Microbial Epidemiology and Outcome of Posttransplant Bloodstream Infection: An Analysis of 222 Consecutive Liver Transplant Recipients

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Background

- Effective antimicrobial prophylaxis strategies
  - ↓ incidence of infections among liver transplant recipients
- Morbidity and mortality due to infectious complications are major problems
- **Bloodstream infection (BSI): Bacteremia**
  - Most frequently occurring infectious complication after liver transplantation (LT) (incidence 21~49%)
  - Significant predictor for Posttransplant death

Del Pozo et al. World J Gastroenterol 2008; Bert F et al. Liver transpl 2010

Background

- Most BSI are caused by
  - **Intra-abdominal** sepsis or **biliary tract infections**
  - Hematogenous spread from the portal blood
- Other sources of BSI
  - Respiratory, urinary, central venous catheter-related or wound infections
- Growing concern for the increased **resistance to antimicrobial agents**
  - Multi-drug resistant Gram (+) and G (-) pathogens are emerging with increased antimicrobial resistance.

Linares L et al. Transplant Proc 2009; Zhong L et al. J Infect 2011; Serefhanoglu K et al. Braz J Infect Dis 2011

Background

- Detailed knowledge of posttransplant BSI
  - Improve empirical antimicrobial strategies
  - Aid in overcoming antimicrobial resistance
  - Help infection control practices
- The aim of this study
  - To assess the **frequency, source, timing and antimicrobial resistance of bacterial pathogens** responsible for BSI during 1st year after LT
  - To evaluate the associated **risk factors** of BSI and of mortality in LT recipients with BSI

Materials and Methods

- Pateints who was performed LT from February 2005 to May 2011
- Ajou University Hospital
- 231 LT operations including
  8 re-transplantation in 222 recipients
- 11 ABO-incompatible LT since 2007
- 33 salvage LT after hepatic resection for HCC

Materials and Methods

- Definition of **Bloodstream infection**
  - A positive blood culture with a pathogenic organism
    - At least 2 sets of blood culture for potential skin contaminant
  - Each isolated organisms were counted as a single case
- Definition of **source of BSI**
  - The same organism found in the blood culture is isolated from a clinically significant site of infection (eg. Bile, urine, intravascular catheter, liver aspiration…)

Definitions by CDC criteria

Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM: **CDC definitions for nosocomial infections, 1988**. *American journal of infection control* 1988, **16**(3):128-140

Demographic Characteristics of the Study Population (N=222)

Age (years), mean ± SD	49.1	±8.9
Gender, **male, N. (%)**	168	**(75.7%)**
Hepatitis B virus	**170**	**(76.6%)**
Alcohol	**58**	**(26.1%)**
Hepatocellular carcinoma	**106**	**(47.7%)**
Hepatitis C virus	3	(1.4%)
Acute hepatic failure	5	(2.3%)
Malignant neoplasm	5	(2.3%)
Primary biliary cirrhosis	4	(1.8%)
Cryptogenic cirrhosis	3	(1.4%)
Others	4	(1.8%)

Demographic Characteristics of the Study Population (N=222)

Child-Pugh score	9.3	±3.1
MELD score	**18.9**	±10.4
Broad-spectrum antibiotics in 1 month	125	**(56.3%)**
Salvage liver transplantation	33	(14.8%)
Diabetes Mellitus	23	(10.3%)

Materials and Methods

- Antimicrobial prophylaxis
  - Cefoperazone/sulbactam (2005~2007)
    Piperacillin/tazobactam (2007~) for 3~5 days
  - **Vancomycin** for 3~5 days
  - **Amphotericin B deoxycholate** (2005~2009)
    Liposomal Amphotericin B (2009~) for 5 days
  - **Gancyclovir**
  - Selective bowel decomtamination
  - Trimethoprim/sulfamethoxazole
- Immunosuppression
  - Tacrolimus or cyclosporine, prednisone, basiliximab

Materials and Methods

- Pretransplant variables
  - Age, gender, B-viral hepatitis, alcoholic liver cirrhosis, CTP[1] score, MELD[2] score, HCC[3], DM[4], broad spectrum antibiotics in 1 month
- Operative variables
  - Living donor graft, pRBC transfusion, op time, ABO-I[5], splenectomy
- Posttransplant variables
  - Posttransplant hemodialysis, reoperation within 3 months, acute rejection, Intensive care unit (ICU) stay, admission days, retransplantation, biliary complications

[1] Child-Pugh-Turcotte, [2]Model of end stage liver disease, [3]hepatocellular carcinoma, [4]Diabetes mellitus, [5]Incompatible

Results

- **Frequency**
  - **28.8%** (64 of 222) of LT recipients underwent 112 episodes of BSI
    - 50.4 BSI episodes per 100 patients 1 YR pottransplant
  - One patient can have more than one episode
    - 1 BSI in 59.3% (38 /64) of patients
    - **Multiple BSI in 40.6%** (26 /64) of patients

- Total follow-up days in median with range: 1306 with 2-1803 days

Results: Timing

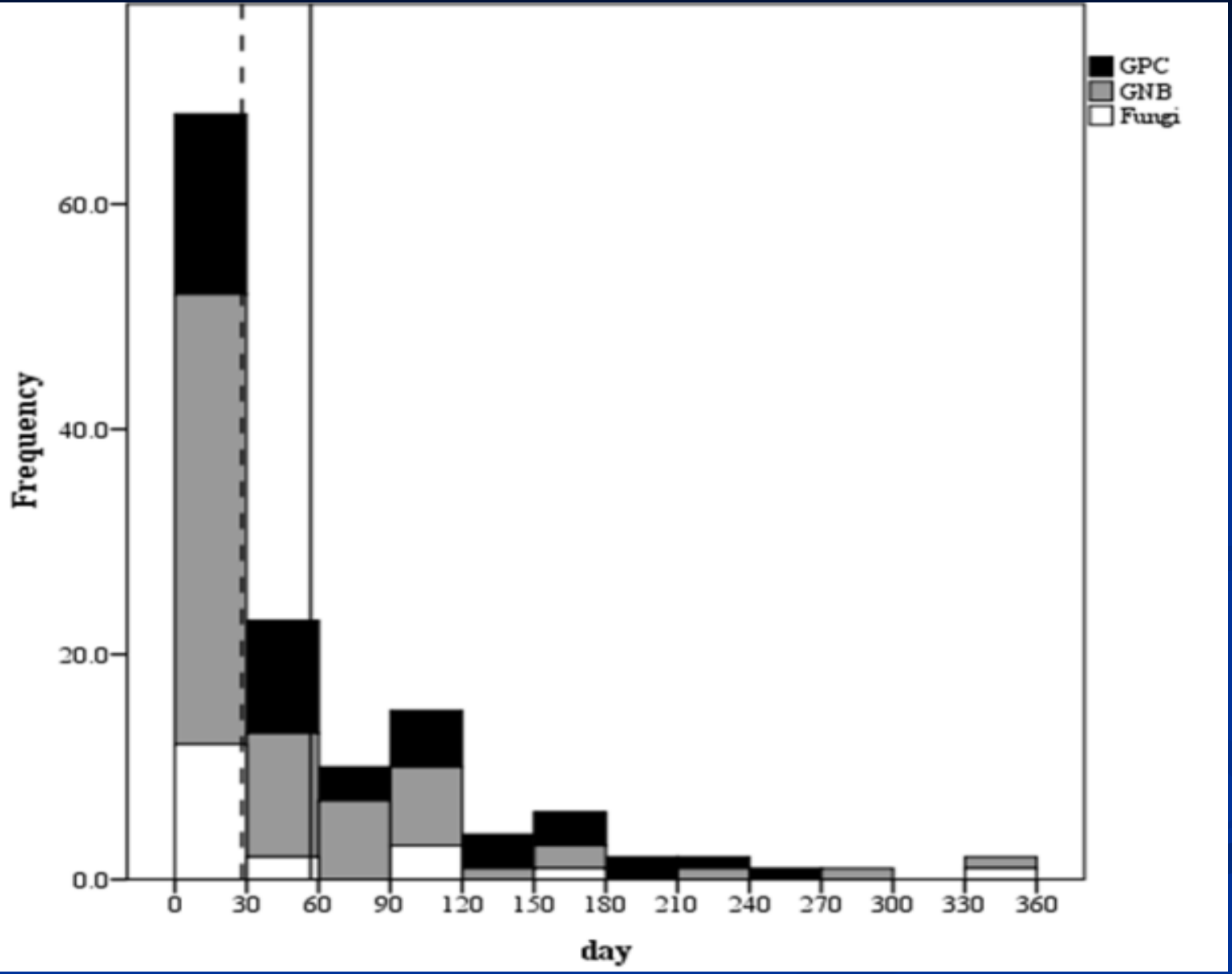
- Most BSI episodes occurred **within a month** after LT
  - Median time with interquartile range from the day of LT to the day of BSI

    Total (n=134): **28 days** with 6-89 days

    GPC (n=44): **40 days** with 19-113 days

    GNB (n=71): **23 days** with 6-66 days

    Fungi (n=19): **12 days** with 5-95 days
- The median time to onset (median with IQR)
  - *K. pneumoniae,* the earliest: 8 with 4-83 days
  - Enterococcus, the last: 101 with 24-153 days


GPC
GNB
Fungi
Frequency
60.0
40.0
20.0
0.0
0
30
60
90
120
150
180
210
240
270
300
330
360
day

Causative pathogens of BSI

	Organisms (n=135)	N. (%)
Gram positives n= 44 (32.8%)	*Staphylococcus aureus*	14 (10.4)
	Coagulase negative Staphylococcus	5 (3.7)
	Enterococcus	24 (17.8)
	Other GP	1 (0.7)
Gram negatives n=72 (52.9%)	*Klebsiella pneumoniae*	19 (14.2)
	Escherichia coli	17 (11.9)
	Enterobacter cloacae	6 (4.4)
	Acinetobacter baumannii	14 (10.4)
	Pseudomonas species[a]	12 (8.9)
	Other GN	6 (4.4)
Fungi n=19 (14.2%)	*Candida albicans*	9 (6.7)
	Candida tropicalis	5 (3.7)
	Other candida species	5 (3.7)

Antimicrobial susceptibility of bloodstream infection

- Most pathogens were highly multi-drug resistant
  - *Enterococcus faecium:* **38% (8/21) Vancomycin-R**
  - *K. pneumonia:* **68.4% (13/19) ESBL-producing**
  - *Escherichia coli:* **82.3% (14/17) ESBL-producing**
  - *S. aureus:* **92.8% (13/14) Methicillin-R**
  - *A. baumannii:* **92.8% (13/14) Carbapenem-R**
  - *P. aeruginosa:* **91.6% (11/12) Carbapenem-R**

  - All candida were susceptible to fluconazole. Carbapenem-R enterobacteriaceae or Vancomycin-R S. aureus were not identified.

ESBL, extended spectrum beta-lactamase

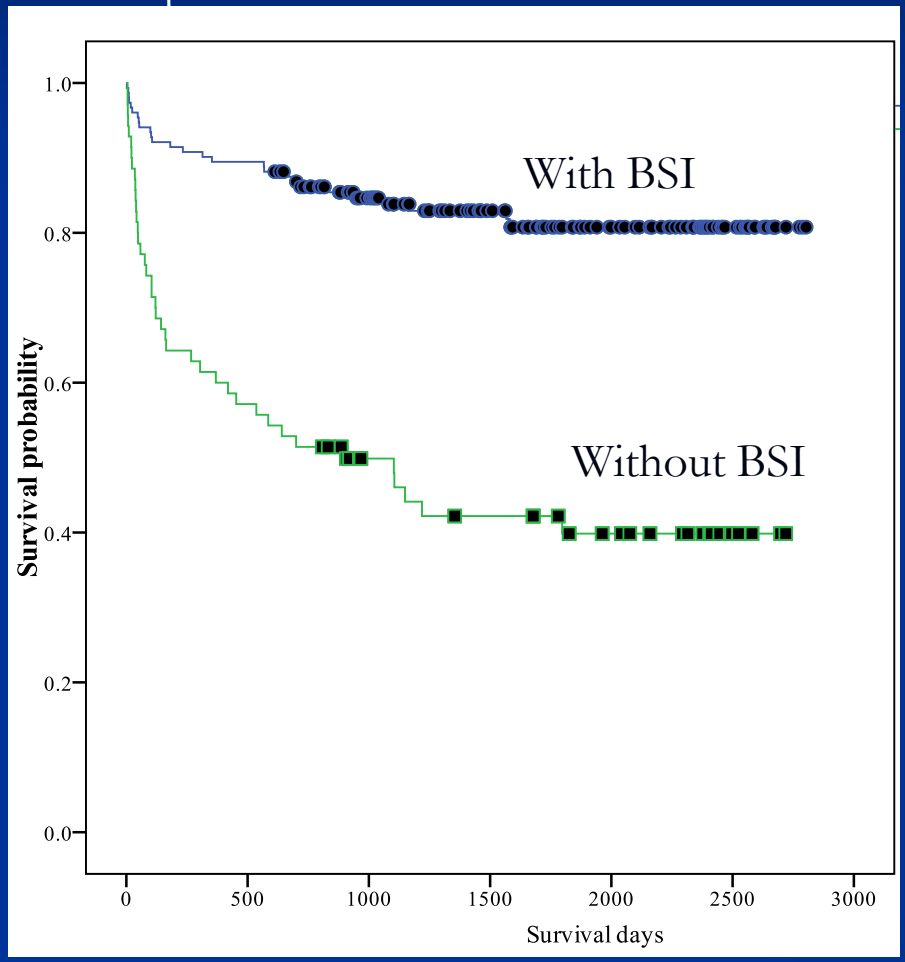
Source of Bloodstream infection

- Source of infection and the m/c causative pathogen
  - **Biliary 36.2%** (49/135 isolates): Enterococci
  - **Abd/wound 28.1%** (38/135): *K. pneumoniae*
  - **IVC related 18.5%** (25/135): *Candida*
  - Lung 5.9% (8/135): *Pseudomonas*
  - Urinary 2.2% (3/135), Unknown 8.9% (12/135)

IVC, intravascular catheter; m/c most common

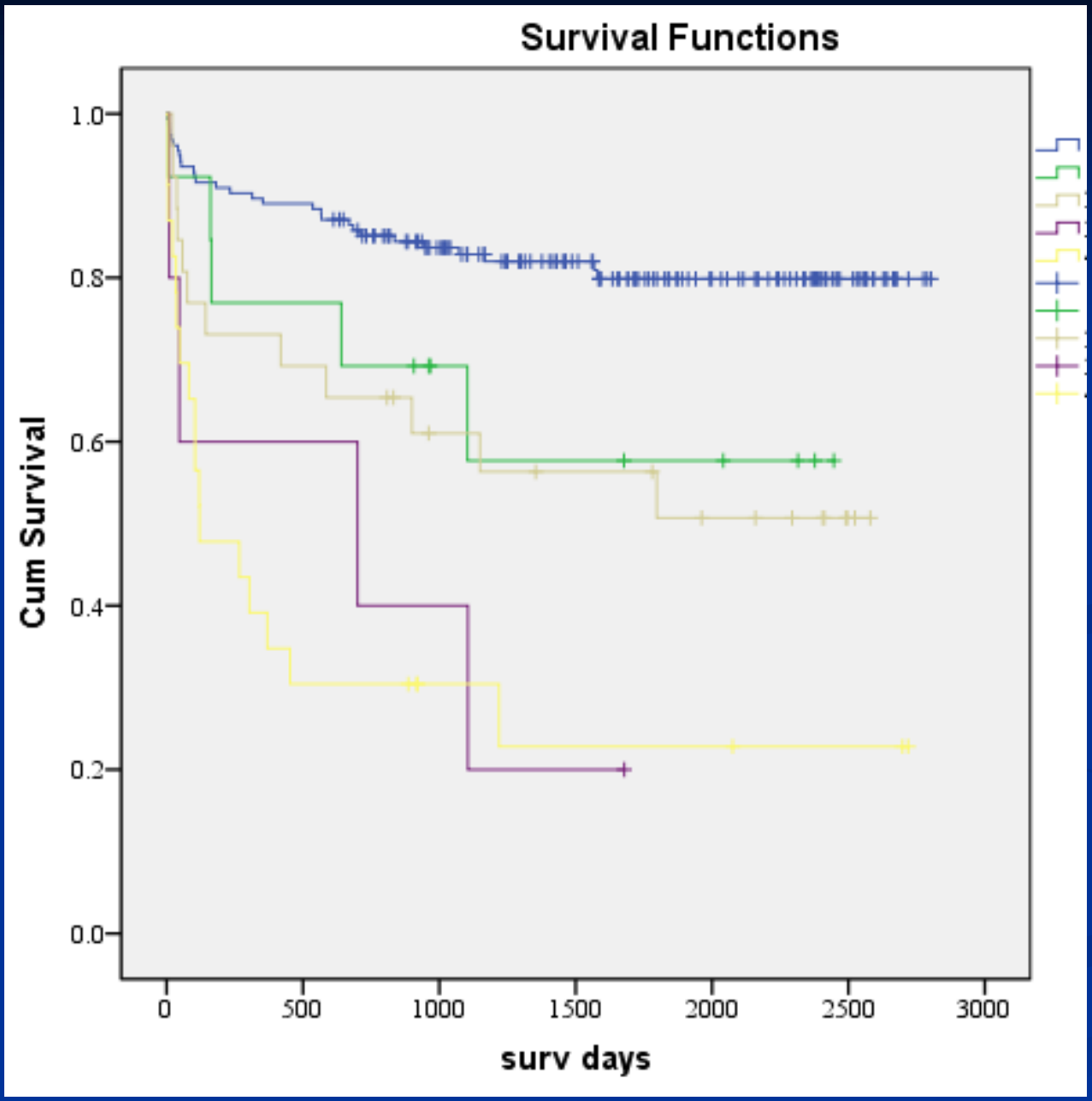
Patient survivals

Kaplan-Meier Survival Curves



	Patients with BSI	Patients without BSI
1YR Surv rate	**60.0%**	**89.5%**
30 D Mortality	22.9%	5.9%
1YR Mortality	40.0%	10.5%

P<0.0001



Without BSI
GP
GN
Fungi
polymicrobial

1YR SR

Fungal BSI	Non-fungal BSI
35.7%	66.1%
Poly microbial	Mono microbial
26.7%	69.1%

Risk factors for Posttransplant Bloodstream infection

- Univariate Analysis
  - CTP score, MELD score, transfusion, posttransplant HD, re-op episodes, postop ICU stay, total postop adm days, retransplantation and biliary complication.

- Multivariate Analysis
  - **Biliary Complication:** OR 2.91, CI 1.29-6.59; P=0.010
  - **Longer ICU stay:** OR 1.04, CI 1.00-1.08; P<0.001.

Predictor for Death after LT

	All patients			Patients with BSI		
Variables	HR	95% CI	*P* value	HR	95% CI	*P* value
Age	1.00	0.97-1.03	0.670	**1.05**	**1.01-1.10**	**0.016**
B-viral hepatitis	0.51	0.28-0.95	0.034	0.18	0.07-0.50	0.001
HCC	**2.14**	**1.20-3.82**	**0.009**	**3.82**	**1.57-9.32**	**0.003**
Post-transplant HD	**3.38**	**1.70-6.70**	**<0.001**	**2.44**	**1.02-5.84**	**0.044**
ICU stay after LT	**1.02**	**1.00-1.04**	**0.004**	**1.03**	**1.01-1.05**	**0.001**
Post-transplant adm	0.97	0.95-0.98	<0.001	0.96	0.94-0.97	<0.001
Bloodstream infection	**3.92**	**2.22-6.91**	**<0.001**			
Candidemia				**3.71**	**1.58-8.71**	**0.003**
Polymicrobial BSI				**3.18**	**1.39-7.28**	**0.006**

Discussion

- Clinical significance of BSI during 1 yr after LT
  - **Common Cx: 28.8%** (64/222) of recipients
  - Strongest predictor for death: HR 3.92, CI 2.22-6.91; *P*<0.001
    BSI group **1YR SR 60.0%** (vs 89.5% of non-BSI group)
  - Particularly high mortality in patients with candida or polymicrobial BSI
- Relatively **higher** rate of BSI
  - **Poor general condition**: higher MELD (18.9) and CTP score (9.3)
  - Possible **learning curve effect** in the early transplant period

Discussion:

- Common type of BSI
  - Enterococcemia originated from **biliary infection** in the later posttransplant period
  - Enteric GN bacilli or nonfermenting GN bacteremia from abdominal or/and wound infection
  - Candidemia or *A. baumannii* bacteremia originated from **the intravascular catheter infection**
    - 18.5% of posttransplant BSI was Catheter related: CRBSI is **nosocomial** that warrants additional action for infection control practices

Discussion

- Most pathogens were highly MDR
  - **ESBL: 68.4%** *K. pneumoniae*, **82.3%** *E. coli*
  - **VRE: 38%** *E. faecium*
  - **Methicillin-R: 92.8%** MRSA, **100%** MRCoNS
  - **Carbapenem-R: 92.8%** *A. baumannii*, **91.6%** *Pseudomonas*
- Factors increase MDR
  - Extensive exposure to **broadspectrum antibiotics** before LT
  - Routine use of **broadspectrum antibiotics** as a prophylaxis: Antipseudomonal penicillin + Vancomycin
- Posttransplant hemodialysis as a significant predictor for death
  - Cautious and selective use of **nephrotoxic agents** including antimicrobial prophylaxis for LT

Conclusion

- Posttransplant BSI **occurred frequently during 1 year** after LT and it leads to low patient survival rate.
- **Biliary complication** was the strongest predictor for BSI and **biliary origin enterococcemia** was the most common type of BSI after LT.
- **Fungal and polymicrobial BSI** showed particularly high mortality.
- Most of the pathogens in BSI were **highly MDR**.
- This study provides detailed microbiology and clinical feature of posttransplant BSI which help **to guide selection of antimicrobial therapy** in LT recipients with suspected BSI and to improve infection control practices.