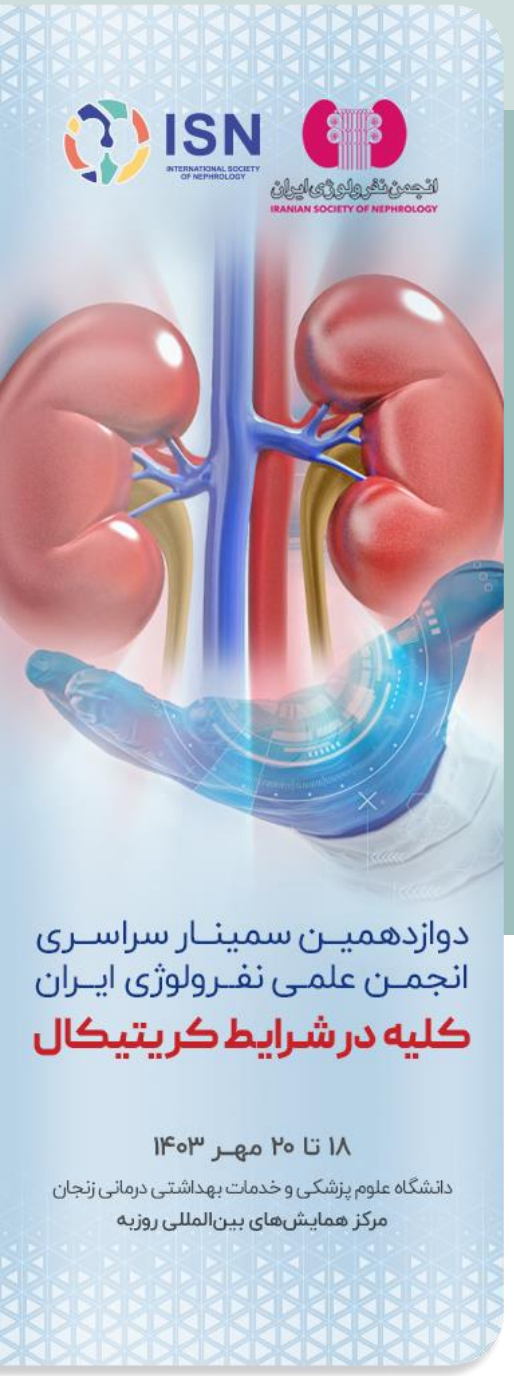


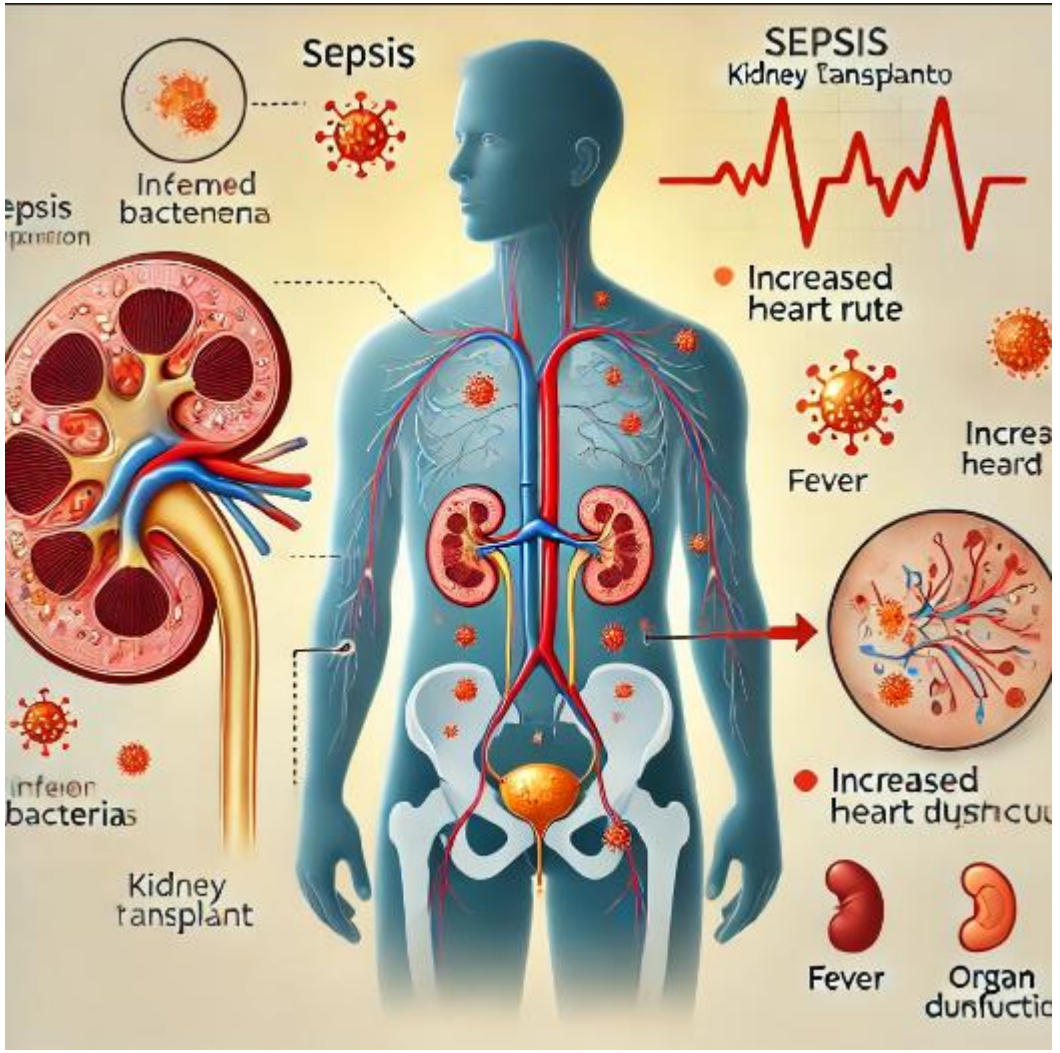
SEPSIS IN KIDNEY TRANSPLANT RECIPIENTS

DR F. POURREZAGHOLI
SBMU

The advances in care for patients with immunocompromised status have been remarkable over the last 2 decades, but sepsis continues to be a major cause of death.

Transplant recipients are more frequently admitted than other patients and they experience more frequent nosocomial infections and sepsis.

Classic features of sepsis, such as leukocytosis and fever, may be absent, whereas thrombocytopenia and organ failure may be more pronounced



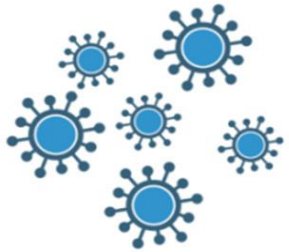
KTRs have a 40% higher rate of sepsis compared to the general population.

Other conditions such as **old age, DM, pneumonia** as a site of infection, and being **underweight** or **obese**, also increase the risk of sepsis.

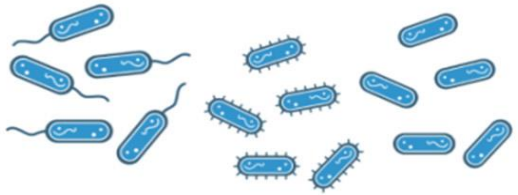
Up to 6% of KTRs experience life-threatening complications requiring **ICU admission**.

One of the most common medical complications requiring ICU is infection.

Virus



Bacteria



Prevalent system involved in disease control

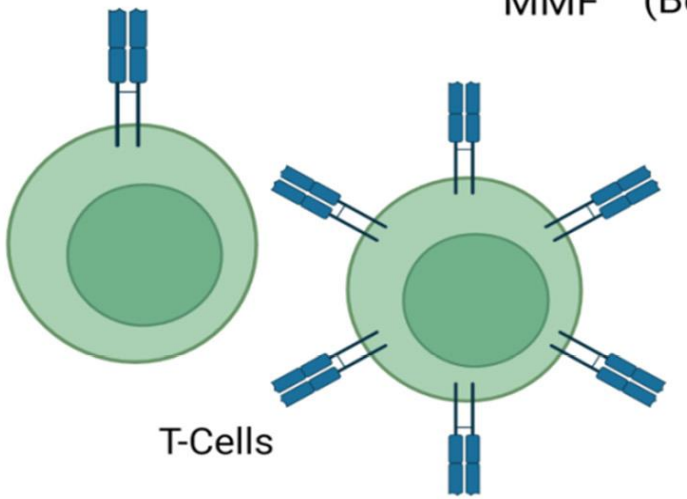
Prevalent risk according to specific drug-induced immune deficit

CNI
MMF

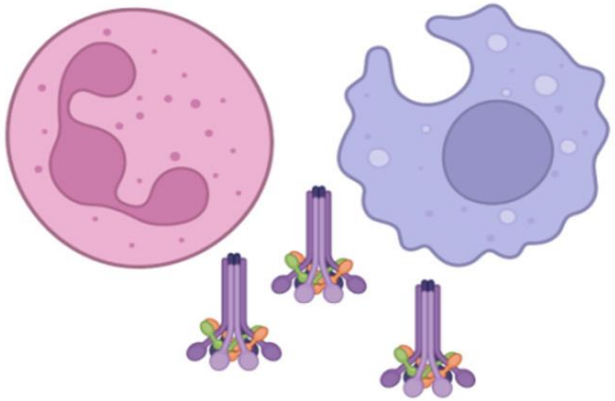
ATG
(Belatacept)

Steroids
mTORi

Eculizumab
(Tocilizumab)



T-Cells



Innate immune system

Drug	Immunosuppressive Class	Effect on Infection Risk	Mechanism
Tacrolimus	Calcineurin inhibitor	Increased risk of bacterial, viral, and fungal infections	Suppresses T-cell-mediated immune response
Mycophenolate mofetil	Antiproliferative agent	High risk of viral (CMV, BK) and bacterial infections	Inhibits proliferation of T and B cells
Prednisone	Corticosteroid	Risk of bacterial, viral, and fungal infections	General immunosuppression
Cyclosporine	Calcineurin inhibitor	Similar to tacrolimus	Suppresses T-cell activation

DEFINITION

Sepsis in KTRs is defined as a life-threatening organ dysfunction resulting from a dysregulated host response to infection.

In these patients, sepsis is challenging due to the combination of their compromised immune system, driven by immunosuppressive therapies to prevent rejection, and their heightened susceptibility to infections.

Sequential Organ Failure Assessment (SOFA) Score:

- A useful tool to assess the degree of organ dysfunction.
- A SOFA score ≥ 2 points is indicative of sepsis.
- Parameters include respiratory, cardiovascular, liver, coagulation, renal, and central nervous system function.

- **Quick SOFA (qSOFA)**:
- Simple bedside tool using three criteria:
  - Respiratory rate > 22/min
  - Altered mentation (Glasgow Coma Scale < 15)
  - Systolic blood pressure ≤ 100 mmHg
- A score ≥ 2 suggests poor outcomes and the need for further investigation.

DEFINITIONS	SEPSIS – 1 (1991)	Sepsis – 2 (2001)	Sepsis – 3 (2016)
Sepsis	Systemic response to infection manifested by 2 or more of SIRS criteria as a result of infection	Same definitions as Sepsis-1 with greater number & detail of signs and symptoms	A life threatening organ dysfunction caused by dysregulated host response to infection Suspected or documented infection & increase SOFA >2
Severe Sepsis	Sepsis associated with organ dysfunction, hypoperfusion, or hypotension	Same definitions as Sepsis-1 with greater number & detail of signs and symptoms	No longer applicable
Septic shock	Sepsis-induced, wit hypotension despite adequate fluid resuscitation along with presence of perfusion abnormalities	Same definitions as Sepsis-1 with greater number & detail of signs and symptoms	Can be identified with a clinical construct of sepsis with persistent hypotension, requiring vasopressor therapy to elevate MAP to 65 mm Hg despite adequate fluid resuscitation

BOSNIAN JOURNAL OF BASIC MEDICAL SCIENCES RESEARCH ARTICLE WWW.BJBMS.ORG

Risk factors for complications and graft failure in kidney transplant patients with sepsis

Syuan-Hao Syu[1], Yung-Wei Lin[1,2], Ke-Hsun Lin[1], Liang-Ming Lee[1], Chi-Hao Hsiao[1], Yu-Ching Wen[1,2*]

- CMV serologic mismatch (because of CMV reactivation, through immunomodulatory mechanisms, the risk of subsequent bacterial and fungal infections is increased)
- Cold ischemia time
- length of surgical procedure
- Amount of blood loss and transfusions during transplant
- The net state of immunosuppression
- The use of T-cell–depleting antibodies

Risk Factor Category	Specific Risk Factors	Description/Impact
Immunosuppressive Therapy	- Calcineurin inhibitors (e.g., tacrolimus, cyclosporine) - Corticosteroids - Antimetabolites (e.g., mycophenolate mofetil)	Suppresses the immune system, increasing susceptibility to infections (bacterial, viral, fungal), leading to sepsis.
Recent Surgery or Catheter Use	- Recent kidney transplant surgery - Presence of central venous catheters, urinary catheters	Surgical wounds or catheters act as entry points for infections, increasing the risk of bacteremia and sepsis.
Urinary Tract Infections (UTIs)	- Frequent UTIs - Ureteric stents or other urological interventions	Kidney transplant recipients are prone to recurrent UTIs, a common source of sepsis, especially from resistant organisms.
Opportunistic Infections	- **Viral**: CMV, BK virus - **Fungal**: Candida, Aspergillus - **Bacterial**: Pseudomonas, Enterobacter, MRSA	Opportunistic infections thrive in immunocompromised patients and may cause overwhelming sepsis if untreated.

Previous Infections	- History of bacteremia or systemic infections - Recurrent respiratory infections	Previous episodes of infection can indicate underlying risk and make patients more prone to subsequent sepsis.
Chronic Illnesses	- Diabetes mellitus - Chronic obstructive pulmonary disease (COPD) - Cardiovascular disease	Comorbid conditions exacerbate the risk of infections and organ dysfunction, increasing sepsis risk.
Delayed or Subclinical Presentation	- Fever masked by immunosuppressants - Atypical or subtle signs of infection	Immunosuppressive drugs can mask typical signs of infection, delaying diagnosis and increasing the severity of sepsis upon recognition.
Antibiotic Resistance	- Use of broad-spectrum antibiotics - Multi-drug resistant organisms (e.g., MRSA, VRE, CRE)	Overuse or misuse of antibiotics can lead to resistant infections, complicating sepsis treatment in transplant recipients.

Transpl Infect Dis. 2017 Jun;19(3). doi: 10.1111/tid.12695. Epub 2017 May 9.

Sepsis after renal transplantation: Clinical, immunological, and microbiological risk factors

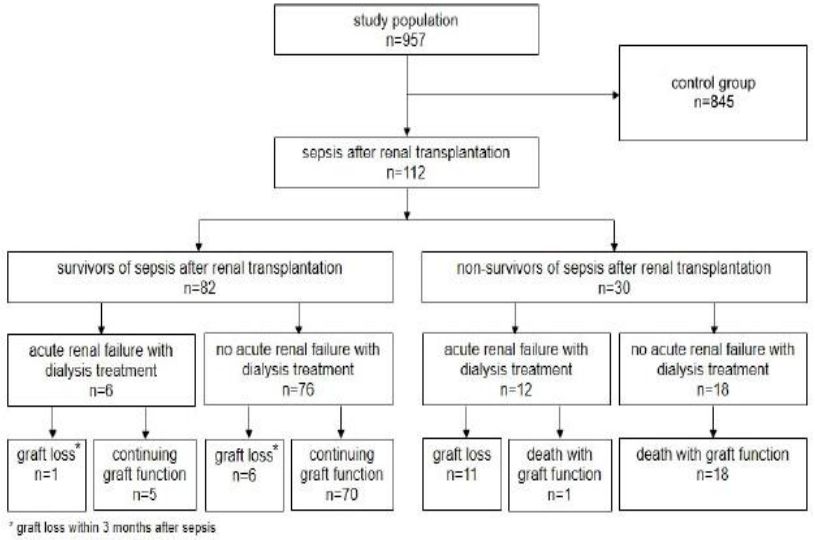


TABLE 3A. Multivariate regression analysis of risk factors associated with sepsis.

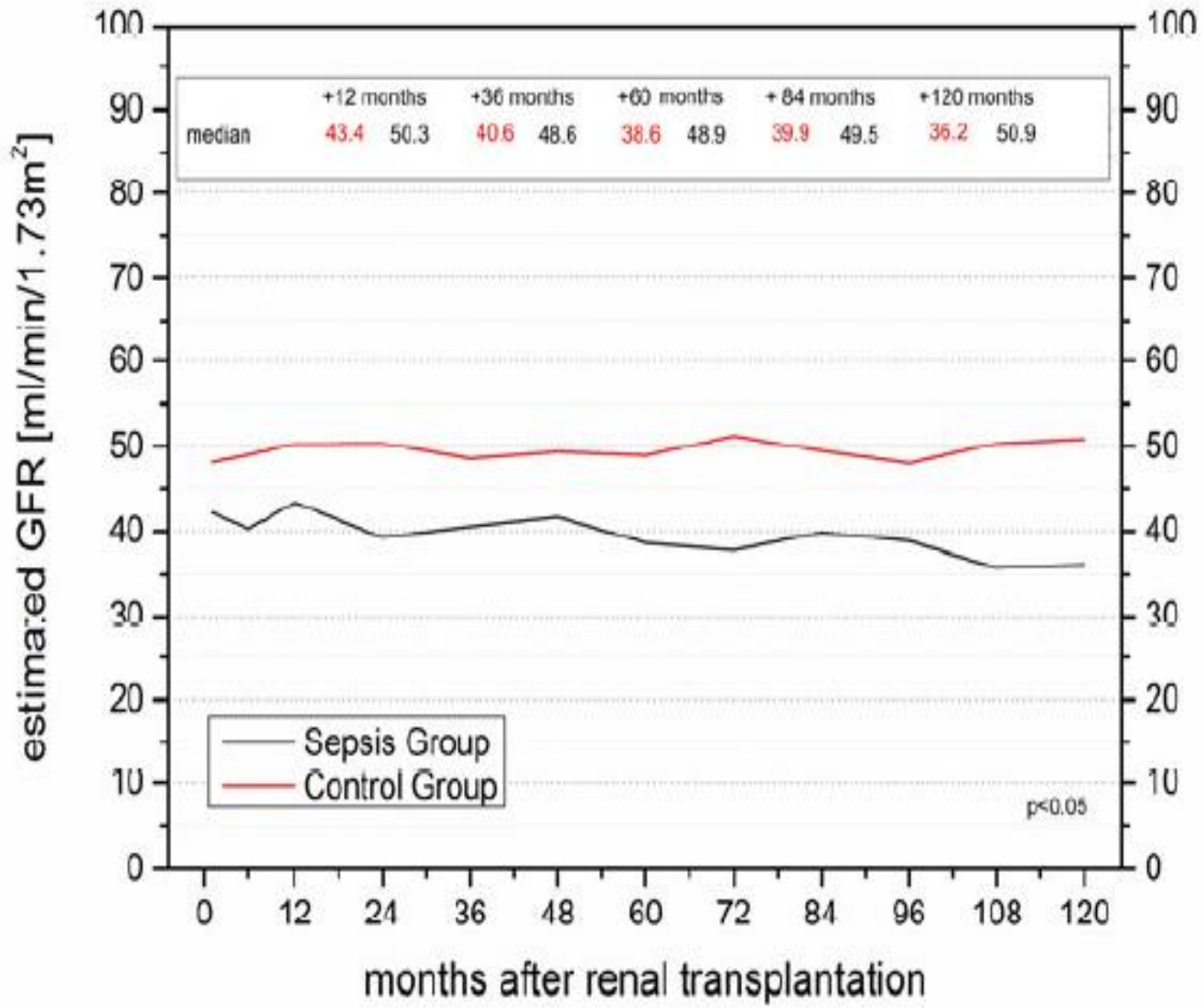
A) Risk factors for sepsis after renal transplantation	OR (95% CI)	*P*-value
Age	1.014 (0.994-1.034)	*.164*
Diabetes mellitus	2.258 (1.440-3.540)	*<.001**
Induction with lymphocyte depletion	2.179 (1.253-3.789)	*.006**
2 HLA-B mismatches	1.380 (0.885-2.153)	*.156*
Donor Age	1.020 (1.003-1.036)	*.019**

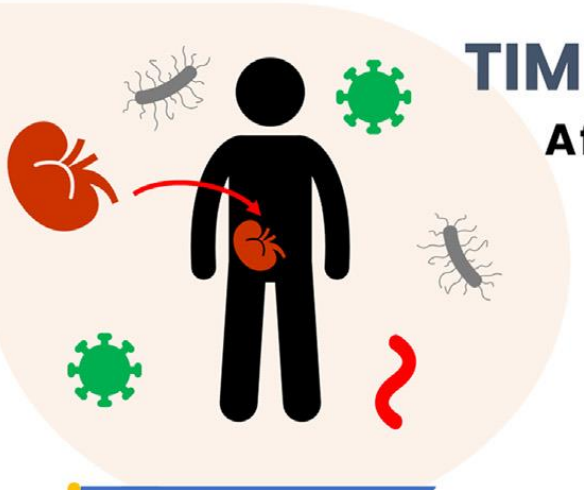
OR, odds ratio; CI, confidence interval; HLA, human leukocyte antigen.

TABLE 3B. Time-dependent covariate analysis of CMV viremia and acute cellular rejection with the development of sepsis.

B) Risk factors for sepsis after renal transplantation	HR (95% CI)	*P*- value
CMV viremia	1.820 (1.174-2.820)	.001*
Acute cellular rejection	1.510 (1.021-2.235)	.039*

**P*-values significant.
HR, hazard ratio; CI, confidence interval; CMV, cytomegalovirus.


+12 months
+36 months
+60 months
+84 months
+120 months
median
43.4 50.3
40.6 48.6
38.6 48.9
39.9 49.5
36.2 50.9
estimated GFR [ml/min/1.73m²]
Sepsis Group
Control Group
p<0.05
months after renal transplantation



TIMELINE OF INFECTIONS

After a kidney transplant

Within 30 Days

Early post-kidney transplant infections

Usually Health care associated infections

- Bacterial > viral > fungi
- SSIs, UTIs, CRBSIs, Pneumonia, Clostridium difficile infection.
- Donor derived infections (Rare) – CMV, Bacteremia, EBV, BK Virus, Dengue, TB

Within first 12 months

Opportunistic infections

Due to intense immunosuppression from anti-rejection therapy.

- Arise from new infection or reactivation of latent infection
- Increased risk due to lymphocyte depleting agents like Anti-thymoglobulin antibody, rituximab, alemtuzumab
- Antimicrobial prophylaxis reduces incidence, timing & severity of infections

After 12 months

Community Acquired infections

Minimal net immunosuppression

Pneumonia, Upper respiratory tract infections, UTI, Gastrointestinal infection

Abbreviations:
SSI-Surgical site infection, UTI – Urinary tract infection,
CRBSI – catheter related blood stream infections,
TB – tuberculosis, EBV – Epstein Barr Virus,
CMV – Cytomegalo Virus

Seminars inNephrology,Vol43,No5,September2023,

There is no current biomarker available that alone allows for a rapid and reliable sepsis diagnosis.

DIAGNOSTIC METHODS

Laboratory Tests

- **Blood Cultures:**
  - *Gold standard for identifying bloodstream infections.*
  - At least two sets of blood cultures (from different sites) should be drawn before initiating antibiotics.
- **Inflammatory Markers:**
  - **CRP:** Elevated levels indicate inflammation.
  - **Procalcitonin:** Can help distinguish bacterial infections from other causes of inflammation.

CBC:Leukocytosis or leukopenia may indicate infection.

Serum Lactate:Elevated serum lactate levels (> 2 mmol/L) indicate tissue hypoxia and are a marker of severe sepsis.

- **Urine Cultures**:
  - Important in diagnosing UTIs, which are frequent in KTRs and a common cause of sepsis.
- **Viral PCR Testing**:
  - For viruses such as **CMV** and **BK virus**
  - **Fungal Cultures**:
  - For patients at risk of fungal sepsis
  - **Sputum and Bronchoalveolar Lavage (BAL)**:
  - For respiratory pathogens in cases of suspected pneumonia.

World Journal of Transplantation

World J Transplant. 2020 Sep 18; 10(9): 230–255.
Published online 2020 Sep 18. doi: 10.5500/wjt.v10.i9.230

Biomarker	Role in Sepsis	Utility in Kidney Transplant Patients	Limitations
Procalcitonin (PCT)	Rises quickly in bacterial infections	Helps differentiate bacterial sepsis from rejection, particularly in immunosuppressed patients	May be influenced by surgery or trauma; less reliable in viral infections
C-Reactive Protein (CRP)	General marker of inflammation	Elevated in both sepsis and rejection; useful when combined with other biomarkers (e.g., PCT or IL-6)	Non-specific; can be elevated in rejection and other inflammatory conditions
Interleukin-6 (IL-6)	Early pro-inflammatory cytokine	Rises early in sepsis; can help distinguish sepsis from rejection when used with other markers	Elevated in various inflammatory conditions, including rejection
Soluble Urokinase Plasminogen Activator Receptor (suPAR)	Associated with immune activation	High levels indicate poor outcomes in sepsis; may be useful in assessing risk of graft dysfunction	Non-specific; can be elevated in non-septic inflammation
Endotoxin	Indicates Gram-negative bacterial infection	Helps identify Gram-negative sepsis in kidney transplant recipients	Less useful in viral or fungal sepsis
Presepsin (sCD14-ST)	Released in response to bacterial infection	Promising marker for bacterial sepsis in transplant patients; may be more specific than PCT or CRP	Not widely available in all clinical settings
Neutrophil-to-Lymphocyte Ratio (NLR)	Marker of systemic inflammation	May aid in early diagnosis of sepsis; easy and inexpensive to measure	Non-specific; requires combination with other markers
Triggering Receptor Expressed on Myeloid Cells-1 (TREM-1)	Amplifies immune response to bacterial infection	Can help distinguish bacterial sepsis from rejection in transplant recipients	Limited use in viral or fungal infections; not commonly used

Lactate	Marker of tissue hypoperfusion	Useful for assessing severity of sepsis and risk of septic shock	Elevated in various conditions (shock, hypoperfusion), not specific to sepsis
HLA-DR Expression on Monocytes	Reduced expression indicates immune dysfunction	Helps identify immune paralysis in sepsis, guiding immunomodulatory therapy	Not routinely used in clinical practice
Neopterin	Indicates macrophage activation	Can help differentiate bacterial infections from rejection and viral infections	Elevated in many inflammatory conditions
Cystatin C	Marker of kidney function	Useful for assessing renal function in septic kidney transplant recipients, more reliable than creatinine	Not a direct marker of sepsis; influenced by kidney function

PROCALCITONIN

Procalcitonin (PCT) is a propeptide biomarker that is released by a host of human tissues in response to inflammatory cytokines and endotoxin

After transplant surgery, PCT levels expected to peak on the first or second day, with reduction over the next week if the course is uncomplicated Although the peak does not seem to correlate with complication, a PCT level that fails to decrease during the first postoperative week should prompt suspicion of infection

Thus, the kinetics of PCT may be more useful than a measurement at a single point in time.

PROCALCITONIN

- ATG has been associated with significantly elevated PCT levels, whereas interleukin 2 antagonists and steroids do not affect PCT levels

- Among patients who are chronically immunosuppressed, baseline PCT levels are not thought to be altered in the absence of infection

THE LANCET
Infectious Diseases

This journal Journals Publish Clinical Global health Multimedia Events About

ARTICLES · Volume 13, Issue 5, P426-435, May 2013

Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis

Christina Wacker, Cand Med [a] · Anna Prkno, Cand Med [a] · Prof Frank M Brunkhorst, MD [*,b] · Prof Peter Schlattmann, PhD [*,a]

Situation	Action
High PCT (> 2 ng/mL)	Start empiric antibiotics immediately, consider sepsis
Moderate PCT (0.5 - 2 ng/mL)	Consider infection, observe and repeat PCT; if increasing, start antibiotics
Low PCT (< 0.5 ng/mL)	Unlikely bacterial infection; consider acute rejection or non-bacterial cause
Declining PCT	Indicates response to antibiotics; consider stopping antibiotics
Rising or Persistent PCT	Investigate for resistant infections or complications (e.g., abscess)

Condition	Procalcitonin (PCT)	CRP	IL-6	Presepsin (optional)	Clinical Features
Bacterial Sepsis	Elevated (> 2 ng/mL)	Elevated	Elevated	Elevated	Fever, chills, hypotension, elevated lactate, source of infection likely
Viral/Fungal Infection	Normal or mildly elevated (< 1 ng/mL)	Elevated	Normal to mildly elevated	May be low or elevated	Subacute onset, may present without fever, viral PCR/cultures positive
Acute Rejection	Normal or mildly elevated (< 0.5-1 ng/mL)	Elevated	Elevated or normal	Normal	Rise in serum creatinine, signs of graft dysfunction, negative cultures

A NOVEL CONCEPT

Torque Teno Virus (TTV)

Immune monitoring by TTV

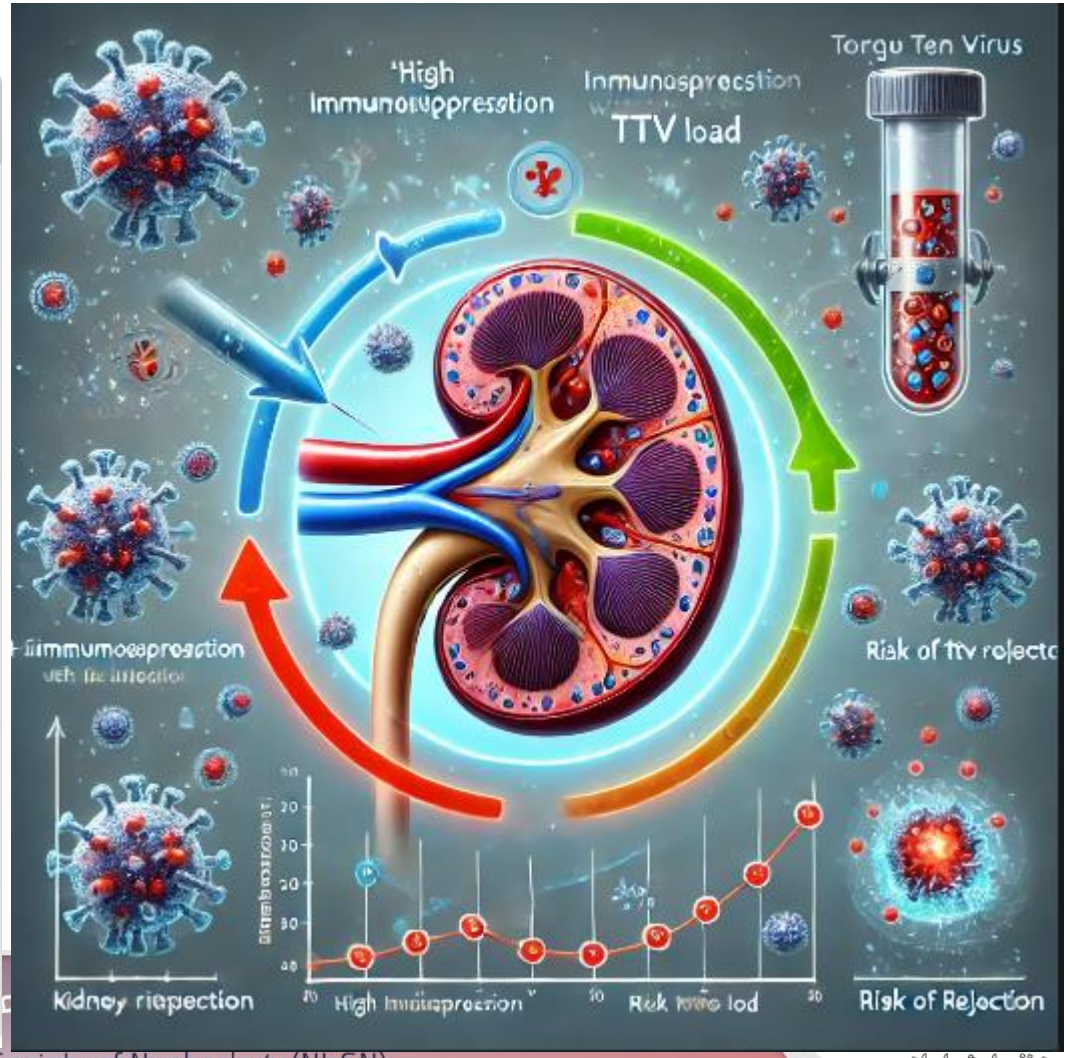
- DETECTABLE IN THE BLOOD OF ALL KIDNEY TRANSPLANT RECIPIENTS
- CAUSES NO DISEASE
- REFLECTS THE IMMUNE FUNCTION OF THE HOST
- TTV LEVEL IN THE BLOOD ASSOCIATES WITH INFECTION AND GRAFT REJECTION

Open Access Article

Torque Teno Virus: A Promising Biomarker in Kidney Transplant Recipients

Int. J. Mol. Sci. **2024**, *25*(14), 7744; https://doi.org/10.3390/ijms25147744

Step	TTV Viral Load	Action
Baseline Pre-Transplant	Measure baseline	Establish pre-transplant viral load for future comparison.
0-3 months post-transplant	Low or undetectable	Consider increasing immunosuppression, monitor for signs of rejection.
	High or increasing	Reduce immunosuppression to minimize risk of infection.
>3 months post-transplant	Steady or stable	Continue current immunosuppression regimen.
	Sudden increase	Check for infections or over-immunosuppression, consider dose reduction.
	Sudden decrease	Check for signs of rejection, consider increasing ↓ unosuppression.



Study protocol | Open access | Published: 22 March 2023

A multicentre, patient- and assessor-blinded, non-inferiority, randomised and controlled phase II trial to compare standard and torque teno virus-guided immunosuppression in kidney transplant recipients in the first year after transplantation: TTVguideIT

TTV Load (log_{10} copies/mL)	Interpretation	Clinical Action
< 4.6	Insufficient immunosuppression	Increase immunosuppressive therapy (risk of rejection)
4.6 - 6.2	Optimal immunosuppression	Maintain current regimen
> 6.2	Excessive immunosuppression	Reduce immunosuppressive therapy (risk of infection)

Immune Function Tests

- A test of leucocyte function known as the ***QuantiFERON Monitor***

- The assessment of lymphocyte function using the ***ImmuKnow***

MINI REVIEW article
Front. Nephrol., 08 November 2023
Sec. Kidney Transplantation
Volume 3 - 2023 | https://doi.org/10.3389/fneph.2023.1293907

Immune monitoring of allograft status in kidney transplant recipients

ImmuKnow (Eurofins Viracor) test

Test Purpose	Measures T-cell function by evaluating ATP production after stimulation.
Prognostic Value	Predicts **risk of infections** due to over-immunosuppression.
Limitations	Does not predict **graft rejection.**
Type of Test	Blood test, specifically measuring cellular immune response.
Clinical Use	Helps tailor immunosuppressive therapy to avoid infections in transplant patients.

Low immune response: ATP levels ≤225 ng/mL
Moderate immune response: ATP levels 226-524 ng/mL
Strong immune response: ATP levels ≥525 ng/mL

QuantiFERON Monitor (Qiagen)

Test Purpose	Measures leukocyte (white blood cell) function and immune response.
Prognostic Value	Effective for predicting **infectious events** in transplant patients.
Limitations	Not effective in predicting **graft rejection.**
Type of Test	Blood test using QuantiFERON technology.
Clinical Use	Monitors immune suppression in solid organ transplant recipients.

Measure the production of (IFNγ) released by the immune cells in response to the antigen stimulation.

Low IFNγ production: Indicates over-immunosuppression.

Normal/Moderate IFNγ production: Suggests balanced immunosuppression.

High IFNγ production: Suggests under-immunosuppression.

MANAGMENT

Managing sepsis in kidney transplant recipients is complex and requires a balance between controlling the infection, preserving the transplanted kidney function, and minimizing the risk of rejection.

The treatment of sepsis in these patients must address the unique challenges posed by immunosuppression, the potential for graft rejection, and complications related to sepsis itself.

Initial Management (First 1–6 Hours)

- **Antibiotic Therapy**:
  - **Empirical Broad-Spectrum Antibiotics**:
    - Initiate as soon as possible, ideally within the first hour after recognizing sepsis.
    - Start broad-spectrum antibiotics that cover **Gram-positive**, **Gram-negative**, and **fungal** pathogens, taking into account local resistance patterns (e.g., Pseudomonas, MRSA).
    - Common empirical regimens: piperacillin-tazobactam, cefepime, meropenem, vancomycin, or linezolid (for MRSA).
    - Modify the antibiotic regimen based on **culture results** and **susceptibility testing**.

Immunosuppression reduction in kidney transplant recipients during bacterial infection–A retrospective study

Article in Clinical Transplantation · September 2019

Variable	Low tacrolimus levels (96 patients)[a]	High tacrolimus levels (87 patients)[a]	*P*-value
Primary outcomes			
Re-hospitalization 90 d and/or death 90 d and/or clinical failure 5 d	43 (44.8%)	43 (49.4%)	.531
Graft loss	9 (9.4%)	11 (12.6%)	.479
Rejection	6 (6.3%)	5 (5.7%)	.886
Secondary outcomes			
Mortality 90 d	1 (1%)	4 (4.6%)	.193
Re-hospitalization 90 d	40 (41.7%)	42 (48.3%)	.369
Clinical failure day 5 of infection	8 (8.3%)	4 (4.7%)	.308
Length of stay (d) of infection hospitalization	2 (4.3-8)	5 (3-8.5)	.243

Immunosuppression reduction in KTRs with moderately severe bacterial infection does not offer a clinical advantage over continuation in terms of mortality, re-hospitalization, or clinical success

Management of Immunosuppressive Therapy in Kidney Transplant Recipients with Sepsis: A Multicenter Retrospective Study

Journal of Intensive Care Medicine
2024, Vol. 39(8) 758-767

DOI: 10.1177/08850666241231495
journals.sagepub.com/home/jic
Sage

Recent studies in SOT recipients with sepsis showed that dose reduction or withdrawal of IST was associated with worse outcomes.

Hospital mortality in KTRs with sepsis is associated with **non-identical HLA relationships**, **septic shock**,and **complete withdrawal of ISTs**.

Clin Infect Dis. 2021 Oct 1; 73(7): e1302–e1317.
Published online 2020 Aug 17. doi: 10.1093/cid/ciaa1189
PMCID: PMC8561260
PMID: 32803228

Immunosuppressive Agents and Infectious Risk in Transplantation: Managing the "Net State of Immunosuppression"

Immune Monitoring (QFM/ImmuKnow):

- Low IFNγ/ATP → Infection risk → Reduce immunosuppression.
- Normal IFNγ/ATP → Balanced → Continue current regimen.
- High IFNγ/ATP → Rejection risk → Increase immunosuppression.

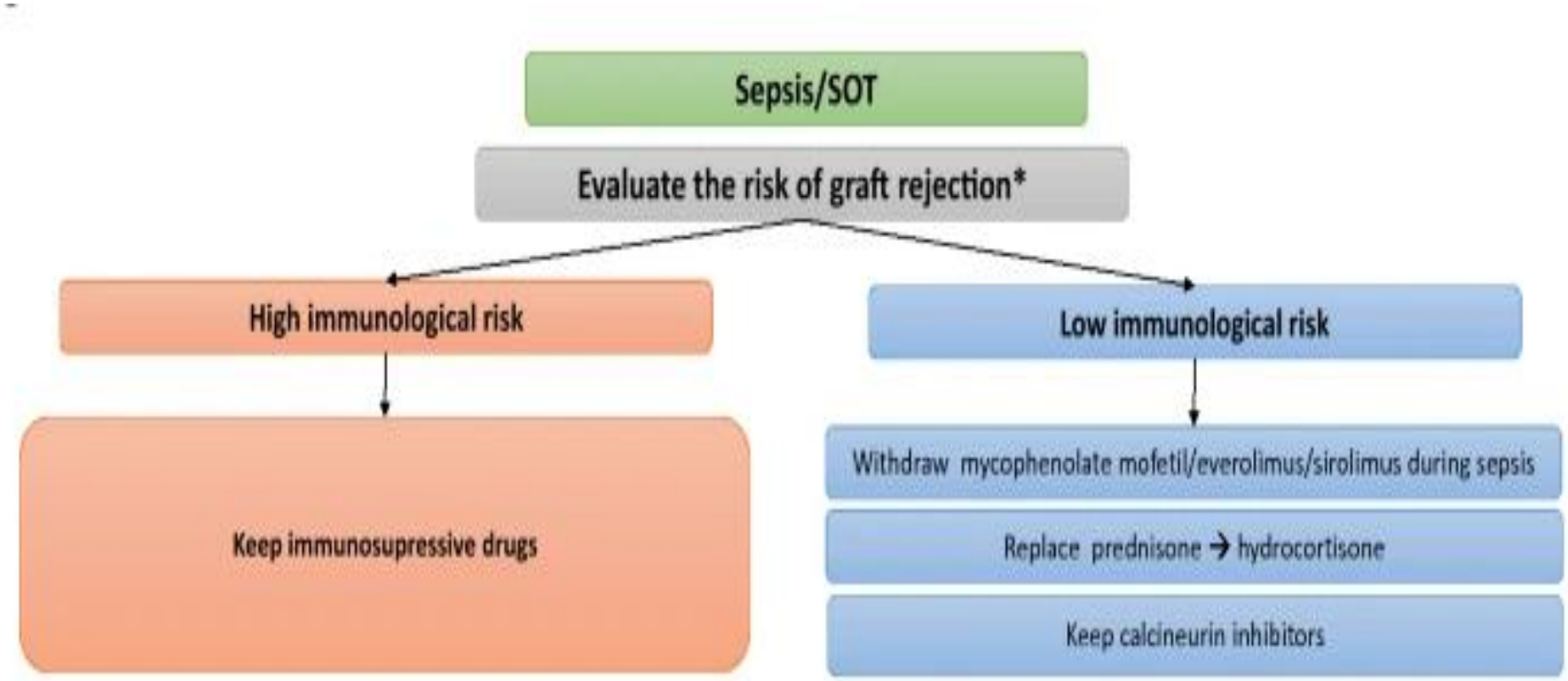
Clinical Signs and Patient History:

- History of infections → Lean towards lowering immunosuppression.
- Signs of rejection (e.g., biopsy, blood tests) → Increase immunosuppression.

Diagnostic and therapeutic approach to infectious diseases in solid organ transplant recipients

Review | Published: 25 March 2019

Volume 45, pages 573–591, (2019) Cite this article



Take-Home Message

Higher Susceptibility: Kidney transplant recipients are at a **significantly higher risk** of developing sepsis due to prolonged use of immunosuppressive medications, which weaken the immune system's ability to fight infections.

Early Detection is Critical: **Early signs of sepsis**—such as fever, rapid heart rate, or confusion—can be subtle, and delayed recognition can result in life-threatening complications, including multi-organ failure.
Prompt identification and intervention are crucial.

Infection Sources: Common sources of infection in kidney transplant patients include UTIs, surgical site infections, and respiratory infections, making it essential to monitor for these conditions closely.

Balancing Immunosuppression: Managing the net state of immunosuppression is key—over-suppression can lead to sepsis, while under-suppression may lead to graft rejection.
Regular immune monitoring tests (e.g**., QuantiFERON**, **ImmuKnow**) help in fine-tuning therapy.

Antibiotic Therapy: Empiric broad-spectrum antibiotics should be started early in suspected sepsis cases, while cultures and diagnostic tests are ongoing.

Mortality Risk: Sepsis is a leading cause of death in kidney transplant recipients, underlining the need for vigilance, preventive care, and quick escalation of care when sepsis is suspected.

Prevention: Routine vaccination, infection control measures, and monitoring for early signs of infection are essential strategies to prevent sepsis in this vulnerable population.

TAKE HOME MESSAGE

- The **net immunosuppressive state** in KTRs heightens the risk for opportunistic infections and sepsis. Close monitoring of immunosuppressive drug levels is crucial to balance infection risk and graft survival.

- Sepsis in KTRs may present with **atypical or masked symptoms** due to immunosuppression. High clinical suspicion and low thresholds for diagnostic testing (e.g., blood cultures, imaging) are key to early detection.

- Beyond infection, factors such as **chronic comorbidities** (diabetes, cardiovascular disease, obesity) and **nosocomial exposures** further elevate sepsis risk.

- Sepsis in KTRs can rapidly lead to multi-organ failure. **Early recognition and aggressive treatment** with broad-spectrum antibiotics and hemodynamic support are essential to improving outcomes.

- Emphasize infection prevention strategies, including **antimicrobial prophylaxis, vaccinations**, and patient education on recognizing early signs of infection.