



Recurrent Urinary Tract Infections and Asymptomatic Bacteriuria in Adults

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Abstract

Purpose of review Our goal was to summarize recent evidence regarding recurrent urinary tract infections and asymptomatic bacteriuria in different adult populations.

Recent findings Several research groups are focused on the description of resident bacterial flora in the bladder and urinary dysbiosis in the microbiome era. Even the definitions might change in light of these discoveries. However, the role of urinary microbiome and bacterial interference has still to be determined.

Summary Systematic treatment of asymptomatic bacteriuria is not recommended and even classic indications such as asymptomatic bacteriuria in pregnant women are controversial. In fact, its treatment is associated with a higher probability of symptomatic UTI and a higher prevalence of antibiotic-resistant bacteria. Improving the diagnosis of asymptomatic bacteriuria and optimizing the management of recurrent urinary tract infections, especially through non-antibiotics measures, are needed in order to minimise antimicrobial resistance.

Keywords Urinary tract infections · Asymptomatic bacteriuria · Urinary microbiota · Prophylaxis

Introduction

Urinary tract infection (UTI) is a colonization of the urinary system by uropathogenic bacteria, leading to different degrees of inflammatory response. The clinical spectrum is highly variable, ranging from uncomplicated UTIs (cystitis or pyelonephritis in healthy, young women without urinary tract abnormalities) to complicated UTIs affecting frail individuals (including transplant patients, elderly population, neurogenic bladder patients, urinary diversion, catheter related UTIs) and being a frequent cause of morbimortality in these populations, with a high risk of developing

urosepsis, acute and/or chronic renal failure, and even death [1].

Recurrent UTIs (rUTIs) are recurrences of complicated or uncomplicated UTIs occurring three or more times per year, or two in the last six months [1]. Non-complicated rUTIs are relatively frequent in healthy, premenopausal, sexually active women, and especially in postmenopausal women. Recurrent cystitis can be considered uncomplicated, but recurrent pyelonephritis must be considered complicated [2] and prompt extended diagnostic evaluation sought to identify specific aetiology such as stones, neurogenic bladder disorders or vesicoureteral reflux.

Classically considered as “sterile” in healthy individuals, the development of expanded quantitative urine cultures (EQUC) and sequencing-based techniques have shifted this paradigm identifying a wide range of bacterial species in the urine of healthy individuals [3•]. This resident microbial community in the urinary tract or urinary microbiome probably has a role in both sporadic and rUTIs, and recent investigations have suggested a relationship between the urinary flora and the response to oral anticholinergics and

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intradetrusor botulinum toxin injections in urge incontinence [4, 5], although its contribution is still not well understood [6].

Given these findings, experts have suggested the use of the term “urinary tract dysbiosis” instead of “UTI” [7••], given that most pathogenic bacteria are part of the resident urinary tract bacteria, and their pathogenicity may occur following an imbalance of this microbiota [8]. Similarly, it has been demonstrated that urinary microbiome changes preceded the development of a catheter-associated UTI (studying the biofilm flora), and that the former returned to normality after treatment [9].

Asymptomatic bacteriuria (AB) is the term used when a microbiologically-significant bacterial growth in the urine is reached in individuals without signs or symptoms of UTI [10] (which will be discussed in the *Diagnosis* section of this review). In view of the previously stated concepts, we can assume that AB does not require antibiotic treatment except in very specific situations. Furthermore, AB has demonstrated a protective role in women with rUTIs, and treating it is associated with a higher probability of symptomatic UTI and a higher prevalence of antibiotic-resistant bacteria [11].

However, AB is frequently unnecessarily treated with antibiotics. This, together with the widespread use of antibiotics to treat UTI, have been identified among the factors involved in the emergence of dangerous multiresistant bacteria with very large morbimortality, and human, social, and health costs [12, 13].

The aim of this review is to summarise the most recent findings and future perspectives in urinary tract infections and asymptomatic bacteriuria in the adult population.

Epidemiology of rUTI and AB

UTIs are extremely frequent, especially in women, with an estimated 50 to 60% of women affected at some point during their lifetime. Except for a spike between 15 and 24 years, the prevalence of UTIs increases with age, with almost 10% of postmenopausal women being referred with a UTI in the past year [14].

They represent significant burden for all health care systems, with more than 10 million outpatient visits per year in the USA [15], and around 100,000 hospital admissions yearly with estimated annual costs of between 1.6 and 3.5 billion dollars [16]. Moreover, UTIs are the most frequent infection within a hospitalized population, especially in Urology units. The *Global Prevalence Study on Infections in Urology* (GPIU) estimates that 9.4% of urological patients hospitalized between 2005 and 2017 developed a complicated UTI during their hospital stay [17]. In general, the prevalence of healthcare-associated

UTIs (HAUTIs) ranges between 13 and 19% in the USA and Europe, to up to 24% in developing countries [18, 19].

The prevalence of AB ranges widely from 1 to 5% for healthy premenopausal women, to 100% in patients with indwelling catheters [20]. In healthy individuals, AB increases with age from 2% in children to 50% in elderly residents of long-term care facilities. Different factors also are associated with a higher incidence of AB such as diabetes, neurogenic lower urinary tract dysfunction (NLUTD) and pregnancy [21••], as we discuss below.

Risk Factors of rUTI and AB

Female gender is one of the main risk factors in the development of UTIs and AB, probably due to anatomical factors such as the proximity of the external urethral meatus to anus, and the shorter urethral length compared to men. Other risk factors associated to rUTI in women are: the use of spermicides, increased frequency of sexual intercourse, family history, reduced oestrogen levels, increased postvoid residual urine, urinary incontinence and pelvic organ prolapse [1].

Pregnancy is also a risk factor for symptomatic UTI. Prevalence of AB is just slightly superior to non-pregnant women (2–9% vs. 1–5%), but the associated anatomical and physiological changes predispose pregnant women affected by AB to develop upper UTIs, that have been associated to adverse perinatal outcomes [22].

Asymptomatic bacteriuria is also more frequent in diabetic patients than in healthy controls (17% vs. 10%), and it can progress to symptomatic UTI in up to 20% of them within 6 months, especially if glycemic control is suboptimal [23, 24].

Catheterization, both indwelling or intermittent, or even the use of a condom catheter, is another well-known risk factor for rUTI and bacteriuria. The daily risk of UTI per catheterization day is approximately 3–7%, and we must assume AB in every patient on permanent catheterization. Patients on clean intermittent self-catheterization also have an increased risk, with 15–85% of them affected by one or more UTIs per year and a prevalence of asymptomatic bacteriuria between 23 and 89% [25].

NLUTD, even in patients voiding spontaneously, is also associated with a higher likelihood of rUTI, with an overall rate of one to 10 UTIs per patient per year. Also, AB rates in this population vary between 42 and 91% depending on the type of bladder emptying method [26]. Specific risk factors that have been proposed in this population are incomplete voiding (postvoid residual urine > 100 cc), bladder or kidney stones, low bladder compliance, vesicoureteral reflux, younger age, and higher levels of disability [27, 28].

Microbiology of rUTI and AB

In the last decade, several groups of investigators have been focusing on the definition of resident bacterial flora of the urinary bladder [8, 29]. The development of 16S rRNA gene amplification and sequencing (and other techniques generally referred to as next-generation sequencing [NGS]) helped in the assessment of microbial diversity in the human microbiota [30•]. This microbial community (also including fungi, protozoa, viruses, and archaeobacteria) is supposed to participate in bladder homeostasis, urothelial integrity, protection against infection, regulation of neurotransmission, and promotion of normal immune functions [31], but the initial steps are focused on investigating the components of commensal and pathogenic flora.

The sensitivity of urine NGS is significantly higher than that of conventional urine culture (69.0% vs. 16.7% in a study by Yoo et al. [32]). Initial approaches to decipher the normal urinary microbiome showed that most frequent taxa are Proteobacteria (*E. coli*), Firmicutes (*Enterococcus faecalis*), Actinobacteria (*Gardnerella*), and Bacteroidetes [8, 33]. In the urine of female patients with acute uncomplicated cystitis, Phylum Proteobacteria and Class Gammaproteobacteria (*Pseudomonas aeruginosa*) have been more frequently detected, whereas in those with recurrent cystitis, a higher proportion of Phylum Bacteroidetes, Class Bacteroidia, Order Bacteroidales, Family Prevotellaceae, and Phylum Firmicutes (*Streptococcus agalactiae*, *Aerococcus urinae*, *Staphylococcus aureus*, *Streptococcus anginosus*) have been found [32, 34, 35]. In fact, the proportion of species comprising the urinary microbiome is dynamic and might change in different states of diseases, as happens with cutaneous, gastric, colon, and gut microbiomes [36].

However, we should consider that not all bacterial strains have the same ability to develop UTI (or virulence potential); furthermore, some strains could be protective. The most studied genus is Enterobacteriaceae, particularly the species *Escherichia coli*. Type 1 pili, with the adhesin FimH in their tip, are essential in bladder colonization and UTI progression. The adhesin binds specifically to mannosylated uroplakins and proteins in both the superficial bladder epithelium and underlying layers, allowing the creation of biofilm-like intracellular bacterial communities (IBC) [37–40]. In a comparative genomic study of *E. coli* isolates from women with recurrent UTI, it was shown that putative urovirulence factors (PUFs) are mostly associated to the phylogenetic clade B2, and that they are not necessarily linked to pathogenicity [37]. Moreover, certain *E. coli* strains were able to outcompete other strains even when presenting with fewer PUFs [37]. The authors also revealed that bacterial gene expression may vary under

certain culture conditions, and that particular mouse models were more reluctant to become infected, hypothesizing that barriers to infection are different among them based on their genetic background [37]. In other words, they suggest that both bacterial virulence phenotypes and host susceptibility are key factors in the development of UTIs.

Diagnosis of rUTI and AB

Diagnosis of AB is based on positive cultures in the absence of urinary symptoms. Two consecutive cultures are necessary in women [1, 21••, 41–43], while only one positive sample is necessary to diagnose men with AB [1, 44•].

rUTI are usually defined, as previously mentioned, as two or more episodes of urinary infection in 6 months or three or more in one year [1, 45, 46]. Every episode of UTI should be assessed through symptoms' consideration and a urine culture (using midstream urine) [41, 46, 47]. This definition entails a period without infection in between recurrences. However, it is not clear whether it is necessary to perform a urine culture to confirm bacteria eradication between episodes given that if a urine culture is positive in an asymptomatic patient in this scenario, it can be considered as AB and there is no indication to treat it [45].

A detailed clinical history should be taken for each UTI episode enquiring about common acute-onset symptoms: i.e., dysuria, frequency, urgency, suprapubic pain, haematuria, malaise, malodorous urine, and, in frail patients, cognitive impairment [45, 48, 49].

A physical exam should be performed in all patients with rUTI. Men with rUTI or AB should undergo a digital examination in order to assess bacterial prostatitis or prostatic enlargement [1]; in peri- and post-menopausal women, pelvic organ prolapse and signs of genital atrophy have to be ruled out [45, 46, 48]. Post-void residual urine may be measured in order to exclude incomplete emptying [45, 48, 50].

Urine culture is essential; up to a 33% of patients complaining of UTI symptoms and 41% of those who have pyuria in the urinalysis will have a negative urine culture that may rule out common microorganisms UTI [51]. Moreover, cultures help in the differential diagnosis of the urinary or pelvic symptoms, which might be caused by other conditions such as sexually transmitted diseases [52], overactive bladder [53, 54], vulvovaginitis [50, 55], genitourinary syndrome of menopause [56], or even COVID-19 [57]. Similarly, if we disregard urinary symptoms and base our diagnosis only in urine culture results, we will diagnose (and might treat) many cases of AB [58]. The most common bacterial genus isolated is *Escherichia*, followed by *Klebsiella species*, *Enterococcus species* and *Pseudomonas species*, but the isolated pathogen may depend upon patients' urological background [59].

In general, a urine culture is considered positive (i) if originating from a mid-stream sample, it shows $\geq 10^5$ colony-forming units (CFU) per ml, or (ii) when collected from a catheterised sample, shows $\geq 10^2$ CFU per ml [1, 43, 60]. However, this threshold has not been updated since 1956, and it is based on a study performed in asymptomatic women; therefore, it may not be useful for symptomatic patients [61].

Some societies recommend lowering this cut-off value in symptomatic uncomplicated infections with only one identified uropathogen to 10^2 CFU/ml [41, 42, 46, 55, 62], as this low count of CFU suggests significant bacteria in these patients. It has even been proposed that for a more accurate diagnosis, each uropathogen should have its own unique threshold [35, 50] due to the fact that even when a low CFU count is found, it might have a role in maintaining persistent inflammation in the bladder, especially for those bacteria having specific virulence factors [63].

New modalities of urine culture, such as the expanded quantitative urinary culture (EQUC), have arisen and have allowed a more precise identification of uropathogens as they use a higher volume of urine, different media for culturing (including anaerobic conditions), and a lower cut-off value for considering the test positive [29, 35, 64•]. Others, such as DNA identification with polymerase chain reaction (PCR), might even detect genes conferring resistance to different antibiotics [59, 65].

For rUTI, imaging and invasive tests are not mandatory except for cases where a complicated UTI is suspected, such as in the presence of cancer, fistulae, bladder outlet obstruction, NLUTD, renal calculi, or other relevant diagnoses [1, 46, 48, 55], as the diagnostic yield of these tests is low [66, 67]. Likewise, for AB, only urinary stones must be ruled out when urine cultures are positive for urease-producing bacteria.

Prophylaxis of Recurrent UTI

It is well-known that antibiotic resistance in common uropathogens is increasing, which jeopardises the efficacy of the treatment of severe infections with multiresistant strains [68, 69], and the *World Health Organization* (WHO) has stated that “the world is heading towards a post-antibiotic era in which common infections could once again kill” [70]. For this reason, Antimicrobial Stewardship programs have been developed, which aim to optimise clinical outcomes and ensure cost-effective therapy whilst minimising unintended side effects of antimicrobial use [1, 71]. Objective 3 of the WHO’s *Global Action Plan on Antimicrobial Resistance* includes the reduction of the incidence of infection through effective sanitation, hygiene and infection prevention measures [70]. In this regard, prophylaxis of recurrent UTIs is

of utmost importance, and should focus on the reduction of risk factors, aetiological treatment, and non-antibiotic prophylactic measures, where possible.

Hormonal Replacement

Vaginal oestrogen is indicated in post-menopausal women with recurrent UTIs [1]. Two types of oestrogenic receptors (ER) can be identified in the urogenital tract: ER β , which is the major ER type in the urinary bladder and is involved in epithelial differentiation and maintenance, whereas ER α dominates in the vagina [72]. Also, the G protein-coupled receptor for oestrogen (GPR30 or GPER-1) has been described, which is a membrane receptor present in the cellular surface that has been widely studied in gynaecological tumours, but also in bladder [73] and prostate cancer [74]. In vitro studies have shown that oestrogen promotes proliferation of epithelial cells of the lower urinary tract and induces the expression of intercellular junction proteins including E-cadherin via the ER β [72]. More pronounced focal adhesions and more stress fibres, predominantly at the cell periphery, can be found in urothelial cells exposed to oestradiol [75].

Dr-adhesins bearing *Escherichia coli* are considered a virulence factor through which the bacteria can evade the host immune system by internalizing into the uroepithelial cells by binding to CD55 expressed on host-cell membranes [76]. A lack of intercellular junction proteins as explained before can favour this mechanism and the development of quiescent intracellular reservoirs in deeper layers of the urothelium, facilitating recurrent UTIs [72].

The human antimicrobial peptide cathelicidin LL-37/hCAP-18 is expressed by various epithelia but also by neutrophils and other immune cells. In a study by Lüthje et al., serum cathelicidin was significantly lower in postmenopausal women, and they showed that peptide levels correlated directly to oestradiol levels, implying that oestrogen has an influence on the expression of this and possibly other antimicrobial peptides like hBD1, hBD2, hBD3, psoriasin, or RNase 7 [75].

Immunoactive Prophylaxis

To understand the mechanism of action of oral immunomodulation or trained immunity for the prevention of UTIs, we must cast our mind back to innate immunity, which is likely to be mediated via toll-like receptors and recognition of lipopolysaccharide in the outer membrane of *E. coli* and most other gram-negative bacteria. Since various classes of uropathogens share similar antigenic structures, they can be recognized by the same pattern

recognition receptor [77]. This trained immunity is based on epigenetic reprogramming of myeloid cells (dendritic cells, macrophages, NK-cells) that result in changes in their phenotypic and metabolic behaviour [78]. It has been described that dendritic cells have the capacity to generate Th1/Th17 and IL-10-producing T cells [79]. Also, modulation of myeloid progenitors in the bone marrow of mice has been shown [80].

The oral immunostimulant OM-89 (Uro-Vaxom®), an oral tablet with an extract of 18 different serotypes of heat-killed uropathogenic *E. coli*, is taken once a day for three months, and afterwards a booster tablet is indicated for the first 10 days of months six–nine [81]. The risk ratio for the development of at least one UTI in the female population was significantly lower in the OM-89 group (RR 0.61, 95% CI 0.48–0.78), and the mean of UTIs was about half compared to placebo [77]. Recently, the utility in neuro-urological patients has also been suggested in a small RCT [82] and in a retrospective study [83], and the results of the clinical trial NCT02591901 are expected [84].

MV140 (also known as Uromune®) is a polyvalent bacterial preparation of whole heat-inactivated bacteria including equal amounts of *Escherichia coli*; *Klebsiella pneumoniae*; *Proteus vulgaris*; and *Enterococcus faecalis*. Giving 2 puffs (each containing 10^8 bacteria) daily sublingually for three months, patients treated with MV140 had significantly higher UTI-free rates (35–90%) than subjects treated with six months of antibiotic prophylaxis (0%) over 15 months [81, 85]. However, these outcomes come from retrospective studies and the results of randomised, placebo-controlled clinical trials are pending.

Urovac® is a vaginal vaccine which contains heat-killed bacteria including six different serotypes of uropathogenic *E. coli*, and one strain each of *Proteus vulgaris*, *Klebsiella pneumoniae*, *Morganella morganii* and *Enterococcus faecalis*. The original dosage was three vaginal suppositories at weekly intervals (of one or two ampules of 2×10^9 organisms per suppository), and afterwards a booster immunization was added which consisted of three additional vaccine suppositories at monthly intervals. Thus, results are heterogeneous and, although a reduction in the occurrence of UTI has been noted [81, 86], no recommendation has been made in the latest EAU Guidelines [1].

Other Preventive Non-antibiotic Measures

No new reports supporting a change in the evidence about the usefulness of other prophylactic measures like probiotics, cranberry preparations (rich in proanthocyanidines), D-mannose, or endovesical instillations of hyaluronic acid and chondroitin sulphate (for glycosaminoglycan [GAG] layer replenishment) have been published [1].

Antibiotic Prophylaxis

In the EAU Guidelines, fosfomycin trometamol 3 g every 10 days and trimethoprim 100 mg once daily are proposed as continuous low-dose prophylaxis for 3 to 6 months; during pregnancy, cephalexin 125 mg or 250 mg or cefaclor 250 mg once daily may also be counselled if the patient has suffered from previous recurrent UTIs [1]. However, we must take into consideration the suggestion that a subinhibitory concentration of antibiotics might cause significant changes in the repertoire of bacterial virulence and biofilm formation in uropathogenic *E. coli*, corresponding to acquired cross-resistance due to genomic changes [87].

Although nitrofurantoin 50 mg or 100 mg once daily can also be recommended, serious pulmonary and hepatic complications have been described in long-term users (usually over six months), specially diffuse interstitial pneumonitis or pulmonary fibrosis [88]. For example, the Spanish Drug Agency (*Agencia Española de Medicamentos y Productos Sanitarios*, AEMPS) prevents the use of this antibiotic agent as a prophylactic treatment and advises limiting its indication to acute UTI episodes for seven days or less [89].

Asymptomatic Bacteriuria

The new evidence summarised above supports the current recommendation in clinical guidelines against treating most cases of AB to decrease or decelerate antibiotic resistance and reduce side effects in patients. Future studies may find even more harmful effects of this inappropriate treatment. In the following paragraphs we shall summarize the most recent advice in specific populations.

Pregnancy

Asymptomatic bacteriuria in pregnancy still indicates screening and treatment according to most international guidelines (for example, EAU, AUA, US Preventive Services Task Force, Infectious Diseases Society of America), but the level of evidence for this recommendation is low due to different reasons. First, there is a lack of complete understanding of the mechanisms linking AB, pyelonephritis, and perinatal complications. Furthermore, most available studies have a high risk of bias and were published between the 1960s and 1980s, making it difficult to compare them with current health protocols and services [90].

The first randomized controlled trial since 1987 with high methodological quality was conducted in 13 centres in The Netherlands between 2011 and 2014, and it did not show any differences between treatment and observation of asymptomatic bacteriuria. They compared the effect of screening and subsequent treatment with nitrofurantoin, placebo, or

observation in more than 5,000 pregnant women. The study showed a slightly higher incidence of UTIs and pyelonephritis (2.4 vs. 0.6%) in those women with asymptomatic bacteriuria without treatment, but no differences in perinatal complications were observed, thus not supporting the policy of screen-and-treat frequently followed in most countries [91]. A systematic review with stricter inclusion criteria (only studies with asymptomatic women were included) failed to show consistent evidence to support routine screening of AB in pregnant women [92].

Postmenopausal Women

AB incidence in postmenopausal women ranges from 2.8 to 8.6% [21••]. This can be explained by the reduction in *Lactobacillus* in the vaginal flora due to low oestrogen levels, the elevation of normal pH, thus facilitating the vaginal colonisation by gut bacteria [72]. However, no advantage has been shown in the development of UTI or AB clearance by antibiotic treatment [44•].

Elderly and Frail Patients

We outlined earlier that approximately half of elderly residents in long-term care facilities may have AB [21••]. Institutionalized adults frequently have a variable association of more comorbidities, functional impairment, and cognitive deficits, which predispose them to higher rates of AB and UTIs [93]. Bowel and/or bladder incontinence, functional disability, and dementia have been classically associated with persistent AB in women [93, 94]. However, no benefit has been proven if AB is systematically treated [44•].

A recent systematic review showed that the studies exploring the relationship between confusion and UTI have poor case definitions for both concepts, and even an inadequate control of confounding factors, thus impeding to determine the association between them [95]. Therefore, the *Infectious Diseases Society of America* recommends investigating other causes of delirium in older patients with functional or cognitive impairment and AB who do not present with systemic signs of infection or genitourinary symptoms [21••, 96].

Neurogenic LUTD

As emphasized before, the prevalence of AB in neurogenic LUTD is high, but only a low proportion of these bacteriuric patients develop symptomatic UTI even after invasive investigations such as urodynamics [26]. Thus, antibiotic treatment in this population must be limited to those with symptomatic UTI. Reducing antibiotics exposure is crucial in a group of patients that have shown up to 50% of multiresistant bacteria in urine due to frequent hospitalizations and

antimicrobial treatments. “Pathological” urine findings such as a positive urine culture, pyuria and/or nitrite positivity do not justify the prescription of antibiotics, and clinical criteria should always prevail [97].

Transplant and Immunosuppressed Patients

Incidence of AB in kidney transplant recipients is between 5 and 27% [98, 99], and current guidelines do not recommend treating it [1, 100•]. In fact, many societies even advise not screening for AB, at least in the first month after surgery [1, 21••, 41]. No recommendations for the first/second months after kidney transplantation can be made [21••, 60, 100•].

Up to 37% of kidney transplant recipients may suffer from a clinically relevant UTI after surgery [101, 102], and these infections are known to cause graft dysfunction and high morbidity and mortality [101, 103, 104]. However, modern studies have not shown these effects in transplant recipient’s patients with AB [105, 106].

A recent systematic review comprising over 200 patients compared treatment of AB versus no treatment and found that antibiotics did not significantly change the risk of suffering a symptomatic UTI (RR 0.86, 95% CI 0.51 to 1.45), alter all-cause mortality (RR 2.23, 95% CI 0.21 to 23.86), graft loss (RR 1.11, 95% CI 0.07 to 17.36), acute rejection (RR 0.93, 95% CI 0.44 to 1.97) or graft function (mean difference in serum creatinine concentration -0.06 mg/dL, 95% CI -0.19 to 0.08) [107]. And one randomized clinical trial found higher rates of resistant bacteria in patients who had received antibiotics for AB compared with those who had not [108]. Therefore, treating AB in organ recipient patients does not seem to be worthwhile.

Nevertheless, outcomes may depend upon the microbe causing the colonization, as some reviews have found *Ureaplasma* spp. and *Mycoplasma* spp. causing severe damage to kidney grafts [109]. It has also been shown that the presence of specific virulence factors may directly influence the pathogenesis of UTI [110].

For other solid organ transplants, screening and treatment of AB is not recommended [21••] as effects of bacteriuria or even UTI do not seem to significantly affect organ function or increase patients’ morbidity [111].

There is a knowledge gap regarding screening and treatment of AB in patients with high-risk neutropenia [21••, 41, 60].

Catheter Associated

Patients with transurethral, suprapubic or nephrostomy catheters must be considered bacteriuric, as a rule. It is crucial to distinguish between catheter-associated UTI, which requires antibiotic treatment, and catheter-associated bacteriuria, which does not. Transurethral and suprapubic catheter

exchanges or placements in patients with AB do not require antibiotic treatment or prophylaxis; however, in case of AB and nephrostomy tube or ureteral stent manipulation, treatment of asymptomatic bacteriuria prior to procedure is recommended [1].

Periprocedural and Perioperative Investigation of Bacteriuria

Urological Procedures (UDS, Endourological Procedures, Prosthesis, etc.)

Strong recommendations have been made by many societies advocating urine culture prior to urological procedures breaking the mucosa. If AB is confirmed in the culture, a short course [112] of directed antibiotic treatment must be administered at least 30 min before the intervention [1, 21••, 41, 43, 46, 113] and it might be continued until catheter removal (if this is intended to be done in the short-term) [41].

However, a recent observational study performed in a cohort of patients undergoing urological surgery showed no association between AB and postoperative infectious complications (HR, 1.02; 95% CI, 0.26–3.96) [114]. Furthermore, another study analysing pre-TURP urine samples and intra-procedure serialised blood cultures found that microbes causing bacteraemia were not the same as those cultured in the urine [115•].

A recent report also assessed the need to treat AB prior to prostate biopsies and found that none of the men with preoperatively diagnosed AB developed any infectious complication after the biopsy [116].

Evidence supports not treating bacteriuria if the urological procedure does not damage the mucosa:

- An observational study made in patients undergoing a cystoscopy showed that less than 5% of patients with AB developed a febrile UTI after the test and none of them progressed to sepsis [117].
- A study assessed the need of AB screening before vesical instillations with BCG and showed the same number of patients having a UTI in both cohorts (screened and unscreened); moreover, they reported delays in 2.5% of BCG treatment in AB patients due to the need to perform urine culture [118].
- Controversy exists regarding AB treatment prior to urodynamic studies or intravesical treatments. Most societies recommend against treating it, as many studies have not found any benefit from antibiotics [119]. Nevertheless, a recent meta-analysis found a higher rate of symptomatic UTI in patients with previous AB who did not receive antibiotic prophylaxis (RR = 0.65, 95% CI: 0.48–0.88) [120]. However, they did not analyse more severe com-

plications (sepsis, hospitalization, and death). In this regard, a study examining the association between AB and adverse events in patients receiving intra-detrusor onabotulinumtoxinA injections found that untreated AB did increase the risk of symptomatic UTI, but it did not increase the risk of urosepsis, hospitalization, or therapy failure [121].

To our knowledge, there are no studies addressing screening and treatment of AB in patients undergoing urological prosthetic surgeries. However, the Infectious Diseases Society of America does not recommend screening for it.

Orthopaedics and Other Surgery (Vascular, and so on.)

Although peri-operative ITU is known to increase the risk of prosthetic infection [122, 123], this is not the case with non-urological prosthetic infection in patients with AB [124, 125•, 126, 127]. Furthermore, some studies have found that bacteria causing prosthetic joint infection are not the same as those producing AB [128, 129]. Therefore, most societies advocate not screening for or treating AB in these patients [1, 21••, 41, 130].

The Spanish Society of Clinical Microbiology and Infectious Diseases only recommends screening and treating AB in neurogenic or incontinent patients, as well as those with indwelling urine catheters, prior to prosthetic spinal surgery to avoid Gram-negative surgical site infections [41]. However, a recent study did not find differences in terms of surgical site infection, readmission or symptomatic UTI [131]; therefore, no consensus exists in these particular cases.

Conclusions

Systematic treatment of asymptomatic bacteriuria is not recommended, and it is associated with a higher probability of symptomatic UTI and a higher prevalence of antibiotic-resistant bacteria. Improving the diagnosis of asymptomatic bacteriuria and optimizing the management of recurrent urinary tract infections, especially through non-antibiotic measures, are needed in order to minimise antimicrobial resistance. Advances in microbiome description and assessment are expected.

Declarations

Conflict of Interest David Hernandez-Hernandez reports speaker honorarium from Pierre Fabre, Astellas, Asofarma, Lacer, Almirall and Alter; and travel grants from Pierre Fabre and Lacer, all outside of the submitted work.

Barbara Padilla-Fernandez reports personal fees and other from QP-harma, outside the submitted work.

David Castro Diaz reports other from Pierre Fabre, other from Astellas, other from Medtronic, other from Lacer, other from Boston Scientific, all outside the submitted work.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of importance
- Of major importance

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