https://www.sworldjournal.com/index.php/swj/article/view/swj33-02-031
DOI: 10.30888/2663-5712.2025-33-02-031

УДК: 616.61-089.843-007.285:616.94-02-053.5:615.37:612.46(048.8)

IMMUNOLOGICAL COMPLEXITY AND SEPSIS-RELATED GRAFT DYSFUNCTION IN A PEDIATRIC KIDNEY TRANSPLANT RECIPIENT: A CASE-BASED REVIEW

ІМУНОЛОГІЧНА ТА СЕПСИС-ПОВ'ЯЗАНА ДИСФУНКЦІЯ ТРАНСПЛАНТАТУ НИРКИ У ДИТИНИ: ОГЛЯД КЛІНІЧНОГО ВИПАДКУ

Vakulenko L./ Вакуленко Л.І.,
MD, SD, Prof./ д.мед. н., проф.
orcid.org/0000-0003-3823-6134
Obolonska O./ Оболонська О.Ю.
MD, PhD, Associate Professor/доц., PhD
orcid.org/0000-0001-9863-1828
Rhenita Rajkumar/ Реніта Раджкумар
MD/ MD
orcid.org/0009-0001-2017-613X
Dnipro State Medical University, , Dnipro, Vernadsky str., 9. 49044
Дніпровський державний медичний університет,
Дніпро, вул. Вернадського, 94904
Medvedska O./ Медведська О.В.
MD/ MD
orcid.org/0009-0007-2173-0503
CE «Regional Medical Center of Family Health» DRC»,
Dnipro, Kosmichna srt,13,49100,
КЗ «Регіональний медичний центр сімейного здоров'я» ДРЦ»,
Дніпро, вул. Космічна, 13 49100,

Abstract. *Pediatric kidney transplantation is a definitive therapeutic intervention for end-stage renal disease, significantly improving both survival and quality of life. However, the procedure comes with unique challenges, primarily due to a child's still-developing immune system. This immaturity often leads to ambiguous immunological responses and a heightened vulnerability to infections. According to statistics, nearly 70% of young kidney transplant recipients experience an infectious complication within the first three years post-transplant. The main challenge for doctors is to find a delicate balance between two conflicting goals: maintaining enough immunosuppression to prevent organ rejection while preserving the immune system's ability to fight off infections. This dilemma is most critical when a patient develops sepsis, an uncontrolled systemic inflammatory response that is a leading cause of death among transplant recipients.*

A unique difficulty in pediatric transplantation is the accurate interpretation of immunovirological tests, particularly for the Epstein-Barr virus (EBV) and antinuclear antibodies (ANA).The EBV status is vital because it guides the strategy to prevent post-transplant lymphoproliferative disorder (PTLD), a potentially fatal complication, especially in children who have never been exposed to the virus. However, test results can be misleading due to immune system dysfunction from the underlying end-stage renal disease. For example, a positive VCA IgG antibody result without other markers may be a false positive—a phenomenon known as pseudopositivity—caused by an over-activation of the immune system's B-cells.

The article provides an analysis of the literature on infectious and immunological features of patients with a transplanted kidney and gives an example of a 15-year-old patient with a transplanted kidney from a living donor (mother). The treatment tactics after the development of complications in

the form of sepsis associated with tonsillogenic bacterial carriage are presented. The analysis of the tactics of reducing immunosuppressive therapy and the development of complications in the form of transplant rejection is presented.

Keywords. *Pediatric renal transplantation, sepsis, immunosuppression. EBV pseudopositivity, ANA positivity.*

Introduction.

Pediatric kidney transplantation remains the definitive therapeutic intervention for end-stage renal disease (ESRD), significantly improving survival and quality of life. However, pediatric patients present unique challenges due to their evolving immune systems, frequent immunological ambiguities, and vulnerability to infections. Approximately 70% of kidney transplant recipients experience an infectious episode within the first three years. Immunovirological parameters such as Epstein–Barr virus (EBV) serology and antinuclear antibody (ANA) titers can produce ambiguous or misleading results, complicating clinical decisions and post-transplant management.

Analysis of recent research and publications. A case-based systematic review methodology was employed, combining detailed clinical data from a pediatric renal transplant recipient at Dnipro State Medical University with a comprehensive literature synthesis from PubMed and EMBASE databases (2020–2024). Relevant guidelines from KDIGO, ISOT, IPTA, WHO, and the Polish Transplant Society (PTS) were included for evidence-based recommendations. End-stage renal disease (ESRD) in children necessitates renal replacement therapy, with transplantation being the gold standard due to improved survival, growth, and neurodevelopmental outcomes compared to dialysis [1-3]. However, pediatric patients present a complex immunological milieu shaped by age-related immune maturation, underlying kidney pathology, and comorbidities, which can complicate transplant candidacy and post-transplant care.

The central challenge confronting the medical community is the pursuit of a delicate balance between two critical yet contradictory objectives: maintaining an adequate level of immunosuppression to protect the allograft from rejection and restoring immune function to effectively combat infection. This dilemma becomes most acute in cases where a patient develops sepsis—an uncontrolled systemic inflammatory response to infection that is a leading cause of intensive care unit

admissions and a significant contributor to mortality among kidney transplant recipients. In the first month after transplantation, infections associated with surgery and hospitalization, such as urinary tract infections, wound infections, and pneumonia, predominate. These are often nosocomial in origin. Up to 6 months, during the period of peak immunosuppression, opportunistic infections resulting from reactivation of latent pathogens, particularly cytomegalovirus (CMV), are the most common. After 6 months, immunosuppression usually decreases, but the patient still remains more susceptible to community-acquired infections. Significant challenge in pediatric renal transplantation is the interpretation of immunovirological parameters, particularly Epstein–Barr virus (EBV) serology and antinuclear antibody (ANA) testing. EBV infection status guides prophylactic strategies to prevent post-transplant lymphoproliferative disorder (PTLD), a potentially fatal complication, especially in EBV-naïve recipients receiving T-cell–depleting immunosuppression [4]. However, serological profiles may be confounded by ESRD-related immune dysregulation. In particular, EBV viral capsid antigen (VCA) IgG positivity in the absence of Epstein–Barr nuclear antigen (EBNA) antibodies may reflect false-positive results or pseudopositivity due to polyclonal B-cell activation [5,6].

Similarly, low-titer ANA positivity can occur in pediatric ESRD patients due to uremia-induced immune activation rather than autoimmune disease. Misinterpretation of ANA results may delay transplantation or prompt unnecessary interventions in the absence of systemic lupus erythematosus (SLE) clinical criteria [7–9].

Pre-transplant infectious screening is crucial to detect latent foci such as tonsillitis or dental infections, which can precipitate severe infections post-transplant due to immunosuppression [10-14]. Additionally, vaccination coverage against hepatitis A and B, pneumococcus, and SARS-CoV-2 is critical to reduce infectious morbidity [15–17]. The absence of clear, universal protocols for managing such patients underscores the need for a deep understanding of the pathophysiological mechanisms, an individualized diagnostic approach, and a balanced adjustment of therapy. Immunosuppressive therapy following kidney transplantation is typically administered as a "triple immunosuppression" regimen. This gold-standard approach involves a

combination of three drug classes, each targeting different stages of the immune response, providing a synergistic effect while minimizing adverse reactions [18].

Aims. To present a case of a pediatric patient undergoing living-donor renal transplantation complicated by EBV pseudopositivity, ANA positivity without systemic lupus erythematosus (SLE), and sepsis-related graft dysfunction.

Presentation of the main material. A systematic review of recent literature was conducted to contextualize clinical observations, focusing on immunosuppressive management, vaccination, and infection control strategies.

This report describes a complex pediatric kidney transplant case emphasizing the interplay of ambiguous immunological markers, incomplete vaccination, infectious complications. A systematic review contextualizes these findings and proposes practice recommendations [19-21] . Recommendations of the main guidelines are presented in the (table 1).

Table 1-Dosing of immunosuppressive drugs for sepsis [19-21]

Clinical management stage	Recommendation for calcineurin inhibitors	Recommendation for antimetabolites	Recommendation regarding glucocorticoids
Suspected sepsis	reduce dose by 25-50%	Temporarily pause	Maintain current dose or increase
Septic shock	Temporarily suspend until stabilization	Temporarily pause	Increase to stress doses
Stabilization (after sepsis)	Gradually return to initial dose, monitor levels	Gradually return to initial dose, monitor levels	Gradually reduce the dose to a maintenance dose

This case study describes a 15-year-old girl who experienced neonatal asphyxia, complicated by acute kidney injury (AKI), which likely led to a significant loss of nephrons. Until the age of 15, she had no episodes of kidney dysfunction. After a viral infection, she acutely developed oliguria and an extremely elevated creatinine level (2000 μmol/L). The child was admitted to a regional hospital. She received renal replacement therapy (hemodialysis), but kidney function did not recover. Her glomerular filtration rate progressively decreased from 15% to 5%.

Immunovirological Testing:Epstein–Barr virus (EBV) serology: Viral capsid antigen (VCA) IgG, Epstein–Barr nuclear antigen (EBNA). Antinuclear antibodies (ANA): Indirect immunofluorescence; anti-dsDNA for SLE exclusion. Hepatitis panel: Hepatitis A, B, and C. ANA Status Low-titer positive (1:80), speckled pattern; dsDNA negative. Hepatitis Panel HAV vaccinated; HBV and HCV negative.

EBV infection status is critical in transplant recipients due to the risk of PTLD, a malignancy driven by unchecked EBV replication under immunosuppression [4]. The conventional serological assessment includes antibodies against viral capsid antigen (VCA) and Epstein–Barr nuclear antigen (EBNA). Typically, VCA IgG positivity with EBNA positivity indicates past infection and immunity. However, pediatric ESRD patients frequently exhibit EBV pseudopositivity characterized by VCA IgG positivity but absent EBNA antibodies. This phenomenon arises from polyclonal B-cell activation and cross-reactivity induced by chronic immune stimulation and uremic milieu [5,9]. Without confirmatory EBV DNA PCR or p18 antigen testing, false assumptions about immunity may lead to underestimation of PTLD risk and inappropriate immunosuppression adjustments. ANA testing is a cornerstone in diagnosing autoimmune disorders such as SLE. However, ESRD, especially in pediatric patients, can induce low-titer ANA positivity unrelated to systemic autoimmunity [6–8]. Uremic toxins may cause immune dysregulation, leading to nonspecific autoantibody production. The absence of anti-dsDNA antibodies and clinical features of lupus strongly suggests a benign serological finding. This underscores the need to prioritize clinical over serological criteria when evaluating transplant eligibility [10].

A kidney transplant was performed with her mother as the donor. Initially, the postoperative course was stable. She was discharged home a month later on standard triple-drug immunosuppressive therapy (tacrolimus, corticosteroids, mycophenolate) and prophylactic treatment (valganciclovir and cotrimoxazole).

The child's history included episodes of tonsillitis at ages 5-6 y.o., but there were no exacerbations in the last 8 years. Bacterial cultures taken before the operation did not identify any pathogenic flora.

Two months later, the child developed bacterial tonsillitis caused by multidrug-resistant Klebsiella pneumoniae and Staphylococcus aureus.

The KDIGO and ISOT guidelines recommend a gradual taper of immunosuppressive drugs with the use of a corticosteroid bridge to balance infection control and graft preservation [12–14,20]. However, a gradual taper was not possible due to the development of septic shock. This was considered a recurrence of chronic tonsillitis. In response to the infection, the tacrolimus dose was reduced by 50%, but this did not improve the course of sepsis; septic shock developed. Tacrolimus and mycophenolate were temporarily discontinued. The corticosteroid dose was not changed. This helped improve the septic condition. When the blood tacrolimus level dropped to 0.4 ng/mL, which occurred on the third day after discontinuing the drug, signs of graft rejection appeared—an increase in creatinine level. Rejection was confirmed by biopsy. On the fifth day, the rejection had cytological signs of a chronic type. Tacrolimus and mycophenolate were resumed, followed by another episode of sepsis. Against the background of massive antibacterial therapy, a tonsillectomy was performed. A balance of antibacterial therapy and adjusting the tacrolimus dose to achieve a blood concentration of up to 2 ng/mL, along with a course of prednisone pulse therapy, allowed the child's condition to stabilize. The child was discharged home.

Conclusion.

Pediatric kidney transplantation requires a carefully coordinated approach balancing immunosuppression and infection control. These cases underscore the necessity of comprehensive preoperative infectious evaluation and highlight the potential impact of unrecognized infection history on clinical outcomes. Based on the analysis of this case, we believe that the reduction of the tacrolimus dose in cases of bacterial complications should be around 30%. It is mandatory to increase the dose of corticosteroids, despite the presence of sepsis. The presence of chronic foci of infection should be considered regardless of the time since the last exacerbation (if there are doubts about whether to remove the tonsils or adenoids, they should be removed). EBV serology must be interpreted with adjunctive molecular testing to avoid

misclassification. Low-titer ANA positivity in ESRD should not delay transplantation absent clinical autoimmunity. Pre-transplant infectious screening, comprehensive vaccination, and nuanced immunosuppression management during infections are paramount to improving outcomes. Sudden cessation of calcineurin inhibitors can provoke immune rejection and should be replaced by tapering strategies supported by corticosteroids.

References

1. Winterberg P. D., Garro R. Long-Term Outcomes of Kidney Transplantation in Children. Pediatric Clinics of North America. 2019. Vol. 66, № 1. P. 269–280. DOI: 10.1016/j.pcl.2018.09.008.

2.Danziger-Isakov L., Kumar D. Vaccination in solid organ transplantation. American Journal of Transplantation. 2013. Vol. 13. Suppl. 4. P. 311–317. DOI: 10.1111/ajt.12122.

3.Hariharan S. et al. Long-term Kidney Transplant Survival Across the Globe. Transplantation. 2024. Vol. 108, № 9. P. e254–e263. DOI: 10.1097/TP.0000000000004977.

4.Zhang Y. et al. Characteristics of immunological events in Epstein-Barr virus infection in children with infectious mononucleosis. Frontiers in Pediatrics. 2023. Vol. 11. Art. 1060053. DOI: 10.3389/fped.2023.1060053.

5. Martins M. E. C. C. et al. Detection of the Presence of Epstein−Barr Virus and Cytomegalovirus Using Polymerase Chain Reaction in Patients With Chronic Kidney Disease. Journal of Oral Diagnosis. 2023. Vol. 8. P. 1–7. DOI: 10.5935/2525-5711.20230220.

6.Hatton O. L. et al. The interplay between Epstein-Barr virus and B lymphocytes: implications for infection, immunity, and disease. Immunology Research. 2014. Vol. 58, № 2–3. P. 268–276. DOI: 10.1007/s12026-014-8496-1.

7. Yang X., Lin B., Shen T. Clinical features of renal damage associated with Epstein-Barr virus infection in children. Frontiers in Pediatrics. 2023. Vol. 11. Art. 1123941. DOI: 10.3389/fped.2023.1123941.

8. Roger S. D. et al. Long-term safety and efficacy of sodium zirconium cyclosilicate for hyperkalaemia in patients with mild/moderate versus severe/end-stage chronic kidney disease: comparative results from an open-label, Phase 3 study. Nephrology Dialysis Transplantation. 2021. Vol. 36, № 1. P. 137–150. DOI: 10.1093/ndt/gfz285.

9. Luderer R. et al. Real-time Epstein-Barr virus PCR for the diagnosis of primary EBV infections and EBV reactivation. Molecular Diagnosis. 2005. Vol. 9, № 4. P. 195–200. DOI: 10.1007/BF03260091.

10. Mejdoub S. et al. Antinuclear antibodies in children: clinical signification and diagnosis utility. La Tunisie medicale. 2021. Vol. 99, № 10. P. 980–984. PMID: 35288899.

11.Schachtner T., Stein M., Reinke P. Sepsis after renal transplantation: Clinical, immunological, and microbiological risk factors. Transplant Infectious Disease. 2017. Vol. 19, № 3. DOI: 10.1111/tid.12695.

12. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. American Journal of Transplantation. 2009. Vol. 9. Suppl. 3. P. S1–S155. DOI: 10.1111/j.1600-6143.2009.02834.x.

13. Indian Society of Organ Transplantation (ISOT). Pediatric transplant protocols. URL: https://notto.mohfw.gov.in/WriteReadData/Portal/News/858_1_Updated_NOTTO_ANNUAL_REPORT__08-05-24_.pdf (дата звернення: 09.09.2025).

14.Oomen L. et al. Pediatric kidney transplantation in Europe, a clinical snapshot pilot. Frontiers in Pediatrics. 2024. Vol. 12. Art. 1432027. DOI: 10.3389/fped.2024.1432027.

15.MacDonald N. et al. Global vaccine action plan lessons learned I: Recommendations for the next decade. Vaccine. 2020. Vol. 38, № 33. P. 5364–5371. DOI: 10.1016/j.vaccine.2020.05.003.

16. Moore D. L. Immunization of the immunocompromised child: Key principles. Paediatr Child Health. 2018. Vol. 23, № 3. P. 203–205. DOI:

10.1093/pch/pxx180.

17.Casotti V. et al. Vaccinations in Paediatric Solid Organ Transplant Candidates and Recipients. Vaccines (Basel). 2024. Vol. 12, № 9. Art. 952. DOI: 10.3390/vaccines12090952.

18.Park S. et al. European Society of Organ Transplantation Consensus Statement on Testing for Non-Invasive Diagnosis of Kidney Allograft Rejection. Transplantation International. 2024. Vol. 36. Art. 12115. DOI: 10.3389/ti.2023.12115.

19. Furian L. et al. European Consensus on the Management of Sensitized Kidney Transplant Recipients: A Delphi Study. Transplantation International. 2024. Vol. 37. Art. 12475. DOI: 10.3389/ti.2024.12475.

20. Bafi A. T., Tomotani D. Y., de Freitas F. G. Sepsis in Solid-Organ Transplant Patients. Shock. 2017. Vol. 47. Suppl. 1. P. 12–16. DOI: 10.1097/SHK.0000000000000700.

21. Bolaños-Meade J. et al. Three prophylaxis regimens (...) versus tacrolimus and methotrexate for prevention of graft-versus-host disease with haemopoietic cell transplantation with reduced-intensity conditioning: a randomised phase 2 trial with a non-randomised contemporaneous control group (BMT CTN 1203). Lancet Haematology. 2019. Vol.6, №3. P.e132–e143. DOI:10.1016/S2352-3026(18)30221-7.

Анотація. *Трансплантація нирки у дітей – це остаточне терапевтичне втручання при термінальній стадії ниркової недостатності, яке значно покращує як виживання, так і якість життя. Однак ця процедура пов'язана з унікальними труднощами, головним чином через те, що імунна система дитини все ще розвивається. Ця незрілість часто призводить до неоднозначних імунологічних реакцій та підвищеної вразливості до інфекцій. Згідно зі статистикою, майже 70% молодих реципієнтів трансплантата нирки переживають інфекційне ускладнення протягом перших трьох років після трансплантації. Головним завданням для лікарів є пошук делікатного балансу між двома суперечливими цілями: підтримка достатньої імуносупресії для запобігання відторгненню органу та збереження здатності імунної системи боротися з інфекціями. Ця дилема є найбільш критичною, коли у пацієнта розвивається сепсис, неконтрольована системна запальна реакція, яка є основною причиною смерті серед реципієнтів трансплантата.Унікальною складністю в дитячій трансплантації є точна інтерпретація імуновірусологічних тестів, особливо на вірус Епштейна-Барр (ВЕБ) та антинуклеарні антитіла (АНА). Статус ВЕБ є життєво важливим, оскільки він керує стратегією запобігання посттрансплантаційному лімфопроліферативному розладу (ПТЛР), потенційно фатальному ускладненню, особливо у дітей, які ніколи не стикалися з вірусом. Однак результати тестів можуть бути оманливими через дисфункцію імунної системи, спричинену термінальною стадією ниркової недостатності. Наприклад, позитивний результат на антитіла IgG до VCA без інших*

маркерів може бути хибнопозитивним — явищем, відомим як псевдопозитивність — спричиненим надмірною активацією В-клітин імунної системи. у статті наводиться аналіз літератури щодо інфекційних та іммунологічнії особливостей пацієнтів з транплантованою ниркою та наведено приклад пацієнтки 15 років з трансплантованою ниркою від живого донора (матері). Педставлена тактика лікування після розвитку ускладнень у вигляді сепсису, що по'язаний з тонзилогенним бактеріоносійством. Аналіз тактики зниження імуносупресивної терапії та розвиток ускладнень у вигляді віддторгнення трансплантату.

Ключові слова. *Дитяча трансплантація нирки, сепсис, імуносупресія. псевдопозитивність EBV, позитивність ANA.*