



Comparative Clinical Outcomes of Varicella Infection in Immunosuppressed Pediatric Patients: Hematology-Oncology vs. Other Causes

Hematoloji-Onkoloji Hastaları ile İmmünsüprese Hastalarda Su Çiçeği Enfeksiyonu Klinik Sonuçları

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Abstract

Aim: Varicella infection (chickenpox) is one of the most common infectious diseases in childhood, yet it may lead to morbidity and mortality, especially in immunosuppressed patients. This study aimed to perform a comparative evaluation of complications, duration of hospitalization, antibiotic and acyclovir use and intensive care need of patients who were immunosuppressed due to hematological/oncological diseases (Group A) or due to other causes (Group B).

Material and Method: The medical records of patients diagnosed with varicella infection at Pediatric Infectious Diseases Clinic between 2008 and 2016 were retrospectively evaluated. Patients who were immunosuppressed due to hematological/oncological diseases or due to other causes were included in the study.

Results: A total of 68 patients were enrolled to the study. Hospitalization peaked in spring and early summer. Acute lymphoblastic leukemia was the most common diagnosis in Group A, nephrological diseases in Group B. Sepsis was more frequent in Group A, while skin infections were more common in Group B. Acyclovir use was significantly higher in Group A since the treatment was started as soon as diagnosis was made in Group A but upon clinical course in Group B. There was no significant difference in the duration of hospitalization and antibiotic therapy between the two groups.

Conclusion: Varicella infection may lead to severe complications, particularly in immunosuppressed patients. We observed that sepsis was more frequent in hematology-oncology patients while skin infections in Group B, suggesting that neutrophil count or functions affected by the disease or immunosuppressant agents such as steroids may lead differences in the course and complications of varicella infection. Therefore, Group B patients should also be evaluated and treated as risky population just like hematology-oncology patients. Moreover, his study emphasizes the importance of early antiviral therapy in ensuring a favorable prognosis with reduced morbidity and mortality in varicella infection in immunosuppressed patients.

Keywords: Acyclovir, hematology, immunosuppressed, oncology, varicella

Öz

Amaç: Varisella, çocukluk çağının en sık görülen bulaşıcı hastalıklardan biri olmasına rağmen, özellikle immün sistemi baskılanmış hastalarda önemli morbidite ve mortaliteye yol açmaktadır. Bu çalışmada, hematolojik/onkolojik hastalıklar (Grup A) veya diğer nedenlerle (Grup B) immün sistemi baskılanmış hastaların komplikasyonları, hastanede kalış süreleri, antibiyotik ve asiklovir kullanımlarının ve yoğun bakım gereksinimlerinin karşılaştırmalı olarak değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Çocuk Enfeksiyon Hastalıkları Kliniği'nde 2008-2016 yılları arasında suçiçeği enfeksiyonu tanısı alan hastaların tıbbi kayıtları retrospektif olarak incelenmiştir. Hematolojik/onkolojik hastalıklar veya diğer nedenlerle immün sistemi baskılanmış hastalar bu çalışmaya dahil edilmiştir.

Bulgular: Çalışmaya toplam 68 hasta dahil edilmiştir. Hastaneye yatışlar ilkbahar ve yaz aylarının başında en yüksek seviyeye ulaşmıştır. Akut lenfoblastik lösemi, Grup A'da, nefrolojik hastalıklar ise Grup B'de en sık görülen tanı olarak saptanmıştır. Sepsis, Grup A'da daha sık görüldüğü, cilt enfeksiyonları Grup B'de daha sık görülmüştür. Sepsis ve asiklovir kullanımının Grup A'da anlamlı olarak daha sık olduğu belirlenmiştir. Çalışmaya toplam 68 hasta dahil edildi. Hastaneye yatış ilkbahar ve yaz başında zirve yaptı. Akut lenfoblastik lösemi Grup A'da, nefrolojik hastalıklar Grup B'de en sık tanıydı. Sepsis Grup A'da, cilt enfeksiyonları ise Grup B'de daha sık görülmüştür. Grup A'da tanı anında, Grup B'de ise klinik gidişe göre başlanan asiklovir tedavisi Grup A'da anlamlı olarak daha yüksek bulunmuştur. İki grup arasında hastanede kalış süresi ve antibiyotik tedavisi açısından anlamlı bir fark saptanmamıştır.

Sonuç: Suçiçeği enfeksiyonu özellikle immünsüpresif hastalarda ciddi komplikasyonlara yol açabilmektedir. Hematoloji-onkoloji hastalarında sepsisin, Grup B'de ise cilt enfeksiyonlarının daha sık görüldüğünü gözlemlenmiştir. Bu durum, hastalığın veya steroidler gibi immünsüpresif ajanların etkilediği nötrofil sayısı veya fonksiyonlarının suçiçeği enfeksiyonunun ve komplikasyonlarının seyrini değiştirebileceğini düşündürmektedir. Bu nedenle, Grup B hastaları da hematoloji-onkoloji hastaları gibi riskli grup olarak değerlendirilmeli ve tedavi edilmelidir. Ayrıca, bu çalışma, immün baskılanmış hastalarda su çiçeği enfeksiyonunda erken antiviral tedavinin daha az morbidite ve mortalite ile daha iyi bir prognoz sağlanmasında önemli olduğunu vurgulamaktadır.

Anahtar Kelimeler: Asiklovir, hematoloji, immünsüprese, onkoloji, su çiçeği



INTRODUCTION

Varicella infection (chickenpox) is a prevalent infectious disease and also one of the most common exanthematous diseases. It is often a benign infection that is usually self-limiting without treatment. However, it can potentially have severe complications such as secondary bacterial infection or neurological and respiratory complications that may require hospitalization even in healthy children. In addition, severe complications including persistent or hemorrhagic skin lesions, pneumonia, and disseminated intravascular coagulation may develop, leading to significant morbidity and mortality in immunosuppressed patients.^[1] Vaccination remains the primary step for prevention and it was included in the National Immunization Program in Türkiye in 2013. Antiviral treatment is recommended when complications are present in otherwise healthy children. The prognosis and treatment strategies for immunocompromised patients are an important issue. Previous studies have shown that early acyclovir treatment is effective in reducing infection-related morbidity and mortality by preventing complications and dissemination.^[2]

In this study, we aimed to conduct a comparative evaluation of complications, duration of hospitalization, antibiotic and acyclovir use, and the need for intensive care of patients who were immunosuppressed due to hematological / oncological diseases or due to other causes, in the Pediatric Infectious Diseases Clinic. In addition, the main objective of defining the patient groups was to determine the effect of awareness of varicella infection in hematology-oncology patients on the course of the infection to identify the approach and outcomes in patients with immunosuppression due to other reasons and to explore unrecognized risk factors for varicella infection.

MATERIAL AND METHOD

This study is a retrospective investigation of patients diagnosed with varicella infection in the Pediatric Infectious Diseases Clinic between 2008 and 2016. This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee (decision number 2017/0078). All participants included in the study or their parents provided written informed consent.

This study included patients with immunosuppression. Patients who were immunosuppressed due to hematological/ oncological diseases or other causes were enrolled in the study and children who were previously healthy or had chronic diseases not leading to immunosuppression, and neonates were excluded. The patients' data including demographics, duration of hospitalization, antibiotic therapies and intensive care requirements, were collected from medical records.

The patients were categorized in two groups. Group A consisted of immunosuppressed patients diagnosed with hematologic or oncologic diseases. Group B consisted of patients with immunosuppression due to other diseases or treatments. Group A included diseases such as hematological malignancies,

solid tumors, idiopathic thrombocytopenic purpura (ITP) requiring immunosuppressant therapy, chemotherapy and/or steroids, and hemophagocytic syndrome. Group B included patients who received long-term or intermittent high dose of oral or inhaled steroid therapy, patients with secondary immunosuppression due to chronic diseases, patients receiving immunosuppressant drug therapies such as tumor necrosis factor (TNF)-alpha antagonist, and patients with congenital or acquired (e.g. due to HIV infection, etc.) defect in their immune system. Patients' data were obtained from medical records such as current age, gender, duration of hospitalization, comorbidities, vaccination history, physical examination and laboratory test findings, use and duration of acyclovir and antibiotic therapies, need for intensive care, and complications. The complications observed among the study patients were grouped as follows: secondary bacterial skin infection, respiratory system complications, and sepsis.

The statistical analysis was carried out using the Number Cruncher Statistical System (NCSS) 2007 Statistical Software (Utah, USA).

Data analyses included descriptive statistical methods (expressed as mean and standard deviation) along with the use of independent t-test for bivariate comparison of variables with normal distribution (mean age, duration of acyclovir therapy and duration of hospitalization), and Chi-square test for comparison of qualitative data (for gender, antibiotic therapies, acyclovir use and complications). The results were evaluated at a significance level of $p < 0.05$.

RESULTS

A total of 68 patients were enrolled, with 42 assigned to Group A and 26 to Group B. The cohort included 40 males (58.82%) and 28 females (41.18%). The mean age was 6.12 ± 4 years (range: 1 month to 17 years). No significant difference in gender distribution was found between the two groups ($p=0.171$). Similarly, there was no significant difference in mean age ($p=0.070$).

The peak of hospitalization was in January (11.76%), February (13.24%), April (13.24%), May (13.24%), and July (13.24%). Groups A and B did not differ significantly in terms of age ($p=0.070$), gender ($p=0.171$), or vaccination status ($p=0.964$).

In Group A, more than half of the patients ($n=23$, 54.76%) were diagnosed with acute lymphoblastic leukaemia (ALL). Eleven (26.19%) patients had solid tumours, five (11.9%) had idiopathic thrombocytopenic purpura (ITP), one (2.38%) had acute myeloblastic leukemia (AML), one (2.38%) had Burkitt's lymphoma, and one (2.38%) had hemophagocytic syndrome.

Among those diagnosed with solid tumors, two (4.76%) patients had neuroblastoma, one (2.38%) had ependymoma, one (2.38%) had optic glioma, one (2.38%) had pons glioma, two (4.76%) had retinoblastoma, and four (9.52%) had Wilms tumor. None of the patients in Group A had undergone hematopoietic stem cell transplantation.

Acyclovir was administered to all patients in Group A, except for one patient who did not present with an obvious skin rash or systemic infectious symptom (97.62%). The mean duration of acyclovir therapy was 7.78 ± 2.67 days (range: 1–15 days). Among the 42 patients, pneumonia developed in 2 (4.76%) and sepsis in 13 (30.96%) patients, while no secondary skin lesions were observed. Antibiotics were administered to 16 (38.10%) patients. The mean duration of hospitalization was 7.98 ± 2.66 days (range: 1–17 days), and none of the patients required intensive care.

Group B included 26 patients. Thirteen (50%) were diagnosed with nephrotic syndrome, seven (26.93%) with asthma, two (7.70%) with chronic renal failure, one (3.85%) with familial Mediterranean fever, one (3.85%) with Henoch-Schönlein purpura nephritis, one (3.85%) with polymyositis, and one (3.85%) with Schwachman-Diamond syndrome. Overall, these conditions were classified as nephrological diseases in 57.7% of patients, allergic diseases in 26.93%, rheumatologic diseases in 11.55%, and congenital immunodeficiency syndromes in 3.85%.

Since the introduction of varicella vaccination into the national immunization program in Türkiye in 2013, five patients in Group A and three in Group B had been vaccinated, including one patient with congenital immunodeficiency syndrome. The difference in vaccination status between the two groups was not statistically significant.

Among the 26 patients in Group B, 19 (73.08%) received acyclovir therapy, with a mean duration of 7.32 ± 1.16 days (range: 1–15 days).

The use of acyclovir was significantly higher in Group A (97.62%) compared to Group B (73.08%) ($p=0.002$).

The complications observed in Group B included pneumonia, sepsis, and skin infections. Pneumonia developed in 4 patients (15.38%), sepsis in 2 (7.7%), and secondary skin infections in 3 (11.5%).

Sepsis was significantly more frequent in Group A ($p=0.007$), whereas skin infections were more common in Group B ($p=0.024$). Antibiotics were administered to 9 patients in Group B (34.62%), with no significant difference between the two groups ($p=0.772$).

Only one patient (3.85%) with asthma required intensive care due to sepsis secondary to a skin infection, and was discharged after full recovery. The mean duration of hospitalization for the 26 patients in Group B was 7.27 ± 3.01 days (range: 1–17 days). There was no significant difference in the duration of hospitalization between the two groups ($p=0.316$). The comparative data of both groups are presented in **Table 1**.

Table 1. Complications, acyclovir and antibiotic treatment and duration of hospitalization of in Group A and Group B patients

	Group A n:42		Group B n:26		p values
	n	%	n	%	
Pneumonia					
No	40	95.24%	22	84.62%	0.133
Yes	2	4.76%	4	15.38%	
Sepsis					
No	29	69.05%	25	96.15%	0.007
Yes	13	30.95%	1	3.85%	
Skin infection					
No	42	100.00%	23	88.46%	0.024
Yes	0	0.00%	3	11.54%	
Acyclovir treatment					
No	1	2.38%	7	26.92%	0.002
Yes	41	97.62%	19	73.08%	
Acyclovir treatment (days)	7.78 ± 2.67		7.32 ± 1.16		0.471
Antibiotic treatment					
No	26	61.90%	17	65.38%	0.772
Yes	16	38.10%	9	34.62%	
Hospitalization (days)	7.98 ± 2.66		7.27 ± 3.01		0.316

DISCUSSION

The clinical course of immunosuppressed patients hospitalized due to varicella infection was evaluated in this study. It was observed that the patients were hospitalized more frequently during January, February, April, May, and July, reflecting a seasonal pattern similar to that reported in other countries with comparable climates.^[3]

In the United Kingdom and Canada, varicella infections were shown to peak in the same months, with lower frequencies in summer, probably because schools were closed.^[4] In the VARICOMP study, conducted with 824 patients hospitalized due to varicella infection in 27 centers in Türkiye, it was reported that most cases occurred in spring and early summer, with two peaks observed in January–February and May–June. This finding indicates high-risk periods for disease transmission and is consistent with data from other countries.^[5,6]

We observed no significant difference in either gender distribution or mean age between the two groups, which is consistent with the literature.^[5–9] However, the mean age of varicella infection in the VARICOMP study was reported to be under 5 years, probably because the vaccination program had not yet started in Türkiye at the time the study was conducted.^[5] Moreover, we observed no difference in the clinical manifestations according to vaccination status between the two groups.

In Group A, the majority of patients were diagnosed with ALL, followed by solid tumors. In the VARICOMP study, only 26% of 824 patients had a history of underlying chronic disease, and the most common condition was also ALL.^[5] In studies conducted with immunosuppressed patients, particularly those with hematological/oncological diagnoses, ALL was

reported as the most frequent underlying disease, which is consistent with our findings.^[9,10] However, in the study conducted by Öcal Demir et al., solid tumors represented the most common malignancy among 33 patients.^[7]

Virus-specific cellular immunity is very important in preventing or controlling viral activation and dissemination. The reason for a more severe course of varicella-zoster virus (VZV) infections and more frequent complications in patients with primary or acquired immunodeficiency is associated with insufficient cellular immunity in these patients.^[11,12] Therefore, VZV may be more severe in patients with malignant diseases receiving immunosuppressive treatment, those with underlying chronic diseases affecting immunity, or those with immunodeficiency.^[13] Thus, it is a life-threatening infection in hematology–oncology patients due to serious complications such as pneumonia, encephalitis, hepatitis, coagulopathy, and bacterial superinfections.^[14] Feldman et al. reported that one-third of children with malignancy developed progressive disease, and that patients with lymphoproliferative disorders receiving ongoing chemotherapy had the highest risk of visceral involvement. It is also known that patients with acute leukemia have a higher risk of varicella pneumonia compared to other types of cancer.^[15] Studies have reported that VZV infection can develop at any time in 2–3% of patients who undergo stem cell transplantation or have leukemia.^[16] Early initiation of antiviral therapy has been shown to reduce mortality and morbidity, which is consistent with our findings of no fatal complications in this study.^[17]

In our study, dissemination did not occur in any of immunosuppressed patients who were treated in over eight years period in our hospital. Since the patients were follow-up due to their underlying malignancies, they were admitted to the hospital as soon as the first lesions were observed. The acyclovir therapy recorded more frequently in Group A patients, most probably because it was started at same the time of diagnosis of Varicella infection, while in Group B patients, the use of acyclovir was considered upon clinical course of the infection. Overall, acyclovir treatment was started in the early stage in almost all of the patients and continued for approximately seven days; and the early onset of the treatment is thought to contribute to the benign course of the infection without serious complication. In many studies, the duration of acyclovir treatment was similar to our study,^[5,7,9,18] and the duration of hospitalization did not vary either.^[7,9]

The complications were compared between hematology–oncology patients and immunosuppressed patients due to other causes. Sepsis was significantly more common in Group A. Neutrophil counts and functions were considered to play a role in the higher rate of sepsis observed in Group A; however, these parameters could not be evaluated in this retrospective study, which was a limitation. In contrast, secondary skin infections were more frequent in Group B. Similar to nonsteroidal anti-inflammatory drugs, which have been shown to increase the risk of serious skin and soft tissue

complications of varicella-zoster virus infection—particularly in children—systemic steroids also affect neutrophil function through different pathways, leading to a reduced immune response to opportunistic infections.^[19,20]

Complication rates vary across studies, which may be attributed to differences in vaccination status, age, underlying disease, and timing of treatment among study populations. In the VARICOMP study from Türkiye, conducted both in healthy children and in those with underlying chronic diseases, the most frequently observed complication was secondary bacterial infection.^[5] Similarly, studies from Türkiye and the United States have reported bacterial skin/soft tissue infections and neurological complications as the most common outcomes.^[6] Although secondary bacterial infection appears to be the most common complication in previously healthy children, pneumonia is also reported frequently.^[8,21] In contrast, in a study including 41 patients with malignancy, three patients developed severe respiratory complications such as acute respiratory distress syndrome (ARDS), highlighting the importance of close monitoring, particularly in immunosuppressed patients.^[18]

Although the risk of varicella infection in hematology–oncology patients is well documented, there are only a few studies investigating the clinical course of varicella infection in immunosuppressed patients due to other causes. Patients receiving steroid regimens for asthma have been shown to be at high risk for severe varicella infection.^[22] Therefore, it has been suggested that such patients should be treated with acyclovir immediately and should adhere to the two-dose varicella vaccination policy.^[23] In our study, one patient receiving steroid therapy for asthma required intensive care due to sepsis following secondary bacterial skin infection, and she had not received acyclovir before the complications developed. These data underline the importance of early acyclovir treatment in patients with chronic diseases such as asthma. It is well known that varicella infection is one of the most important causes of death in patients receiving steroid treatment.^[24,26] Not only asthma but also other chronic diseases, such as nephrotic syndrome and juvenile idiopathic arthritis requiring immunosuppressive therapy (e.g., steroids, methotrexate), are considered risk factors for the development of severe varicella complications. Therefore, acyclovir is recommended for all such patients without delay.^[27,28]

CONCLUSION

Treatment strategies are defined according to the clinical course and complications of the disease, particularly in patients with chronic illnesses. Severe complications and fatal outcomes of infectious diseases in hematology–oncology patients are frequent and familiar to both caregivers and healthcare professionals, raising awareness of the importance of early intervention. Our study evaluated the approaches of the hematology–oncology clinic and other clinics treating patients with chronic diseases leading to

immunosuppression. We observed that severe complications can also develop to a considerable extent in Group B patients, indicating that the severity of varicella infection should not be underestimated or regarded as a self-limiting illness. Therefore, it may be suggested that these patients should be considered a high-risk population for varicella infection, requiring early treatment and close monitoring.

In conclusion, varicella infection may lead to severe morbidity and mortality, particularly in immunosuppressed patients. Our study emphasizes that early acyclovir therapy prevents the dissemination of varicella infection, ensures a milder clinical course, and significantly reduces the incidence of complications not only in hematology–oncology patients but also in those with chronic diseases requiring immunosuppressive agents. Furthermore, the differences in complications between the two groups highlight the need for tailored management strategies to achieve a more favorable clinical outcome.

Abbreviations

ALL: acute lymphoblastic leukemia, **AML:** acute myeloblastic leukemia, **HIV:** human immunodeficiency virus, **ITP:** idiopathic thrombocytopenic purpura, **TNF:** tumor necrosis factor, **VZV:** Varicella-Zoster virus

ETHICAL DECLARATIONS

Ethics Committee Approval: The research protocol was approved by the Istanbul Medeniyet University Göztepe Training and Research Hospital Ethics Committee (Date: 28.02.2017, Decision No: 2017/0078).

Informed Consent: All participants included in the study or their parents provided written informed consent.

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REFERENCES

- Heininger U, Seward JF. Varicella. *Lancet*. 2006;368(9544):1365-76.
- Kara A. Varisella Zoster Virüs Enfeksiyonlarında Asiklovir Kullanımı. *Çocuk Enf Derg*. 2007;1:162-6.
- Grimpel E, Levy C, de La Rocque F, et al. Pediatricians Working Group. Paediatric varicella hospitalisations in France: a nationwide survey. *Clin Microbiol Infect*. 2007;13(5):546-9.
- Brisson M, Edmunds WJ, Law B, et al. Epidemiology of varicella zoster virus infection in Canada and the United Kingdom. *Epidemiol Infect*. 2001;127(2):305-14.
- Dinleyici EC, Kurugol Z, Turel O, et al. The epidemiology and economic impact of varicella-related hospitalizations in Türkiye from 2008 to 2010: a nationwide survey during the pre-vaccine era (VARICOMP study). *Eur J Pediatr*. 2012;171(5):817-25.
- Peterson CL, Mascola L, Chao SM, et al. Children hospitalized for varicella: a prevaccine review. *J diatr*. 1996;129(4):529-36.
- Öcal Demir S, Kepenekli Kadayıfçı E, Karaaslan A, et al. The role of acyclovir in the treatment of herpes zoster virus infections in immunocompromised children. *J Pediatr Inf*. 2015;9:142-6.
- Dilek M, Helvacı M, Aksu N. Evaluation of varicella complications. *Abant Med J*. 2015;4(4):360-5.
- Celik U, Alhan E, Aksaray N, et al. Varicella-zoster virus infection in children with malignancy. *J Pediatr Inf*. 2008;3:105-8.
- Streng A, Wiegner V, Liese JG. Varicella in pediatric oncology patients in the post-vaccine era: analysis of routine hospital data from Bavaria (Germany), 2005–2011. *Pediatr Hematol Oncol*. 2016;33(7-8):468-79.
- Whitley RJ. Varicella-zoster virus. In: Mandell GL, Bennett JE, Dolin R, editors. *Mandell, Douglas and Bennett's principles and practice of infectious diseases*. 7th ed. Philadelphia: Elsevier; 2010. p.1963-9.
- Whitley RJ. Varicella-zoster virus. In: Mandell GL, Bennet JE, Dolin R, editors. *Principles and practice of infectious diseases*. 6th ed. Philadelphia: Elsevier; 2005. p.1780-5.
- Cohen JL, Brunell PA, Straus SE, Krause PR. Recent advances in varicella-zoster virus infection. *Ann Intern Med*. 1999;130(11):922-32.
- Liese JG, Grote V, Rosenfeld E, Fischer R, Belohradsky BH, von Kries R, ESPED Varicella Study Group. The burden of varicella complications before the introduction of routine varicella vaccination in Germany. *Pediatr Infect Dis J*. 2008;27(2):119-24.
- Feldman S, Hughes WT, Daniel CB. Varicella in children with cancer: seventy-seven cases. *Pediatrics*. 1975;56(3):388-95.
- Han CS, Miller W, Hake R, et al. Varicella zoster infection after bone marrow transplantation: incidence, risk factors, and complications. *Bone Marrow Transplant*. 1994;13:277-83.
- Arvin AM. Antiviral therapy for varicella and herpes zoster. *Semin Pediatr Infect Dis*. 2002;13(1):12-21.
- Düzgöl M, Özek G, Bayram N, et al. Varicella-zoster virus infections in pediatric malignancy patients: a seven-year analysis. *Turk J Haematol*. 2016;33(4):346-8.
- Mustafa S. Steroid-induced secondary immune deficiency. *Ann Allergy Asthma Immunol*. 2023;130(6):713-7.
- Mikaeloff Y, Kézouh A, Suissa S. Nonsteroidal anti-inflammatory drug use and the risk of severe skin and soft tissue complications in patients with varicella or zoster disease. *Br J Clin Pharmacol*. 2008;65(2):203-9.
- Theodoridou M, Laina I, Hadjichristodoulou C, Syriopoulou V. Varicella-related complications and hospitalisations in a tertiary pediatric medical center before vaccine introduction. *Eur J Pediatr*. 2006;165(4):273-4.
- Umaretiya PJ, Swanson JB, Kwon HJ, Grose C, Lohse CM, Juhn YJ. Asthma and risk of breakthrough varicella infection in children. *Allergy Asthma Proc*. 2016;37(3):207-15.
- Lantner R, Rockoff JB, DeMasi J, Boran-Ragotzy R, Middleton E Jr. Fatal varicella in a corticosteroid-dependent asthmatic receiving troleandomycin. *Allergy Proc*. 1990;11(2):83-7.
- Aljebab F, Choonara I, Conroy S. Long-course oral corticosteroid toxicity in children. *Arch Dis Child*. 2016;101(9):e2.
- Dowell SF, Bresee JS. Severe varicella associated with steroid use. *Pediatrics*. 1993;92(2):223-8.
- Hill G, Chauvenet AR, Lovato J, McLean TW. Recent steroid therapy increases severity of varicella infections in children with acute lymphoblastic leukemia. *Pediatrics*. 2005;116(4):e525-9.
- Wiegner V, Schick J, Beer M, et al. Varicella-zoster virus infections in immunocompromised patients: a single-centre 6-year analysis. *BMC Pediatr*. 2011;11:31.
- Leuvenink R, Aeschlimann F, Baer W, et al. Clinical course and therapeutic approach to varicella zoster virus infection in children with rheumatic autoimmune diseases under immunosuppression. *Pediatr Rheumatol Online J*. 2016;14:34.