



HAL
open science

Antibiotics versus no therapy in kidney transplant recipients with asymptomatic bacteriuria (BiRT): a pragmatic, multicentre, randomized, controlled trial

Julien Coussement, Nassim Kamar, Marie Matignon, Laurent Weekers, Anne Scemla, Magali Giral, Judith Racapé, Éric Alamartine, Laurent Mesnard, Mireille Kianda, et al.

► To cite this version:

Julien Coussement, Nassim Kamar, Marie Matignon, Laurent Weekers, Anne Scemla, et al.. Antibiotics versus no therapy in kidney transplant recipients with asymptomatic bacteriuria (BiRT): a pragmatic, multicentre, randomized, controlled trial. *Clinical Microbiology and Infection*, 2020, 27 (3), pp.398 - 405. 10.1016/j.cmi.2020.09.005 . hal-03197692

HAL Id: hal-03197692

<https://hal.sorbonne-universite.fr/hal-03197692v1>

Submitted on 14 Apr 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Original article

Antibiotics versus no therapy in kidney transplant recipients with asymptomatic bacteriuria (BiRT): a pragmatic, multicentre, randomized, controlled trial

Julien Coussement^{1, 2, *}, Nassim Kamar³, Marie Matignon^{4, 5, 6, 7}, Laurent Weekers⁸, Anne Scemla⁹, Magali Giral¹⁰, Judith Racapé¹¹, Éric Alamartine¹², Laurent Mesnard¹³, Mireille Kianda¹⁴, Lidia Ghisdal¹⁵, Concetta Catalano², Emine N. Broeders², Olivier Denis¹⁶, Karl M. Wissing¹⁷, Marc Hazzan¹⁸, Daniel Abramowicz¹⁹ on behalf of the Bacteriuria in Renal Transplantation (BiRT) study group†

¹ Division of Infectious Diseases, CUB-Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium

² Department of Nephrology, Dialysis and Renal Transplantation, CUB-Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium

³ Department of Nephrology and Organ Transplantation, Hôpital Rangueil, Centre Hospitalier Universitaire de Toulouse, Université Paul Sabatier, INSERM U10403, Toulouse, France

⁴ Centre d'Investigation Clinique Biothérapie, Hôpital H. Mondor-A. Chenevier, APHP (Assistance Publique-Hôpitaux de Paris), Créteil, France

⁵ Université Paris-Est, UMR_S955, UPEC, Créteil, France

⁶ INSERM U955, Equipe 21, Créteil, France

⁷ Nephrology and Transplantation Department, Hôpital H. Mondor-A. Chenevier, APHP (Assistance Publique-Hôpitaux de Paris), Créteil, France

⁸ Department of Nephrology, Centre Hospitalier Universitaire de Liège, Liège, Belgium

⁹ Department of Nephrology - Transplantation, Hôpital Necker Enfants Malades, APHP (Assistance Publique-Hôpitaux de Paris), Université Paris Descartes Sorbonne Paris Cité, Paris, France

¹⁰ Institute for Transplantation, Urology and Nephrology (ITUN), Nantes University Hospital, Nantes, France

¹¹ Research Centre 'Biostatistiques, Epidémiologie et Recherche Clinique', École de Santé Publique, Université Libre de Bruxelles, Brussels, Belgium

¹² Department of Nephrology, Centre Hospitalier Universitaire de Saint-Étienne, Saint-Étienne, France

¹³ Department of Nephrology and Kidney Transplantation, Hôpital Tenon, APHP (Assistance Publique-Hôpitaux de Paris), Sorbonne Université, Paris, France

¹⁴ Department of Nephrology, Centre Hospitalier Universitaire Brugmann, Brussels, Belgium

¹⁵ Department of Nephrology, Centre Hospitalier EpiCURA, Baudour, Belgium

¹⁶ Laboratory of Microbiology, CHU UCL Namur, Université Catholique de Louvain, Yvoir, Belgium

¹⁷ Department of Nephrology, Universitair Ziekenhuis Brussel, Vrije Universiteit Brussel, Brussels, Belgium

¹⁸ Nephrology Department, University Hospital of Lille, INSERM U995, Lille, France

¹⁹ Department of Nephrology, Universitair Ziekenhuis Antwerpen, Universiteit Antwerpen, Antwerp, Belgium

ARTICLE INFO

Article history:

Received 8 July 2020

Received in revised form

30 August 2020

Accepted 1 September 2020

Available online 10 September 2020

Editor: L. Leibovici

Keywords:

Asymptomatic bacteriuria

Bacteriuria

Kidney transplantation

Pyelonephritis

Urinary tract infection

ABSTRACT

Objectives: Many transplant physicians screen for and treat asymptomatic bacteriuria (ASB) during post-kidney-transplant surveillance. We investigated whether antibiotics are effective in reducing the occurrence of symptomatic urinary tract infection (UTI) in kidney transplant recipients with ASB.

Methods: We performed this multicentre, randomized, open-label trial in kidney transplant recipients who had ASB and were ≥ 2 months post-transplantation. We randomly assigned participants to receive antibiotics or no therapy. The primary outcome was the incidence of symptomatic UTI over the subsequent 12 months.

Results: One hundred and ninety-nine kidney transplant recipients with ASB were randomly assigned to antibiotics (100 participants) or no therapy (99 participants). There was no significant difference in the occurrence of symptomatic UTI between the antibiotic and no-therapy groups (27%, 27/100 versus 31%, 31/99; univariate Cox model: hazard ratio 0.83, 95%CI: 0.50–1.40; log-rank test: p 0.49). Over the 1-year study period, antibiotic use was five times higher in the antibiotic group than in the no-therapy group (30 antibiotic days/participant, interquartile range 20–41, versus 6, interquartile range 0–15, $p < 0.001$). Overall, 155/199 participants (78%) had at least one further episode of bacteriuria during the follow-up.

* Corresponding author. Julien Coussement, Department of Infectious Diseases, Peter MacCallum Cancer Centre, 305 Grattan Street, Melbourne, VIC, 3000, Australia.

E-mail address: juliencoussement@gmail.com (J. Coussement).

† The members of the Bacteriuria in Renal Transplantation (BiRT) study group are listed in the [Appendix](#).

Compared with the participant's baseline episode of ASB, the second episode of bacteriuria was more frequently caused by bacteria resistant to clinically relevant antibiotics (ciprofloxacin, cotrimoxazole, third-generation cephalosporin) in the antibiotic group than in the no-therapy group (18%, 13/72 versus 4%, 3/83, p 0.003).

Conclusions: Applying a screen-and-treat strategy for ASB does not reduce the occurrence of symptomatic UTI in kidney transplant recipients who are more than 2 months post-transplantation. Furthermore, this strategy increases antibiotic use and promotes the emergence of resistant organisms. **Julien Coussement, *Clin Microbiol Infect* 2021;27:398**

© 2020 The Authors. Published by Elsevier Ltd on behalf of European Society of Clinical Microbiology and Infectious Diseases. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Symptomatic urinary tract infection (UTI) is the commonest infection following kidney transplantation [1]. Given the frequency of symptomatic UTI and its associated morbidity [2], it has been suggested that bacteriuria should be screened for, and if present treated, with the intent to eradicate bacteriuria and reduce the incidence of symptomatic UTI [3–6]. There is also a concern that post-transplant pyelonephritis may present asymptotically due to graft denervation and immunosuppression [5,7]. As observed in a recent European survey, more than 70% of transplant physicians always screen for asymptomatic bacteriuria (ASB) during post-kidney transplant surveillance, and ASB is often treated [8].

The historical practice of screening for and treating ASB after kidney transplantation potentially results in significant antibiotic exposure because the cumulative incidence of ASB is high when urine cultures are systematically repeated during post-transplant surveillance (e.g. 51% of patients in the first 3 years post-transplant [3]). Furthermore, the use of fluoroquinolones (which are the most commonly prescribed antibiotics to treat post-transplant ASB) significantly promotes the selection and amplification of resistant organisms, which is a major issue in solid-organ transplantation [3,8–11].

To date, two randomized controlled trials (RCTs) [10,12] and one quasi-RCT [13] have compared antibiotics versus no therapy in kidney transplant recipients with ASB. An updated meta-analysis of these studies found no significant effect of antibiotics on the incidence of symptomatic UTI (see Supplementary Appendix p. 3: data for 287 participants, risk ratio (RR) 1.02, 95% confidence interval (CI) 0.66–1.59) [14]. However, all three studies had significant limitations. In particular, sample sizes were relatively small, and there was limited compliance to the intervention in both RCTs (29–51% of the participants allocated to antibiotics did not receive antibiotics exactly as planned). Additionally, in both RCTs the primary endpoint of pyelonephritis occurred much less frequently than expected (in five or fewer participants/group). As a consequence, the certainty of evidence was low for important outcomes such as symptomatic UTI [15,16].

We therefore conducted the Bacteriuria in Renal Transplantation (BiRT) study to determine whether antibiotics reduce the risk of symptomatic UTI in kidney transplant recipients with ASB.

Methods

Study design

We conducted a prospective, randomized, parallel-group, multicentre, open-label, superiority trial in France (seven sites) and Belgium (six sites) to compare antibiotics with no therapy in kidney transplant recipients with ASB. The protocol was developed in

accordance with SPIRIT guidelines [17], with support from the Centre for Evidence in Transplantation (Oxford, UK), and was published in *The Lancet* (www.thelancet.com/protocol-reviews/14PRT-5447). The study was designed to be pragmatic (see Supplementary Appendix p. 11). The trial was approved by ethics committees and authorities in France and Belgium, and registered with the European Clinical Trials Database, 2012-003857-26, and ClinicalTrials.gov, NCT01871753.

Participants

Adult kidney transplant recipients (≥ 18 years of age) were eligible if they had ASB, and were ≥ 2 months post-transplantation. Participants were recruited through usual follow-up clinics, using the fact that we routinely perform life-long screening for bacteriuria after kidney transplantation. ASB was defined as isolation of a single bacterial species at $\geq 10^5$ cfu/mL in a urine specimen from a patient without symptoms of UTI. Following routine practice in our centres [8], a second positive culture was not necessary before enrolment. A second specimen was, however, sent for culture before randomization when possible for the patient. Patients developing ASB while on cotrimoxazole prophylaxis were eligible for inclusion; cotrimoxazole was routinely used as prophylaxis for *Pneumocystis jirovecii* for a duration ranging from 3 months post-transplant to life-long. Patients who had an indwelling urinary (bladder and/or ureteral) catheter were excluded. Other exclusion criteria are listed in the Supplementary Appendix p. 4. All participants provided written informed consent.

Randomization and masking

Patients were centrally assigned (1:1) to either antibiotics or no therapy using an internet-based randomization service. Randomization was stratified by sex and age (< 50 versus ≥ 50 years). The randomization sequence was computer-generated and used blocks of four. Investigators were masked to the randomization sequence. Participants and clinicians were not blinded to allocation.

Procedures

In the antibiotic group, antibiotics were administered for 10 days. The antibiotic was selected by the treating physician, but had to be active *in vitro* against the causative bacteria. In the control group, no antibiotics were prescribed for ASB.

In both groups, participants were followed for 12 months post-randomization, with study visits scheduled at 1, 2, 4, 6, 8, 10 and 12 months. For each follow-up visit, a urine culture was performed to screen for bacteriuria. All seven visits used a pre-established questionnaire, and also included history taking, temperature measurement, and blood analysis. If ASB occurred again at a study follow-up visit, antibiotics were re-administered in the antibiotic

group but not in the control group (see Supplementary Appendix p. 5 for details regarding the screen-and-treat strategy). Participants were asked to contact the local staff if they developed symptoms of infection. Data were collected prospectively using an electronic case report form.

To ensure data quality, we monitored all participant data using central reviewing (i.e. monthly online monitoring of study data) and on-site visits with the help of an independent monitoring team (Clinical Research Centre, Lille University Hospital, France).

Outcomes

The primary outcome was the incidence of symptomatic UTI during the 1-year follow-up, defined as the association of (a) one or more symptoms/signs from a prespecified list (of cystitis, pyelonephritis, prostatitis, or bloodstream infection due to UTI – see Supplementary Appendix p. 6), and (b) a positive urine culture (i.e. isolation of a bacterial organism at $\geq 10^4$ cfu/mL). To limit the risk of bias associated with the open-label design of this trial, primary outcomes were adjudicated before analysis with the help of three co-investigators blinded to allocation and not involved in patient care. All secondary outcomes are listed in the Supplementary Appendix p. 6. All outcomes were prespecified.

Sample size calculation

We estimated that the 1-year cumulative incidence of symptomatic UTI would be 20% among untreated patients [1,3,13]. We considered a reduction in the incidence of symptomatic UTI from 20% to 6% to represent the minimal clinically important difference (taking into account the impact of antibiotics on the spread of antibiotic resistance, and the fact that many symptomatic UTIs occurring after kidney transplantation are cystitis which has a limited impact on the patient and his/her graft) [1]. This 70% decrease was consistent with the effect of antibiotics reported in pregnant women with ASB [18]. A sample size of 198 participants was needed to have an 80% chance of detecting a reduction in the incidence of symptomatic UTI from 20% to 6% as significant at the 5% level, considering a potential 10% loss to follow-up.

Statistical analysis

Baseline participant characteristics are expressed as proportions for categorical variables, means and standard deviations (SDs) for normally distributed continuous variables, and median and interquartile ranges (IQRs) for non-normally distributed continuous variables. Primary analysis was by intention-to-treat. For the primary outcome, we used Kaplan–Meier survival curves to estimate the cumulative incidence of symptomatic UTI. The curves were compared using the log-rank test. The hazard ratios (HRs) and their 95% CIs were derived from a univariate Cox model, with p values corresponding to the Wald's test. To investigate the consistency of the study conclusions among different subpopulations, an analysis of the primary endpoint was undertaken in three pre-specified subgroups: (a) time between transplantation and study inclusion <6 versus ≥ 6 months; (b) baseline estimated glomerular filtration rate <40 versus ≥ 40 mL/min/1.73 m²; and (c) resistant organism at baseline versus other organism (details in Supplementary Appendix p. 12). A per-protocol analysis was also conducted, excluding participants with a protocol deviation (see Supplementary Appendix p. 13). For secondary outcomes, we compared categorical variables between study groups using Pearson's χ^2 test or Fisher's exact test (as appropriate), and continuous variables using Student's t test or Mann–Whitney–Wilcoxon test (as appropriate). Change in serum creatinine throughout the follow-up period was

compared using a two-way repeated measures ANOVA. A two-sided p value of <0.05 was considered as statistically significant. Additional details related to the statistical analysis are provided in the Supplementary Appendix p. 8.

Results

Study population

One hundred and ninety-nine kidney transplant recipients with ASB were enrolled and randomly assigned to receive antibiotics (100 participants) or no therapy (99 participants). These 199 participants constituted the intention-to-treat population (Fig. 1). Baseline characteristics are shown in Table 1. At study inclusion, 27.1% of the patients (54/199) were in the first post-transplant year. The most common organism responsible for the inclusion episode of ASB was *Escherichia coli* (63.3%, 126/199). Overall, 98% of the participants (195/199) completed (188/199) or died (7/199) before the 12-month follow-up.

Interventions and protocol compliance

At baseline, 198/199 participants (99.5%) received the planned intervention (i.e. antibiotics versus no therapy). In the antibiotic group, fluoroquinolones were the most commonly prescribed agents at baseline (27%, 27/100), followed by second-/third-generation cephalosporins (26%, 26/100), amoxicillin (18%, 18/100), amoxicillin–clavulanic acid (17%, 17/100), nitrofurantoin (5%, 5/100), cotrimoxazole (4%, 4/100), and fosfomycin-trometamol (3%, 3/100). During the 1-year follow-up period, more than 90% of the scheduled urine cultures were performed (1272/1393, 91.3%), and 19 participants (9.5%) had a protocol deviation (details in Supplementary Appendix p. 13). Therefore, the per-protocol analysis included 92 participants in the no-therapy group and 87 participants in the antibiotic group (Fig. 1).

Outcomes

Overall, 58/199 participants (29.1%) developed at least one symptomatic UTI during the follow-up period. On an intention-to-treat basis, the risk of symptomatic UTI did not differ significantly between participants in the antibiotic group and those in the no-therapy group (27/100, 27% versus 31/99, 31%, univariate Cox model: HR 0.83, 95%CI: 0.50–1.40, p 0.49; log-rank test: p 0.49, Fig. 2). The characteristics of these 58 symptomatic UTI episodes are summarized in Table 2. The per-protocol analysis confirmed these findings (incidence of symptomatic UTI: 23/87 (26%) in the antibiotic group versus 30/92 (33%) in the no-therapy group, univariate Cox model: HR 0.78, 95%CI: 0.45–1.34, p 0.36; log-rank test: p 0.36). Antibiotics did not significantly reduce the cumulative incidence of symptomatic UTI in any of the pre-specified subgroups (Supplementary Appendix p. 12).

Antibiotics had no significant impact on any secondary clinical outcome (Table 3). Specifically, the incidence of pyelonephritis did not differ significantly between study groups (17/100 (17%) in the antibiotic group versus 16/99 (16%) in the no-therapy group, RR 1.05, 95%CI 0.56–1.96, p 0.87). Treating ASB did not significantly improve kidney function (Table 3).

One month after randomization, 93% of the participants (186/199) had a urine specimen sent for culture. Among them, the prevalence of ASB was significantly lower in the antibiotic group than in the no-therapy group (29%, 27/92 versus 66%, 62/94, p < 0.001). Compared with untreated participants, those in the antibiotic group also had a significantly lower total number of ASB

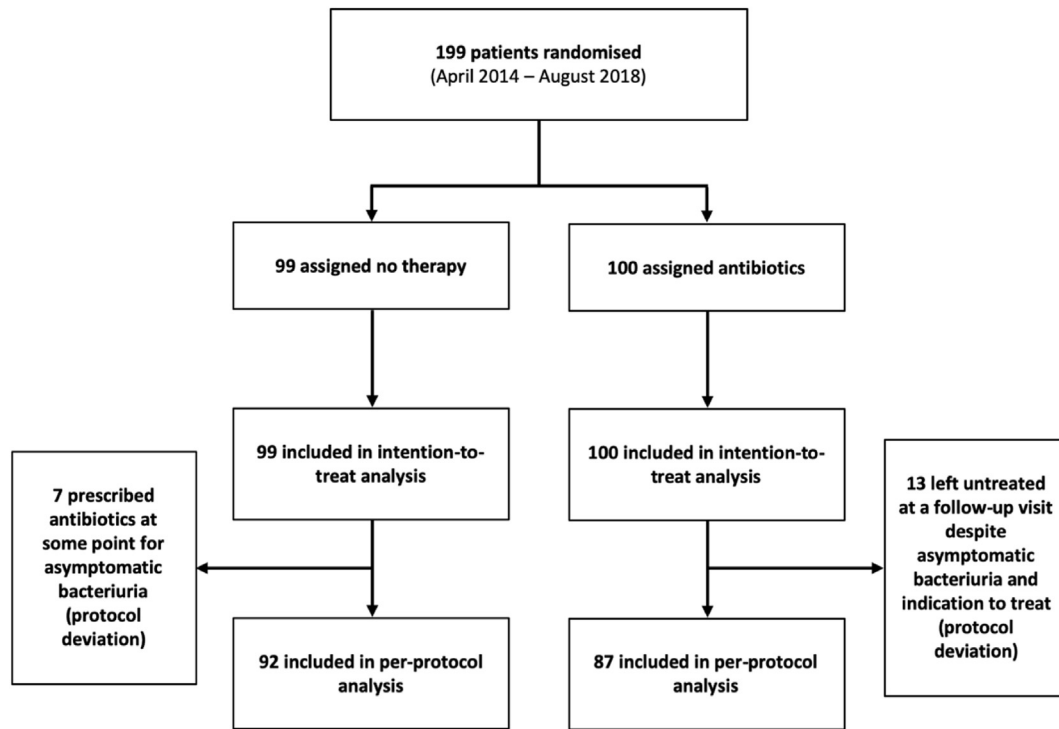


Fig. 1. Trial profile.

episodes during the complete follow-up period, and were significantly less likely to have ASB at end of study (Table 3).

Antibiotic use varied significantly between groups (Table 3 and Supplementary Appendix p. 15). Especially, the median number of days receiving antibiotics for any cause was five times higher in the antibiotic group than in the no-therapy group (30 days per patient throughout the 1-year study period (IQR 20–41) versus 6 days (IQR 0–15), respectively, $p < 0.001$, excluding antibiotic prophylaxis, e.g. cotrimoxazole used to prevent *Pneumocystis pneumonia*).

To determine the impact of antibiotics on antibiotic resistance, we focused on the 155/199 participants (77.9%) who had at least one further episode of bacteriuria during the follow-up. Compared with the participant's baseline episode of ASB, this second episode of bacteriuria was more frequently caused by bacteria resistant to clinically relevant antibiotics (i.e., ciprofloxacin, cotrimoxazole, or third-generation cephalosporin) in the antibiotic group than in the no-therapy group (18%, 13/72 participants versus 4%, 3/83 participants, $p 0.003$, details in Supplementary Appendix p. 16). Overall, 93 serious adverse events (SAEs) were reported: 50 SAEs among 28/100 participants (28%) in the antibiotic group versus 43 SAEs among 23/99 participants (23%) in the no-therapy group ($p 0.44$, details in Supplementary Appendix p. 18).

Discussion

The present study was designed to determine whether antibiotics are beneficial in kidney transplant recipients who have ASB beyond the first 2 months post-transplant. Although antibiotic use was associated with fewer subsequent cases of bacteriuria, this microbiological effect did not translate into significant clinical benefit over the 1-year study period, including in our primary outcome of symptomatic UTI. Furthermore, antibiotic consumption was five times higher among participants from the antibiotic group than among those from the no-therapy group, and treating ASB

significantly promoted the emergence of more resistant organisms in the urine.

While symptomatic UTIs represent a heterogeneous group of events ranging from mild episodes of cystitis to more severe episodes of graft pyelonephritis, it is remarkable that treating ASB did not reduce the incidence of pyelonephritis or improve any of the other graft-related outcomes (i.e. kidney function, graft rejection, and graft loss). These results argue against the hypothesis that ASB may represent 'silent pyelonephritis' among kidney transplant recipients as a consequence of both transplant denervation and immunosuppression [5,7].

This study has several strengths, including its randomized design. Compared with previously published trials focusing on kidney transplant recipients with ASB, we had double the number of participants assigned to antibiotics (100 participants in the current study versus 41–53 participants/study in previous trials) [10,12,13]. The high level of compliance with study protocol and the clear microbiological effect of antibiotics support our conclusions that antibiotics are not clinically beneficial in this situation. Also, benefits and harms of antibiotics were rigorously examined, using comprehensive data monitoring for all patients.

This study also has several limitations. First, participants and physicians were not blinded to treatment allocation, and this may have biased our results for the primary outcome because symptoms of UTI are partly subjective. However, the open-label design was selected to reflect usual care. To minimize the risk of bias, primary outcomes were adjudicated with the help of assessors blinded to treatment allocation.

Second, our trial was powered to detect a large effect, and hence we cannot rule out a small to moderate effect of antibiotics on the risk of symptomatic UTI. This is illustrated by the relatively wide confidence interval surrounding the hazard ratio for the primary outcome (HR 0.83, 95%CI: 0.50–1.40). However, our results confirm those of three previous trials, which also did not demonstrate a significant clinical benefit associated with the use of a screen-and-

Table 1
Baseline characteristics (intention-to-treat analysis)

	No therapy (n = 99)	Antibiotics (n = 100)
Female, n (%)	74 (75)	77 (77)
Age (years), mean ± SD	60.1 ± 11.6	60.2 ± 11.5
Primary kidney disease diagnosis		
Glomerular disease (other than diabetes)	26 (26)	24 (24)
Polycystic kidney disease	16 (16)	17 (17)
Diabetes	11 (11)	13 (13)
Tubulo-interstitial nephritis	8 (8)	17 (17)
Vascular nephropathy	13 (13)	8 (8)
Uropathy	11 (11)	5 (5)
Unknown	14 (14)	16 (16)
Dialysis before transplantation	85 (86)	90 (90)
Duration (months), median (IQR)	28 (16–43)	33 (18–52)
Oliguria/anuria at time of transplant (≤ 500 mL/day), n (%), n = 168	37 (46)	48 (55)
Haemodialysis (versus peritoneal dialysis), n (%)	71 (84)	77 (86)
Time from transplantation to study inclusion (months), median (IQR)	49 (18–109)	26 (10–77)
Study inclusion in the first 12 months post-transplant, n (%)	21 (21)	33 (33)
1st transplant (versus 2nd or 3rd transplant), n (%)	85 (86)	77 (77)
Single (versus dual) kidney transplant, n (%)	98 (99)	97 (97)
Urinary catheterization in the month prior to inclusion, n (%)	1 (1)	0 (0)
Diabetes, n (%)	29 (29)	39 (39)
Deceased donor (versus living), n (%)	90 (91)	93 (93)
Donor age (years), mean ± SD, n = 198	52 ± 19	54 ± 17
History of biopsy-proven acute rejection since transplantation, n (%)	11 (11)	13 (13)
Induction immunosuppressive therapy at transplantation, n (%), n = 198		
Anti-CD25	50 (51)	45 (45)
Thymoglobulin	29 (30)	35 (35)
Other induction regimen	7 (7)	11 (11)
None	12 (12)	9 (9)
Number of antirejection drugs at time of study inclusion, n (%)		
Three-drug immunosuppressive therapy	65 (66)	72 (72)
Two-drug immunosuppressive therapy	33 (33)	27 (27)
Single drug immunosuppressive therapy	1 (1)	1 (1)
Antirejection drugs used at time of study inclusion, n (%)		
Calcineurin inhibitor (tacrolimus or cyclosporin)	86 (87)	92 (92)
Antiproliferative drug (mycophenolic acid or azathioprine)	84 (85)	88 (88)
Steroids	78 (79)	78 (78)
Belatacept	8 (8)	7 (7)
mTOR inhibitors	6 (6)	7 (7)
Use of cotrimoxazole prophylaxis after transplantation, n (%), n = 198	91 (93)	87 (87)
Ongoing cotrimoxazole prophylaxis at time of study inclusion, n (%)	12 (12)	27 (27)
Major events in the year before study enrolment, n (%)		
UTI requiring hospital admission, n = 197	13 (13)	8 (8)
Antibiotics for symptomatic UTI or asymptomatic bacteriuria, n = 198	51 (52)	42 (42)
Antibiotics for infection other than UTI, n = 197	16 (16)	23 (23)
Infection or colonization by an ESBL-producing organism, n = 197	9 (9)	4 (4)
Urine test results at study entry, n (%)		
Pyuria (i.e. ≥ 25 leucocytes/mm ³ of urine)	81 (82)	78 (78)
Bacterial species		
Enterobacteriaceae	86 (87)	87 (87)
<i>Escherichia coli</i>	62 (63)	64 (64)
<i>Klebsiella</i> spp.	12 (12)	16 (16)
<i>Enterobacter</i> spp.	5 (5)	1 (1)
<i>Proteus mirabilis</i>	2 (2)	2 (2)
Other	5 (5)	4 (4)
<i>Pseudomonas aeruginosa</i>	2 (2)	1 (1)
<i>Enterococcus</i> spp.	9 (9)	10 (10)
Others	2 (2)	2 (2)
Second urine specimen sent for culture before randomisation, n (%)	66 (67)	73 (73)
Same organism identified, n = 139	61 (92)	71 (97)
Same organism identified, at $\geq 100,000$ CFU/mL, n = 138	54 (83)	66 (90)
Numbers of baseline urinary samples with antimicrobial resistant isolates, n (%)		
Ciprofloxacin-resistant Gram-negative bacteria, n = 178	26 (29)	23 (26)
Cotrimoxazole-resistant Gram-negative bacteria, n = 178	39 (43)	51 (58)
3rd generation cephalosporin-resistant Gram-negative bacteria, n = 168	18 (21)	7 (9)
Blood analysis at time of study inclusion		
White blood cell count (/mm ³), mean ± SD	7239 ± 2567	7462 ± 2842
Neutrophil count (/mm ³), mean ± SD, n = 177	5102 ± 2364	5248 ± 2338
CRP (mg/L), median (IQR), n = 195	3 (1–6)	3 (1–9)
Serum creatinine level (mg/dL), mean ± SD	1.5 ± 0.6	1.4 ± 0.5
Estimated glomerular filtration rate (mL/min/1.73 m ²) ^a , mean ± SD	44 ± 19	45 ± 15

CRP, C-reactive protein; ESBL, extended spectrum β -lactamase; IQR, interquartile range; mTOR, mammalian target of rapamycin; SD, standard deviation; UTI, urinary tract infection; n, number of participants analysed (if < 199).

^a According to Modification of Diet in Renal Disease formula.

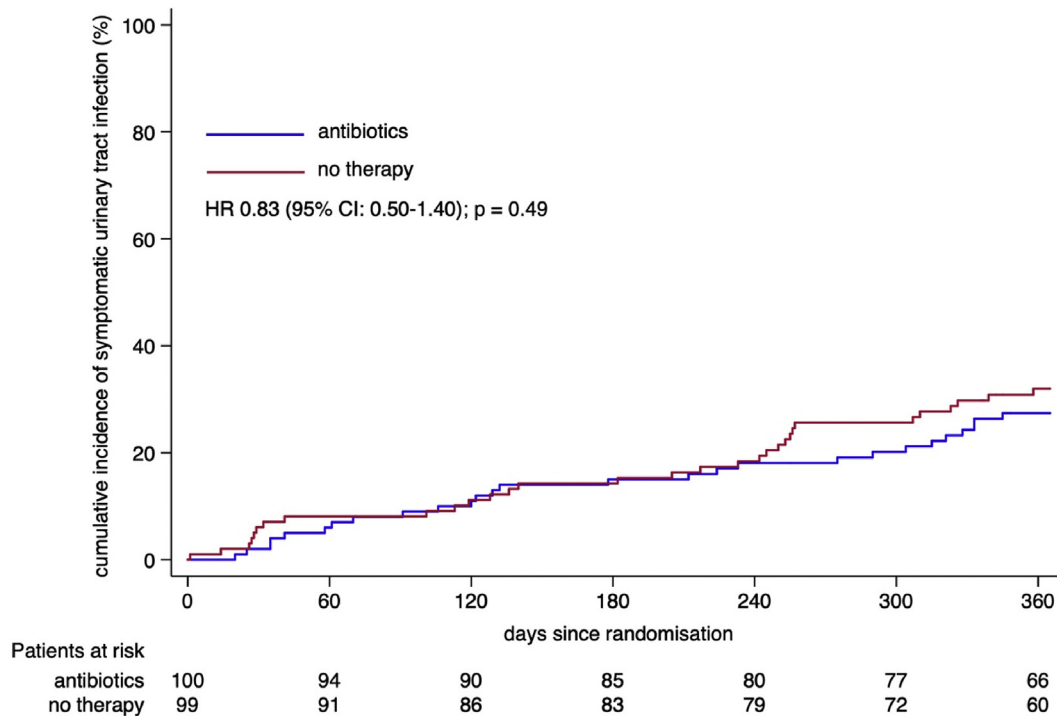


Fig. 2. Cumulative incidence of symptomatic urinary tract infection (intention-to-treat analysis). CI: confidence interval, HR: hazard ratio; p-value refers to log-rank test.

Table 2

Characteristics of first episode of symptomatic urinary tract infection (UTI) (primary endpoint; intention-to-treat analysis)

	No therapy (31 episodes)	Antibiotics (27 episodes)	p
Need for hospital admission, n (%)	10 (32)	6 (22)	0.39
If hospital admission: length of stay (days), median (IQR)	7 (5–13)	5 (3–36)	0.66
Symptoms of cystitis, n (%) ^a	22 (71)	22 (81)	0.35
Symptoms of pyelonephritis (i.e. fever and/or chills and/or kidney pain), n (%) ^a	14 (45)	16 (59)	0.28
Blood test results ^b :			
White blood cell count (/mm ³), mean ± SD	9252 ± 3489	10022 ± 5030	0.53
Neutrophil count (/mm ³), mean ± SD, n = 43	7322 ± 3658	7873 ± 5239	0.69
CRP (mg/L), median (IQR)	24 (3–68)	52 (4–65)	0.60
Serum creatinine level (mg/dL), mean ± SD, n = 49	1.8 ± 0.7	1.7 ± 0.6	0.85
Acute kidney injury ^c , n (%), n = 49	10 (36)	6 (29)	0.60
Bloodstream infection, n (%), n = 17	6 (60)	3 (43)	0.64
Microbiological findings:			
Pyuria (i.e. ≥25 leucocytes/mm ³ of urine), n (%)	30 (97)	26 (96)	1
Pathogen causing symptomatic UTI, n (%):			0.21
<i>Escherichia coli</i>	19 (61)	19 (70)	
<i>Klebsiella spp.</i>	4 (13)	1 (4)	
<i>Enterococcus faecalis</i>	3 (10)	0 (0)	
Other pathogens ^d	5 (16)	7 (26)	
Same species present without symptoms at study visit immediately preceding the symptomatic UTI, n (%)	18 (58)	6 (22)	0.006

IQR, interquartile range; SD, standard deviation; n, number of participants analysed (if < 58).

^a some patients had symptoms of cystitis and of pyelonephritis.

^b Blood analysis performed in 50/58 participants.

^c Acute kidney injury was defined as an increase in serum creatinine of ≥0.3 mg/dL from previous value (i.e. previous study visit).

^d UTIs due to *Proteus mirabilis* (n = 2), *Enterobacter spp.* (n = 1), *Serratia spp.* (n = 1), *Citrobacter spp.* (n = 1), *Pseudomonas aeruginosa* (n = 1), *Staphylococcus saprophyticus* (n = 1), or *Staphylococcus epidermidis* (n = 1), or mixed UTIs associating *Escherichia coli* and another pathogen (*Proteus mirabilis* n = 1, *Enterobacter spp.* n = 1, *Citrobacter spp.* n = 1, *Streptococcus agalactiae* n = 1).

treat strategy for ASB after kidney transplantation [10,12,13]. We updated our meta-analysis with the data from the current trial and, again, found no significant effect of antibiotics on the prevention of symptomatic UTI (four studies, data for 486 participants, RR 0.94, 95%CI 0.69–1.28, see Supplementary Appendix p. 22).

A third potential limitation is that we are unable to determine what proportion of patients assessed for eligibility were enrolled,

because we did not keep a log of subjects screened but not included. To assess the external validity of our trial findings, we instead performed an observational co-study in some of the trial sites [19]. This co-study showed that the characteristics of the BiRT study participants resembled those of kidney transplant recipients who have ASB in usual care in terms of sex, age, kidney function, and time post-transplant [19].

Table 3
Secondary outcomes during the 1-year follow-up (intention-to-treat analysis)

	No therapy (n = 99)	Antibiotics (n = 100)	p
Death, n (%)	3 (3)	4 (4)	1
Graft loss (death-censored), n (%)	3 (3)	2 (2)	0.68
Biopsy-proven graft rejection, n (%)	2 (2)	3 (3)	1
Increase in serum creatinine level (mg/dL) from baseline to end of study, n = 196, mean ± SD	0.09 ± 0.50	0.19 ± 0.61	0.2
Pyelonephritis, n (%)	16 (16)	17 (17)	0.87
Bloodstream infection due to UTI, n (%)	6 (6)	4 (4)	0.51
Hospital admission due to symptomatic UTI, n (%)	12 (12)	8 (8)	0.33
Number of symptomatic UTI episodes per participant :			
no episode, n (%):	68 (69)	73 (73)	0.76
1 episode, n (%):	23 (23)	21 (21)	
≥2 episodes, n (%):	8 (8)	6 (6)	
<i>Clostridioides difficile</i> -associated diarrhoea, n (%)	0 (0)	0 (0)	NA
Asymptomatic bacteriuria at 1 month post-study inclusion, n = 186 ^a , n (%)	62 (66)	27 (29)	<0.001
Asymptomatic bacteriuria at 12 months post-study inclusion (end-of-study), n = 186 ^a , n (%)	49 (53)	31 (33)	0.008
Total number of asymptomatic bacteriuria episodes per participant during the 1-year follow-up, median (IQR)	3 (1–6)	1 (0–3)	<0.001
Number of participants in whom second episode of bacteriuria (asymptomatic or symptomatic) was caused by a more resistant bacteria than was their baseline episode of asymptomatic bacteriuria ^b , n = 155 ^c	3 (4)	13 (18)	0.003
Number of participants in whom first episode of symptomatic UTI was caused by a more resistant bacteria than was their baseline episode of asymptomatic bacteriuria ^b , n = 53	4 (15)	4 (15)	1
Antibiotic consumption during the 1-year study period:			
Median (IQR) number of antibiotic days per patient, for any cause	6 (0–15)	30 (20–41)	<0.001
Median (IQR) number of antibiotic days per patient, for asymptomatic bacteriuria only	0 (0–0)	20 (10–30)	<0.001
Median (IQR) number of antibiotic days per patient, for symptomatic UTI only	0 (0–8)	0 (0–7)	0.54

IQR, interquartile range; SD, standard deviation; UTI, urinary tract infection; n, number of variables included (if < 199); NA, not available.

^a 186/199 participants performed a urine culture at this follow-up visit (other participants either did not do a urine test at this visit, or had died).

^b Defined as isolation of Gram-negative bacteria resistant to one or more clinically relevant antibiotics (i.e. ciprofloxacin, cotrimoxazole, or third-generation cephalosporin), if not already present at baseline.

^c 155/199 participants had one or more further episodes of bacteriuria during the 1-year study follow-up (and were therefore included in this analysis).

Fourth, trial participants were relatively late after transplant, as illustrated by the fact that only 13% of the participants were included in the first 6 months after transplantation. In particular, we cannot extrapolate our conclusions to the first 2 months post-transplant, as such patients were not eligible for our trial. Similarly, patients developing ASB in the first weeks/months after transplant were excluded from the previously published trials comparing antibiotics versus no therapy [10,12,13].

Last, the 10-day antibiotic duration used in the current trial to treat ASB was relatively long. While this duration was selected to be of sufficient length to be potentially effective (especially because, as described above, there is concern that post-transplant pyelonephritis may present asymptotically), this choice may also have impacted our estimates for the outcomes of antimicrobial resistance and antibiotic consumption.

Our findings support the recent recommendation made by the Infectious Diseases Society of America (IDSA), the American Society of Transplantation, and the European Association of Urology against systematic antibiotic use in kidney transplant recipients with ASB [20–22]. However, as acknowledged by the IDSA [15], this recommendation was made despite a low certainty of evidence for important outcomes such as symptomatic UTI. Although our trial results reinforce the existing body of evidence against a systematic screen-and-treat strategy for ASB, effectively reducing antibiotic prescribing may be challenging. Importantly, treatment of ASB persists in various settings despite publication of negative trials and guidelines advocating the contrary [23]. Because antibiotic prescribing for ASB typically occurs in response to the positive result of a urine culture, efforts should be made to stop the routine use of urine cultures in kidney transplant recipients who are asymptomatic and more than 2 months post-transplant.

In summary, using a screen-and-treat strategy for ASB did not significantly improve clinical outcomes of kidney transplant recipients who were more than 2 months post-transplant. By contrast, this strategy drastically increased antibiotic use and promoted the emergence of more resistant organisms in the urine. More research is needed to determine the effects of screening for and treating ASB in the first 2 months post-transplant. While we agree with the recent suggestion by the IDSA that the efficacy of this strategy needs to be studied early after transplant [20], it is also important to consider the potential risks of leaving ASB untreated in these patients who are heavily immunocompromised and often have a ureteral catheter, which may facilitate the ascent of pathogens from the bladder to the graft.

Author contributions

JC was the chief investigator. JC, LW, AS, JR, KMW, MH, OD and DA contributed to the design of the study. JC, NK, MM, LW, AS, MG, EA, LM, MK, LG, ENB, KMW, MH and DA were the site principal investigators, responsible for participant recruitment and data collection. JC and DA were responsible for the day-to-day running of the trial. JC, JR, KMW, MH and DA did the data analysis. JC wrote the first draft of the manuscript; all authors revised this draft. All authors read and approved the final version. JC had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Transparency declaration

All authors have completed the ICMJE uniform disclosure form. Julien Coussement reports research grants from Fonds Erasme pour

la Recherche Médicale, Fonds David et Alive Van Buuren, and Fonds Carine Vyghen (during the conduct of the study), and personal fees from Sanofi (outside the submitted work). Magali Giral reports grants from Novartis and Sanofi (outside the submitted work), and travel funding and/or honoraria from Astellas, Chiesi, Novartis, Sandoz and Sanofi (also outside the submitted work). Nassim Kamar reports personal fees from Abbvie, Amgen, Astellas, Biotest, CSL Behring, Chiesi, Gilead, Fresenius Medical care, Merck Sharp and Dohme, Neovii, Novartis Pharma, Sanofi, Sandoz, and Shire (outside the submitted work). Anne Scemla reports non-financial support from Bristol-Myers Squibb (outside the submitted work). Other authors declare no competing interests. This work was supported by three research grants: Fonds Erasme pour la Recherche Médicale, Fonds David et Alive Van Buuren, and Fonds Carine Vyghen (all to JC). The funders of the study had no role in the study design, in the collection, analysis and interpretation of data, or in the report writing.

Access to data

Data collected for the study—including de-identified individual participant data and a data dictionary defining each field in the set—will be made available to researchers who provide a methodologically sound proposal to the corresponding author with a signed data access agreement at any point.

Acknowledgments

We thank Liset Pengel (Peter Morris Centre for Evidence in Transplantation, Oxford, UK) for her help with study design. We thank Alexandre Jacq for his precious help regarding the electronic data collection system and the randomization service. We thank our colleagues from the Cochrane Kidney and Transplant Group (Fiona Russell, Gail Y. Higgins) for help with the systematic review process. We also thank James R. Johnson, David Lebeaux and Karen Pickett for their careful reviews of the manuscript. We thank all trial participants, and everyone who contributed to recruitment and follow-up of participants.

Appendix

Members of the bacteriuria in renal transplantation (BIRT) study group: Audrey Beq (Toulouse, France), Tatiana Besse-Hammer (Brussels, Belgium), Marie-Noëlle Blondel-Halley (Paris, France), Arnaud Borsu (Liège, Belgium), Vianney Charpy (Nantes, France), Lionel Couzi (Bordeaux, France), Frédéric Debelle (Baudour, Belgium), Arnaud del Bello (Toulouse, France), Marie de Solere (Lille, France), Sara Frade (Lille, France), Luc Frimat (Nancy, France), Philippe Grimbert (Créteil, France), Pierrick Guerif (Nantes, France), Rachel Hellemans (Antwerp, Belgium), Bénédicte Hodemon-Corne (Nantes, France), Jean-Michel Hougardy (Brussels, Belgium), Alain Le Moine (Brussels, Belgium), Nicole Lietaer (Brussels, Belgium), Olivier Lortholary (Paris, France), Kirsty Loudon (Stirling, United Kingdom), Annick Massart (Antwerp, Belgium), Els Meersman (Antwerp, Belgium), Thavarak Ouk (Lille, France), Lissa Pipeleers (Brussels, Belgium), Sandrine Roisin (Brussels, Belgium), Sarah Tollot (Lille, France), Sabine Verhofstede (Antwerp, Belgium), Martin Wojcik (Lille, France).

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cmi.2020.09.005>.

References

- [1] Vidal E, Torre-Cisneros J, Blanes M, Montejó M, Cervera C, Aguado JM, et al. Bacterial urinary tract infection after solid organ transplantation in the RESITRA cohort. *Transpl Infect Dis* 2012;14:595–603.
- [2] Pelle G, Vimont S, Levy PP, Hertig A, Ouali N, Chassin C, et al. Acute pyelonephritis represents a risk factor impairing long-term kidney graft function. *Am J Transplant* 2007;7:899–907.
- [3] Fiorante S, Lopez-Medrano F, Lizasoain M, Lalueza A, Juan SR, Andrés A, et al. Systematic screening and treatment of asymptomatic bacteriuria in renal transplant recipients. *Kidney Int* 2010;78:774–81.
- [4] Lee JR, Bang H, Dadhania D, Hartono C, Aull MJ, Satlin M, et al. Independent risk factors for urinary tract infection and for subsequent bacteremia or acute cellular rejection: a single-center report of 1166 kidney allograft recipients. *Transplantation* 2013;96:732–8.
- [5] Snyderman DR. Posttransplant microbiological surveillance. *Clin Infect Dis* 2001;33:S22–5.
- [6] Rifkind D, Marchioro TL, Waddell WR, Starzl TE. Infectious diseases associated with renal homotransplantation. *JAMA* 1964;189:397–407.
- [7] Al-Khayyat H, Toussaint N, Holt S, Hughes P. Gram-negative sepsis following biopsy of a transplant recipient with asymptomatic allograft pyelonephritis. *CEN Case Rep* 2017;6:46–9.
- [8] Coussement J, Maggiore U, Manuel O, Scemla A, Lopez-Medrano F, Nagler EV, et al. Diagnosis and management of asymptomatic bacteriuria in kidney transplant recipients: a survey of current practice in Europe. *Nephrol Dial Transplant* 2018;33:1661–8.
- [9] Stewardson AJ, Gaia N, Francois P, Malhotra-Kumar S, Delémont C, Martínez de Tejada B, et al. Collateral damage from oral ciprofloxacin versus nitrofurantoin in outpatients with urinary tract infections: a culture-free analysis of gut microbiota. *Clin Microbiol Infect* 2015;21:344 e1–11.
- [10] Origen J, Lopez-Medrano F, Fernandez-Ruiz M, Polanco N, Gutierrez E, Gonzalez E, et al. Should asymptomatic bacteriuria be systematically treated in kidney transplant recipients? Results from a randomized controlled trial. *Am J Transplant* 2016;16:2943–53.
- [11] Cervera C, van Delden C, Gavalda J, Welte T, Akova M, Carratala J, et al. Multidrug-resistant bacteria in solid organ transplant recipients. *Clin Microbiol Infect* 2014;20:49–73.
- [12] Sabé N, Oriol I, Melilli E, Manonelles A, Bestard O, Polo C, et al. Antibiotic treatment versus no treatment for asymptomatic bacteriuria in kidney transplant recipients: a multicenter randomized trial. *Open Forum Infect Dis* 2019;6:ofz243.
- [13] Moradi M, Abbasi M, Moradi A, Boskabadi A, Jalali A. Effect of antibiotic therapy on asymptomatic bacteriuria in kidney transplant recipients. *Urol J* 2005;2:32–5.
- [14] Coussement J, Scemla A, Abramowicz D, Nagler EV, Webster AC. Antibiotics for asymptomatic bacteriuria in kidney transplant recipients. *Cochrane Database Syst Rev* 2018;2:CD011357. <https://doi.org/10.1002/14651858.CD011357.pub2>.
- [15] Nicolle LE, Siemieniuk R. Reply to Coussement et al. *Clin Infect Dis* 2020;70:988–9.
- [16] Coussement J, Scemla A, Abramowicz D, Nagler EV, Webster AC. Management of asymptomatic bacteriuria after kidney transplantation: what is the quality of the evidence behind the IDSA guidelines? *Clin Infect Dis* 2020;70:987–8.
- [17] Chan AW, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586.
- [18] Smaill F, Vazquez JC. Antibiotics for asymptomatic bacteriuria in pregnancy. *Cochrane Database Syst Rev* 2007:CD000490.
- [19] Coussement J, Scemla A, Hougardy JM, Sberro-Soussan R, Amrouche L, Catalano C, et al. Prevalence of asymptomatic bacteriuria among kidney transplant recipients beyond two months post-transplant: a multicenter, prospective, cross-sectional study. *PLoS One* 2019;14:e0221820.
- [20] Nicolle LE, Gupta K, Bradley SF, Colgan R, DeMuri GP, Drekonja D, et al. Clinical practice guideline for the management of asymptomatic bacteriuria: 2019 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2019;68:e83–110.
- [21] Goldman JD, Julian K, Practice ASTIDCo. Urinary tract infections in solid organ transplant recipients: guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant* 2019;33:e13507.
- [22] European Association of Urology EAU. Guidelines on urological infections. Limited update March 2018. Available from: <https://uroweb.org/wp-content/uploads/EAU-Guidelines-on-Urological-Infections-2018-large-text.pdf>. [Accessed 15 June 2020].
- [23] Gupta K, Trautner BW. The 2019 USPSTF report on screening for asymptomatic bacteriuria—lessons from history. *JAMA Netw Open* 2019;2:e1912522.