SCUOLA DI SPECIALIZZAZIONE IN MALATTIE INFETTIVE E TROPICALI

PANDORA ID - 25

TIME TO WEBINAR IN INFECTIOUS DISEASES

PROGETTO DI FORMAZIONE

Anno Accademico 24/25

TMT CONGRESS & EVENTS

PREVENZIONE E TRATTAMENTO DELLE INFEZIONI BATTERICHE NEL PAZIENTE SOTTOPOSTO A TRAPIANTO DI ORGANO SOLIDO: UN APPROCCIO PER APPARATI

Lunedì 7 Aprile 2025 – Ore 16.00-19.00 VIRTUAL EDITION

Responsabili scientifici: Prof.ssa Alessandra Bandera, Prof. Andrea Lombardi

INFEZIONI DELLE VIE URINARIE

Maddalena Peghin MD PhD, Associate Professor
Infectious and Tropical Diseases Unit
University of Insubria-ASST-Sette Laghi, Varese, Italy

UNIVERSITÀ DEGLI STUDI DELL'INSUBRIA

Rete Nazionale Trapianti

Sistema Socio Sanitario
Regione Lombardia
ASST Sette Laghi
Polo Universitario

Disclosures

- Dia Sorin, MDS, Menarini, Pfizer, Thermofisher

Outline

- Epidemiology and risk factors for UTI
- Typical and atypical pathogens as causes of UTI
- Direct and indirect effects of UTI
- Treatament indication and duration for UTI
- Prevention

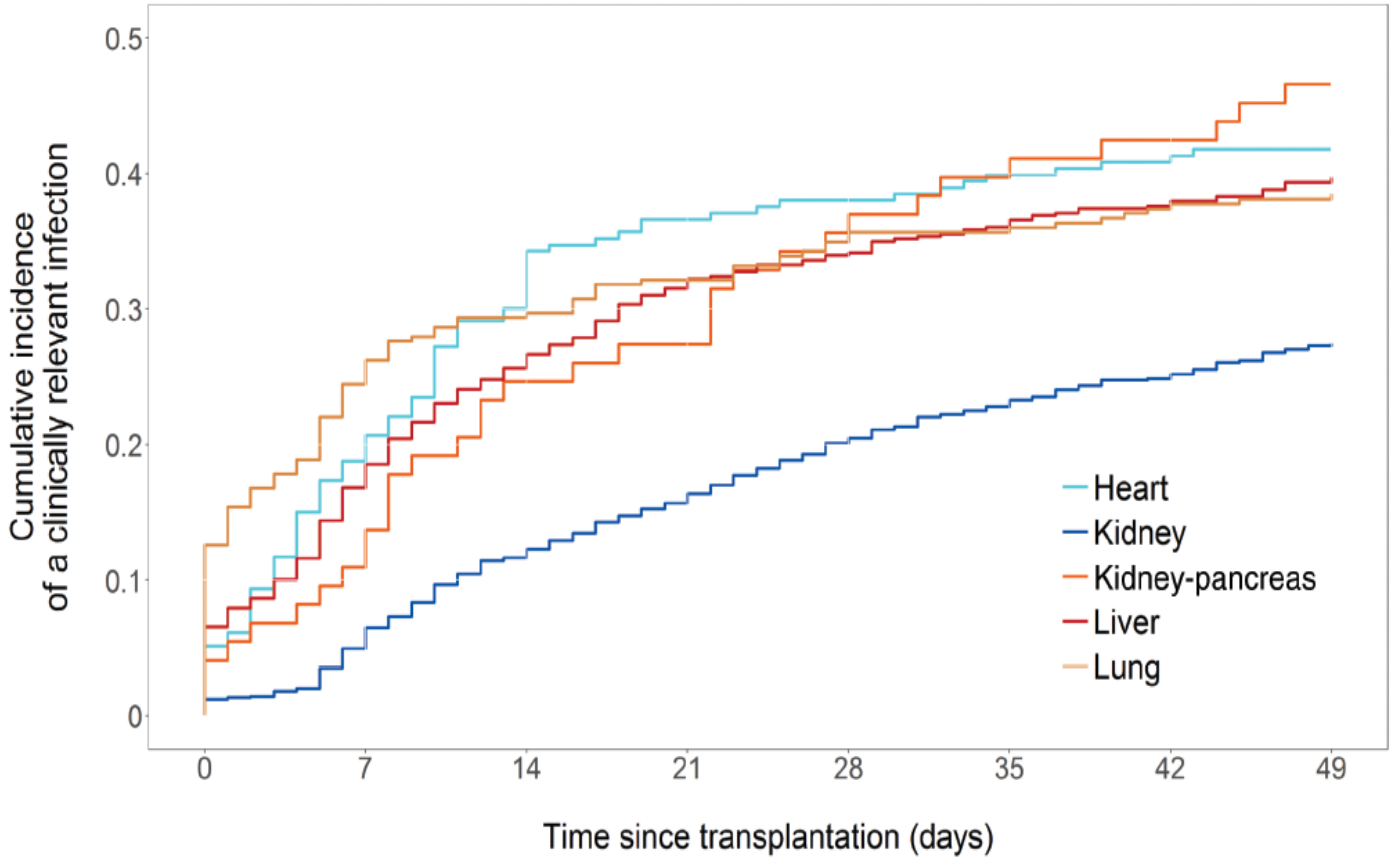
Outline

- **Epidemiology and risk factors for UTI**
- Typical and atypical pathogens as causes of UTI
- Direct and indirect effects of UTI
- Treatament indication and duration for UTI
- Prevention

Burden and timeline of infectious diseases in the first year after SOT

prospective study -the Swiss Transplant Cohort
SOT between 2008 -2014 with ≥12 months of follow-up: 2761 SOT

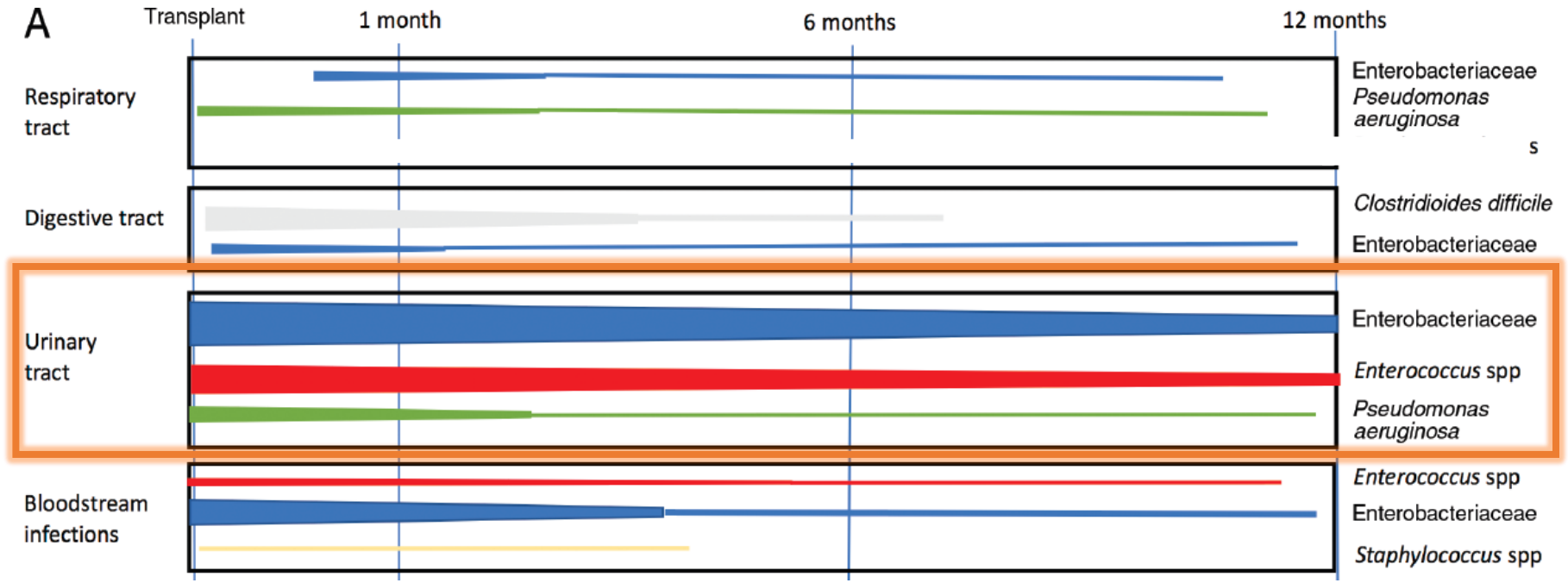
55% suffered 3520 infections during the first year after SOT
62.6% bacterial infections



Cumulative incidence 1 year after SOT

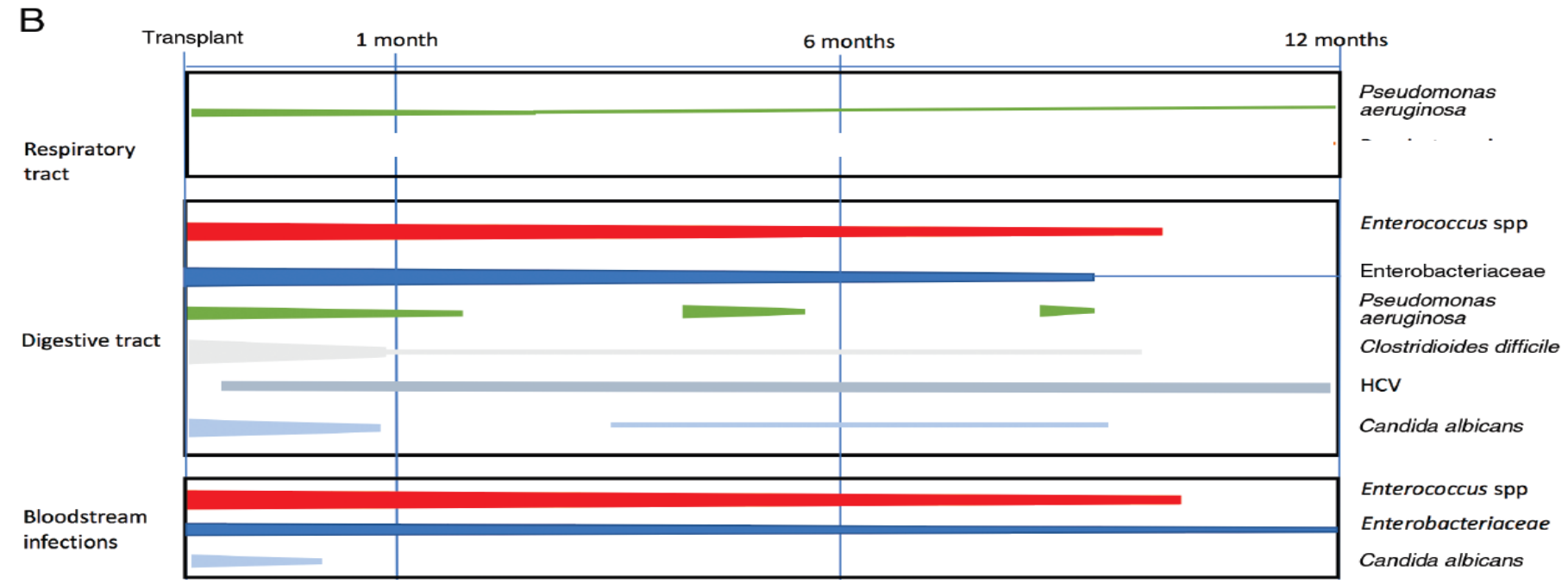
- 53% for kidney
- 55% for liver
- 60% for heart and kidney-pancreas
- 62% for lung transplant

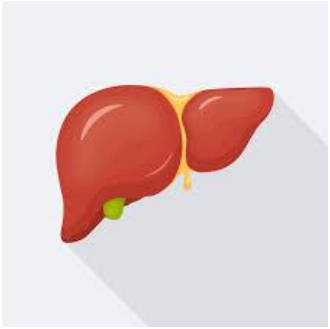
van Delden et al Clinical Infectious Diseases 2020;71(7)



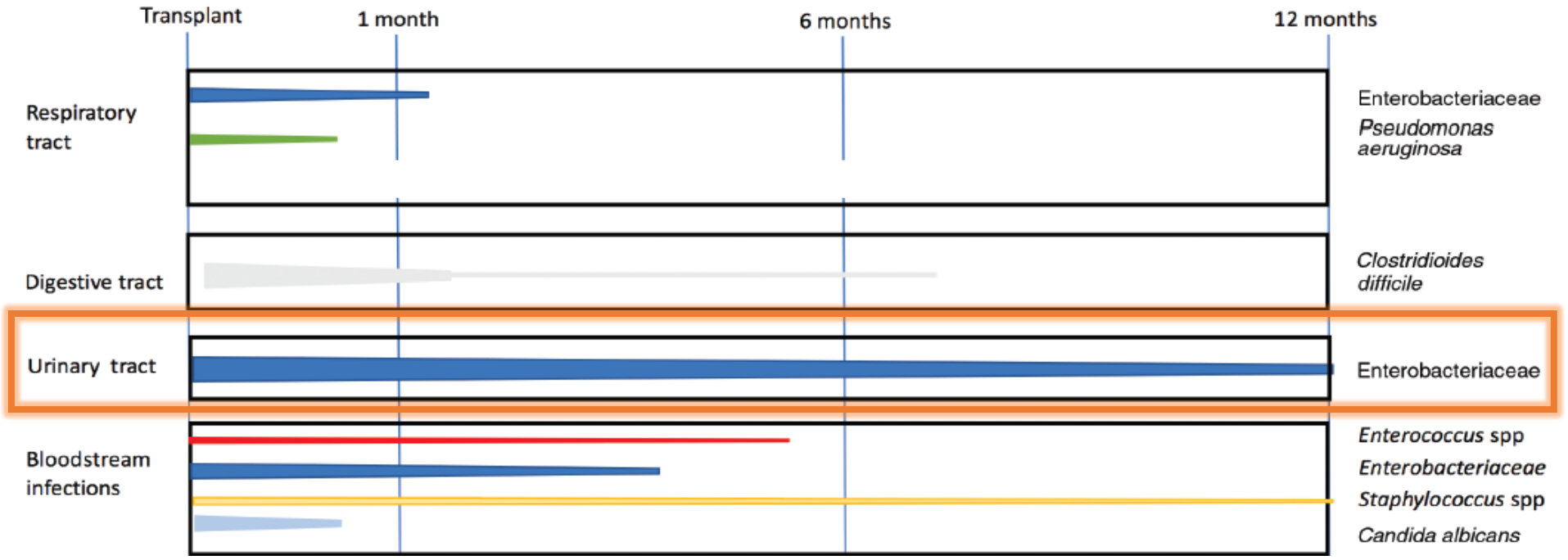
- **UTI throughout the year**

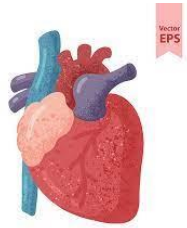
- **prevalence range 8-70%**
- **30% of hospitalizations for sepsis**
- **40% of bacteremia source**



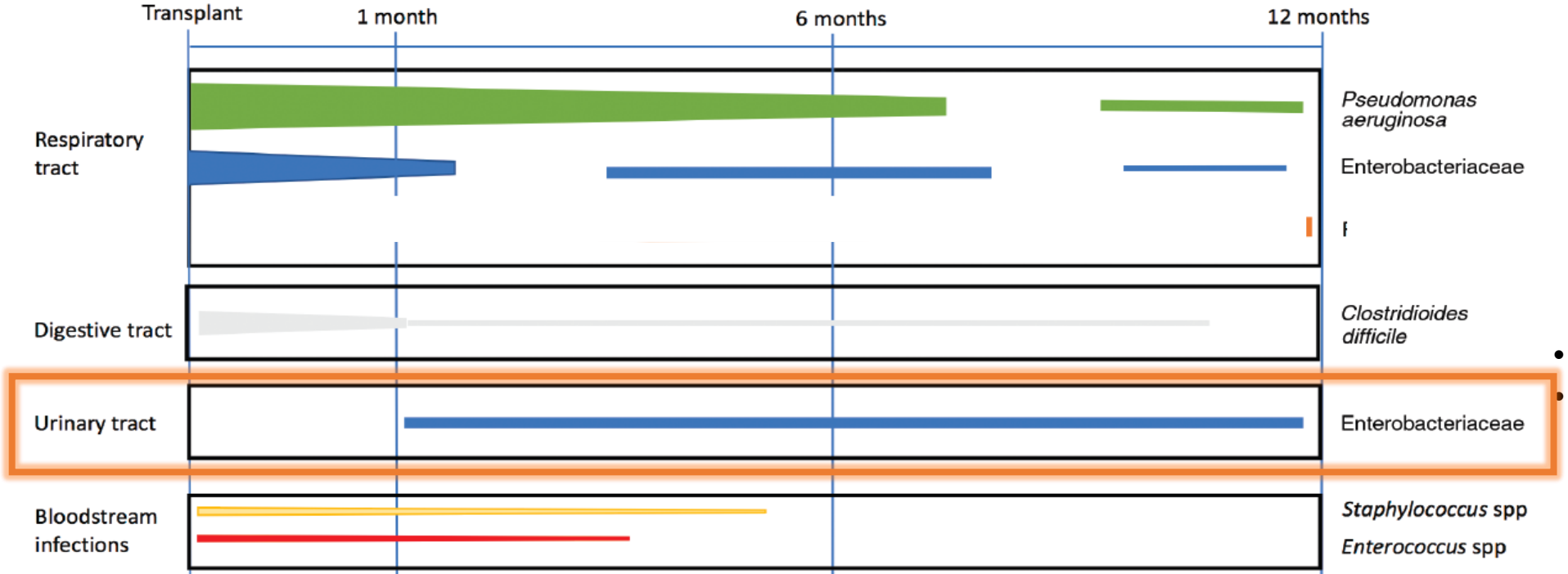


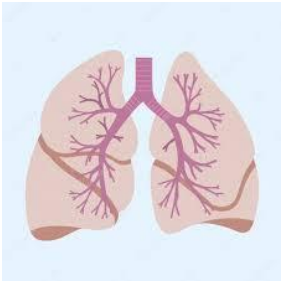
- IAI throughout the year
- BSI throughout the year





- **UTI throughout the year**
- BSI throughout the year
- RTI (< 1 m)





- RTI throughout the year
- **UTI throughout the year**

Table 3
Risk factors for urinary tract infections in solid organ transplantation.

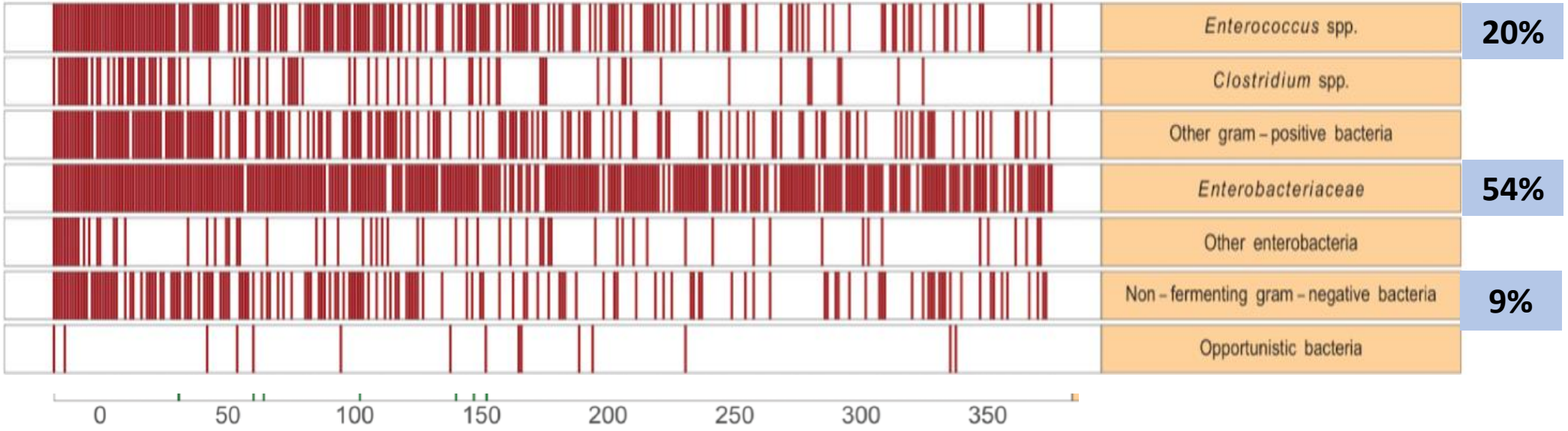
Female gender
Age
Mycophenolate mofetil
Antithymocyte globulin
Need for immediate post-transplant dialysis
Ureteral stent placement > 30 days
Diabetes mellitus
Deceased-donor kidneys
Number of episodes of acute rejection
Reflux kidney disease prior to transplantation
Length of hospitalization
Length of urinary catheterization
Number of episodes of acute rejection
Post-transplant urinary obstructions
Increase in immunosuppression

E. Vidal et al. / Enferm Infecc Microbiol Clin. 2015;

Outline

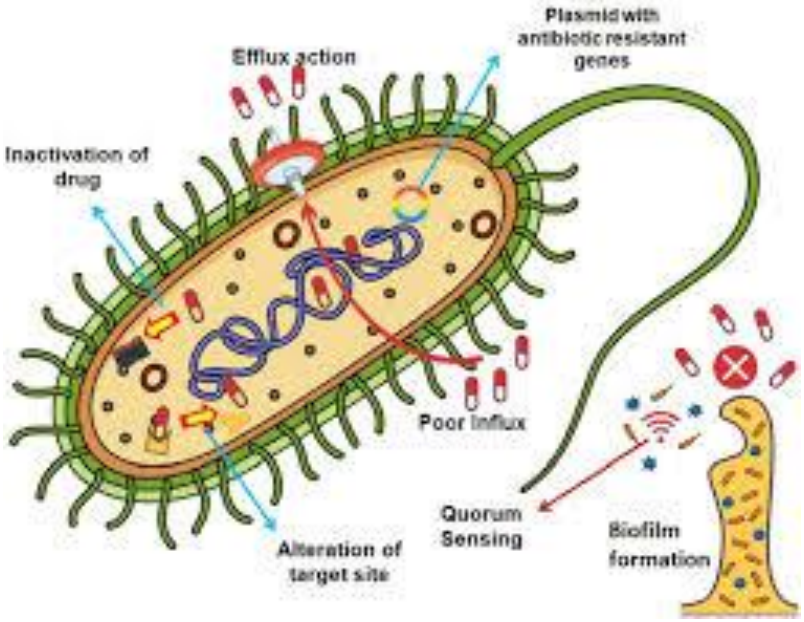
- Epidemiology and risk factors for UTI
- **Typical and atypical pathogens as causes of UTI**
- Direct and indirect effects of UTI
- Treatament indication and duration for UTI
- Prevention

Timeline of bacterial infections by pathogen



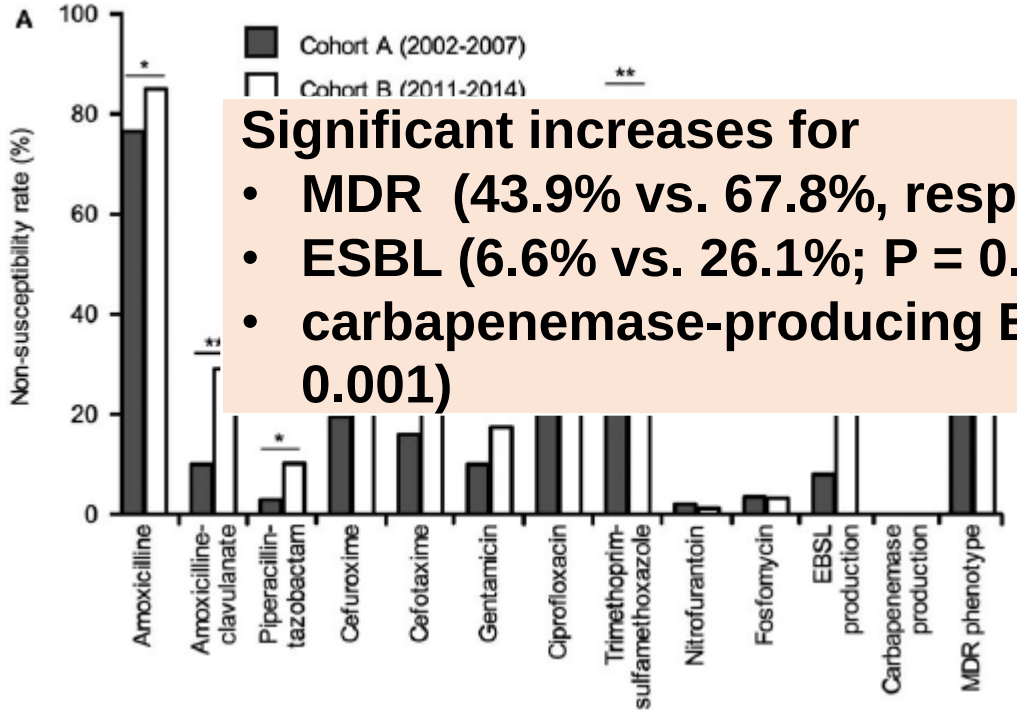
- **UTI etiology**
  - GNB: 56-90%
  - *E.coli* is the most common cause of UTI in all types of SOT and is cause of 85.7% of bacteremic UTI
  - Other causes: *Klebsiella* spp., *P. aeruginosa*, *Enterococcus* spp.and other GNB

MDR pathogens are an important issue in UTI in SOT

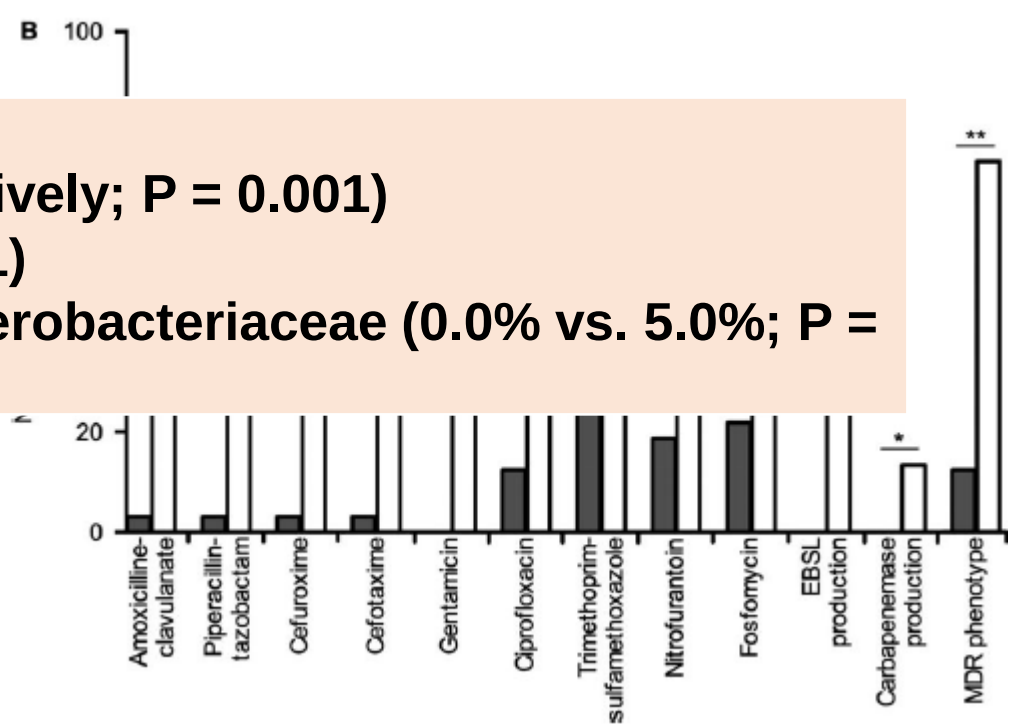


Progressive increase of resistance in Enterobacteriaceae urinary isolates from KTR over the past decade: narrowing of the therapeutic options

- Madrid Hospital: 2 cohorts of KTR : Cohort A (n= 189) 2002-2004; Cohort B (n= 115), 2011- 2013



E.coli



K.pneumoniae

Significant increases for

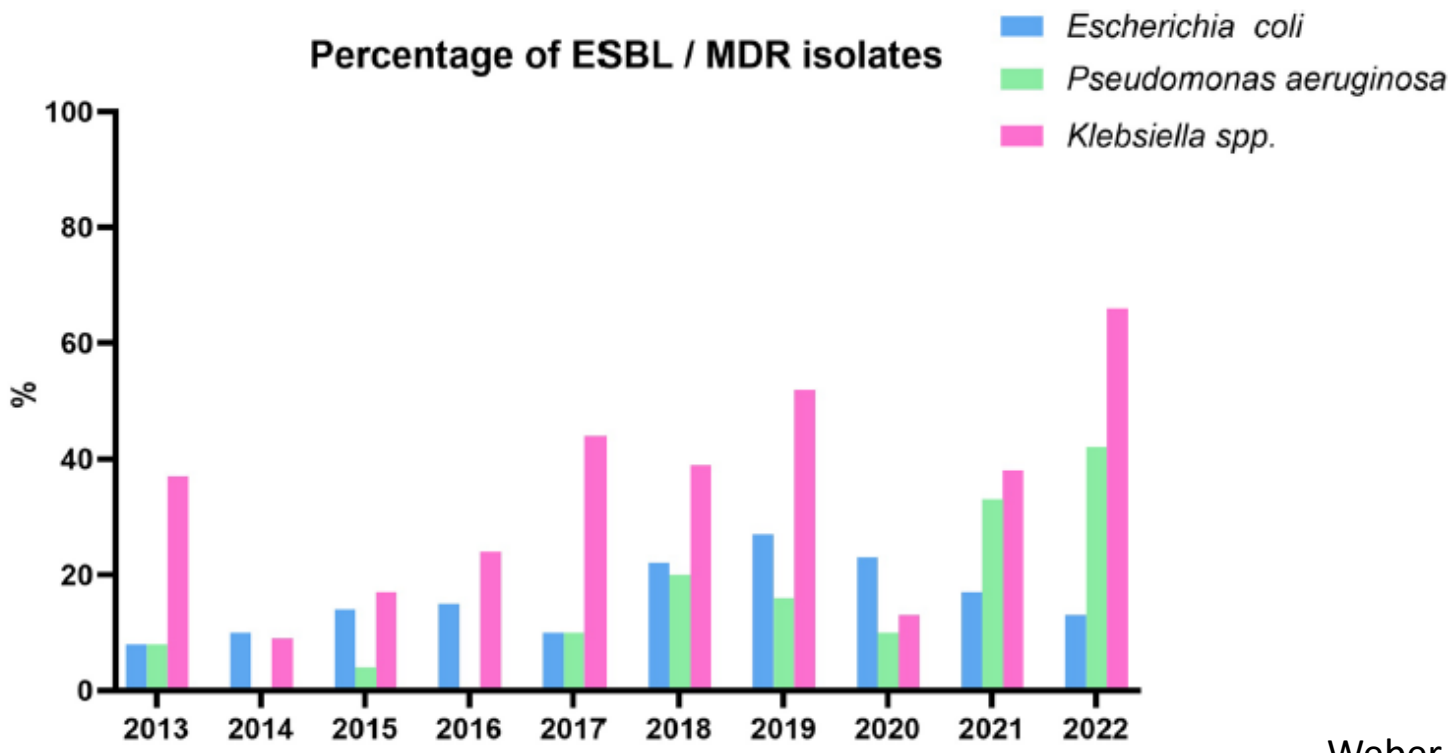
- **MDR (43.9% vs. 67.8%, respectively; P = 0.001)**
- **ESBL (6.6% vs. 26.1%; P = 0.001)**
- **carbapenemase-producing Enterobacteriaceae (0.0% vs. 5.0%; P = 0.001)**

Origuen et al. Transpl Infect Dis 2016: 18

Antibiotic resistance of urinary pathogens after kidney transplantation a 10-year single-center survey in Germany

University Hospital Essen 2013-2022

- 10.508 urine samples collected from 6962 patients, 39% of positivity
- *E.coli* accounted for 41% of UTI, *Klebsiella spp*. for 11.7%
- increasing resistance to piperacillin/tazobactam and ceftazidime



Weber et al. Infection. 2025 Mar 10.

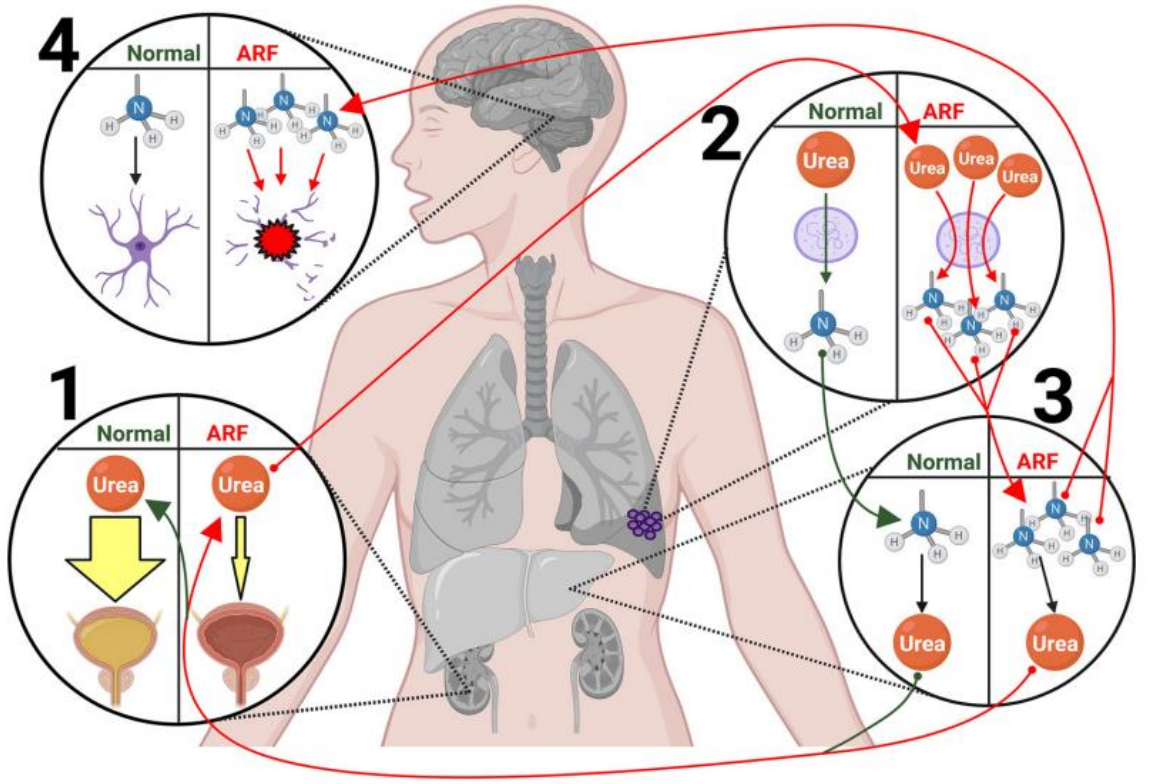
Emerging underrecognized pathogens : the role of mollicutes

- Lack cell walls and do not grow in routine culture media
- *Mycoplasma* and *Ureaplasma* species
  - *Mycoplasma pneumoniae*
  - *Mycoplasma genitalium*
  - *Mycoplasma hominis*
  - *Ureaplasma urealyticum*
  - *Ureaplasma parvum*
- **Commensals of the urogenital tract, colonizers of the oral cavity**
- **Diseases that affect primarily the respiratory or urogenital tracts**
- Diagnosis:
  - Specialized media and techniques
  - Molecular-based assays
  - Serology

Waites et al. Manual of Clinical Microbiology. ASM Press; 2015. pp.1088–1105

Fatal hyperammonaemia syndrome can be caused by disseminated Mollicute infections.

- SOT are vulnerable to hyperammonemia syndrome (HR) > LTR
- *Ureaplasma* and *Mycoplasma* spp. harbor ureases
- Early in the post-transplant period
- HR SOT: 4 % (> lung) ; mortality 70%



High serum ammonia levels can lead to increased cerebral pressure, coma, and death

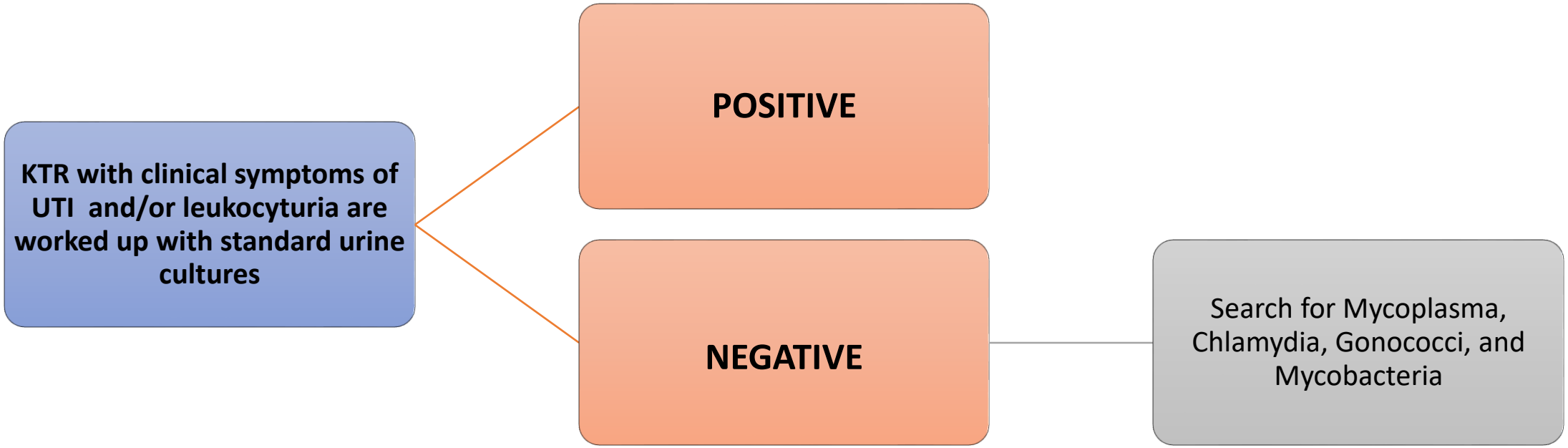
Fleming et al. Microbiol Spectr 2022 Feb 23;10(1)

Donor derived or recipient derived infection?

- Initially hypothesis: that HS occurred due to dissemination of *Mollicutes* from the transplant recipient's own urogenital tract in the setting of immunosuppression
- This theory has been debunked in lung transplant recipients where infections appear to be mostly donor derived
- Further studies are needed to better elucidate the mechanism of HS secondary to *Ureaplasma* and *M. hominis* infections in other organ transplant recipients

Ureaplasma and Mycoplasma in kidney transplant recipients

Zurich Hospital: consecutive cases over a 3-year period



10 positive KTR

- 5 asymptomatic
- 5 symptomatic with dysuria or pain at the graft site
  - 4 patients developed biopsy-proven acute graft pyelonephritis with graft dysfunction
  - 1 of these patients additionally showed a renal abscess

Gerber et al. *Transpl Infect Dis.* 2018

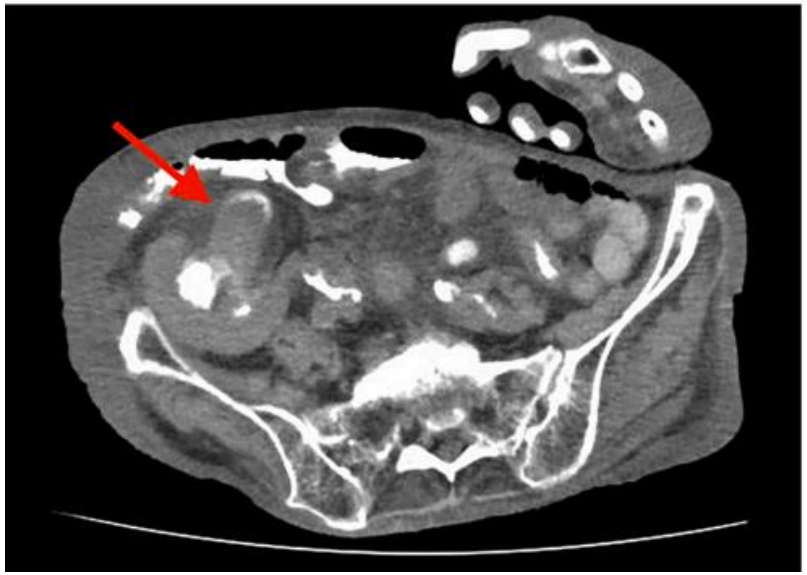
TABLE 2 Reported cases of transplant patients with infections due to *U. urealyticum* and *M. hominis*

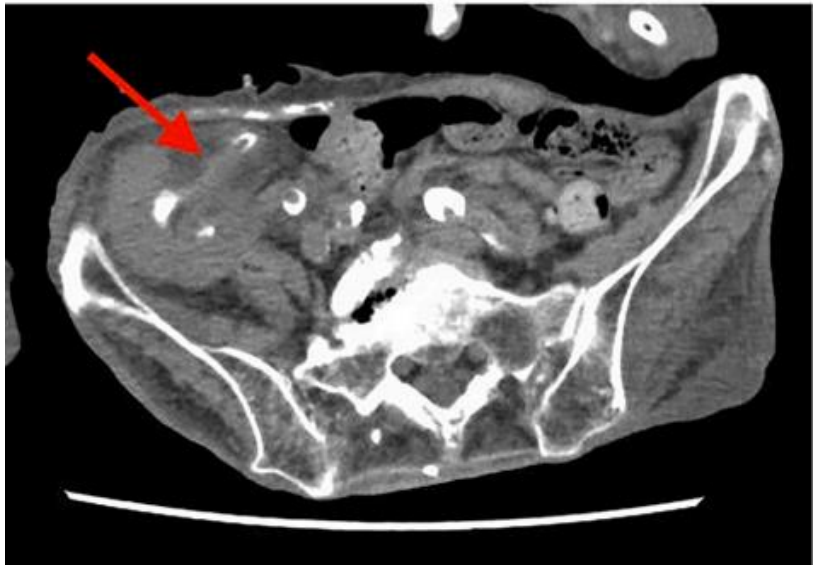
Author (Year)	Organ trans-planted	Additional risk factors	Clinical presentation	Microorganism	Treatment	Outcome
Geissdoerfer (2008)[9]	Kidney	Early postoperative, hemorrhagic shock, infected hematoma	Meningitis	*Ureaplasma urealyticum*	Graft removal, Tobramycin, Meropenem, Ciprofloxacin, Doxycyclin	No response initially, recovery after switch to chloramphenicol
Loupy (2008)[19]	Kidney	Early postoperative	Wound infection	*M. hominis* + *U. urealyticum*	Moxifloxacin	Recovery
	Kidney	Early postoperative	Wound infection	*M. hominis*	Levofloxacin	Recovery
	Kidney	Early postoperative	Wound infection	*M. hominis*	Ofloxacin	Recovery
Camara (2007)[6]	Kidney	Anti-CD3 antibodies	Peritonitis, Perinephric abscess, Raised liver enzymes	*M. hominis*	Imipenem, Gentamycin, Peritoneal lavage	Recovery
Eilers (2007)[4]	Kidney	PTLD, Rituximab	Multiple renal abscesses	*U. urealyticum*	Levofloxacin	Recovery
Cordtz (2006)[20]	Kidney	CVID, IVIG	Pyonephrosis native kidney, foot cellulitis, sepsis	*U. urealyticum*	Nephrectomy, Clarithromycin, Doxycyclin	Recovery
Pastural (2002)[8]	Kidney	Early postoperative, hemorrhagic shock	Sepsis, wound infection	*M. hominis*	Ofloxacin, graft removal	Recovery
Miranda (1990)[15]	Kidney	Early postoperative	Wound infection, Perirenal abscess	*M. hominis*	Docycyclin	Recovery
	Kidney	Early postoperative	Ureter anastomosis leak, acute renal failure, T-cell-mediated rejection	*M. hominis*	Doxycyclin	Recovery
	Kidney	Early postoperative	Wound infection	*M. hominis*	Doxycyclin	Recovery
Burdge (1988)[16]	Kidney	Early postoperative	Septic arthritis	*M. hominis* + *U. urealyticum*	Doxycyclin	Improvement, but 2 relapses after cessation of antibiotics
Fernandez (2017)[17]	Lung	Early postoperative	Hyperammonemia, Sepsis, Pneumonia	*U. parvum*	Azithromycin, Doxycyclin	Recovery
Bharat (2015)[14]	Lung	Early postoperative	Hyperammonemia	*U. urealyticum*	Azithromycin	Improvement, then relapse, Fatal
	Lung	Early postoperative	Hyperammonemia, Cerebral edema	*U. urealyticum*	No antibiotics	Fatal
	Lung	Early postoperative	Hyperammonemia, Cerebral edema	*M. hominis* + *U. parvum*	No antibiotics	Fatal
	Lung	Early postoperative	Hyperammonemia	*U. urealyticum*	No antibiotics	Fatal
	Lung	Early postoperative	Hyperammonemia	*U. parvum*	Levofloxacin, Azithromycin	Recovery
	Lung	Early postoperative	Hyperammonemia	*U. parvum*	Levofloxacin	Recovery

Gerber et al. *Transpl Infect Dis.* 2018

Corynebacterium urealyticum

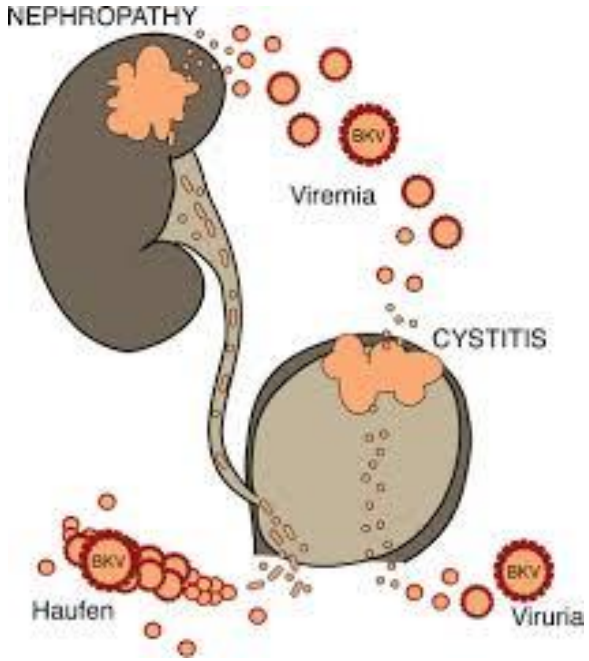
- Corynebacterium urealyticum UTI has been associated with obstructive uropathy, symptoms > 1 one month, and encrusting pyelitis in KTR
- Long-term incubation and special media are needed for its isolation

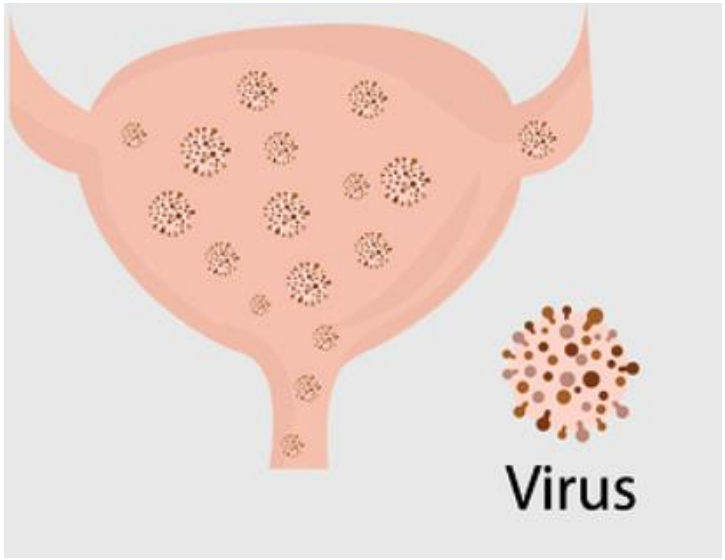




Ohyama et al. J Infect Chemother 2025 Feb

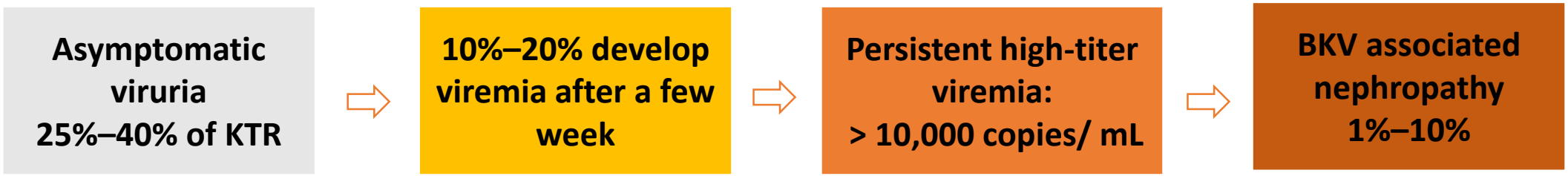
Viral Pathogens Causing UTI





BK polyomavirus

- The BK polyomavirus is a human polyomavirus
- Primary BKV infection occurs during childhood, with 80%–90% adults exposed
- The virus remains latent in the kidney tubules and uroepithelium



Agrawal et al. CJASN 17: 286–295, 2022.

Adenovirus infections in SOT and ITU in KTR

- ADV in SOT : from asymptomatic to severe disseminated disease with impact on morbidity, mortality, and graft survival
- Clinical manifestations depend on site of infection and type of transplanted organ
- Kidney Disease: Improving Global Outcomes (KDIGO)
  - does not recommend routine screening of Adenovirus in KTR
  - KTR with fever, dysuria and hematuria: reccomended ADV nephritis screening
- Hemorrhagic cystitis and graft dysfunction more often described in adult than pediatric KTR

https://kdigo.org/guidelines/

Differences in ADV nephritis and BK virus nephropathy

Characteristics	Adenovirus nephritis (n = 11)	BK virus nephropathy (n = 33)	p value
Microhematuria	10 (91%)	4 of 21 (19%)	<0.001
Granulomas	9 (82%)	0	<0.001
Pure tubulointerstitial nephritis	1 (9%)	32 (97%)	<0.001

Jagannathan G, et al. Kidney Int 2023

Outline

- Epidemiology and risk factors for UTI
- Typical and atypical pathogens as causes of UTI
- **Direct and indirect effects of UTI**
- Treatament indication and duration for UTI
- Prevention

TABLE 1 Classification of asymptomatic bacteriuria (AB) and urinary tract Infection (UTI) in renal transplant recipients

Classification	Description	Laboratory investigations of urine	
Asymptomatic bacteriuria	No urinary or systemic symptoms of infection	>10^5 CFU/mL uropathogen[ab]	44%
Acute simple cystitis	Dysuria, urinary urgency/frequency, or suprapubic pain; but no systemic symptoms and no ureteral stent/nephrostomy tube/ chronic urinary catheter	>10 WBC/mm^3[c] >10^3 CFU/mL uropathogen[b]	32%
Acute pyelonephritis/ Complicated UTI	Fever, chills, malaise, hemodynamic instability, or leukocytosis (without other apparent etiology); flank/allograft pain; or bacteremia with same organism as in urine Dysuria, urgency, frequency, suprapubic pain may or may not be present	>10 WBC/mm^3[c] >10^4 CFU/mL uropathogen[b]	24%
Recurrent UTI	≥ 3 UTIs in prior 12-month period	As above	14%

- KTR with UTI may present without symptoms localized to the urinary tract
- In immunosuppressed patients, symptoms can be subtle and the denervated kidney allograft may not reliably be tender in pyelonephritis
- Acute elevations in serum creatinine may also be seen

Goldman et al *Clinical Transplantation.* 2019

Important questions- UTI and KTR

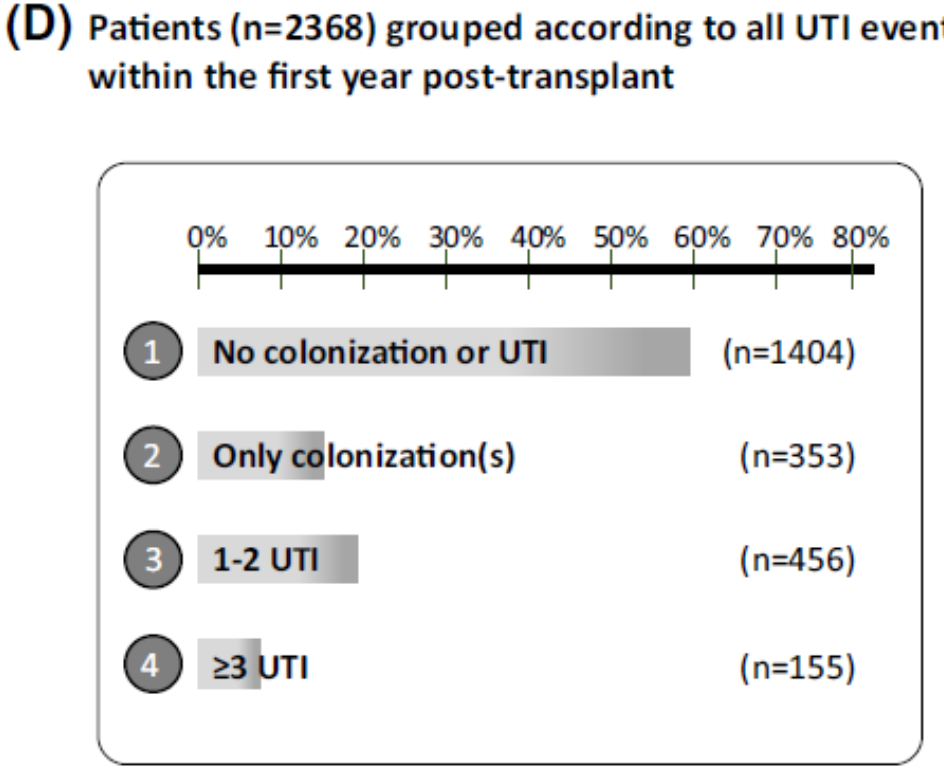
Occurrence of UTI in KTR and association with

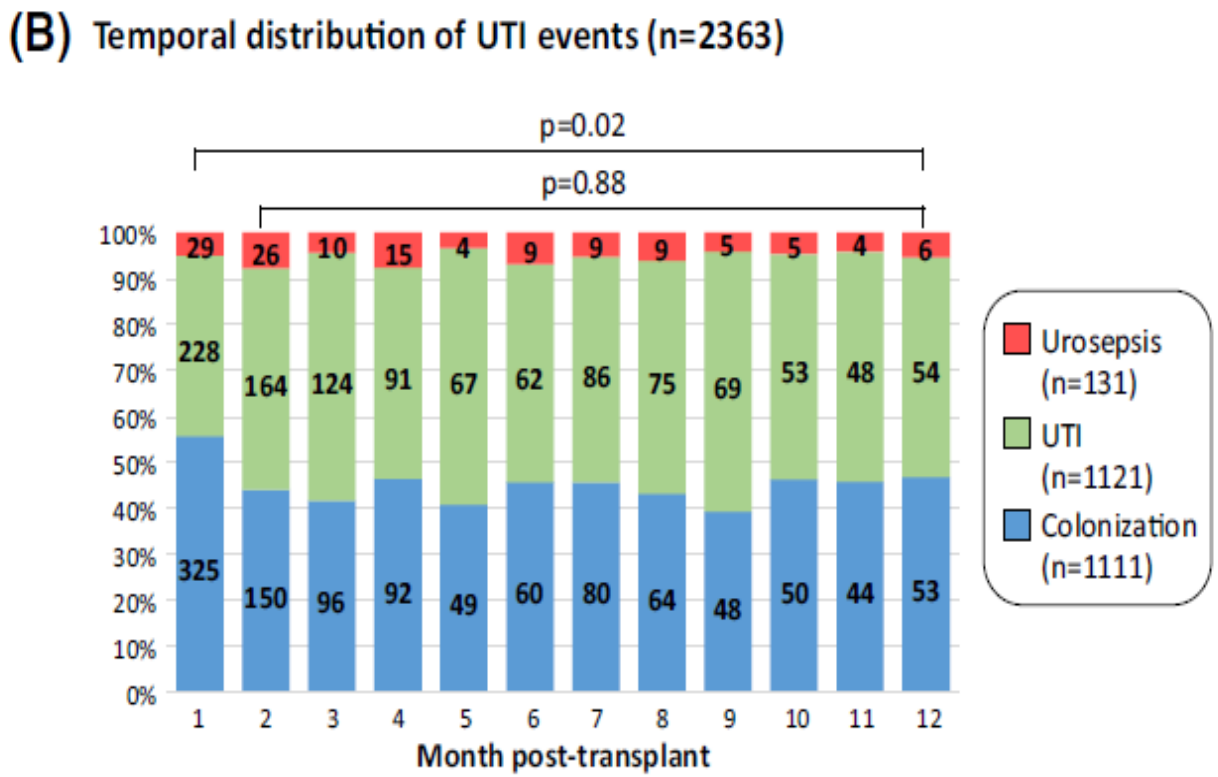
- impaired allograft function
- lower patient and allograft survival

- These divergent results might be related to limitations due
  - low number of included patients
  - retrospective
  - short follow-up time
  - different definitions and incomplete inclusion of UTI phenotypes

Impact of different urinary tract infection phenotypes within the first year post-transplant on renal allograft outcomes

2008-2017: SOT followed for a median of 4.9 years

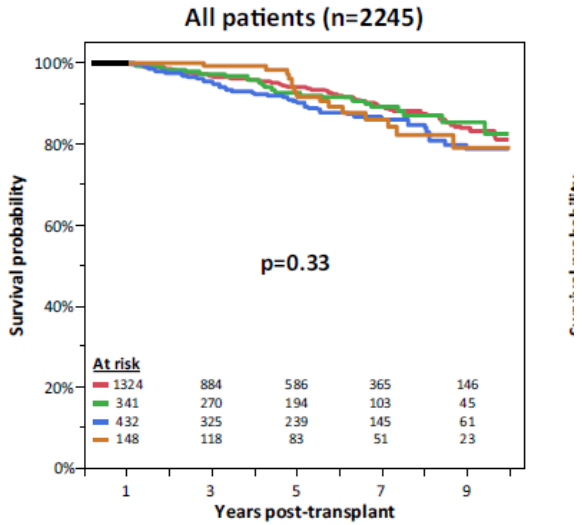




Brune et al Am J Transplant. 2022 April 2, 1823–1833

Recurrent UTI is a strong and independent risk factor for lower eGFR at one year and a lower long-term death-censored allograft survival

(A) Patient survival

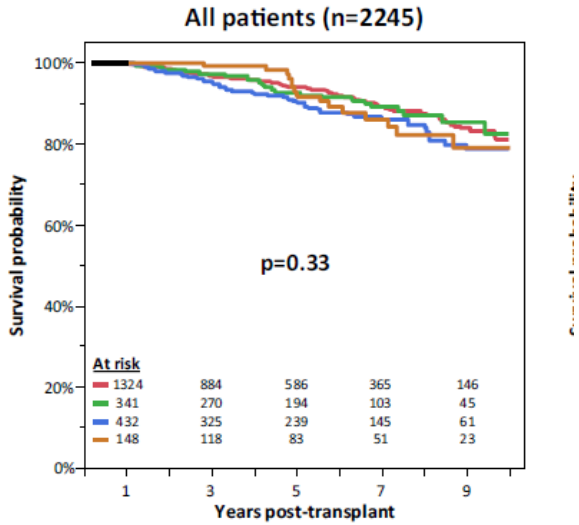


Parameter	Total (n = 2368)	No colonization or UTI (n = 1404)	Colonization only (n = 353)	1–2 UTI (n = 456)	≥3 UTI (n = 155)	p-Value
Graft loss or death	123 (5.2%)	80 (5.7%)	12 (3.4%)	24 (5.3%)	7 (4.5%)	.36
Death	49 (2.1%)	27 (1.9%)	5 (1.4%)	12 (2.6%)	5 (3.2%)	.45
Graft loss	74 (3.1%)	53 (3.8%)	7 (2.0%)	12 (2.6%)	2 (1.3%)	.13
eGFR [ml/min]	53 (41–66)	54 (42–67)	53 (43–67)	51 (39–66)	44 (34–58)[a]	<.001
Patients with eGFR <25	107 (4.5%)	50 (3.6%)	8 (2.3%)	30 (6.6%)	19 (12.3%)	<.001

Brune et al Am J Transplant. 2022 April 2, 1823–1833

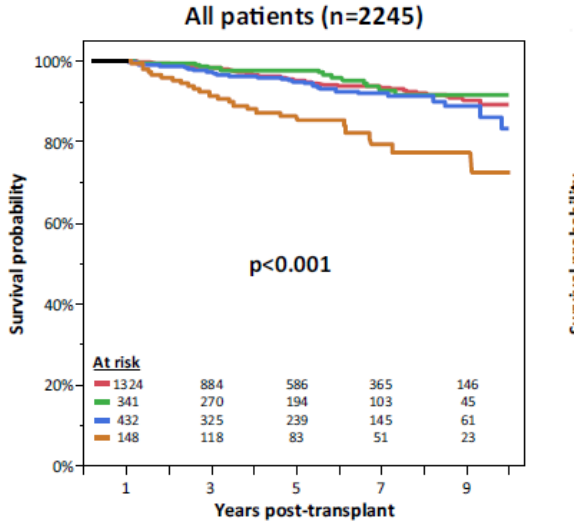
Recurrent UTI is a strong and independent risk factor for lower eGFR at one year and a lower long-term death-censored allograft survival

(A) Patient survival



Parameter	Total (*n* = 2368)	No colonization or UTI (*n* = 1404)	Colonization only (*n* = 353)	1–2 UTI (*n* = 456)	≥3 UTI (*n* = 155)	*p*-Value
Graft loss or death	123 (5.2%)	80 (5.7%)	12 (3.4%)	24 (5.3%)	7 (4.5%)	.36
Death	49 (2.1%)	27 (1.9%)	5 (1.4%)	12 (2.6%)	5 (3.2%)	.45
Graft loss	74 (3.1%)	53 (3.8%)	7 (2.0%)	12 (2.6%)	2 (1.3%)	.13
eGFR [ml/min]	53 (41–66)	54 (42–67)	53 (43–67)	51 (39–66)	44 (34–58)[a]	<.001
Patients with eGFR <25	107 (4.5%)	50 (3.6%)	8 (2.3%)	30 (6.6%)	19 (12.3%)	<.001

(B) Death-censored graft survival



Variable	HR (95%CI)	*p*-value
UTI phenotype at 1 year post-transplant		
No colonization or UTI	Reference	
Colonization only	1.00 (0.55–1.81)	.98
1–2 UTI	1.52 (0.93–2.47)	.10
≥3 UTI	4.41 (2.53–7.68)	<.001

Brune et al Am J Transplant. 2022 April 2, 1823–1833

Outline

- Epidemiology and risk factors for UTI
- Typical and atypical pathogens as causes of UTI
- Direct and indirect effects of UTI
- **Treatament indication and duration for UTI**
- Prevention

Diagnosis and management of asymptomatic bacteriuria in kidney transplant recipients: a survey of current practice in Europe

244 participants in 25 countries

- 72% always screen for asymptomatic bacteriuria in KTRs
- 6% never treated asymptomatic bacteriuria with antibiotics
- 24% would start empirical antibiotics
- Fully susceptible microorganism , mostly used antibiotics :
  - fluoroquinolones
  - amoxicillin/clavulanic acid
  - oral cephalosporins

Nephrol Dial Transplant (2018) 3

RCT for the treatment of asymptomatic bacteriuria among KTRs

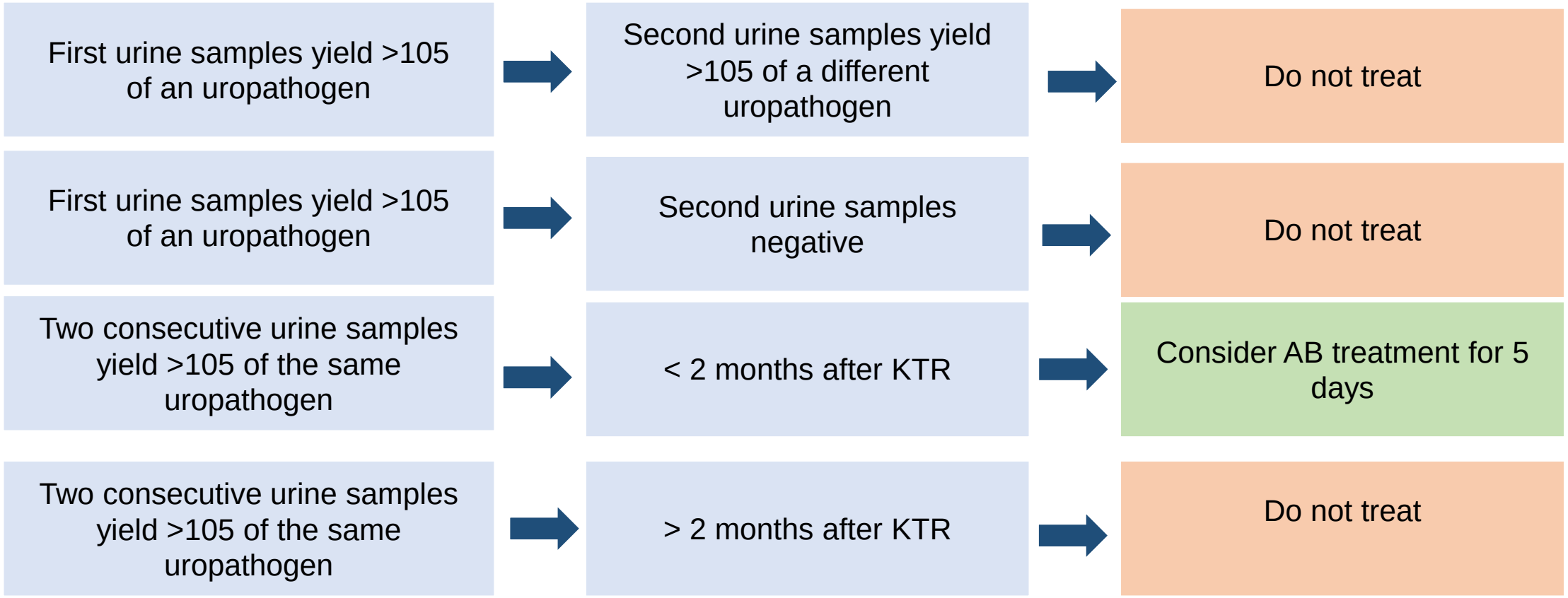
Treatment of asymptomatic bacteriuria does not prevent symptomatic UTI or allograft pyelonephritis BUT

dramatically increases the risk of overall antibiotic exposures and increases the risk of subsequent resistant organisms

Mendoza et al 2022
Coussement et al.2021
Sabe et al.2019
Origüen et al.2016
Moradi et al.2005

Treatment of asymptomatic bacteriuria in KTR

two consecutive urine samples yield >105 of the same uropathogen



Treatment of asymptomatic bacteriuria in KTR
specific patogens

2 Urine samples yield >105 of an MDR uropathogen → Do not treat

2 Urine samples yield >105 of Candida spp. → Change urinary catether

Exclude obstructing fungal balls or systemic infections → Do not treat asymptomatic candiduria **except** prior to urologic procedures or when the patient is neutropenic

Treatment recomendations dor UTI in KTR

Clinical presentation	Duration of treatment
• **Asymptomatic bacteriuria**	5 days
• **Simple cystitis**	5-7 days (late) 10-14 days (early)
• **Pyelonephritis** • **Complicated UTI—moderate/severe**	14-21 days

Goldman et al *Clinical Transplantation.* 2019

Shorter antibiotic courses in SOT : the impossible dream?

- Growing number of studies have demonstrated similar outcomes with shorter courses of antibiotics for bacterial infections
- Under representation of SOT recipients severely limits extrapolation of the findings to these patients
- Recommendations guiding antibiotic duration for SOT are rarely addressed in clinical guidance
- Short vs long antibiotic therapy in SOT
  - no comparative studies for CAP, VAP, IAI, SSTI
  - some studies on UTIs, bacteriuria, GNB BSI and peri-operative antibiotic use

Imlay et al. Clin Microbiol Infect 2022 Aug 18

Short versus prolonged antibiotic treatment for complicated UTI after kidney transplantation

- Retrospective study n= 214 kidney transplant recipients
- Duration of treatment : **short (6–10 days) and prolonged (11–21 days)**
- Composite outcome: 30-day readmission/mortality or recurrent UTI at 6 months

	Short treatment *N* = 115	Long treatment *N* = 99	All cohort *N* = 214	*P*-value
Primary outcomes				
Composite outcome	33 (28.7%)	30 (30.3%)	63 (29.4%)	0.797
Relapse of UTI	19 (16.5%)	21 (21.2%)	40 (18.7%)	0.38
Secondary outcomes				
30-day mortality	2 (1.7%)	0	2 (0.9%)	0.500
Readmission 30 days	31 (27%)	30 (30.3%)	61 (28.5%)	0.589
Readmission 90 days	42 (36.5%)	44 (44.4%)	86 (40.2%)	0.239
Days of hospital stay- all cohort, (median, 25–75%)	9 (7–15)	10 (8–18)	10 (8–16)	0.103
Days of hospital stay (alive at day 30), (median, 25–75%)	9 (7–15)	10 (8–18)	10 (8–16)	0.114
Bacteraemia within 30 days	20 (17.4%)	24 (24.2%)	44 (20.6%)	0.216
MDR development within 180 days	26/113 (23%)	23/98 (23.5%)	49/211 (23.2%)	0.937
Creatinine 30 days, *N* = 153 (median, 25–75%)	1.5 (1.01–2.01)	1.47 (1.11–2.12)	1.49 (1.09–2.05)	0.630
Creatinine 90 days, *N* = 147 (median, 25–75%)	1.41 (0.95–2.04)	1.34 (1.01–1.81)	1.41 (0.99–1.87)	0.779

MDR, multidrug resistance.

Avni-Hachman et al. Transpl Int 2021 Dec;34(12):2686-2695

Outline

- Epidemiology and risk factors for UTI
- Typical and atypical pathogens as causes of UTI
- Direct and indirect effects of UTI
- Treatament indication and duration for UTI
- **Prevention**

Prevention of both AB and UTI post-transplant

- Introduction of routine perioperative antibiotic prophylaxis

- Minimization of use of indwelling catheters:
    - < 4 week: early ureteral stent removal
    - early urinary catheter removal

- Long-term use of antimicrobial prophylaxis to prevent PCP and other infections
    - TMP/SMX antibiotic prophylaxis significantly decreases AB, symptomatic UTI and bacteremia in KTR

Pinchera et al. *Microorganisms* 2024, *12*(11), 2217

- KDIGO guidelines suggest prophylaxis with TMP-SMX for at least 6 months after transplantation in order to prevent UTIs and opportunistic infections (such PCP)

https://kdigo.org/guidelines/

Prophylaxis and MDR

- TMP-SMX prophylaxis has become less effective as uropathogens have become more resistant to this regimen
- No consensus among transplant clinicians regarding the optimal preventive strategy for UTI in the era of increasing antibiotic resistance

Fosfomicin

1-Randomized, double-blind, placebo-controlled trial

- TMP-SMX plus a single dose of IV FOS (41 KTR)
- TMP-SMX plus placebo (41 KTR)

- Lower incidence of symptomatic UTIs during the first 7 weeks posttransplant in the fosfomycin group (7 versus 37 %)

2-Controlled clinical trial

- FOS PO (3 g) every 10 days and TMP-SMX (160/800 mg) three times per week
- TMP-SMX (160/800 mg) daily

- No difference in the incidence of UTI during the first 6 months posttransplant

Rosado Canto et el. Nephrol Dial Transplant. 2020; Arreola-Guerra J et al TID 2018

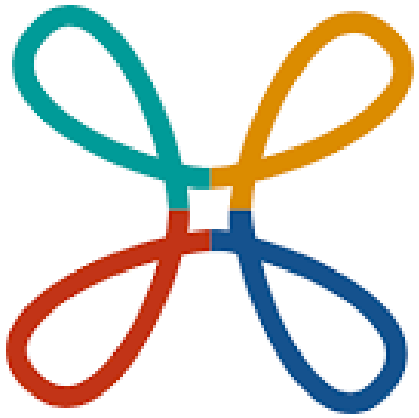
Recurrent UTI, approach to prevention

- Exclude for anatomic or functional abnormalities of the urinary tract
- Counselling on the risk factors for recurrent UTI and behavioral changes that might reduce the risk
- Long-term antibiotic prophylaxis should be individualized
- For postmenopausal females, topical estrogen may prevent recurrence of UTIs.
- Use of methenamine hippurate (1g twice daily) +/- ascorbic acid (1g twice daily) for prevention of recurrent UTI

Pinchera et al. *Microorganisms* 2024, *12*(11), 2217

Conclusions

- UTI, particularly in KTR, are an important clinical problem in transplantation
- Antimicrobial resistance is a rapidly evolving and worrisome issue
- In the setting of SOT, both typical and atypical pathogens should be included in the diagnostic approach
- Treatment of asymptomatic bacteriuria does not prevent symptomatic UTI but increases the risk of MDR pathogens
- Shorter antibiotic courses should be considered for SOT with bacterial infections
- Preventive strategies should be optimized to prevent UTI recurrence



Donare è una scelta naturale

CAMPAGNA NAZIONALE PER LA DONAZIONE
DI ORGANI, TESSUTI E CELLULE