

La Gestione Multidisciplinare delle Infezioni Complicate delle Vie Urinarie nel Terzo Millennio

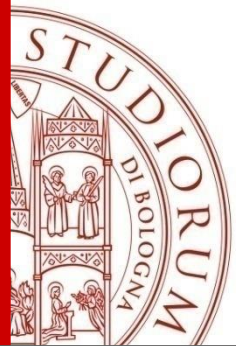


Ferrara, 5 Maggio 2017
Azienda Ospedaliera-Universitaria Ferrara
Nuovo "Arcispedale S. Anna", Cona
Aula Congressi

Infezioni nel trapianto di rene: aspetti epidemiologici, clinici e terapeutici

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Fattori di rischio

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Outcome del trapianto

3

Infezioni complesse

The prevalence and predictive factors of urinary tract infection in patients undergoing renal transplantation: A meta-analysis

Xiaohui Wu MS^{a,b}, Yanyan Dong MD^c, Yunhong Liu MS^b, Yingxia Li MS^d, Yu Sun MS^e, Jingna Wang MS^f, Shuihui Wang MD^{a,*}

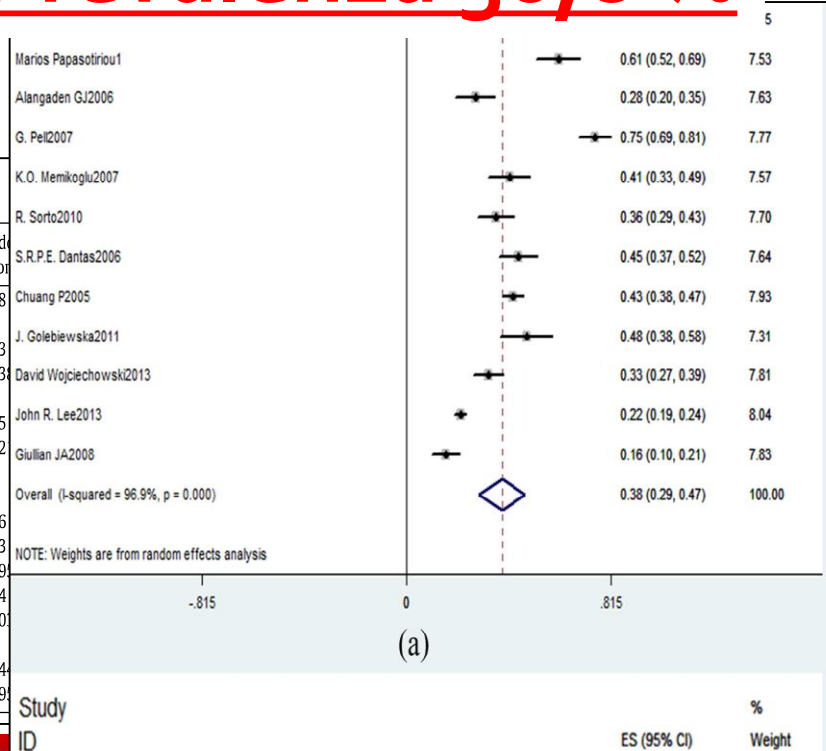
American Journal of Infection Control 44 (2016)

13 studi (dal 2005 al 2014),
3364 pazienti

Prevalenza 30,8 %

Table 1
Characteristics of the articles included in the meta-analysis

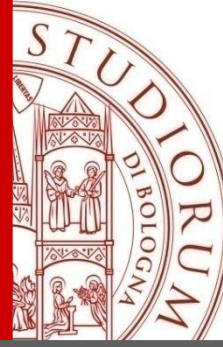
Study design	Country	No. of participants	No. of urinary tract infections	Male/female (n)	Mean age (y)	Mean follow-up (mo)	Deceased or living donor
G. Bonkat ¹¹ 2012	Switzerland	78	3	51/27	56	24	50/28
P.A. Cepeda ¹² 2005	Spanish	226	55	na	na	48	na
G. J. Alangaden ¹³ 2006	USA	127	35	76/51	47.1	21	94/33
R. Sorto ¹⁴ 2010	Mexico	176	63	96/80	37	48	38/138
J. Golebiewska ¹⁵ 2011	Poland	89	49	52/37	48.13	12	88/1
D. Wojciechowski ¹ 2013	San Francisco	236	77	145/91	51.6	12	141/95
A. Farr ¹⁶ 2014	Austria	598	185	389/209	54	18	57/52
M. Papisotiriou ¹⁷ 2011	Greece	122	74	75/47	44	67.8	na
E. Vidal ¹⁸ 2012	Spain	2,172	156	1,381/671	52	18	na
J. A. Giullian ¹⁹ 2008	USA	158	25	109/49	47	36	67/76
S. Dantas ²⁰ 2006	Brazil	163	73	98/65	42.5	24	110/53
P. Chuang ²¹ 2005	USA	500	213	331/169	44	42	105/39
G. Pellè ²² 2007	France	177	133	117/60	46.5	21.84	153/24
K. O. Memikoglu ²³ 2007	Turkey	136	56	88/48	32	38	33/10
F. López-Medrano ²⁴ 2014	Spain	163	16	107/56	44.8	26.2	na
N. Safdar ²⁵ 2005	USA	384	192	166/218	47	96	140/24
J. R. Lee ⁴ 2013	New York	1,166	247	714/452	53	60	607/59



Major Article

The prevalence and predictive factors of urinary tract infection in patients undergoing renal transplantation: A meta-analysis

Xiaohui Wu MS^{a,b}, Yanyan Dong MD^c, Yunhong Liu MS^b, Yingxia Li MS^d, Yu Sun MS^e, Jingna Wang MS^f, Shuihui Wang MD^{a,*}



American Journal of Infection Control 44 (2016)

USA: 41 %

Profilassi con beta lattami: 38 %

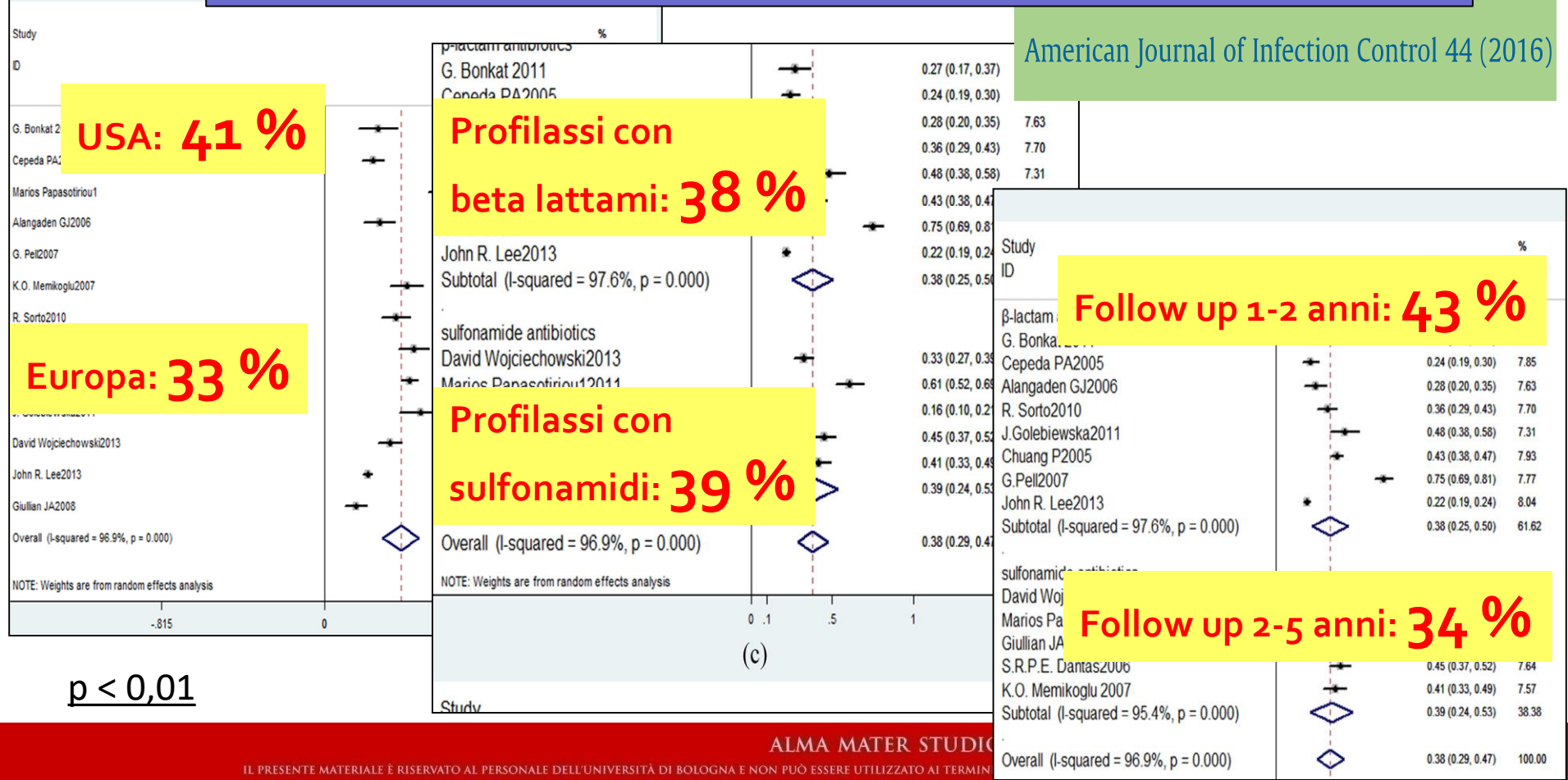
Europa: 33 %

Profilassi con sulfonamidi: 39 %

Follow up 1-2 anni: 43 %

Follow up 2-5 anni: 34 %

p < 0,01



Urinary Tract Infections in Solid Organ Transplantation

R. Parasuraman^{a,*}, K. Julian^b and the AST Infectious Diseases Community of Practice

American Journal of Transplantation 2013; 13: 327–336
Wiley Periodicals Inc.

Prevalenza infezioni vie urinarie negli studi: tra il 21% e il 79 %

- definizioni non univoche
- diverso follow up negli studi
- differenze nell'uso della profilassi antibiotica post trapianto

DEFINIZIONI

Table 1: Diagnostic criteria for UTI (18,19)

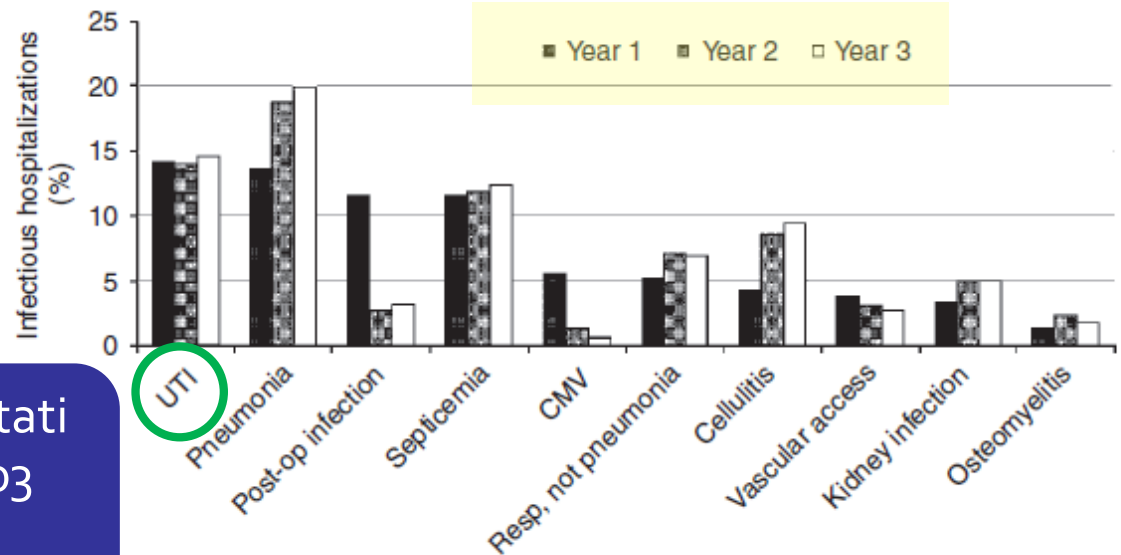
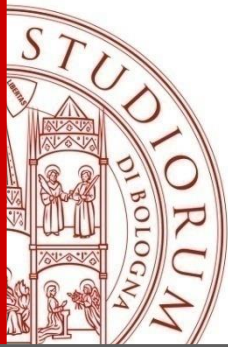
Category	Description	Clinical features	Laboratory investigations
Batteriuria non complicata	cystitis in women	Frequency, suprapubic pain, no symptoms 4 weeks before this episode	>10 WBC/mm ³ >10 ³ cfu/mL ¹
Pielonefrite lieve		Fever, chills, flank/allograft pain; other diagnoses excluded; no history or clinical evidence of urological abnormalities (ultrasonography, radiography)	>10 WBC/mm ³ >10 ⁴ cfu/mL ¹
Infezione urinaria complicata		From categories 1 and 2 with a complicated UTI (see text for definition)	>10 WBC/mm ³ >10 ⁵ cfu/mL ¹ in women >10 ⁴ cfu/mL ¹ in men, or in straight catheter urine in women
Batteriuria asintomatica		Asymptomatic	>10 WBC/mm ³ >10 ⁵ cfu/mL ¹ in two consecutive MSU cultures >24 h apart
UTI ricorrente		At least three episodes of uncomplicated infection documented by culture in past 12 months: women only; no structural/functional abnormalities	>10 ³ cfu/mL ¹

Modified according to IDSA/European Society of Clinical Microbiology and Infectious Diseases guidelines. All pyuria counts refer to unspun urine.

Rates of first infection following kidney transplant in the United States

Kidney International (2009) **75**, 317–326

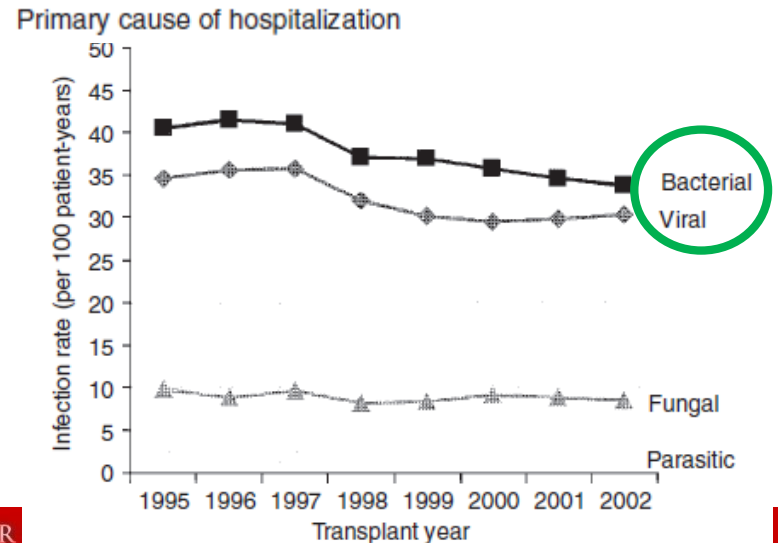
Jon J. Snyder¹, Ajay K. Israni^{2,3}, Yi Peng¹, Lin Zhang⁴, Teresa A. Simon⁴ and Bertram L. Kasiske²



46471 trapiantati dal 1995-2003 (Registro Medicare)

UTI è la seconda causa di ospedalizzazione per infezione

Tasso ospedalizzazione 45 x100 pazienti/anno



Risk and outcome of pyelonephritis among renal transplant recipients

BMC Infectious Diseases

2016

Mette Elneff Graversen^{1*}, Lars Skov Dalgaard¹, Søren Jensen-Fangel¹, Bente Jespersen², Lars Østergaard¹ and Ole Schmeltz Søgaard¹

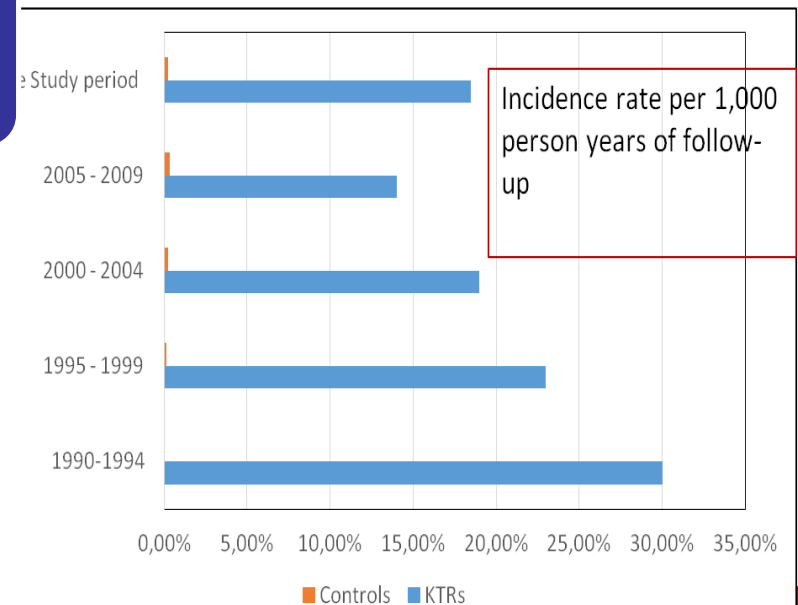
Purpose of the study: determine the incidence of pyelonephritis

Numbers: **2656** Kidney transplant recipients vs **49226** controls

Outcome: A first time hospitalization for pyelonephritis identified in 261 KTRs (**9.8%**) and in 115 population controls (**0.2%**)

Renal Transplant Recipients had **72-fold higher** risk of first time hospitalisation for pyelonephritis compared to matched population controls.

«studio che analizza l'incidenza di ricovero per pielonefrite in una popolazione di trapiantati rispetto a una di controllo»



Fattori di Rischio

Table 3: Risk factors for UTI in renal transplant recipients (6,15, 26-30)

Risk factors	OR (95% CI)
Bacterial urinary tract infection	
Female gender	5.8 (3.79-8.89)
Age (per year)	0.02 (1.01-1.04)
Reflux kidney disease prior to transplantation	3.0 (1.05-8.31)
Deceased donor	3.64 (1.0-12.7)
Duration of bladder catheterization	1.50 (1.1-1.9)
Length of hospitalization prior to UTI	0.92 (0.88-0.96)
Increase in immunosuppression	17.04 (4.0-71.5)
Candiduria	
Female gender	12.5 (6.70-23.0)
ICU care	8.8 (2.3-35.0)
Prior antibiotic use	3.8 (1.7-8.3)
Indwelling urethral catheter	4.4 (2.1-9.4)
Neurogenic bladder	7.6 (2.1-27)
Malnutrition	2.4 (1.3-4.4)
Acute pyelonephritis	
Female gender	5.14 (1.86-14.20)
Acute rejection episodes	3.84 (1.37-10.79)
Number of UTIs	1.17 (1.06-1.30)

Parasuraman R et al, Am J Transplant, 2013

2013

Khaled Abdel Tawab et al. Experimental and Clinical Transplantation (2017)

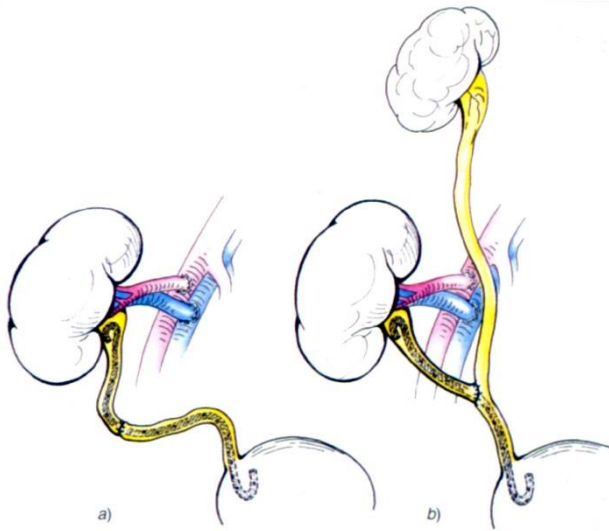
- Women
- Adult age (than elderly and childhood)
- Deceased donors
- Induction with ATG
- Pretransplant urologic problems
- Hepatitis C infection

Metanalisi di Wu X et al, Am J Inf Cont, 2016

- **Women** (OR 3.11; 95% CI, 2.10-4.13)
- **Longer duration of catheter** (OR 1.53; 95% CI, 1.03-2.03)
- **Deceased donor** (OR 1.28; 95% CI, 1.09-1.52)
- **Acute Cellular Rejection** (OR 1.64; 95% CI, 1.11-2.41)

Il Trapianto Oggi è ...

Bologna



→ Catetere vescicale tenuto in sede per 7-10 giorni

→ Stent endoureterale tenuto in sede per 4-6 settimane

- Tx in ricevente con problemi urologici **SI**
- Tx doppio **SI**
- Tx nell'anziano (età > 70 anni) **SI**
- Tx con donatore Marginale (età > 65 anni) **SI**
- Tx in pz iperimmuni (2° o 3° trapianti) **SI**
- Tx da vivente ABO o HLA incompatibile **SI**
- Tx in pz HIV+ , HCV+ **SI**
- Tx pediatrico (donatore vivente o cadavere) **SI**
- Tx multiorgano (rene-cuore, rene-fegato, ...) **SI**
- Tx da donatore a cuore fermo **SI**

Fc-gamma receptor 3A polymorphism predicts the incidence of urinary tract infection in kidney-transplant recipients



Lalit Kumar Das, Kentaro Ide*, Asuka Tanaka, Hiroshi Morimoto, Seiichi Shimizu, Naoki Tanimine, Yuka Tanaka, Hideki Ohdan*



Table 2

Genomic characteristics of recipients with and without urinary tract infection (UTI) episode.

	Total (n = 81)	UTI (+) (n = 31)	UTI (-) (n = 50)	p-Value
<i>CTQA</i> [276 A/G], n (%)				0.51
276 A/A	16 (19.8)	5 (16.1)	11 (22.0)	
276 A/G or G/G	65 (80.2)	26 (83.9)	39 (78.0)	
<i>FCGR2A</i> [131 H/R], n (%)				0.20
131 H/H	56 (69.1)	24 (77.4)	32 (64.0)	
131 H/R or R/R	25 (30.9)	7 (22.6)	18 (36.0)	
<i>FCGR3A</i> [158 F/V], n (%)				0.02*
158 V/V	42 (51.9)	11 (35.5)	31 (62.0)	
158 F/V or F/F	39 (48.1)	20 (64.5)	19 (38.0)	

A difference was considered significant if the p-value was <0.05.

Table 5

Impact of *FCGR3A* single nucleotide polymorphism (SNP) on post-transplant infectious complications after propensity score matching.

Type of infection	[158 V/V] (n = 26)	[158 F/V or F/F] (n = 26)	p-Value
CMV, n (%)	2 (7.7)	4 (15.4)	0.33
Fungal, n (%)	0 (0)	1 (3.8)	0.50
UTI, n (%)	5 (19.2)	14 (53.8)	<0.01

Table 3

Multivariate analysis of urinary tract infection (UTI) episode after primary renal transplantation.

	OR	95% CI	p-value
Sex [Female]	3.53	1.34 - 9.81	0.009*
<i>FCGR3A</i> [158 F/F or V/F]	3.26	1.24 - 9.08	0.015*

Vitamin D Deficiency Is an Independent Risk Factor for Urinary Tract Infections After Renal Transplants

Young Eun Kwon, MD, Hyunwook Kim, MD, PhD, Hyung Jung Oh, MD, Jung Tak Park, MD, Seung Hyeok Han, MD, PhD, Dong-Ryeol Ryu, MD, PhD, Tae-Hyun Yoo, MD, PhD, and Shin-Wook Kang, MD, PhD

Medicine • Volume 94, Number 9, March 2015

TABLE 3. Outcomes According to Baseline 25(OH)D3 Levels

	25(OH)D3		P Value
	Group 1 <10 ng/mL (n = 171)	Group 2 ≥10 ng/mL (n = 239)	
UTI, n (%)	52 (30.4)	40 (16.7)	0.001
Early UTI, n (%)*	8 (4.7)	7 (2.9)	0.35
Late UTI, n (%)*	45 (26.3)	36 (15.1)	0.005
Frequency of UTI events/1000 patient-years	68.6	33.8	
Graft failure, n (%)	7 (4.1)	9 (3.8)	0.87
Mortality, n (%)	4 (2.3)	11 (4.6)	0.23

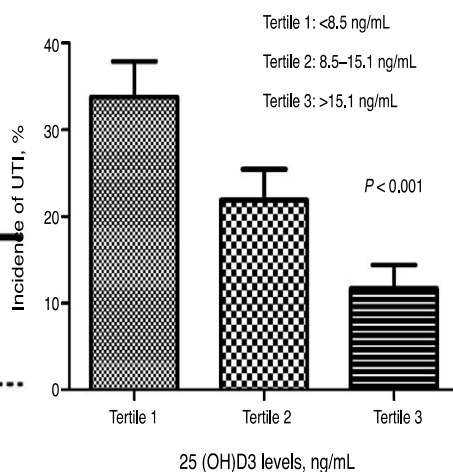
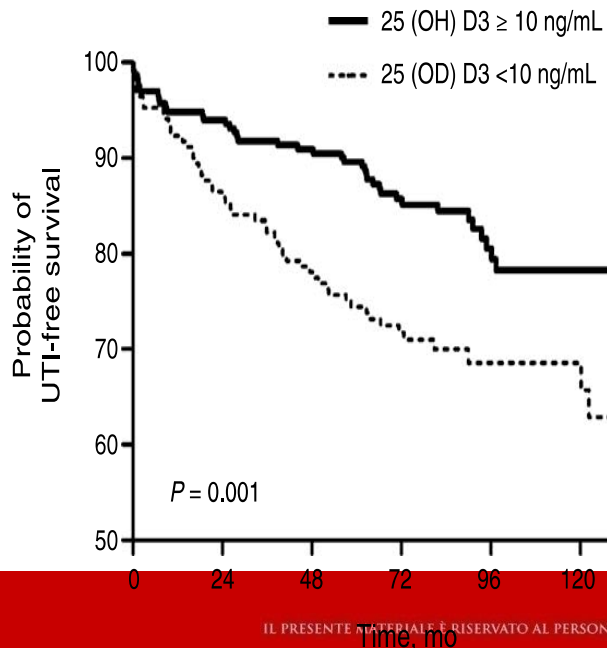
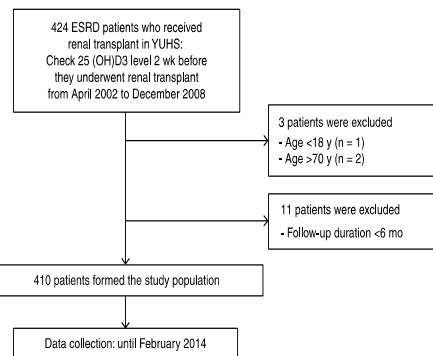
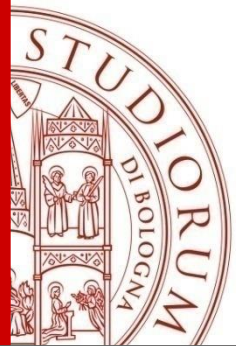


TABLE 4. Multivariate Cox Regression Analysis for the Incidence of UTIs With Adjustments for Various Factors

	Model 1		Model 2	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Vitamin D deficiency (vs ≥10 ng/mL)	1.56 (1.03-2.38)	0.04	1.81 (1.11-2.97)	0.02
Female (vs male)	6.58 (3.74-11.56)	<0.001	6.79 (3.85-11.96)	<0.001
BMI (per 1 kg/m ²)	1.00 (0.93-1.07)	0.94	1.00 (0.93-1.08)	0.95
Smoker (vs nonsmoker)	0.99 (0.46-2.13)	0.98	0.97 (0.45-2.10)	0.94
Donor		0.10		0.19
Living-related donor	Reference		Reference	
Living-unrelated donor	1.16 (0.69-1.95)	0.57	1.19 (0.69-2.05)	0.52
Deceased donor	1.71 (1.04-2.80)	0.03	1.64 (0.96-2.80)	0.07
Age (per 1 y increase)	—	—	1.00 (0.98-1.02)	0.99
Albumin (per 1 g/dL decrease)	—	—	1.23 (0.75-2.03)	0.42
Hemoglobin (per 1 g/dL decrease)	—	—	0.96 (0.84-1.10)	0.58
Seasons				0.70
Spring	—	—	0.75 (0.40-1.42)	0.38
Summer	—	—	Reference	
Autumn	—	—	0.75 (0.40-1.39)	0.36
Winter	—	—	0.95 (0.53-1.70)	0.86
Pretransplantation treatment mode				0.67
Preemptive	—	—	Reference	
Hemodialysis	—	—	1.44 (0.76-2.72)	0.26
Peritoneal dialysis	—	—	1.10 (0.55-2.18)	0.79
Previous kidney transplantation	—	—	1.51 (0.56-4.17)	0.42



1

Fattori di rischio

2

Outcome del trapianto

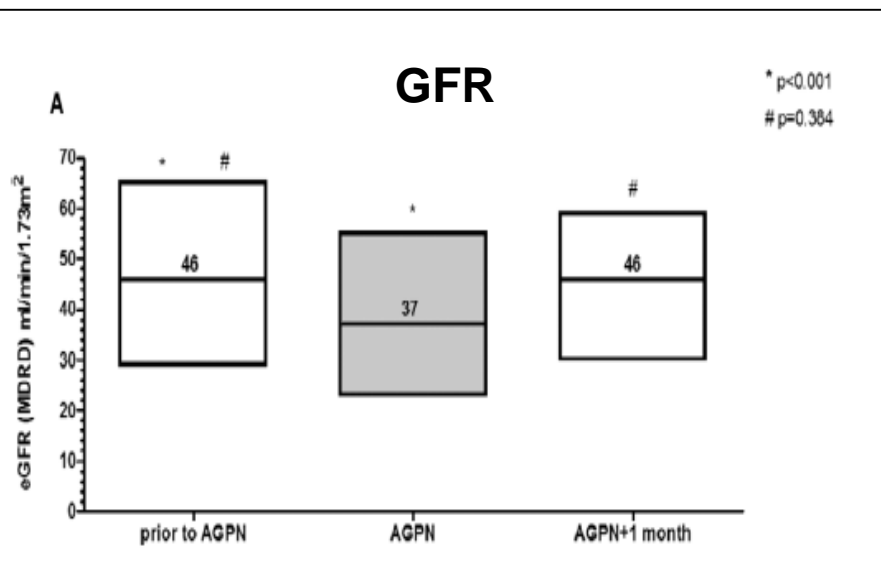
3

Infezioni complesse

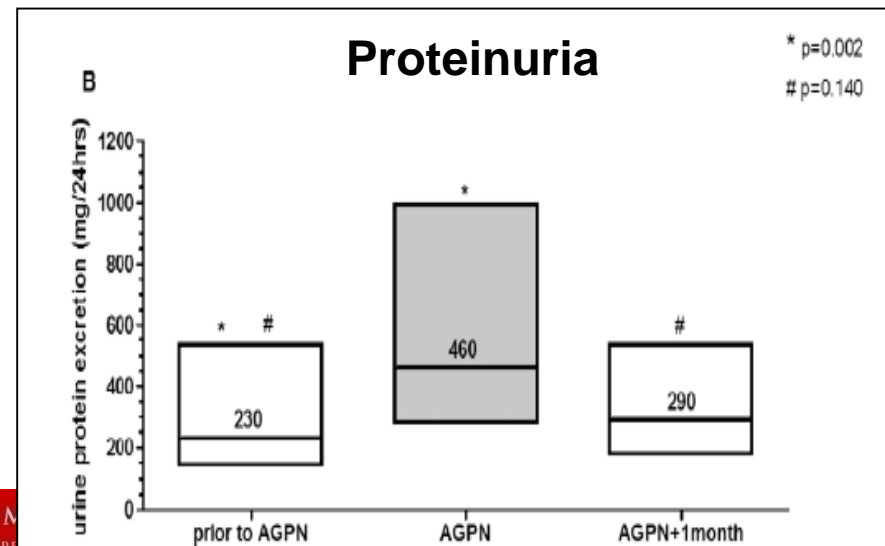
Incidence, risk factors, and the impact of allograft pyelonephritis on renal allograft function

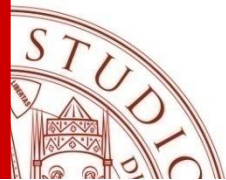
Sing R et al, Transplant Inf Dis, 2016

- Study design: RETROSPECTIVE COHORT STUDY
- Population: Kidney transplant recipients transplanted between 2004 and 2009 in a single center in Netherlands
- Follow up = 1 year for all patients



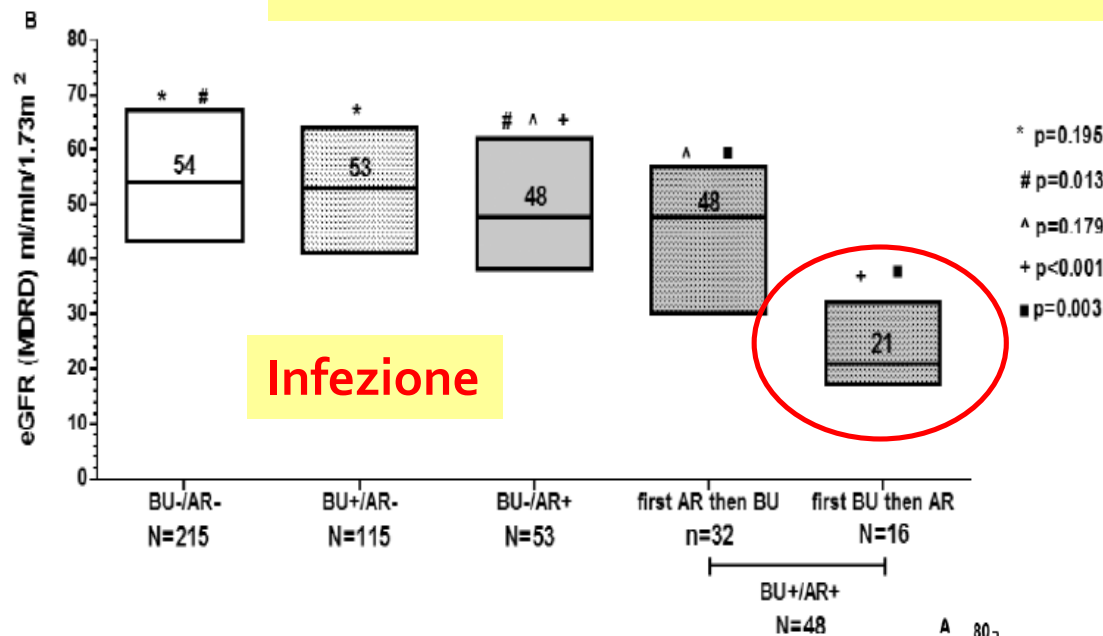
Effetto in acuto della pielonefrite



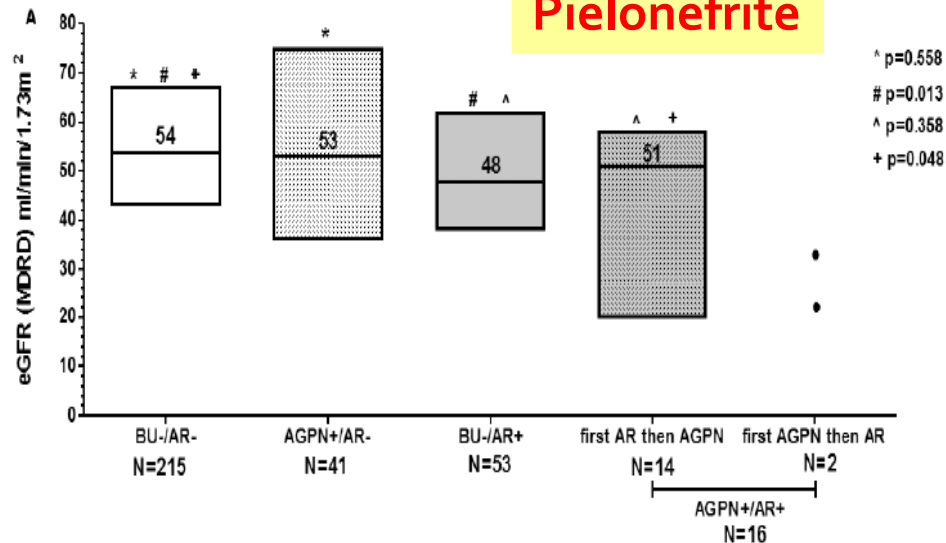


Incidence, risk factors, and the impact of allograft pyelonephritis on renal allograft function

Sing R et al,
Transplant Inf
Dis, 2016



Pielonefrite



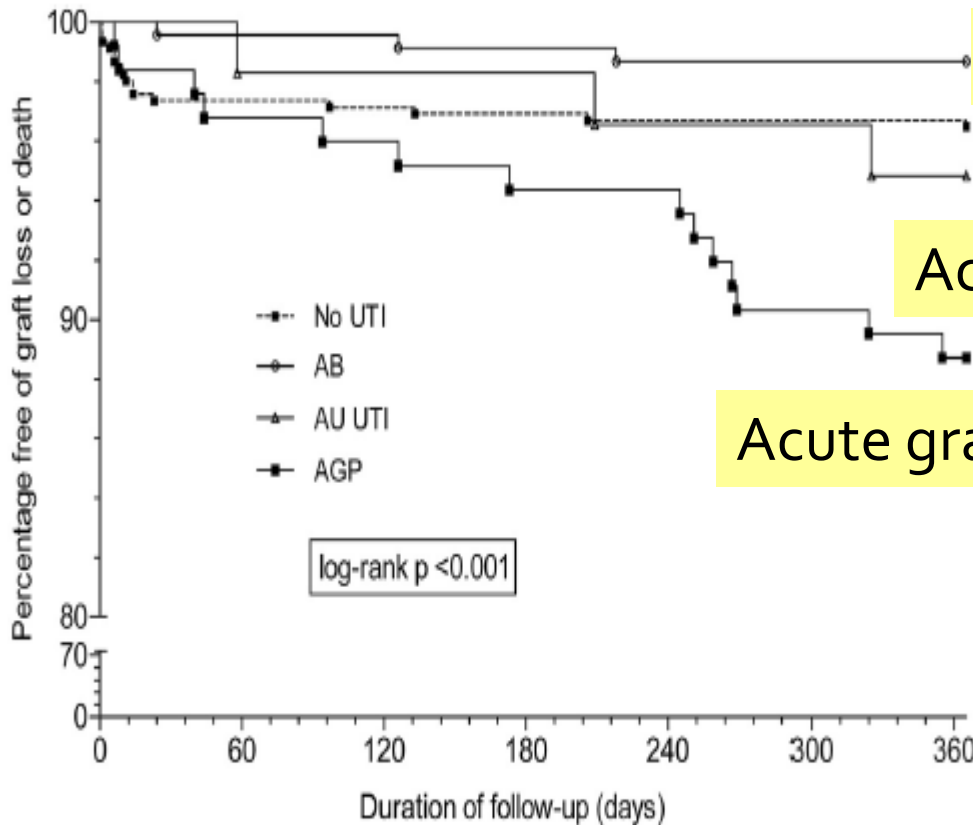
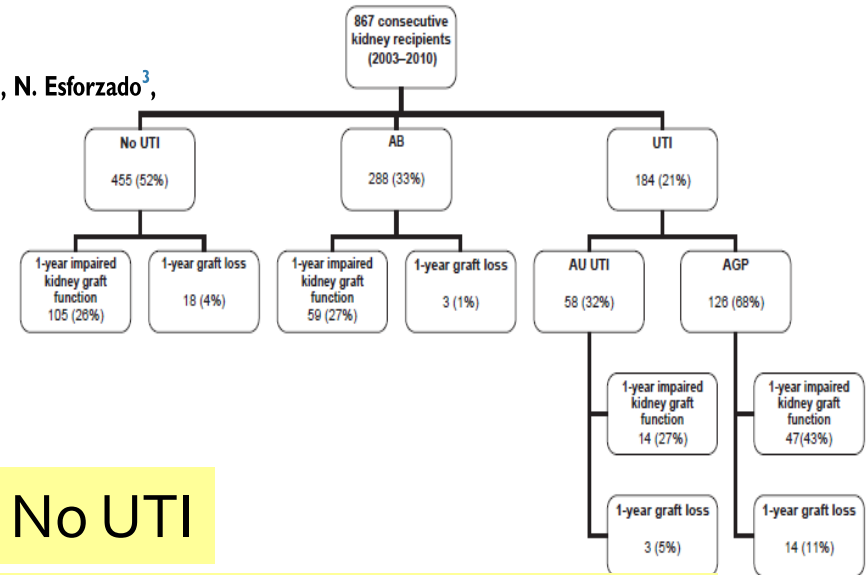
The subtypes of acute rejection (AR) among the renal allograft recipients who experienced bacteriuria

	Subtypes of acute rejection				P-value
	Cellular	Humoral	Combined	Steroid-resistant cellular	
Only rejection (n = 53)	36 (67.9%)	9 (17.0%)	3 (5.7%)	5 (9.4%)	
Both bacteriuria and AR (n = 48)					
First AR then bacteriuria (n = 32)	19 (59.4%)	5 (15.6%)	5 (15.6%)	3 (9.4%)	0.502
First bacteriuria then AR (n = 16)	7 (43.8%)	2 (12.5%)	5 (31.3%)	2 (12.5%)	0.039

Compared to the group that only experienced AR, there were significantly (chi-square $P = 0.039$) more episodes of combined rejections among the group that experienced AR after a bacteriuria event. The subtypes of AR did not differ between the group that experienced their first bacteriuria event after AR compared with those who only experienced AR (chi-square $P = 0.502$).

Impact of urinary tract infections on short-term kidney graft outcome

M. Bodro¹, G. Sandemonte¹, I. Lipperheide¹, M. Allali¹, F. Marco², J. Bosch², F. Cofan³, M. J. Ricart³, N. Esforzado³,
 F. Oppenheimer¹, A. Moreno¹ and C. Cervera¹



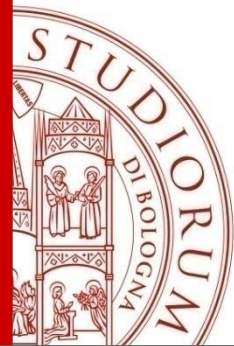
No UTI

Asimptomatic bacteriuria

Acute uncomplicated UTI

Acute graft Pyelonephritis

Bodro M et al, Infec Dis, 2015



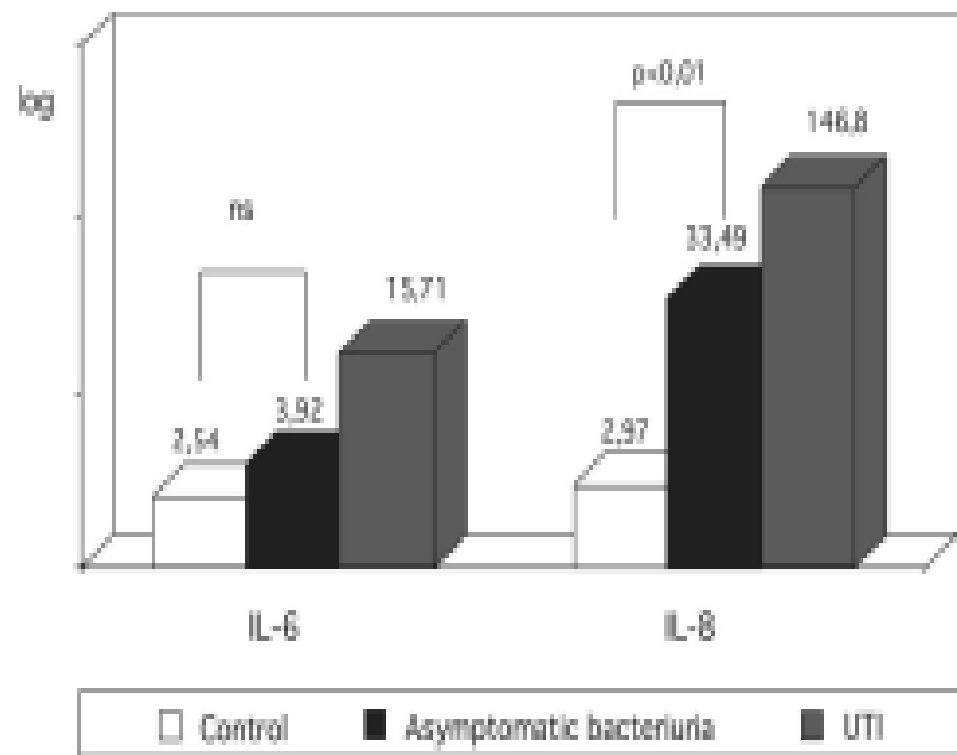
Urine Cytokines Profile in Renal Transplant Patients with Asymptomatic Bacteriuria

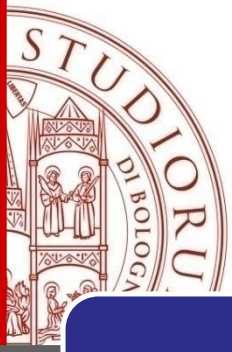
Transplantation, 2006

Michał Ciszek, Leszek Pączek, Irena Bartłomiejczyk, and Krzysztof Mucha

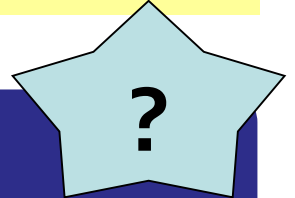
TABLE 1. Demographic data

	Asymptomatic bacteriuria	Control
n	22	25
Age (years)	45.2±10.6	43.7±11.8
Women/men	17/5	18/7
Time posttransplantation (months)	34.1±18.9	36.4±21.1
Cause of end-stage renal disease (n)		
Glomerulonephritis	7	6
Chronic pyelonephritis	6	1
Vesicoureteral reflux	3	2
Diabetic nephropathy	2	4
APKD	2	3
Unknown	2	9
Diabetes mellitus (n)	5	8





Elementi considerabili

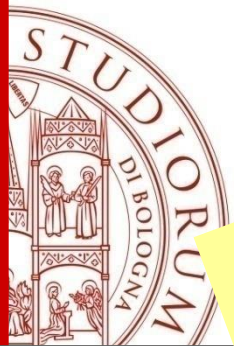


Ritardo terapeutico

Confondimento diagnostico

Riduzione della terapia immunosoppressiva

Ruolo dell'immunità innata



L'immunità
innata ?

Th17 e Th1

However, a similar study indicates that IFN- γ plays a role in this setting as well, suggesting that Th17 cells have the capacity to cause rejection, but may be redundant.

Porrett PM, et al. Mechanisms underlying blockade of allograft acceptance by TLR ligands. J Immunol. 2008; 181:1692–1699

Table 4: Treatment of UTI in transplant recipients (52)

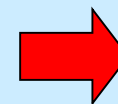
Clinical presentation	Suggested management
Asymptomatic bacteriuria	No consensus on management. Repeat culture with appropriate technique (consider straight catheterization) to rule-out contamination. In the first 1–3 months posttransplant, consider treatment for 5–7 days; beyond 3 months posttransplant, avoid treatment unless associated rise in creatinine. No need for empiric treatment—await culture susceptibility and select the most narrow-spectrum antibiotic available.

171 trapianti, screening ad 1 mese con urinocultura:
130 px senza batteriuria, 41 pazienti con batteriuria
asintomatica in 41, trattati per 14 giorni con antibiotico
su antibiogramma

Variable	Relative risk ratios	95% confidence interval	P
Female Gender	2.6	1.2 to 5.6	.019
Deceased donor kidney transplantation	7.7	1.9 to 3.1	<.001

Fattori di Rischio per Batteriuria

Nonostante il trattamento della batteriuria
asintomatica, vi era aumentata incidenza di
infezioni complicate e ospedalizzazioni



Outcome del trapianto

Clinical outcome	With AB (N=41)	Without AB (N=130)	P
Delayed graft function, N (%)			
No	23 (56.1)	90 (69.2)	.12
Yes	18 (43.9)	40 (30.8)	
Acute rejection 1 Y, N (%)			
No	38 (92.7)	116 (89.2)	.52
Yes	3 (7.3)	14 (10.8)	
Graft survival 1 Y, N (%)			
No	2 (4.9)	6 (4.7)	.95
Yes	39 (95.1)	123 (95.3)	
Patient survival 1 Y, N (%)			
No	0 (0)	4 (3.1)	.25
Yes	41 (100)	129 (96.9)	
Hospital admissions for symptomatic UTI 1 Y, N (%)			
0	20 (48.8)	106 (81.5)	<.001
1	14 (34.2)	12 (9.3)	
2	3 (7.3)	6 (4.6)	
3 or more	4 (9.7)	6 (4.6)	

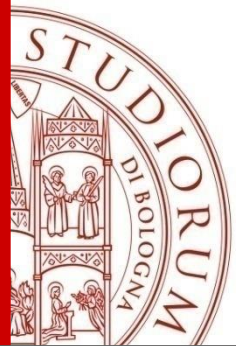
Terapia Immunosoppressiva e

46471 trapiantati dal 1995-2003
(Medicare)

Rischio di Infezioni

Characteristic (%)	Viral		Bacterial		Fungal		Any	
	Relative risk (95% CI)	P	Relative risk (95% CI)	P	Relative risk (95% CI)	P	Relative risk (95% CI)	P
<i>Steroid use</i>								
Steroids (92.4)	0.98 (0.90–1.07)	0.6721	0.95 (0.88–1.02)	0.1729	0.91 (0.78–1.06)	0.2287	0.95 (0.90–1.01)	0.1289
<i>Calcineurin inhibitor use</i>								
Cyclosporine (52.5)	1.00		1.00		1.00		1.00	
Tacrolimus (34.7)	0.93 (0.89–0.98)	0.0033	0.91 (0.87–0.95)	<0.0001	0.85 (0.78–0.93)	0.0002	0.91 (0.88–0.94)	<0.0001
Neither (12.8)	1.10 (1.03–1.18)	0.0030	1.09 (1.02–1.15)	0.0080	0.97 (0.86–1.09)	0.6354	1.06 (1.01–1.11)	0.0181
<i>Antimetabolite use</i>								
Azathioprine (15.2)	1.00		1.00		1.00		1.00	
Mycophenolate mofetil (65.6)	1.10 (1.03–1.16)	0.0020	0.98 (0.93–1.04)	0.5383	0.90 (0.81–0.99)	0.0340	1.02 (0.98–1.07)	0.3608
Neither (19.2)	1.05 (0.98–1.13)	0.1510	1.07 (1.00–1.15)	0.0387	0.92 (0.80–1.04)	0.1852	1.06 (1.01–1.12)	0.0295
<i>mTOR inhibitor use</i>								
Rapamycin (8.6)	0.90 (0.83–0.97)	0.0075	1.27 (1.18–1.36)	<0.0001	1.04 (0.91–1.20)	0.5579	1.07 (1.02–1.14)	0.0099
<i>Induction antibody</i>								
IL-2R blocker (23.8)	1.00		1.00		1.00		1.00	
Other (24.4)	0.88 (0.83–0.93)	<0.0001	0.95 (0.90–1.00)	0.0443	0.99 (0.90–1.09)	0.8566	0.93 (0.89–0.96)	0.0001
None (51.8)	1.04 (0.99–1.09)	0.1147	1.08 (1.03–1.13)	0.0007	1.10 (1.02–1.20)	0.0201	1.06 (1.03–1.10)	0.0005

Snyder JJ et al, Kidney Int, 2009



1

Fattori di rischio

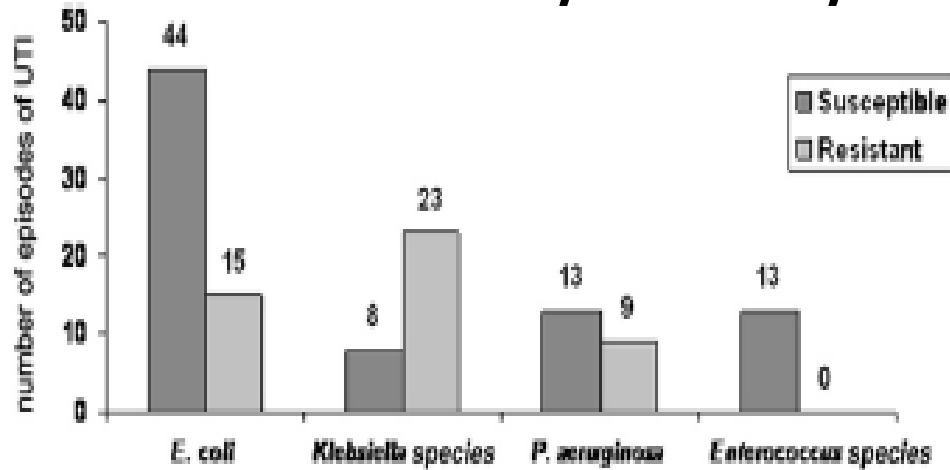
2

Outcome del trapianto

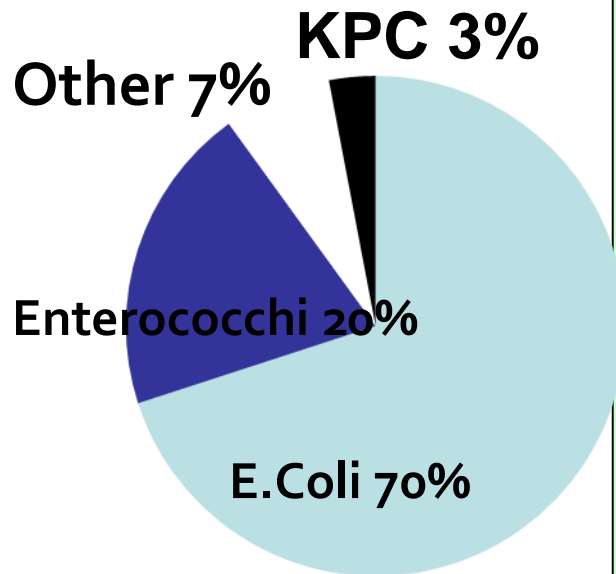
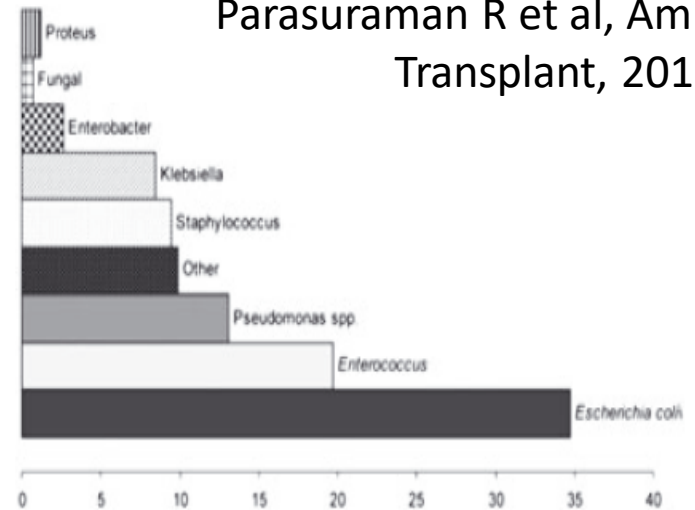
3

Infezioni complesse

Bodro M et al, Infec Dis, 2015



Parasuraman R et al, Am J Transplant, 2013

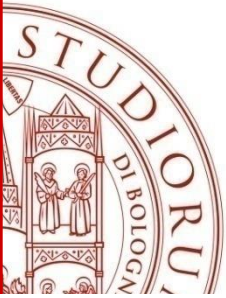


Epidemiology and outcomes of carbapenem-resistant *Klebsiella pneumoniae* bacteriuria in kidney transplant recipients

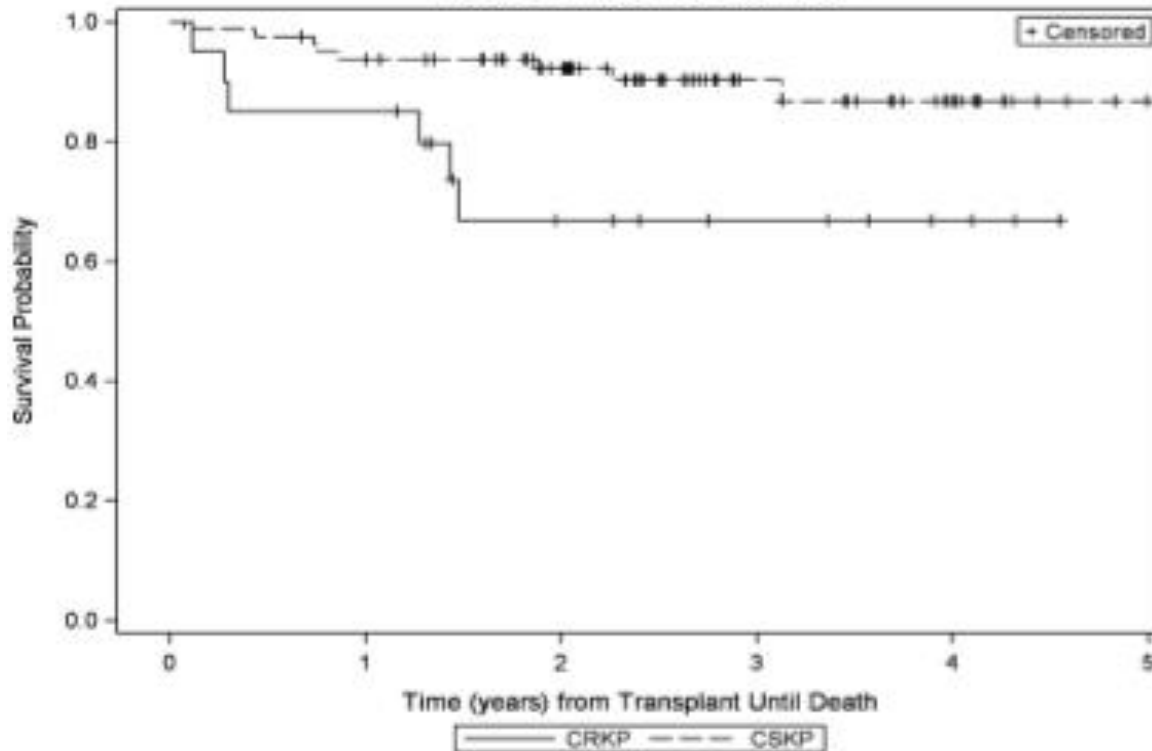
Pouch SM et al, Transplant Infectious Disease 2015

- **1852** adult kidney transplant between Jan 2007 and Dec 2010
- The incidence of CRKP bacteriuria and CSKP bacteriuria during the study period was **1.1%** and **13.6%**, respectively.

Epidemiology and outcomes of carbapenem-resistant *Klebsiella pneumoniae* bacteriuria in kidney transplant recipients



Product-Limit Survival Estimates



Kaplan–Meier analysis of mortality

«**Mortality** from any cause was **higher** among subjects with CRKP bacteriuria than among those with CSKP bacteriuria (30% vs. 10%, respectively, $P=0.03$)»

Pouch SM et al,
Transplant Infectious Disease 2015

A review on colistin nephrotoxicity

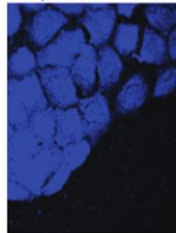
Eur J Clin Pharmacol (2015) 71:801–810

Atefeh Ordooei Javan¹ · Shervin Shokouhi² · Zahra Sahraei¹

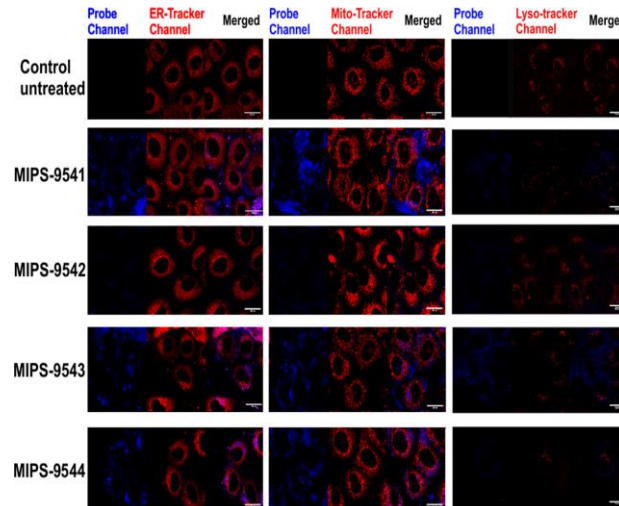
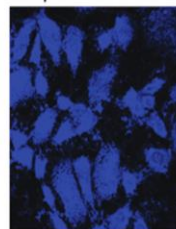
- Antibiotico ciclico lipopetidico che aumenta la permeabilità di membrana delle cellule tubulari prossimali con accumulo del farmaco intracellulare e attivazione di stress ossidativo e apoptosi
- Se protratta determina insorgenza di danno tubulo interstiziale a glomeruli indenni

Cellular Uptake and Localization of Polymyxins in Renal Tubular Cells Using Rationally Designed Fluorescent Probes

500 μ M MIPS-9541



200 μ M MIPS-9541



Yun et al, Antimicrobial Agents and chemotherapy, 2015

Clinical and Economic Consequences of First-Year Urinary Tract Infections, Sepsis and Pneumonia in Contemporary Kidney Transplantation Practice

Naik et al, *Transplant Int*, 2016

OPTN + Medicare data, 2000-2011

60700 trapianti di rene

Total predicted year 1 costs according to first-year infection status

