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Original Article

Antimicrobial use for asymptomatic bacteriuria—First, do no harm

Yana Shpunt MD[1], Inna Estrin BS[1], Yossef Levi BS[2], Hodaya Saadon BS[1], Galit Ben-Yossef BS[1], Lili Goldshtein MSc[1], Dan Klafter MA[1], Shani Zilberman-Itskovich MD[1], Debby Ben-David MD[3], David E. Katz MD, MPH[4], Tsillia Lazarovitch PhD[5], Ronit Zaidenstein MD[2] and Dror Marchaim MD[1,2]

[1]Unit of Infection Control, Shamir (Assaf Harofeh) Medical Center, Zerifin, Israel, [2]Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel, [3]Unit of Infection Control, Wolfson Medical Center, Holon, Israel, [4]Division of Internal Medicine, Shaare Zedek Medical Center, Jerusalem, Israel and [5]Clinical Microbiology Laboratory, Shamir (Assaf Harofeh) Medical Center, Zerifin, Israel

Abstract

Objective: Administration of antimicrobials to patients with asymptomatic bacteriuria (ASB) is a common error that can lead to worse outcomes. However, controlled analyses quantifying the commonality and impact of this practice are lacking. We analyzed the independent predictors for antimicrobials misuse in ASB and quantified the impact of this practice on clinical outcomes.

Design: Retrospective case-control and cohort analyses for calendar year 2017.

Setting: Tertiary-care, university-affiliated medical center.

Patients: The study included adult (>18 years) patients with positive urine culture. Pregnant women, renal transplant recipients, and patients who underwent urologic procedures were excluded.

Methods: ASB was determined according to US Centers for Disease Control and Prevention (CDC) criteria. Multivariable logistic regression models were constructed to analyze predictors and outcomes associated with antimicrobial use for patients with ASB.

Results: The study included 1,530 patient-unique positive urine cultures. Among these patients, 610 patients (40%) were determined to have ASB. Of the 696 isolates, 219 (36%) were multidrug-resistant organisms (MDROs). Also, 178 (29%) patients received antimicrobials specifically due to the ASB. Independent predictors for improper administration of antimicrobials were dependent functional status (adjusted odds ratio [aOR], 2.3; 95% CI, 1.4–3.6) and male sex (aOR, 2; 95% CI, 1.25–2.6). Use of antimicrobials was independently associated with re-hospitalizations (aOR, 1.7; 95% CI, 1.1–2.6) and later, acute Clostridioides difficile infections (CDI) in the following 90 days (aOR, 4.5; 95% CI, 2–10.6).

Conclusions: ASB is a common condition, frequently resulting from an MDRO. Male sex and poor functional status were independent predictors for mistreatment, and this practice was independently associated with rehospitalizations and CDI in the following 90 days.

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Asymptomatic bacteriuria (ASB) is defined as the presence of up to 2 pathogens in a properly obtained urine sample, at a concentration of at least 10^5 colony-forming units (CFU)/mL, in a person with no symptoms or signs indicating a urinary tract infection (UTI) (eg, urgency, increased frequency, dysuria, flank pain, or fever).[1,2] ASB is commonly misdiagnosed as a UTI.[3] Although ASB is common, its prevalence varies in the population depending on age, gender, hormonal status, sexual activity, and presence of genitourinary structural disorders.[4]

Among patients with urinary catheters, it is often difficult to distinguish ASB from symptomatic UTI or other fever-related sources. In 100% of patients with urine catheter for >1 month, bacteria will grow if a culture is obtained but does not necessarily represent a UTI.[5] Febrile illness among patients with a urinary catheter and positive urine culture can lead to a misdiagnosis of catheter associated UTI (CAUTI), although in many cases there is another source of infection and the bacterial growth actually represents ASB.[5] This also results in higher rates of CAUTI attributed to the facility. Moreover, urine cultures are frequently ordered from afebrile patients with chronic catheters, for a wide variety of "indications," further increasing rates of ASB misdiagnoses. In common practice, urine cultures are ordered for patients with catheters and impaired cognition (either chronic or acute).[8] However, in a typical report, 22% of urine cultures represent ASB among these frail patients.[13]

The composition of pathogens that cause ASB is similar to that of pathogens that cause symptomatic UTI, with *Escherichia coli* being the most common organism.[6] Among patients with genitourinary disorders or among elderly institutionalized individuals,

Author for correspondence: Dror Marchaim, E-mail: drormarchaim@gmail.com.
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there is a wider range of pathogens, including a high prevalence of multidrug-resistant organisms (MDROs). In the presence of foreign bodies in the urinary system, polymicrobial bacteriuria is also very common.[7]

In certain populations, "treatment" of ASB is recommended by certain professional societies: patients prior to invasive urologic procedures,[8] among pregnant women,[8] and among kidney transplant recipients.[9] However, prescribers often treat ASB as a UTI even when it is not indicated, specifically among the elderly with cognitive impairment, and/or patients with indwelling urinary catheters, where symptoms are absent. This is a common error, but nevertheless, only a limited number of studies have assessed the risk factors for antimicrobial administration and have quantified the impact of this questionable practice. "Treatment" of ASB may lead to undesirable consequences, such as emergence and/or acquisition of MDROs, side effects from antibiotic usage (eg, hypersensitivity reactions), and *Clostridioides difficile* infection (CDI),[10] but quantified controlled data are lacking. Moreover, antimicrobials prescribed for ASB are associated with increased costs to healthcare systems and a negative ecological impact.[11] The lack of scientifically established data might be the reason that preventive resources to curb these practices are not uniformly implemented.[12] We evaluated predictors of antimicrobials misuse among patients with ASB to quantify the impact of this practice on various clinical outcomes.

Methods

Design and setting

We conducted a retrospective case-control and cohort analysis at the Shamir (Assaf Harofeh) Medical Center (SMC), an 877-bed university-affiliated institution in Central Israel, for calendar year 2017. The study was approved prior to its initiation by the local institutional review board committee. The infection control unit at SMC routinely reviews and reports every positive urine culture, as mandated by the Israeli Ministry of Health (MOH).[14]

Data collection

All patient-unique samples were included, including from patients who were cultured in the emergency room and eventually not admitted. The following data were collected: demographics, background/chronic conditions, various exposures to healthcare, acute illness indices, microbiological data, therapeutic data, and various clinical, microbiological, and fiscal outcomes. MDROs included any of the following: methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), *Pseudomonas aeruginosa* (nonsusceptible to ≥3 classes of supposedly effective antibiotics), extended-spectrum β-lactamase–producing Enterobacterales (ESBL), *Acinetobacter baumannii* (non-susceptible to ≥3 classes of supposedly effective antibiotics), and carbapenem-resistant and/or carbapenemase-producing Enterobacterales (CRE, CPE).[15]

Inclusion and exclusion criteria

The study population consisted of patients <18 years of age, with a positive urine culture, according to the definition of the US Centers for Disease Control and Prevention (CDC).[16] Positive urine culture was defined as the growth of 1 or 2 (but not >2) pathogens, at concentrations of $>10^5$ CFU/mL, with isolation of certain pathogens not included if the isolation was from a single sample (eg, *Candida* spp).[1] Patients were not eligible for inclusion if they met any of the following criteria: (1) age younger than 18 years; (2) pregnancy or peripartum period; (3) prior or right after urologic procedure; (4) kidney transplant recipients; and (5) neutropenia (absolute neutrophil count <0.5 cells/μL). Patients with bacteriuria were categorized as having ASB if there was no documentation of signs or symptoms meeting diagnostic criteria for UTI as per CDC criteria.[16] Specifically, patients could not have one of the following documented symptoms: suprapubic tenderness, costovertebral pain, urgency, increased frequency or dysuria. Patients older than 65 years, with no indwelling catheter and fever (>38°C), could still have ASB if the fever was due to a different established (according to CDC criteria[16]) infectious syndrome. Patients with acute alterations in mental status, who often cannot communicate symptoms, were categorized as having ASB if they had none of the aforementioned signs or symptoms.

Statistical analysis

All data were analyzed using SPSS version 25.0 software (2018; IBM, Armonk, NY). We performed 3 analyses according to conventional methods[17]: (1) descriptive statistics to characterize the study population with ASB; (2) univariable and multivariable (logistic regression) case-control analysis of predictors for prescribing antibiotics for ASB; and (3) univariable and multivariable cohort analyses (logistic and Cox regressions), quantifying the impact of prescribing antibiotics for ASB on various clinical outcomes. These outcomes included mortality parameters, length of hospital stay from culture to discharge among survivors of the index hospitalization, functional status deterioration, "acquisition" of MDROs, later acute CDI, additional hospitalizations in 3 months, and discharge to long-term care facility (LTCF) after surviving the index hospitalization and being initially admitted from home.

Results

Descriptive statistics

During the study period, of the 2,557 positive urine cultures, 397 were duplicates (ie, non–patient-unique cultures), 283 were obtained from pediatrics (<18 years), and 586 patients were excluded due to other exclusion criteria (eg, pregnancy, urologic procedure). Of the 1,530 patient-unique cultures, 610 (40%) patients had ASB. The median age of the ASB population was 80 years (IQR, 70–87), 381 (63%) were women, 503 (83%) were older than 65 years, and 209 (34%) were chronically cognitively impaired. In addition, 254 (42%) were hospitalized in the previous 3 months and 309 (51%) stayed in LTCF during the previous 3 months. The median time from admission to ASB diagnosis was one day, which implies that most ASBs were diagnosed upon admission. Also, 186 patients (31%) had fever due to other infectious syndromes on the day of ASB diagnosis. The in-hospital mortality rate was 24%. Among survivors of the index hospitalization, the median length of stay from culture to discharge was 9 days; 40% experienced a functional status deterioration; and 38% of those admitted from home were eventually discharged to a LTCF. In the 3 months after discharge, 40% were readmitted, 18% acquired ≥1 MDRO, and 7% developed acute CDI. The 90-day mortality rate for the entire ASB population was 34%.

In total, 696 pathogens were isolated from 610 patients with ASB: 84% were gram-negative organisms, most commonly *E. coli, K. pneumoniae*, and *P. aeruginosa*. Among the 696 pathogens, 36% of the 610 patients had at least 1 MDRO isolated, most commonly ESBL-producing Enterobacterales (23%) or *P. aeruginosa* (5.4%).

Patients with ASB who received antibiotics

Antimicrobial therapy, which was administered specifically to "cover" the pathogen grown from the urine culture, was administered to a total of 178 (29.2%) patients with ASB. The proportion of febrile patients aged >65 years with no urine catheters and a different nonurinary source of infection was similar between the group of patients who received antibiotics and the group of patients who did not receive antibiotics. Table 1 lists predictors and outcomes associated with antimicrobial therapy. Administration of antimicrobials was more common among men, among patients with dependent functional status, patients admitted to a medical floor, patients with urinary catheter at the time of ASB diagnosis, and patients with a higher Charlson comorbidity scores (Table 1).[18] In multivariable analysis, the independent predictors that remained significantly associated with antibiotic misuse were male sex (aOR, 2; 95% CI, 1.25–2.6; $P < .001$) and dependent functional status in baseline (aOR, 2.3; 95% CI, 1.4–3.6; $P < .001$).

Outcomes of patients with ASB who received antimicrobials

The short-term mortality rates (ie, in-hospital and 14-day rates), were lower among patients with ASB who received antibiotics. In the multivariable regression model, antibiotic administration did not remain independently associated with favorable 14-day survival rates (aOR, 0.7; $P = .30$). The 90-day mortality rate was nonsignificantly ($P = .10$) higher among patients who received antibiotics (Table 1). In the multivariable model, antibiotics administration was not independently associated with 90-day mortality. The length of stay from the date of urine culture to discharge, among survivors of the index hospitalization, was 1 day longer for patients who received antibiotics ($P = .08$ between groups).

Among survivors of the index hospitalization, antibiotic misuse was associated with higher rates of readmissions, and higher rates of CDI, within 90 days (Table 1). In separate multivariable regression outcome models, antibiotic administration for ASB remained independently associated with additional readmissions (aOR, 1.7; 95% CI, 1.1–2.6; $P = .02$) and with later CDI (aOR, 4.5; 95% CI, 2–10.6; $P < .001$), both within 90 days.

Discussion

ASB is a very common condition in hospitals and in the community, especially among elderly patients with indwelling urinary catheters and/or among cognitively impaired individuals, i.e., lacking the capability to provide history information pertaining to symptoms and complaints. One mistake leads to another, and the mistake of ordering a culture, often leads to improper administration of antibiotics. With the exception of certain populations and conditions, numerous recent guidelines have advocated against the use of antibiotics for ASB. However, only a few studies have analyzed and quantified the impact of this practice on various clinical outcomes.[1] This type of controlled data could convince administrators to invest and allocate preventive resources toward the reduction of ASB in general (many measures will reduce the CAUTI rates as well) and could reduce the improper administration of antibiotic to patients with ASB.

In this large study, we reviewed 1,530 patient-unique positive urine cultures. Among them, 610 patients (40%) were diagnosed with ASB and 178 were administered antibiotics. Our findings highlight the high prevalence of ordering urine cultures with no established indication and the burden of improper administration of antibiotics to this population. The study included an elderly population (>80%), with a median age of 80 years, severe baseline comorbidity indexes, multiple recent exposures to health services, and severe acute illness indices. The analyses provided genuine predictors for antibiotic administration, and quantified the independent association of this practice with several outcomes.

The composition of pathogens in this study were reminiscent of analyses recently performed elsewhere.[19] Overall, close to 85% of pathogens were gram negative, and ~15% of patients had a polymicrobial culture. The rate of MDROs was extremely high (36%), specifically ESBLs and *P. aeruginosa*. This situation created a doubled synergistic epidemiological threat because patients "acquired" a condition that could adversely impact their hospitalization outcomes due to possible poor management (ie, the ASB) and also "acquired" a condition that is independently associated with worse outcomes both to current and future hospitalizations (ie, the MDRO acquisition event).[20]

Although multiple potential characteristics were associated with the inappropriate use of antibiotics for ASB (Table 1), only male sex and poor functional status at baseline remained significant and independent predictors. Poor functional status is frequently coupled with the presence of permanent urinary catheter, poor cognition, and lack of ability to provide information pertaining to symptoms, leading to the permissive administration of antibiotics. All other parameters dropped in the regression model. This finding has also been reported recently in a publication that included 46 hospitals from the state of Michigan[19]; therefore, antibiotic administration to functionally dependent patients should be closely monitored and ASB ruled out prior initiation of therapy. Male sex, the additional independent predictor for antibiotic administration, might represent in this cohort a confounding effect to other epidemiological parameters. A subanalysis was performed to investigate this hypothesis but was inconclusive. Future studies, conducted at other facilities and on different populations, should trial the generalizability of this finding.

As depicted in Table 1, the clinical outcomes of patients who received antibiotics were significantly worse, except the early mortality parameters, though this trend was reversed as well after 3 months. In separate regression models, conducted for each outcome with univariable significant association, antibiotics administration was independently associated with a nearly 2-fold increase in the probability of being readmitted within 90 days and with a 4.5-fold increase in the probability to develop acute CDI, within 90 days. The mortality data also imply that the improper administration of antibiotics for ASB might only be evident long after the patient has been discharged. These findings should prompt practitioners and administrators to invest efforts in reducing antibiotic administration for ASB and to discourage the practice of obtaining urine cultures from certain high-risk groups with no signs or symptoms of UTI.

Table 1. Univariable Analyses for Patients With Asymptomatic Bacteriuria (ASB) Who Received Antimicrobials

Parameter		Antimicrobials (n=178)		No Antimicrobials (n=432)		Statistics	
		No.	%	No.	%	OR (95% CI%)	*P* Value
Demographics							
Age, median y (IQR)		82 (72–88)		79 (69–87)			.06
Female sex		93	52	288	67	0.50 (0.4–0.8)	<.001
Exposure to healthcare environments							
Recent (<3 mo) hospitalization		79	45	175	41	1.2 (0.8–1.7)	.4
Recent (<3 mo) LTCF stay prior to hospitalization		93	53	216	50	1.1 (0.8–1.6)	.5
Days from ER admission to ASB diagnosis		1 (0–3)		1 (0–4)			.7
Background medical status							
Cognitive impairment in background		69	39	140	33	1.3 (0.9–1.9)	.14
Dependent functional status upon admission		150	84	302	70	2.3 (1.5–3.6)	<.001
Chronic catheter		22	12	21	5	2.7 (1.5–5.1)	<.001
Past MDR organism isolation[a]		19	11	46	11	1 (0.6–1.8)	>.99
Charlson's score, median (IQR) [44]	Weighted index comorbidity	2 (1–4)		2 (1–3)			.5
	Combined condition score	6 (4–7)		2 (1–3)			.04
	10-year survival, %	5 (0.4–40)		11 (0.1–48)			.04
Acute illness indices							
Fever (>38°C)		53	30	133	31	0.96 (0.7–1.4)	.82
Indwelling urinary catheter in place at culture date		134	78	265	63	2 (1.3–3)	<.001
Mechanical ventilation at culture date		22	12	78	18	0.6 (0.4–0.9)	.08
Total number of urine catheter days, median (IQR)		7 (3–14)		5 (2–12)			.1

Microbiology							
Polymicrobial culture		21	12	66	15	0.7 (0.4–1.3)	.3
Multidrug resistant organism (MDRO)[a]		74	42	145	34	1.4 (1–2)	.06
Extensively drug-resistant organism (XDRO)[b]		8	5	15	4	1.3 (0.5–3.2)	.5
Outcomes							
Died during current hospitalization		35	20	112	26	0.7 (0.5–0.9)	.1
Died within 14 d after culture date		20	11	82	19	0.5 (0.3–0.9)	.02
Died during 90 d after culture date		68	38	137	32	1.3 (0.9–1.9)	.1
Among survivors of the index hospitalization only	LOS from culture to discharge, median d (IQR)	9 (5–17)	8 (4–17)		0.08		
	Functional status deterioration at discharge	66	46	122	37	1.4 (0.96–2.1)	.08
	Discharge to LTCF after being admitted from home	52	37	122	38	0.9 (0.6–1.4)	.8
	Clostridioides difficile infection within 90 d	22	15	10	3	5.6 (2.6–12.2)	<.001
	Readmission within 90 d	62	44	94	30	1.9 (1.3–2.8)	.002
	MDRO[a] acquisition within 6 mo	36	20	75	17	1.2 (0.8–1.9)	.4

Note. ASB, asymptomatic bacteriuria; OR, odds ratio; CI, confidence interval; IQR, interquartile range; LTCF, long-term care facility; ER, emergency room; MDRO, multidrug-resistant organism; ICU, intensive care unit; GFR, glomerular filtration rate; XDRO, extensively drug resistant organism; LOS, length of stay.

[a]MDRO include methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), extended-spectrum β-lactamase (ESBL)–producing Enterobacterales, *Acinetobacter baumannii*, *Pseudomonas aereuginosa*.

[b]XDRO include MRSA with vancomycin MIC ≥2 mg/L, vancomycin-resistant enterococci (VRE), carbapenem-resistant (meropenem MIC>1 mg/L) or carbapenemase-producing Enterobacterales (CRE), carbapenem-resistant *Acinetobacter baumannii*, carbapenem-resistant *Pseudomonas aereuginosa.*

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