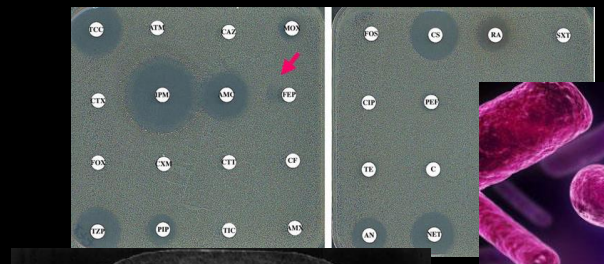
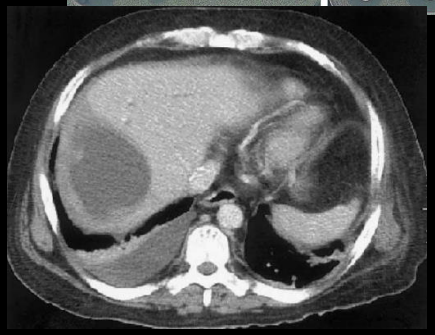
Gram Negative Infections in Solid Organ Transplantation

Christian van Delden MD
Director Transplant Infectious Diseases Unit
Service of Infectious Diseases and
Service of Transplantation
University Hospital Geneva, Switzerland
christian.vandelden@hcuge.ch





SCHOLA GENEVENSIS 1559

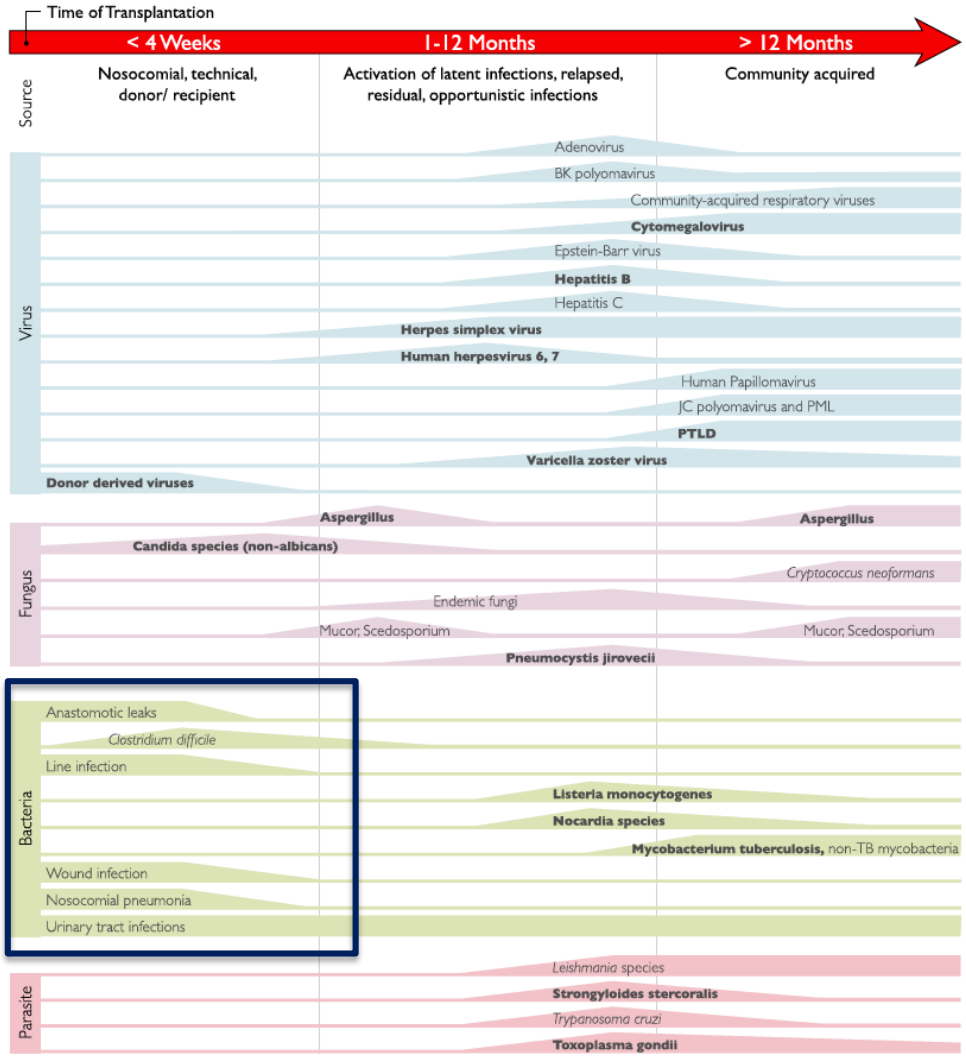
STCS SWISS TRANSPLANT COHORT STUDY

HUG Hôpitaux Universitaires Genève

Disclosures

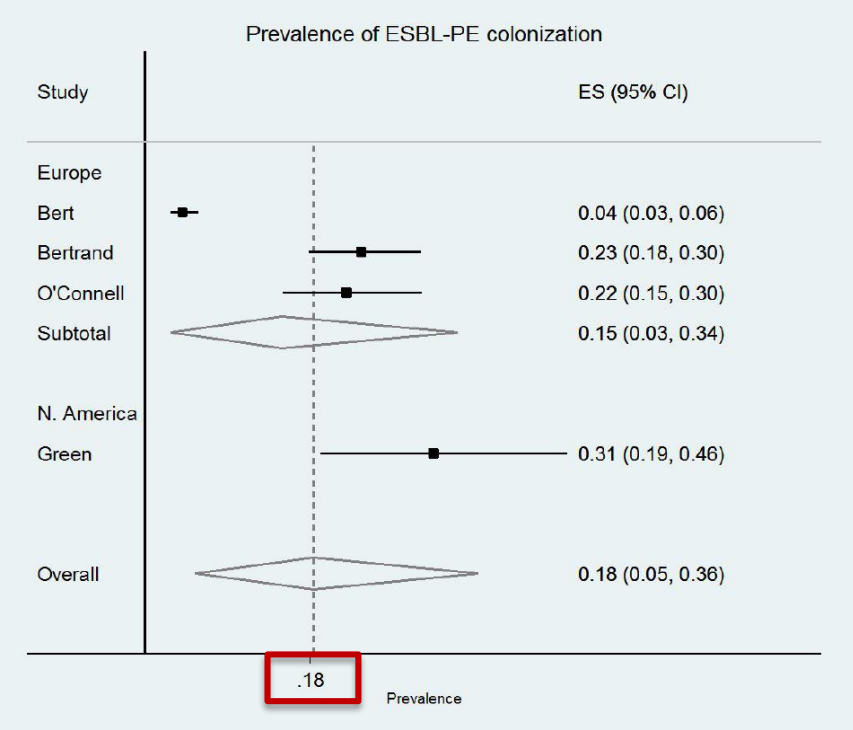
- **Astellas:** grant investigator, scientific advisor
- **Basilea:** grant investigator, scientific advisor
- **Debiopharm:** scientific advisor
- **Gilead:** scientific advisor
- **MSD**: grant investigator, scientific advisor
- **Pfizer:** scientific advisor
- **Sanofi:** scientific advisor

When do gram negative infections occur after solid organ transplantation ?



AJT **2017**;17:856

Prevalence of colonization with ESBL *Enterobacteriaceae* in SOTr



ESBL colonization rate in SOTr :

- Higher than healthy population (14%)
- Similar to patients with malignancies (19%)

Surveillance screening protocols ?

TID **2017**; doi 10.1111

Colonization with ESBL producing *Enterobacteriaceae* in liver transplant recipients

- 317 French liver transplant recipients screened before liver transplantation for ESBL colonization (2009-2011)
- 50 (16%) harbored ESBL producing *Enterobacteriaceae*
- Independent risk factors were:
  - Previous exposure to b-lactams
  - Previous infection with an ESBL producing bacteria
  - History of spontaneous bacterial peritonitis

Patients at risk might benefit from intraoperative prophylaxis and empirical antibiotic treatments

TID **2014**;16:84

Outcome associated with colonization of liver transplant recipients by KPC-producing *K. pneumonia*

- Outbreak in a German center involving 103 patients with a KPC type 2-producing *K. pneumoniae* (2010-2013)
- No routine pre- and post- transplant surveillance during the outbreak

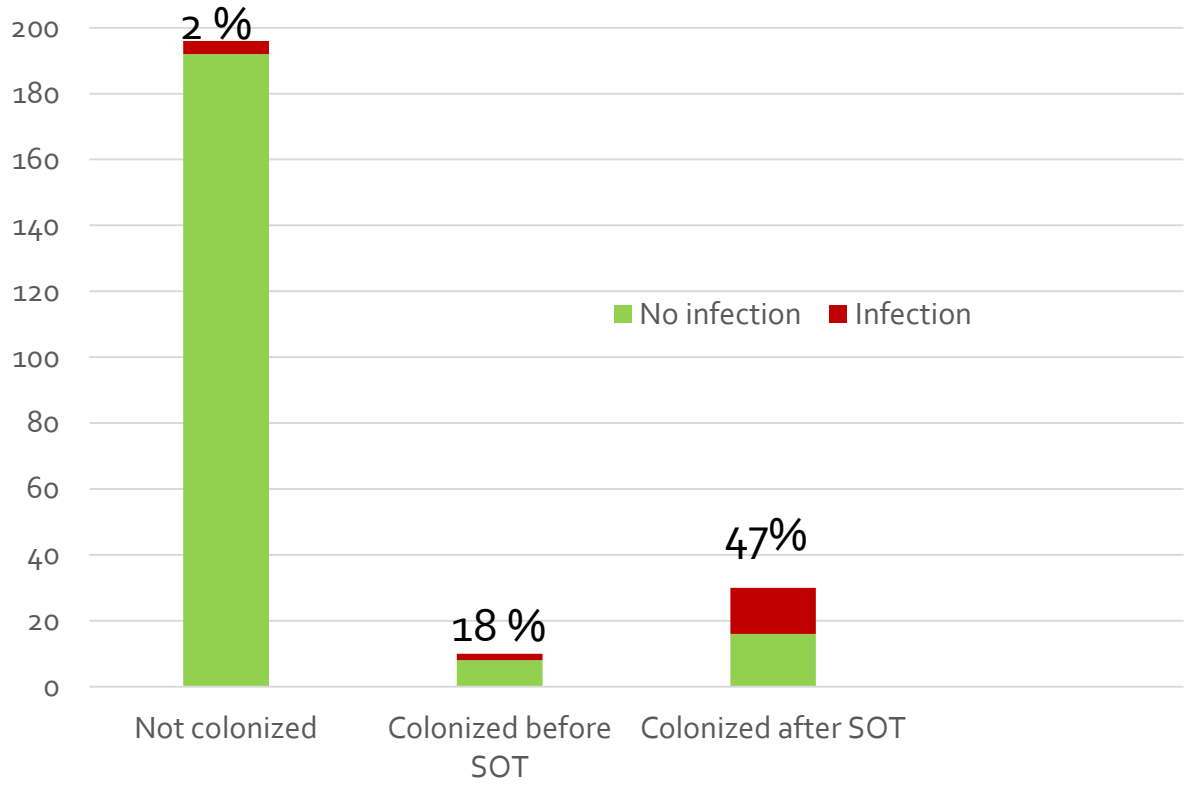
- **During outbreaks regular screening of liver transplant candidates might be indicated**
- **Patients with pre-transplant colonization should be considered liver transplant candidates only with extreme caution**

  - 8 (89%) progressed to infection, 5 (56%) bacteremic
  - Mortality was increased from 11 to 78%

Infect **2014;**42:309 / *Liver Transpl* **2014;**20:736

Infection with carbapenem- resistant *K. pneumoniae* after liver transplantation according to colonization status

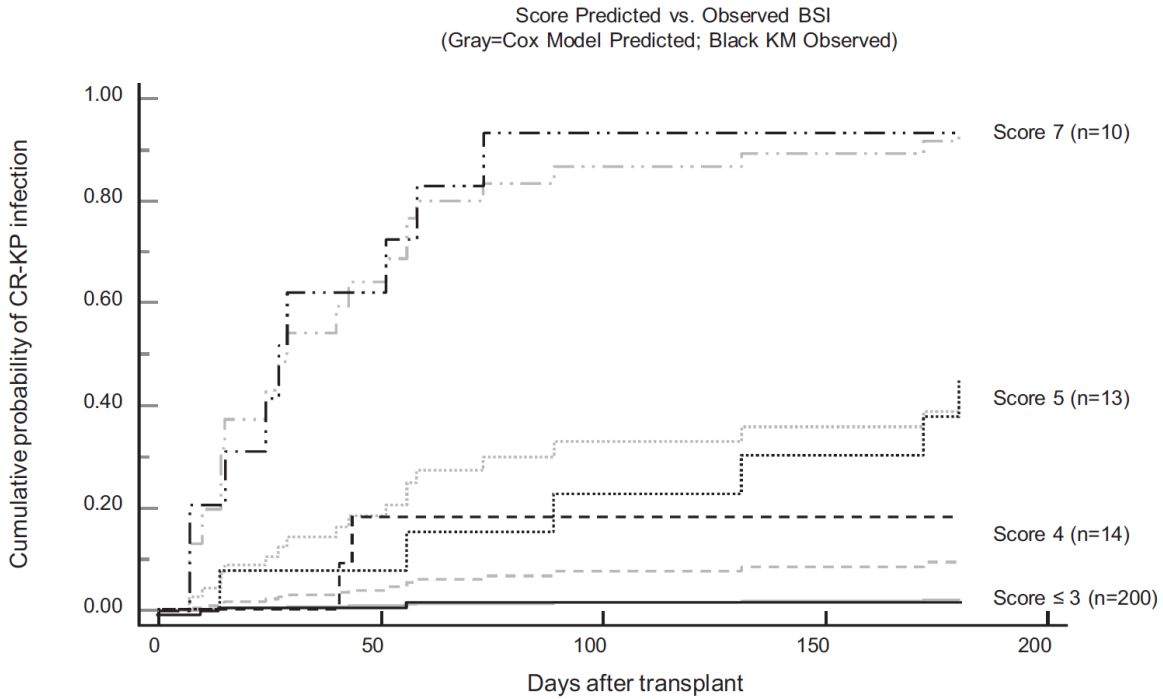
- 237 liver transplant recipients
  - Pre-transplant screening : 11 CR-KP carriers
  - Post-transplant screening: 30 CR-KP carriers



AJT **2015**; 15: 1708

Risk factors and risk score for infection with carbapenem-resistant *K. pneumoniae* after liver transplantation

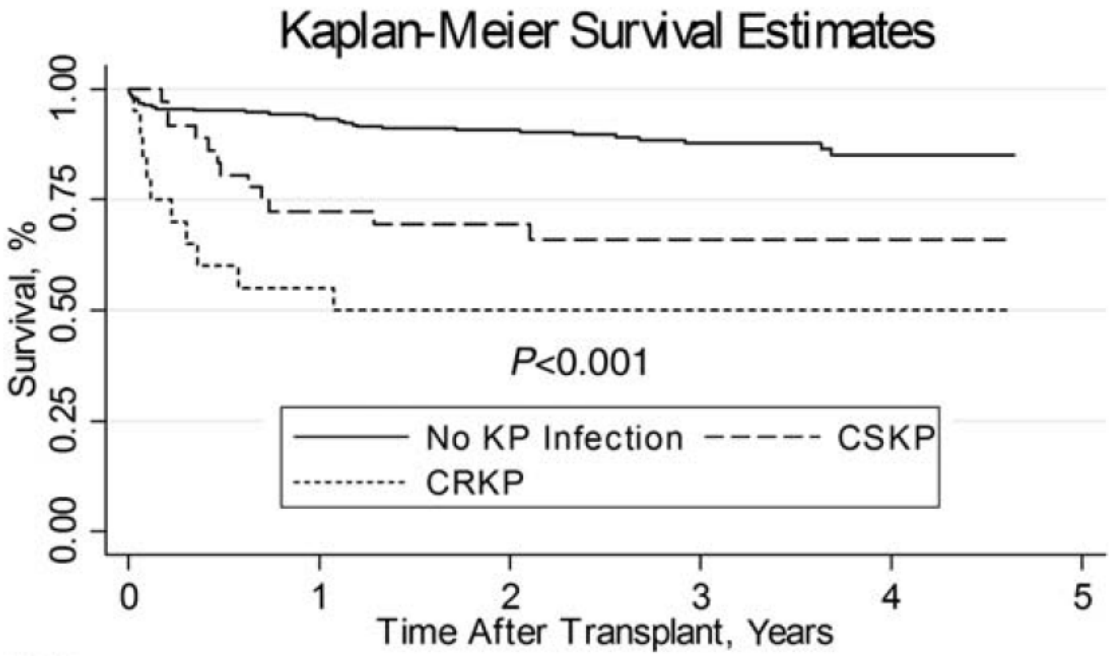
Variable	Hazard ratio	95% CI	p	Risk score points
Renal replacement therapy	4.75	1.64–13.70	0.004	2
Mechanical ventilation >48 h	5.74	1.84–17.82	0.001	2
Histological recurrence of HCV	9.70	2.42–36.09	0.001	2
CR-KP rectal carriage at any time	16.65	5.43–51.01	<0.0001	3



AJT **2015;** 15: 1708

Outcome of liver transplant recipients with infections due to carbapenem-resistant *K. pneumoniae*

Columbia University Medical Center (2010- 2013)



12 months post liver transplant:

- 304 liver transplant recipients
- 20 CRKP infections (7%)
- 36 CSKP infections (12%)

Liver Transpl **2015;** 21:1511

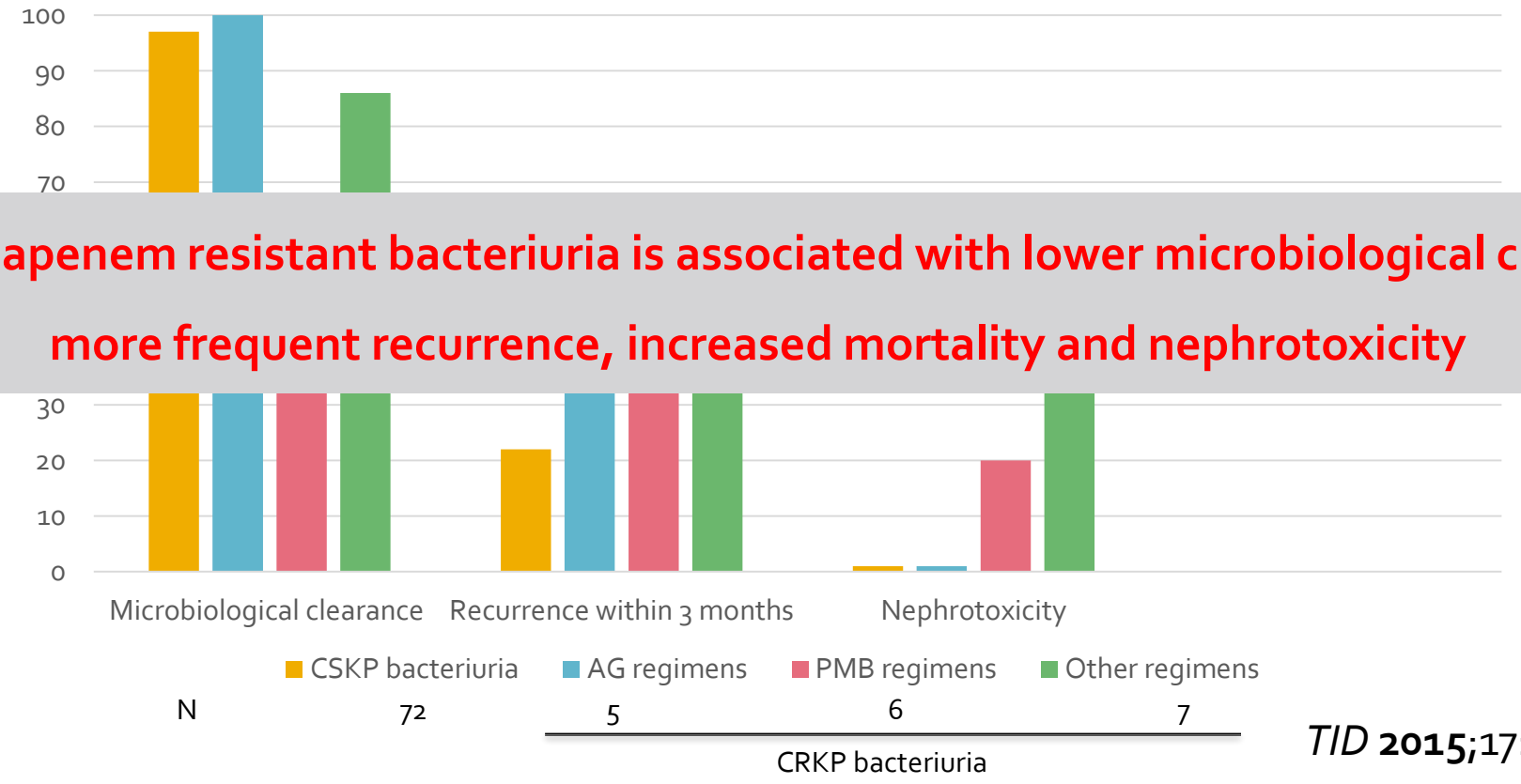
Risk factors for carbapenem-resistant *K. pneumoniae* UTI in kidney transplant recipients

- Diabetes mellitus[1,2]
- Previous antibiotic exposure[1,2]
- Previous UTI/relapsing infection[1, 2]
- Delayed graft function[1]
- Simultaneous SOT[2]
- Deceased donor[2]
- Length of pre-transplant hospitalization[2]
- CRKP infection/colonization[2]

[1] *PlosOne* **2015**;DOI:10.1371
[2] *TID* **2015**;17:800

Outcome of treated episodes of carbapenem-susceptible and resistant *K.pneumoniae* bacteriuria according to treatments

- Columbia University and Weill Cornell Medical Centers
  - 1852 kidney transplant recipients from 2007 to 2010
  - 18 treated CRKP bacteriuria
  - 72 treated CSKP bacteriuria



Carbapenem resistant bacteriuria is associated with lower microbiological cure, more frequent recurrence, increased mortality and nephrotoxicity

TID **2015**;17:800

INCREMENT-SOT

An international consortium for the clinical study of bloodstream infections caused by multidrug-resistant *Enterobacteriaceae* in solid organ transplantation

ClinicalTrials.gov Identifier: NCT02852902

Objectives

Clinical study

- ✓ To assess the efficacy and safety of various antibiotic regimes for the treatment of bloodstream infections caused by MDR *Enterobacteriaceae* in SOT patients.

Microbiological study

- ✓ To generate a collection of isolates associated with the clinical cases recorded in the database.
- ✓ To evaluate the *in vitro* activity of specific antimicrobials against these isolates, study the genetic basis of resistance and the molecular epidemiology of the strains.

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Unión Europea
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ESGICH ESCMID STUDY GROUP FOR INFECTIONS IN COMPROMISED HOSTS
European Society of Clinical Microbiology and Infectious Diseases

SOCIEDAD ANDALUZA DE TRASPLANTE DE ÓRGANOS Y TEJIDOS

Design: International, multicentric, pre-registered, retrospective, cohort study. Clinical episodes occuring from 2000 to 2015.

Courtesy of E. Pérez-Nadales

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Preliminary summary of results

16 countries, 46 centers

Country	Centers
Spain	11
Italy	7
Brazil	4
USA	4
Singapore	1
Israel	1
Turkey	4
UK	1
Switzerland (STCS)	6
Greece	1
Belgium	1
South Africa	1
Sweden	1
France	1
Malta	1

773 clinical cases collected

Type of SOT	n (%)
Kidney	472 (61,1)
Liver	228 (29,5)
Heart	48 (6,2)
Lung	19 (2,5)
Pancreas	3 (0,49)
Pancreas-kidney	9 (1,2)
Multiorgan	12 (1,6)

Enterobacteriaceae	n (%)
E. coli	335 (43,3)
K. pneumoniae	374 (48,4)
Others	64 (8,3)
Betalactamase type	
ESBL	521 (67,4)
Carbapenemase	139 (18)
ESBL+Carbapenemase	48 (6,2)

Microbial collection: 161 isolates

Isolates	n (%)
K.pneumoniae	74 (46,0)
E.coli	32 (38,5)
E.cloacae	8 (5,0)
E.coli BLEE	5 (3,0)

Type of enzyme	n (%)
ESBL	115 (71,4)
Carbapenemase	31 (19,3)
ESBL+carbapenemase	4 (2,5)

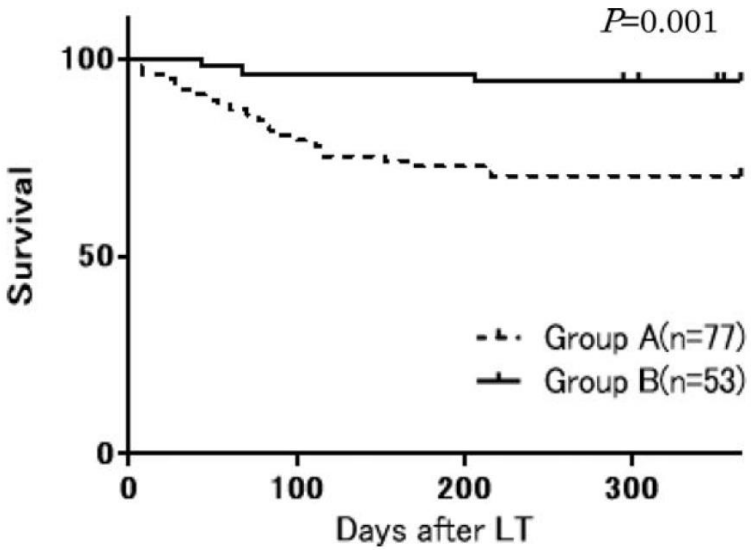
Courtesy of E. Pérez-Nadales

Bundled interventions to control infections following transplantation

- Kyoto University Hospital
  - 130 liver transplant recipients
    - A: 77 LTr 2011-2012 (before intervention)
    - B: 53 LTr 2013-2014 (after intervention)
  - Bundled intervention including:
    - LT candidates required to be able to walk independently (less sarcopenic)
    - Improved hand hygiene and US device decontamination
    - Serum procalcitonin (PCT) measurements to decide on empirical antibiotic therapy (days 2-5-7-10-14-21-28), cut offs 0.5< and >2.0 ng/mL

Liver Transpl **2016;** 22:436

Effectiveness of bundled strategies against infections post-liver transplant



	Group A (n = 77)	Group B (n = 53)	*P* Value
Death within 1 year, n (%)	22 (29)	3 (6)	0.001
Death due to infection, n (%)	9 (12)	1 (2)	0.04
Bacteremia, n (%)	34 (44)	14 (26)	0.03
Detection of multiple bacteria strains, n (%)	14 (18)	2 (4)	0.01
Postoperative hospital length of stay, days	85.4	63.5	0.048
Duration of antibiotic administration, days	42.3	25.1	0.002
Duration of carbapenem administration, days	15.1	5.2	<0.001

Bundled interventions were effective in preventing infections and improving survival

Liver Transpl **2016;** 22:436

How to reduce the risk of gram negative infections in SOT recipients

- Control measures should include
  - Increase compliance with strict hospital hygiene protocols
  - Limitation of pre- and post- transplant antibiotic exposure
    - avoidance of broad-spectrum prophylaxis and of prolonged pre- or post-transplant antibiotic therapies
  - Shorten endotracheal intubation
    - favor non-invasive ventilation and active respiratory physiotherapy
  - Optimize surgical procedures to avoid biliary leaks and need for reoperations

Transplantation of organs from donors infected or colonized by MDR Gram-negative bacteria

- In most countries
  - Patients bacteremic with carbapenem-resistant bacteria are excluded as donors
  - Kidney and lungs are excluded if urine or BAL cultures are positive for carbapenem-resistant bacteria
  - However such culture results might not be known at the time of donation leading to potential donor-derived infections with carbapenem-resistant bacteria

Outcome of SOT using organs from donors infected or colonized by MDR Gram-negative bacteria

- 2011-2012: 219 organs from 170 donors (10 south Italian hospitals)
- 30 organs transplanted from 18 deceased donors infected or colonized by MDR isolates
  - 14 (47%) considered high-risk for transmission (bacteremic/colonization of transplanted organ)
  - 16 (53%) considered low-risk for transmission

AJT **2015**:15:2674

Outcome of SOT using organs from donors infected or colonized by MDR Gram-negative bacteria

- The majority of the low-risk recipients didn't receive donor-targeted antibiotherapy
  - No transmission/infection reported

Risk underestimation and miscommunication leading to inappropriate therapy (wrong antibiotic, short duration, delayed initiation) lead to increased morbidity and mortality

- 4 of the 5 high-risk recipients who did not receive prompt adequate therapy developed infection (n=3) / colonization (n=1)

AJT **2015**:15:2674

Can we safely use organs from colonized / infected donors ?

- Donor colonized by a MDR isolate remaining susceptible to carbapenem can remain candidate for donation
- Donor with deep seated infection of organs not being transplanted
  - Donor should have >48 hours of effective antibiotic therapy
  - Additional consent from recipient/family
  - Recipient should receive at least 14 days of antibiotic therapy
- Donors bacteremic/infected with carbapenemase producing isolates or MDR *Pseudomonas* should be excluded/considered with extreme caution as donors

World J Transplant **2014;**4:43

Conclusions

- Gram negative bacteria predominate as cause of pneumonia, urinary tract infections and bacteremia in the first 12 months post-transplantation
- Increase of MDR isolates especially among the ESKAPE group associated with potential disastrous clinical outcome
- Recipient screening for MDR pathogens and pre-emptive treatment might be indicated
- Bundled interventions (hospital hygiene, reduction of antibiotic therapy…) to prevent bacterial infections might be beneficial
- Donor-derived infections with MDR gram negative pathogens is a serious concern and requires careful evaluation of both potential donor and recipients colonized and/or infected by such pathogens