Asymptomatic bacteriuria in hospitalized patients

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Abstract

Asymptomatic Bacteriuria (ABU) in hospitalized patients is a relatively frequent event and is mainly seen in patients with co-morbidities.

This chapter incorporates the 2016 Guidelines on Urological Infections of the European Association of Urology and the latest Guideline of the Infectious Diseases Society of America for the management of ABU. A systematic literature search in Medline, Cochrane and Embase was also carried out. The following keywords were used: *ABU and hospitalized/inpatients, ABU and elderly institutionalized residents, ABU and diabetes, ABU and urinary stents/catheters, ABU and stones, ABU and surgical procedures, ABU and renal transplantation, ABU and spinal cord injury*. A total of 849 publications were identified and screened by title and abstract. 32 papers were included in the review.

The host immune response in patients with ABU is less intense than usually found in patients with symptomatic urinary tract infections. ABU is more frequent in patients with dementia and pulmonary diseases, and related to well known risk factors for urinary tract infections such as diabetes, presence of permanent urinary devices, infected stones, spinal cord injury, and renal transplantation.

In conclusion, ABU is common in hospitalized patients. Elderly subjects have an increased prevalence of ABU, presumably secondary to concomitant diseases and conditions such as diabetes, urinary retention, urinary incontinence and/or indwelling urinary catheters. In most cases ABU should not be treated with antibiotics. According to the principles of antibiotic stewardship alternative therapeutic approaches should be adopted in hospitalized patients with ABU.

Summary of recommendations

- ABU in hospitalized patients and elderly institutionalized residents is frequently associated with concomitant co-morbidities (LoE 1b).
- Antimicrobial treatment does not have significant benefits in terms of re-infection or uro-sepsis episodes in these patients (LoE 1b, GoR A).
- ABU is associated with an increased risk of urosepsis in women with diabetes; but treatment of ABU does not reduce the risk of symptomatic infections (LoE 2b, GoR B).
- Patients with ABU and risk factors such as permanent urinary devices (stents, catheters, nephrostomy tubes), infected urinary stones and spinal cord injury, should not be treated with antibiotics.
- ABU in kidney transplant patients should not be treated after the first month – it is unknown whether it needs to be treated during the first month (LoE 1b, GoR A) (LoE 1b, GoR A).
- ABU should be treated in patients supposed to undergo endourological procedures with mucosal breakage (LoE 1b, GoR A).

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1 Introduction

The term asymptomatic bacteriuria (ABU) means that one or more bacterial strains have been identified in the urine samples of patients without symptoms of Urinary Tract Infection (UTI) [1]. The critical number of colony forming units is 10^5 in women and men. The prevalence of ABU varies widely in the population and is related to age and presence of significant co-morbidities. Screening and treatment of ABU is generally recommended only during pregnancy [2] and in the preoperative evaluation of men before selected urological procedures [3]. Hospitalized patients may develop ABU related to community-acquired infections, as well as from atypical bacterial strains such as ESBL resistant *E. coli*, Carbapenemase resistant *Klebsiella pneumoniae* or other combined infections often seen in institutions. The microbiological criterium for the diagnosis of ABU in men is not well validated but bacterial concentrations in urine in the range from 10^3 to 10^5 cfu/mL in a single voided urine specimen have been suggested (reproducible in 98% of asymptomatic outpatients when the culture is repeated within a week) whereas it should be $>10^5$ cfu/mL in two consecutive urine specimens in women [4], [5], [6]. Pyuria is a sign of inflammation in the genitourinary tract and is commonly found in subjects with ABU but also in other genitourinary tract diseases with negative urine cultures. Thus, pyuria only is not sufficient to diagnose bacteriuria and the presence or absence of pyuria does not differentiate symptomatic from asymptomatic urinary tract infections [1].

ABU in hospitalized patients is relatively common and is mainly associated with the presence of co-morbidities. It is often seen in elderly people and in patients with urinary tract obstruction and/or urinary incontinence, many of whom are candidates for urological surgical procedures.

Despite the fact that several guidelines regard the test to be of paramount importance to prevent development of UTIs after the procedure, urine culture tests are not always performed before urological procedures [7].

Host variables and bacteria-related virulence factors may be associated with an increased risk of developing ABU in hospitalized patients.

2 Methods

This chapter incorporates the 2014 Guidelines on Urological Infections of the European Association of Urology (EAU) and the latest Infectious Diseases Society of America Guideline for the management of ABU [1], [7]. Moreover, a systematic literature search in Medline, Cochrane, and Embase has been carried out. The following keywords were used: *ABU and hospitalized/inpatients, ABU and elderly institutionalized residents, ABU and diabetes, ABU and urinary stents/catheters, ABU and stones, ABU and surgical procedures, ABU and renal transplantation, ABU and spinal cord injury*. The limitations used were age over 18 years, clinical studies, English language and peer reviewed papers. A total of 849 publications were identified, and screened by title and abstract. 32 papers were included in the review. The studies were rated according to the level of evidence (LoE) and the grade of recommendation (GoR) according to ICUD standards.

3 Results

The outcome of our systematic review is presented and discussed for separate clinical situations.

3.1 Patient characteristics and virulence factors

The host immune response in patients with asymptomatic bacteriuria seems to be less than in patients with symptomatic urinary tract infection. Proteomic data obtained from urine sediment of 120 subjects demonstrated a substantial inflammatory and antimicrobial immune response with high abundance of proteins from activated neutrophils (associated with pathogens in most cases) and confirmed leukocyte esterase activities and abnormal leukocyte counts at microscopy [8]. Lutay and co-workers found that

asymptomatic bacteriuria strain inoculated in human cells is capable of activating a broad suppression of RNA-polymerase II-dependent host gene expression with a subsequent reduced host immune response in comparison with acute pyelonephritis strains [9]. The same results have been found by other authors. The innate host immune response was evaluated in 23 patients with asymptomatic bacteriuria generated by inoculation of *nonvirulent E. coli* 83972 strain. Cytokine/chemokine levels were analyzed in the urine of these patients prior to and after strain inoculation. The authors concluded that the host immune response in patients with asymptomatic bacteriuria is determined by innate immune mediators and that host genetic variability influences the quantifying response [10]. Dobrindt and co-workers confirmed these data and demonstrated that adaptation of *E. coli* 83972 to prolonged growth in the urinary tract involves responses to specific growth conditions present in the individual host [11].

Other variables originating from bacterial virulence factors should also be considered. Bacterial strains isolated from healthy schoolgirls or hospitalized urology patients with ABU were compared with commensal strains isolated from the intestinal flora of children without urinary infection. All isolates from the two populations affected by asymptomatic bacteriuria had similar virulence genetic characteristics but uropathogenic *E. coli* virulence genes were less frequently attenuated in the hospital strains [12]. These results indicate that some ABU related strains undergo a programmed reductive evolution within human hosts and hospitalized patients seem to have higher susceptibility to aggressive infections [13]. Marschall and co-workers demonstrated that *E. coli* related ABU was frequent and more common in patients with dementia and chronic pulmonary disease in a 12-month prospective cohort study on adult inpatients in a tertiary care hospital. Their conclusion was that patient characteristics but not virulence factors discriminate between asymptomatic and symptomatic *E. coli* bacteriuria in the hospital setting [14].

3.2 Elderly institutionalized residents

Some studies aimed to determine the effects of eradicating ABU in nursing home residents regarding the severity of chronic urinary incontinence, infection recurrence, behavioral changes and mortality among non-catheterized men [15], [16], [17], [18], [19].

The results of these studies demonstrated that eradicating bacteriuria had no short term effects on the severity of chronic urinary incontinence among nursing home residents. Ouslander and co-workers found that ABU was temporarily eradicated in about 40% of residents by immediate 6-day antibiotic therapy and another 10% of subjects had persistent ABU after the therapy. The presence of pyuria did not affect the results [15].

Another report evaluated the effectiveness of antimicrobial therapy in decreasing the episodes of bacterial reinfection. The authors found that untreated women experienced higher rates of bacteriuria than those treated by antibiotic therapy but episodes of reinfection as well as adverse events were more common in the treated group [16]. These data suggest that in elderly institutionalized women, bacteriuria is persistent and antimicrobial therapy is harmful and more costly.

Similarly, antimicrobial treatment did not show improvement in physical or mental function and did not significantly change the proportion of patients without bacteriuria compared with placebo (21% vs. 32%) [19]. Moreover, other authors confirmed that mortality was not significantly different among subjects undergoing antimicrobial therapy and subjects undergoing no treatment [17].

Although the institutionalized elderly non-catheterized population has a higher prevalence of ABU, antimicrobial treatment does not appear to have significant benefits for clinical outcomes [20].

3.3 The role of diabetes in hospitalized patients

Patients with diabetes have increased risk of urinary tract infections. Most UTIs in diabetic patients are community acquired infections and patients are treated as outpatients. ABU is often diagnosed by routine urine examination in hospitalized patients. Other host factors that enhance the risk of UTI in diabetics include age, poor metabolic control, and long term complications such as diabetic nephropathy

and cystopathy. Subjective symptoms such as frequency and dysuria may be related to these complications rather than bacteriuria. Thus ABU episodes may be misidentified as symptomatic infection. Autonomic neuropathy involving the genitourinary tract as a consequence of diabetes may result in dysfunctional voiding and urinary retention which decrease the physical bacterial clearance through micturition, thereby facilitating bacterial growth [21].

Elevated glucose concentrations in urine may promote the growth of pathogenic bacteria. Various impairments in the immune system including humoral, cellular, and innate immunity may further contribute to the pathogenesis of ABU and UTI in diabetic patients.

Although ABU has been found to be associated with an increased risk of hospitalization for urosepsis in a prospective observational study among women with diabetes, treatment of ABU did not reduce the risk of symptomatic urinary tract infections [21].

A recently published meta-analysis investigated whether ABU is truly more common in patients with diabetes than among control subjects. 6,281 patients from 21 articles were studied. ABU was present in 12.2% of subjects with diabetes and in 4.5% of controls, with an odds ratio of 3.0 (95% CI 1.1–8) in patients with type I diabetes and 3.2 (2.0–5.2) in patients with type II diabetes as compared to control subjects [22].

3.4 Patients with permanent urinary devices

Urinary infections account for about 40% of hospital acquired/nosocomial infections, and about 80% of urinary tract infections acquired in hospitals are associated with urinary catheters or other devices [23].

Although catheter-associated urinary tract infections (CAUTI) and catheter associated asymptomatic bacteriuria (CAABU) are clinically distinct entities, most papers describing the risk of bacteriuria do not distinguish between them [24]. Kizilbash and co-workers investigated 444 episodes of catheter-associated bacteriuria in 308 patients in a retrospective cohort study with 30 days followup after identification of a positive urine culture. 128 (41.6%) patients had CAUTI, and 180 (58.4%) had CAABU. Three episodes of bacteriuria were followed by bacteremia from a urinary source (0.7%). CAUTI, rather than CAABU, was associated with bacteremia from any source, but neither CAUTI nor CAABU predicted subsequent mortality. Use of antimicrobial agents to treat bacteriuria was not associated with either bacteremia from any source or mortality [24]. Kidd and co-workers investigated the advantages and disadvantages of alternative routes of short term bladder catheterization in adults in terms of infections, adverse events, replacement, duration of use, participant satisfaction, and cost effectiveness. Participants with indwelling catheters had more cases of asymptomatic bacteriuria (RR 2.25, 95% CI 1.63 TO 3.10), although the duration of catheterization was shorter in the indwelling urethral catheter group [25]. On the other hand, some authors demonstrated that ABU overtreatment was greater in the long-term care patients (51.8%) than acute care (30.8%), suggesting a need for increased attention to antibiotic stewardship. Appropriate interventions are able to determine a significant reduction of ABU overtreatment in long-term care (from 1.6 to 0.6 per 1,000 bed-days) [26].

Nephrostomy tube placement has a lower risk of subsequent pyelonephritis compared to urethral catheter placement, although ABU is present in 7.5% [27]. Bahu et al. found 89% ABU events in patients with primary nephrostomy tube placement, and rarely in patients who underwent nephrostomy tube exchange [27]. These results seem to be paradoxical considering the increased risk of slime production and intrarenal migration during a nephrostomy tube replacement manoeuvre. Other authors compared the effect of nephrostomy tube change on the occurrence of asymptomatic bacteremia. They found asymptomatic bacteremia in 11% of cases and no significant effect of antibiotic prophylaxis in bacteremia prevention [28].

Ureteral stenting seems to be unrelated to the frequency of ABU episodes except in patients who have undergone kidney transplantation. These patients have a high incidence of bacteriuria during the first

month after transplantation (56.7%) and ABU in a long term period is seen in about 40% of cases [29], [30]. The most common organism is *E. coli* (40%), but there are also many cases of *Klebsiella* infection (19%). The high incidence of bacteriuria during the early post–kidney transplant period requires increased awareness and surveillance [29].

3.5 Patients with infected stones

Otherwise asymptomatic renal stones may be the cause of bacteriuria. This relationship should be considered before surgical removal of a stone in patients with bacteriuria. Hugosson and co-workers separated stone related infections (70%) from regular lower urinary tract infections (30%) by ureteral catheterization. Even very small stones were shown to be the cause of decade-long bacteriuria with encouraging results obtained from stone removal (87% of infections were eradicated) [31]. In such cases the presence of urinary stones facilitates the formation of small bacterial sanctuaries without being necessarily related to the physical features of the stones.

Urinary stone formation is otherwise closely related to complicated urinary tract infections (urinary obstruction, neurogenic bladder disorders, urinary diversions, indwelling catheters) due to urease-producing bacteria. Infected urinary stones (struvite, carbonate apatite, ammonium urate) are regularly associated with UTI.

Some studies investigated ABU in patients with urinary stones and without associated risk factors who underwent extracorporeal shock wave lithotripsy (ESWL). Mira Moreno reported only 4.6% incidence of ABU suggesting that antibiotic prophylaxis is not justified in these patients unless there are well-defined risk factors [32]. The American Urological Association guidelines recommend universal antibiotic prophylaxis, whereas the European Association of Urology guidelines recommend prophylaxis only for selected patients. Honey and co-workers investigated 526 patients who underwent ESWL for urolithiasis. Urine dipstick and culture excluded infection in 389 of them. Only 2.8% of patients developed ABU and just one patient got a symptomatic urinary infection [33].

3.6 Candidates for surgical procedures (urology, orthopedic, renal transplantation)

Patients with ABU who undergo traumatic genitourinary procedures associated with mucosal bleeding have a high rate of postprocedure bacteremia and sepsis [1]. Bacteremia occurs in up to 60% of bacteriuric patients who undergo prostate trans-urethral resection, and there is clinical evidence of sepsis in 6–10% of these patients [34]. The effectiveness of antimicrobial treatment in preventing these complications is well documented [35].

There is little information concerning other procedures but any intervention involving mucosal bleeding should be considered to increase the risk of developing bacteriuria and infection [36]. Recent studies demonstrated that treatment of bacteriuria is not indicated prior to minor urologic interventions which do not imply mucosal trauma. Bacteriuria was present in 25% of patients who were candidates for BCG intravesical administration and in 17% of subjects who were candidates for cystoscopy [37].

Pretreatment of ABU is not beneficial for minor procedures (e.g. replacement of a long-term indwelled catheter), but it is mandatory for major surgeries such as transurethral prostatectomy and procedures where the urinary tract is opened [1]. Antibiotic prophylaxis should be given with appropriate dosage and timing. In the absence of an indwelled catheter, antimicrobial prophylaxis can be discontinued immediately after the procedure [35], [38], [39]. Conversely, if the indwelling catheter remains in place after prostate resection, some investigators recommend extended prophylaxis until the catheter is removed [34], [38].

Orthopaedic surgery is relatively frequent in the elderly and some authors investigated the efficacy of preoperative antimicrobial treatment in patients with ABU who underwent hip replacement surgery [40]. They evaluated the risk of wound infection related to the presence of asymptomatic bacteriuria. They

found wound contamination in 6% of treated bacteriuric patients and in 4.8% of those without antibiotic treatment, respectively. Thus ABU is not a cause of postoperative orthopedic surgical site infection and treatment of bacteriuria prior to surgery is not required. Other authors prospectively evaluated 215 consecutive patients who underwent knee arthroplasty. ABU was diagnosed in 11 out of 215 patients (5.1%) and four of these were treated with tailored antibiotics. No significant differences between the two groups of patients were found [41].

Renal transplanted patients have an increased risk of developing bacteriuria as previously described. Almost half of all urinary infections found in transplant patients are diagnosed during the first month following transplantation [42]. In particular, ABU occurred in about 65% of cases. The most frequent bacteria are *Enterococcus spp*. (33%) and *E. coli* (31%). Female gender, previous cytomegalovirus infection and a history of an acute rejection episode are independent risk factors for the development of post-transplant urinary infection [42]. It is not clear whether ABU during the first month after transplantation is related to the specific type of surgery with immune depression or the presence of ureteral stenting. ABU is usually found long-term in 40% of patients [29], [30]. Some authors demonstrated an increased risk of symptomatic urinary infection after appropriate antibiotic treatment of ABUs [43]. Origuen et al. recently demonstrated that systematic screening and treatment of ABU beyond the second month after transplantation provided no apparent benefit among kidney transplantation recipients [44].

3.7 Spinal cord injured patients

Subjects with spinal cord injuries have a high prevalence of ABU [45], [46]. Several studies have shown poor effect of antibiotic therapy in the prevention of subsequent symptomatic urinary infections or ABU recurrences. After 7–14 days of antibiotic therapy 93% of subjects were bacteriuric again within 30 days of the completion of the treatment whereas 85% were bacteriuric within 30 days after a 28 day-course [45]. Reinfection strains showed increased antibiotic resistance.

Two randomized studies in patients with ABU using intermittent catheterization showed no difference between antibiotic treatment and placebo on the rates of symptomatic infection and bacteriuria [47] , [48].

Despite the limited number of clinical trials available in this group of patients, the results obtained uniformly recommend antibiotic treatments of symptomatic infections in spinal cord injured patients [1].

Lavado and co-workers recently demonstrated that moderate-intensity aerobic physical training is effective on ABU recurrences in patients with C8 to T12 spinal cord injury with a significant reduced prevalence from 52.3 to 14.2%. The mechanism by which this occurs is not clear [49].

4 Further research

The main aspects of asymptomatic bacteriuria are related to ASB as a risk factor for development of severe infections on one side, and to overtreatment and antibiotic stewardship on the other. Future research should address the importance of the whole urinary microbiome in patient situations where ASB has a role. We also need more data about the immune response to ABU. Finally, we must explore the effects of adherence to present guidelines recommendations and study the effects of non-antibiotic measures in patients with ASB.

5 Conclusions

ABU is a common finding in hospitalized patients. Elderly subjects have an increased risk of developing ABU, usually attributable to concomitant diseases such as indwelling urinary catheter, diabetes, urinary retention and urinary incontinence.

ABU is also frequent in patients who undergo urological surgical procedures with mucosal bleeding including TURP and prostate biopsy. Stone disease seems to be related to ABU only in the case of

urinary tract obstruction including renal calyxes, whereas patients who previously underwent renal transplantation need attention due to the risk of developing significant infections during short and long term followup.

In many cases ABU should not be treated with antibiotics. Exceptions are before mucosa breaking surgery and in transplant patients during the first month after the surgery.

Alternative treatments other than antibiotics should be explored, investigated and adopted to reduce the risk of developing significant infections in hospitalized patients as well as outpatients with ABU.

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