

In the name of God

Asymptomatic Bacteriuria in Pediatric Kidney Transplant Recipients: to Treat or Not to Treat?

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Introduction

- In asymptomatic bacteriuria (ASB), the bacteria do not generate a host response to cause sign and symptom
- ASB in Kidney transplant recipients may be at higher risk for developing **pyelonephritis** and so **impaired graft function**
- Pyelonephritis after renal transplantation may associated with **impaired graft function** and risk of **rejection**

Definition of ASB

Infectious Diseases Society of America(IDSA)-2005

- In men, a single clean-catch voided urine with single organism $\geq 10^5$ cfu/mL colony counts without signs or symptoms of UTI
- In women is two clean-catch voided urine >24 h with the same organism ($\geq 10^5$ cfu/mL) colony counts

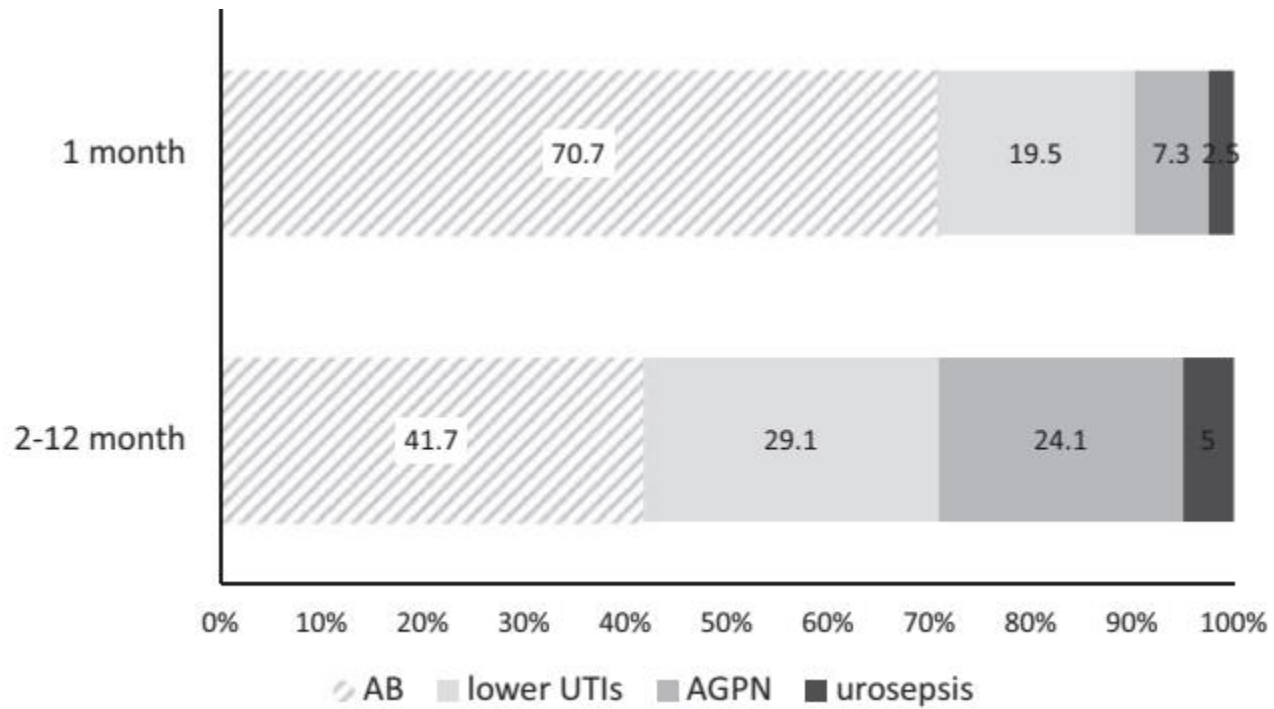
Clin Infect Dis 2005; 40: 643–654

- More than 10^5 CFU/ml of a single organism for extended periods of time
- ASB is positive cultures ($\geq 10^5$ cfu/mL) of the same uropathogens from 2 consecutive urine samples, in the absence of urinary symptoms
- ASB was defined as a significant bacteriuria without any symptom or fever with threshold of $\geq 10^4$ cfu/mL of one or two urinary pathogens

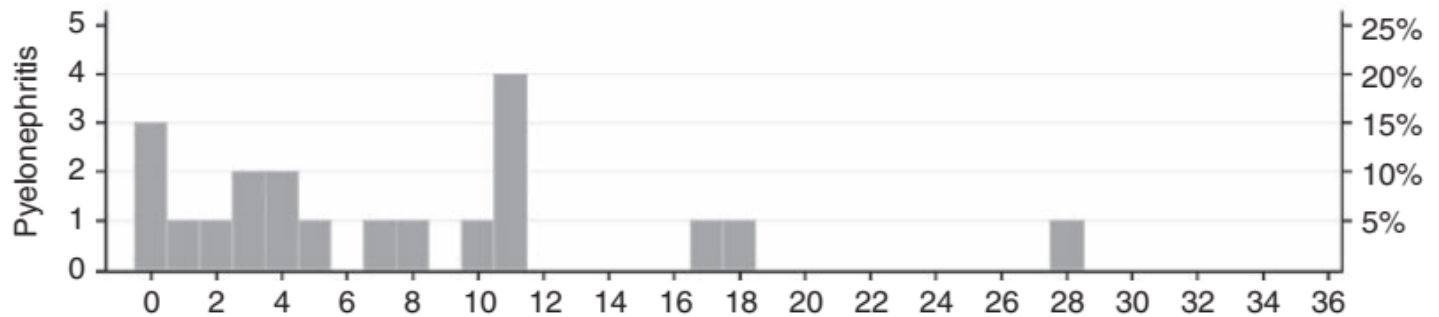
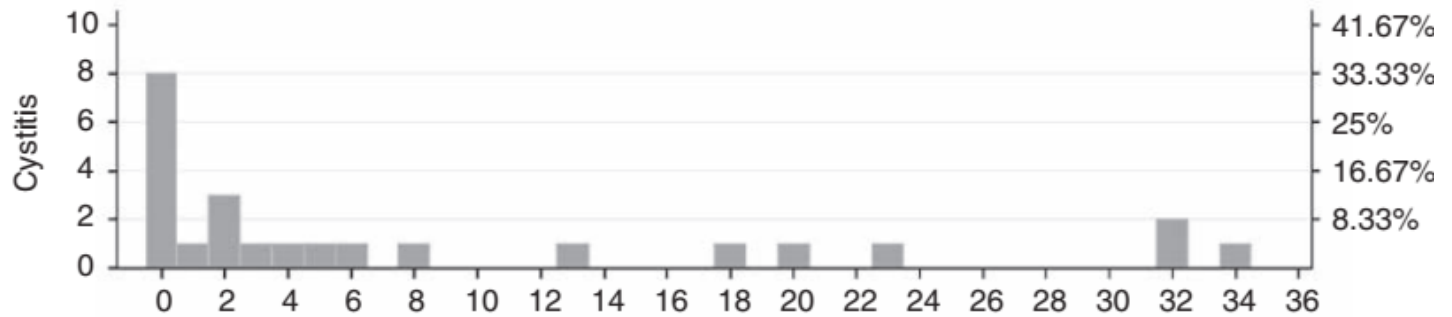
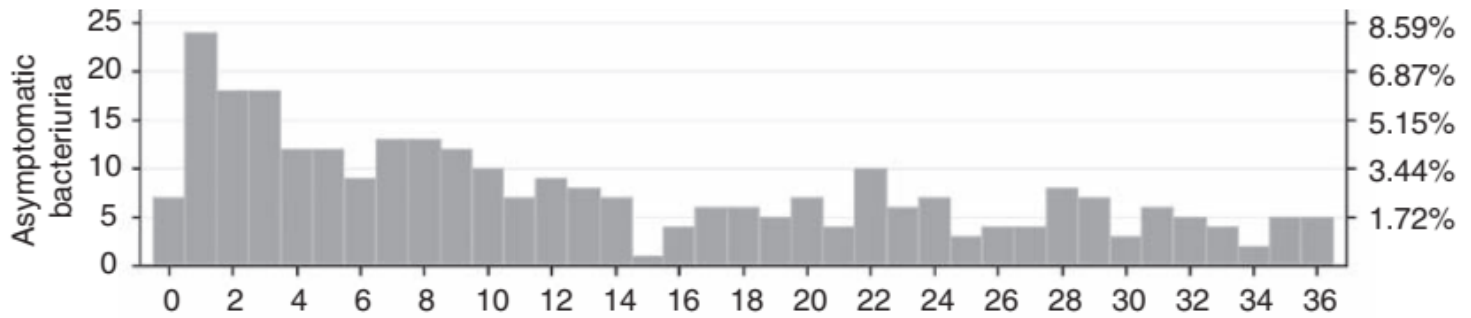
Avner ED, et al. Pediatric Nephrology Seventh Edition. Springer. 2016

Pediatric Nephrology 28 Feb 2019

Dahiya A, et al. Management of asymptomatic bacteriuria in children. NOV 2018



Transplant Infect Dis 2014; 16:605–615.



Original Article

High incidence of bacteriuria following renal transplantation in children

Mostapha Sharifian, Lesley Rees and Richard S. Trompeter

- ❖ 231 episodes of bacteriuria (most asymptomatic) in 66 patients
- ❖ 29% was in first 4 weeks and 52 % in first year

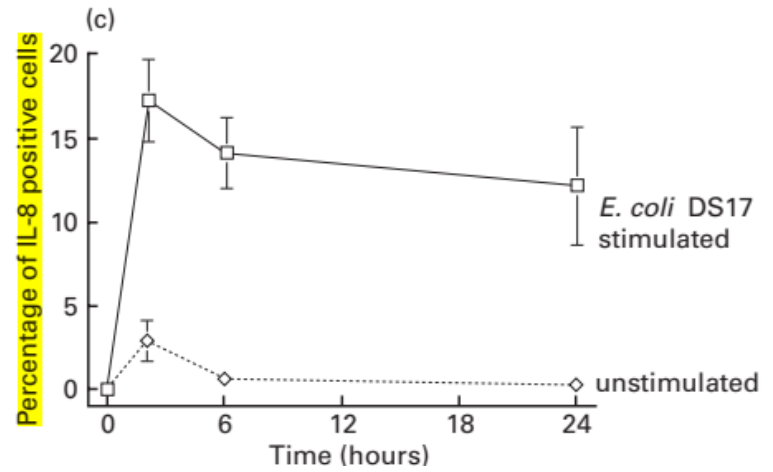
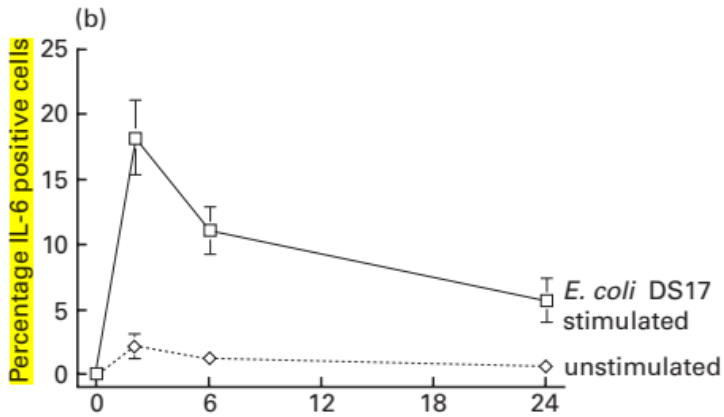
Nephrol Dial Transplant (1998) 13:432-435

Dose ASB cause pyelonephritis, rejection or
allograft dysfunction?

and

Dose treatment of ASB can prevent them?

- Cytokines such as interleukin IL-6 and IL-8 are important mediators in immune responses
- Degree of cytokine response may be due to severity of bacterial infection and inflammation
- Urinary concentration of both IL-6 and IL-8 was elevated in children with symptomatic UTI(PN)
- ASB patients may have lower cytokine response, despite the presence of bacteria in the urinary tract



Clin Exp Immunol 2001; 124:423+428

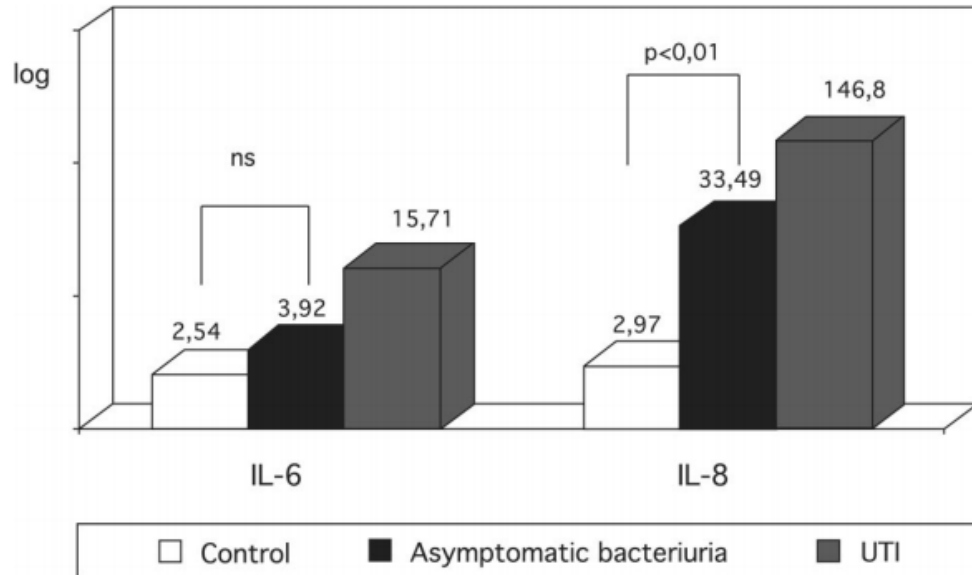
Table 1. Cytokine responses and host and bacterial variables in children with UTI.

	Asymptomatic bacteriuria	Febrile UTI	<i>P</i>
Urine IL-6 (U/mL), <i>n</i>	39 0 (0)	48 28 (0–760)	<.001
Urine IL-8 (pg/mL), <i>n</i>	11/37 (30%) 0 (0–380)	13/18 (76%) 88 (0–3870)	<.01

The Journal of Infectious Diseases 1996;174:1080-4

Urine Cytokines Profile in Renal Transplant Patients with Asymptomatic Bacteriuria

Michał Ciszek, Leszek Paczek, Irena Bartłomieiczvk, and Krzysztof Mucha





- Secretion of IL-8 from renal cells associated with renal inflammation and may influence renal function
- Elevated urinary cytokines in kidney transplant recipients with ASB, which may reflect an impaired immune response to bacterial infection and occult inflammation in the urinary tract (started rejection and impaired graft function)

Dose ASB associate with graft rejection?

Table 5

Multivariable Cox Regression Analysis for the Risk Factors for Biopsy Confirmed ACR

Variable	N (%)	Univariate Analysis		Multivariable Analysis		
		HR (95% CI)	P Value	HR (95% CI)	P Value	
UTI Status						
Untreated UTI (Time Dependent)	100 (8.6%)	2.31 (1.08-4.94)	0.03		2.80 (1.27-6.20)	0.01
Treated UTI (Time Dependent)	147 (12.6%)	0.74 (0.26-2.07)	0.57		0.92 (0.33-2.61)	0.88
Age (per decade increase)	1166 (100.0%)	0.89 (0.74-1.07)	0.21			

❑ Untreated UTI was significantly associated with ACR whereas treated UTI was not associated with ACR

❑ Untreated UTI group had increased risk of ACR

Transplantation. 2013 October 27; 96(8)

Table 4 | Univariate and multivariate analyses of factors associated with kidney allograft rejection

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	P-value	OR	95% CI	P-value
Age (> 60)	0.95	0.49–1.86	0.90			
HCV infection	3.88	1.04–14.39	0.42			
<i>Kidney disease before Tx:</i>						
Glomerulonephritis	1.93	0.97–3.83	0.058			NS
Chronic interstitial nephropathy	1.05	0.83–4.40	0.12			
Diabetic nephropathy	0.96	0.42–2.20	0.93			
Nephroangiosclerosis	0.77	0.30–1.95	0.58			
Congenital nephropathy	0.31	0.03–3.09	0.32			
Kidney polycystosis	0.77	0.30–1.95	0.58			
Non-filiated kidney disease	0.63	0.30–1.32	0.22			
Double transplant	2.87	0.88–9.39	0.07			NS
First renal transplant	0.75	0.30–1.87	0.53			
Second renal transplant	1.68	0.58–4.84	0.33			
Urinary tract surgery after Tx	2.12	1.02–4.41	0.06			NS
Nephrostomy after Tx	1.37	0.52–3.58	0.51			
Cytomegalovirus disease after Tx	2.51	0.84–7.53	0.09			
> 5 Episodes of AB vs 0	22.74	3.89–32.86	0.0005	3.46	1.07–11.18	0.037
2-5 Episodes of AB vs 0	7.83	1.99–8.514	0.0021	1.30	0.52–3.24	NS
1 Episode of AB vs 0	1.68	0.99–2.54	0.019	1.25	0.46–3.38	NS

Abbreviations: AB, asymptomatic bacteriuria; CI, confidence interval; HCV, hepatitis C virus; NS, not significant; OR, odds ratio; Tx, renal transplantation.

□ More than five episodes associated with higher risk of rejection (Not all the episodes of rejection were preceded by ASB)

Kidney International (2010) 78, 774–781

Variable, <i>n</i> (%)	No bacteriuria (<i>n</i> = 98)	AB (<i>n</i> = 37)	Symptomatic UTI+ (<i>n</i> = 74)	<i>P</i> -value
Age in years	44.93 ± 13.52	49.16 ± 14.7	46.9 ± 14.36	¹ 0.15
AR	19 (13.4)	13 (35.1)	27 (36.5)	¹ 0.06

Transplant Infectious Disease 2014: 16: 605–615

Clinical Outcome	With AB (N=41)	Without AB (N=130)	P
Acute Rejection 1 Year			
No	38 (92.7)	116 (89.2)	0.52
Yes	3 (7.3)	14 (10.8)	
Graft Survival 1 Year			
No	2 (4.9)	6 (4.7)	0.95
Yes	39 (95.1)	123 (95.3)	

Clinical Factors and Implications.2017

Table 3. Study Outcomes in Per-Protocol Population

	Antibiotic Treatment if Asymptomatic Bacteriuria n = 29		No Treatment if Asymptomatic Bacteriuria n = 45		P value	RR	95% CI
	n	%	n	%			
Primary endpoint							
KT recipients with acute graft pyelonephritis ^a	4	13.8	3	6.7	.31	2.07	0.50–8.58
Secondary endpoints							
Bacteremic pyelonephritis	0		2	4.4	.25		
Cystitis ^b	4	13.8	3	6.7	.31	2.07	0.50–8.58
Opportunistic infections	5	17.2	10	22.2	.77	0.78	0.30–2.04
Cytomegalovirus infection ^c	5	17.2	10	22.2	.77	0.78	0.30–2.04
BK virus infection	2	6.9	0		.07		
Rejection episodes ^d	1	3.4	2	4.4	.83	0.78	0.07–8.17
Need for hospital admission ^e	16	55.8	26	57.8	1	0.95	0.63–1.44

RCT study:

- ❖ 205 KT recipients were followed in the first year after transplantation

Antibiotic Treatment Versus No Treatment for Asymptomatic Bacteriuria in Kidney Transplant Recipients: A Multicenter Randomized Trial. *Open Forum Infectious Diseases*, 2018

There are conflicting evidence about the relationship between ASB and rejection

Therefore

More studies (especially in children) are needed

Dose ASB associate with decrease graft function?

Pyelonephritis may impair allograft function by:

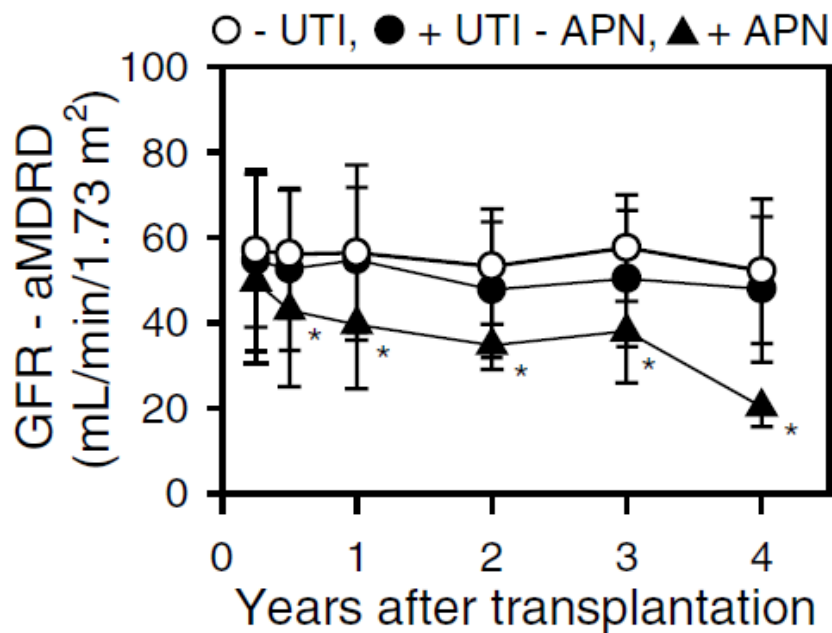
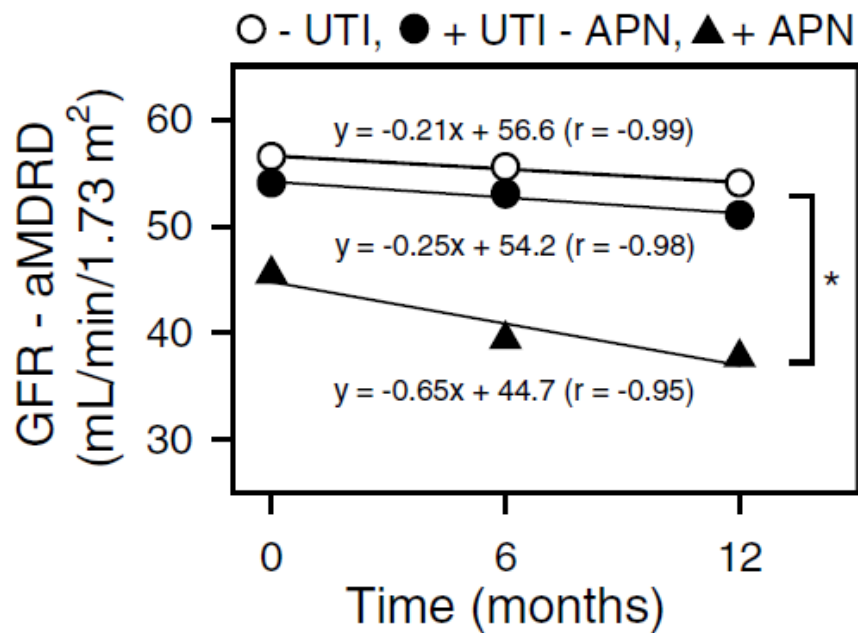
- Release of cytokines
- Activation of the immunological system against the transplanted kidney
- Direct action of the inflammation to the kidney in pyelonephritis

Table 2. AHR for graft loss in transplant recipients who were younger than 18 yr with all UTI after transplantation (inpatient + outpatient)^a

Parameter	AHR	95% CI	P
Early UTI	5.47	1.93 to 15.4	0.000^b
recipient age	1.16	1.06 to 1.34	0.003 ^b
obstructive uropathy	2.39	0.96 to 5.95	0.062
recipient black	2.20	1.01 to 4.83	0.049 ^b
Late UTI	2.09	0.56 to 7.80	0.27
recipient age	1.19	1.06 to 1.33	0.004 ^b
recipient black	2.21	1.01 to 4.85	0.05 ^b

- The US Renal Data System (USRDS) followed pyelonephritis up to 36 m after transplantation (265 Children)
- Early UTI was defined as occurring <6 mo after transplantation
- Late UTI was defined as occurring >6 mo after transplantation

Clin J Am Soc Nephrol 2: 100–106, 2007

B**C**

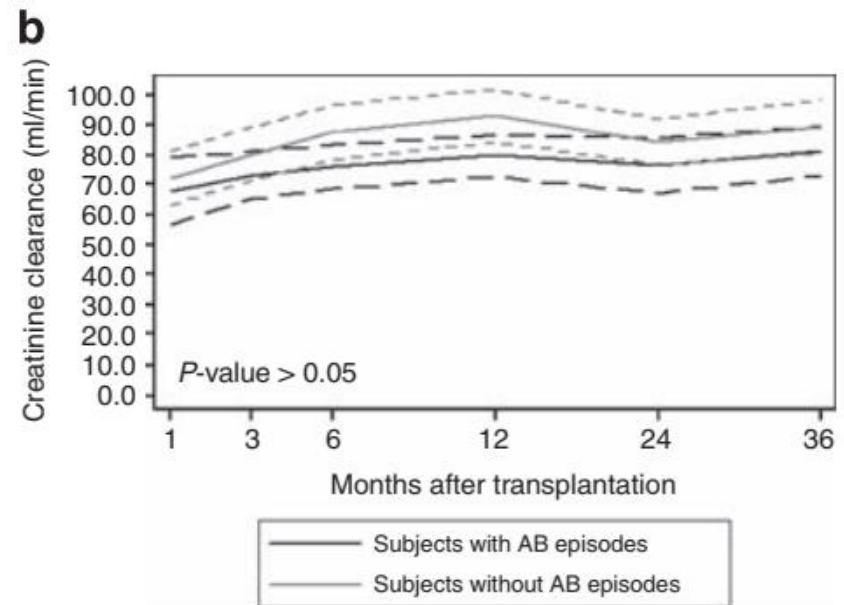
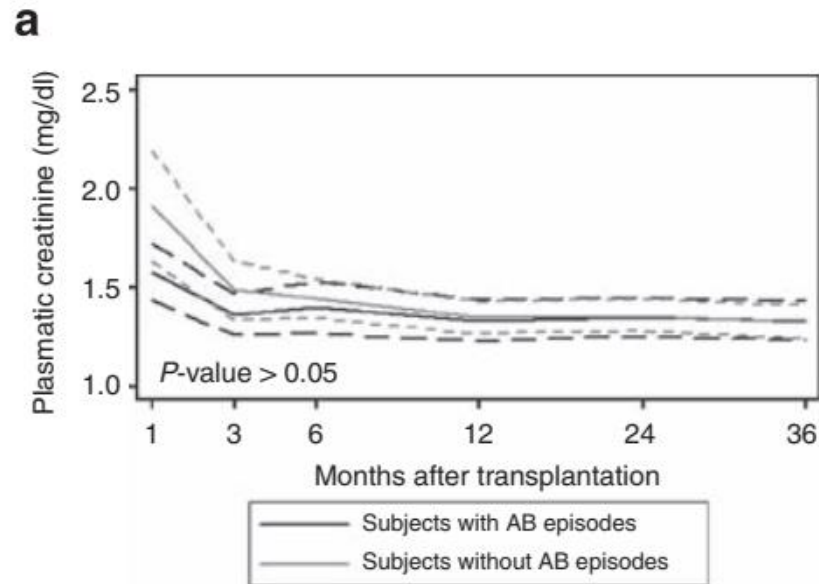
❖ APN is a risk factor for decrease of renal function ($p < 0.05$)

American Journal of Transplantation 2007; 7: 899-907

Table 2. One-year impaired kidney graft function and graft survival by presence and type of UTI.

	Impaired kidney graft function		Graft loss	
	yes n (%)	not n (%)	yes n (%)	not n (%)
No UTI	105 (23)	350 (77)	18 (4)	437 (96)
Asymptomatic bacteriuria	59 (26)	169 (74)	3 (1)	225 (99)
Acute graft pyelonephritis	47 (37) P=0.004	79 (63)	14 (11) P=0.014	112 (89)

Clin Microbiol Infect 2015;21:1104.e1e8]



- No differences in renal allograft prognosis between with and without ASB

Kidney International (2010) 78, 774–781

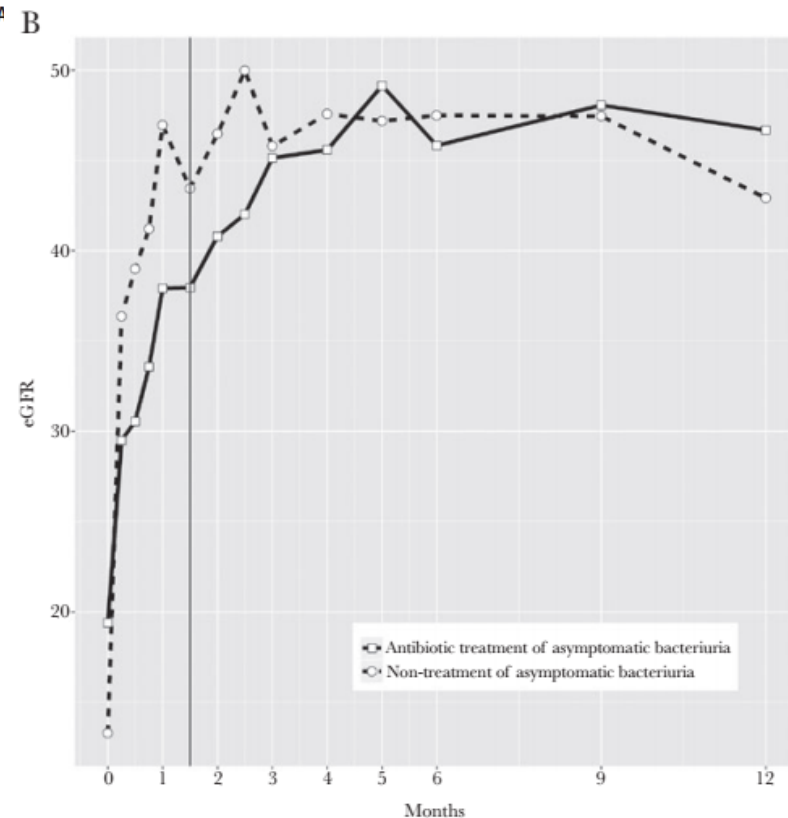
Antibiotic Treatment Versus No Treatment for Asymptomatic Bacteriuria in Kidney Transplant Recipients: A Multicenter Randomized Trial

Núria Sabé,¹ Isabel Oriol,¹ Edoardo Melilli,² Anna Manonelles,² Oriol Bestard,² Carolina Polo,² Ibai Los A
Lluís Riera,⁶ Cristian Tebé,⁷ Óscar Len,³ Francesc Moreso,⁴ Josep M Cruzado,² and Jordi Carratalà¹

❖ Treated vs Untreated ASB:

❖ 102 were antibiotic treatment group

❖ 103 were no treatment group



❖ Treated vs Untreated ASB:

American Journal of Transplantation 2016; 16: 2943–2953
Wiley Periodicals Inc.

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doi: 10.1111/ajt.13829

J. Origüen^{1,*†}, F. López-Medrano^{1,†},

Should Asymptomatic Bacteriuria Be Systematically Treated in Kidney Transplant Recipients? Results From a Randomized Controlled Trial

Table 4: Occurrence of study outcomes in the study groups (modified per-protocol population)

	Treatment group (n = 36)	Control group (n = 50)	OR (95% CI)	p-value
Primary study outcome				
Acute pyelonephritis, n (%)	2 (5.5)	4 (8.0)	0.67 (0.11–3.91)	1.00
Acute graft rejection, n (%)	8 (22.2)	9 (18.0)	1.30 (0.45–3.78)	0.78
Graft loss, n (%)	1 (2.7)	1 (2.0)	1.40 (0.08–23.15)	1.00
All-cause mortality, n (%)	1 (2.7)	1 (2.0)	1.40 (0.08–23.15)	1.00
eGFR, mL/min/1.73 m ² , mean ± SD				
At month 12	46.36 ± 16.4	47.34 ± 15.3		0.79
At month 24	46.3 ± 15.2	47.1 ± 15.2		0.85

American Journal of Transplantation 2016; 16: 2943–2953

Although ,there are several studies that showed
pyelonephritis may be associated with impaired
graft function, but it is not confirmed by **ASB**

- Presence of a microorganism in the urine for a longer period may be a risk factor for microbial invasion

Dose ASB can progress to pyelonephritis?

Table 5 | Univariate and multivariate analyses of risk factors for pyelonephritis

Univariate analysis			
Variable	OR	95% CI	P-value
1 AB episode	5.686	0.994–32.541	0.0508
2–5 AB episodes	9.836	1.994–48.514	0.0050
> 5 AB episodes	22.746	3.894–132.864	0.0005

- ❖ 2–5 or more than 5 episodes of ASB were strongly associated Pyelonephritis (3 year follow up)
- ❖ The incidence of pyelonephritis with ASB was 7 time more than without ASB

Kidney Int 2010; 78:774–781

Clinical Outcome	With AB (N=41)	Without AB (N=130)	P
Hospital Admissions for Symptomatic UTI 1 Year			<0.001
1	14 (34.2)	12 (9.3)	
2	3 (7.3)	6 (4.6)	
3 or more	4 (9.7)	6 (4.6)	

- ✓ Risk of developing symptomatic UTIs requiring hospitalizations were significantly elevated compared with without ASB

Clinical Factors and Implications.2017

- 334 ASB (in 77 RTX) after 1 month post transplantation(77 patients)
- Type I, high-grade bacteriuria($\geq 10^5$ cfu/mL) with pyuria(≤ 10 WBC/field)
- Type II, high-grade bacteriuria without pyuria
- Type III, low-grade bacteriuria($< 10^5$ cfu/mL) with pyuria(≤ 10 WBC/field)
- Type IV, low-grade bacteriuria without pyuria

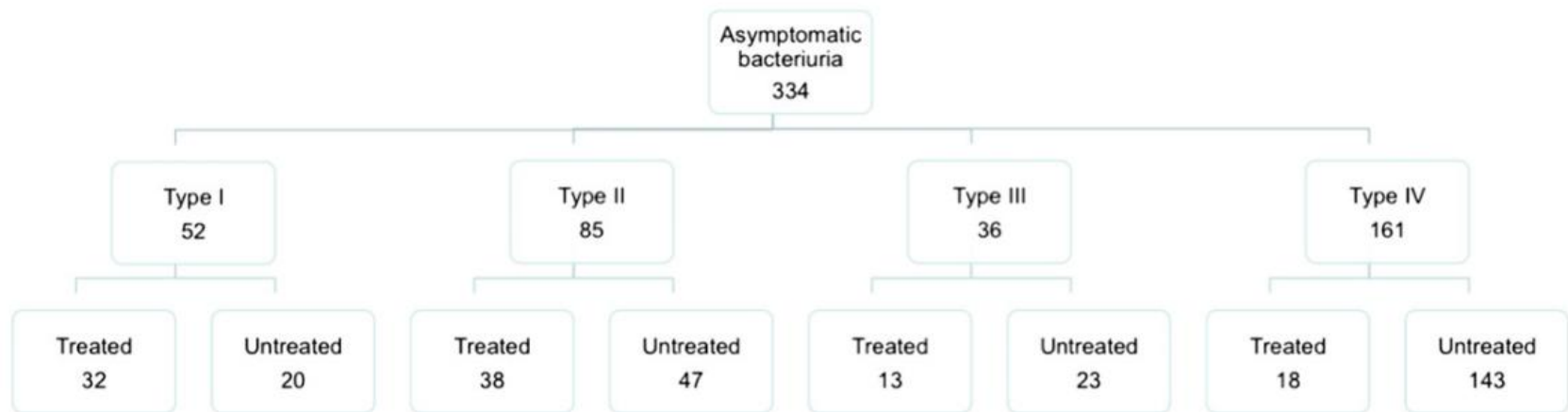


Fig. 1. Flow chart of types and treatments of 334 asymptomatic bacteriuria episodes.

Table 3. Outcome of 101 **treated asymptomatic bacteriuria**

Initial type of treated bacteriuria	Result of control urine culture	
	Symptomatic UTI	Sterile control culture (%)
Type I (<i>n</i> = 32)	0	30 (94%)
Type II (<i>n</i> = 38)	0	11 (29%)
Type III (<i>n</i> = 13)	0	5 (38%)
Type IV (<i>n</i> = 18)	0	9 (50%)

($P = 0.32$)

Table 4. Outcome of 233 **untreated asymptomatic bacteriuria**

Initial type of untreated bacteriuria	Result of control urine culture	
	Symptomatic UTI	Sterile control culture (%)
Type I (<i>n</i> = 20)	1 (5%)	15 (75%)
Type II (<i>n</i> = 47)	0	23 (49%)
Type III (<i>n</i> = 23)	0	9 (39%)
Type IV (<i>n</i> = 143)	3 (2%)	91 (64%)

Nephrol Dial Transplant (2011) 26: 4109–4114

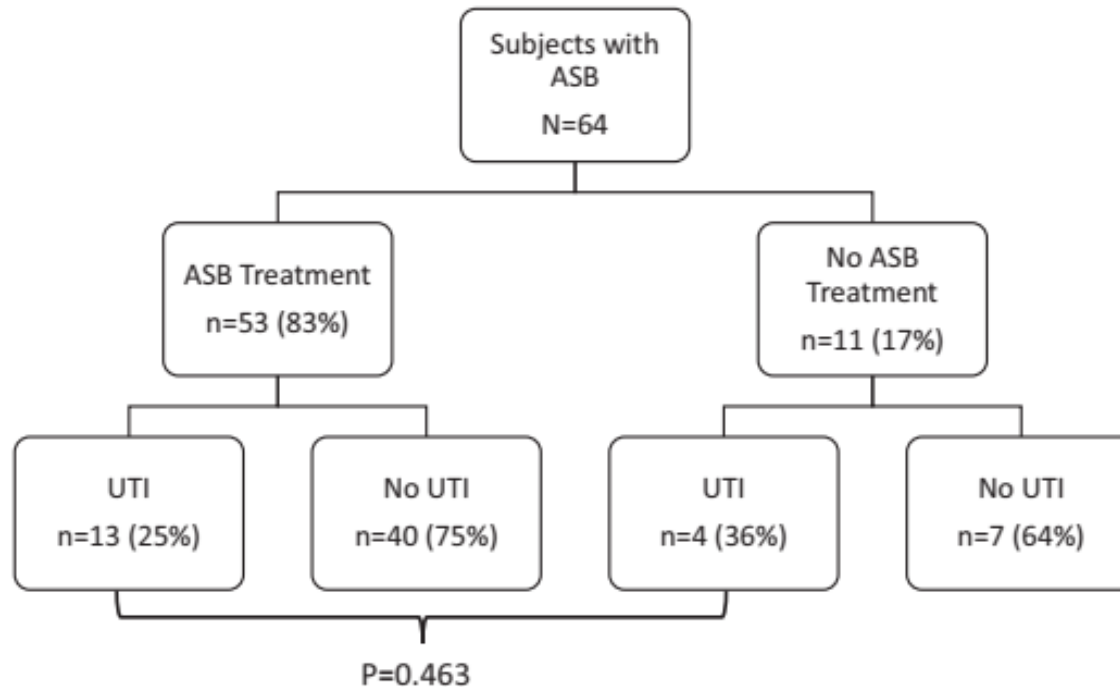


FIGURE 1 ASB-to-UTI progression. ASB, asymptomatic bacteriuria, UTI, symptomatic urinary tract infection

Kidney Transplantation

Effect of Antibiotic Therapy on Asymptomatic Bacteriuria in Kidney Transplant Recipients

MAHMOUDREZA MORADI*, MOHAMMADREZA ABBASI, AS'AD MORADI,

TABLE 3. Comparison of the number of bacteriuric episodes between the two groups

Number of episodes	Case group (%)	Control group (%)	Total
1	11 (25.6)	17 (37.8)	28
2	7 (16.3)	10 (22.3)	17
3	2 (4.6)	1 (2.2)	3
4	3 (6.9)	1 (2.2)	4
5	1 (2.3)	1 (2.2)	2
6	1 (2.3)	2 (2.5)	3
9	-	1 (2.2)	1
Total	25 (58.1)	33 (73.3)	58

88 patients

1 year follow up

(P > 0.05)

Table 3. Study Outcomes in Per-Protocol Population

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Rejection episodes ^d	1	3.4	2	4.4	.83	0.78	0.07–8.17
Need for hospital admission ^e	16	55.8	26	57.8	1	0.95	0.63–1.44

- ❖ Mean number of positive U/C 2.7 in treatment group and 2.8 in no treatment group (p>0.05)
- ❖ No significant differences in the incidence of AGP in the first year after transplantation between treatment and no treatment groups

Antibiotic Treatment Versus No Treatment for Asymptomatic Bacteriuria in Kidney Transplant Recipients: A Multicenter Randomized Trial. *Open Forum Infectious Diseases*, 2018

17th International Congress of Nephrology, Dialysis, and Transplantation

Tabriz, Iran 19-22 November 2019





Asymptomatic bacteriuria in pediatric kidney transplant recipients: to treat or not to treat? A retrospective study

Stéphanie Bonnéric¹ · Anne Maisin¹ · Theresa Kwon¹ · Georges Deschênes¹ · Olivier Niel¹

Received: 20 June 2018 / Revised: 11 January 2019 / Accepted: 18 January 2019

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In conclusion, we suggest that AB episodes should not be systematically treated in pediatric KTR. Indeed, despite a large number of untreated AB in our cohort, few episodes of APN or LUTI occurred after untreated AB; most UTI occurred de novo. Finally, limiting antibiotic treatments have become an urgent and important health issue, in order to reduce multi-drug resistant bacteria emergence in pediatric

So, recent studies on ASB patients can not confirm the higher risk of pyelonephritis in untreated vs treated patients

Clinical Practice Guideline for the Management of Asymptomatic Bacteriuria: 2019 Update by the Infectious Diseases Society of America^a

Lindsay E. Nicolle,¹ Kalpana Gupta,² Suzanne F. Bradley,³ Richard Colgan,⁴ Gregory P. DeMuri,⁵ Dimitri Drekonja,⁶ Linda O. Eckert,⁷ Suzanne E. Geerlings,⁸ Béla Köves,⁹ Thomas M. Hooton,¹⁰ Manisha Juthani-Mehta,¹¹ Shandra L. Knight,¹² Sanjay Saint,¹³ Anthony J. Schaeffer,¹⁴ Barbara Trautner,¹⁵ Bjorn Wullt,¹⁶ and Reed Siemieniuk¹⁷

Clinical Infectious Diseases 2019:1–28

- **RECOMMENDATIONS FOR ASYMPTOMATIC BACTERIURIA**

I. Should Asymptomatic Bacteriuria Be Screened for and Treated in Pediatric Patients?

Recommendation

1. In infants and children, we recommend against screening for or treating ASB (strong recommendation, low-quality evidence).

Clinical Infectious Diseases 2019:1–28

IDSA guideline.....

VII. Should Patients Who Have Received a Kidney Transplant Be Screened or Treated for ASB?

Recommendation:

1. In renal transplant recipients who have had renal transplant surgery **>1 month prior**, we recommend against screening for or treating ASB (*strong recommendation, high-quality evidence*)

Remarks: There is insufficient evidence to inform a recommendation for or against screening or treatment of ASB **within the first month** following renal transplantation

Clinical Infectious Diseases 2019:1–28

IDSA guideline.....

- According this guide line
- Treatment of ASB in renal transplant recipients >1 month may **not prevent pyelonephritis** or graft rejection (high-quality evidence)
- Antimicrobial-resistant organisms are common in renal transplant recipients, and may not effectively treated with oral therapy
- Treatment of ASB may promotes reinfection with organisms increasingly resistant to antimicrobials

Clinical Infectious Diseases 2019:1–28

In Conclusion

- ❖ There is insufficient evidence to support routinely treating or screening of ASB after transplantation
- ❖ The higher risk of rejection by ASB had not confirmed
- ❖ Graft function dose not affected by ASB
- ❖ ASB dose not progress to symptomatic UTI
- ❖ The majority of studies were done in adult and more studies were needed in children