 10.15789/2220-7619-AAB-1765

СВЯЗЬ НИЗКОГО СТАТУСА ВИТАМИНА D С ТЯЖЕСТЬЮ ДЕТСКОЙ ПНЕВМОНИИ У ГОСПИТАЛИЗИРОВАННЫХ БОЛГАРСКИХ ПАЦИЕНТОВ

Римпова Н.[1],
Вылчева В.[2],
Цакова А.[3],
Шивачев Х.[4],
Илиев Д.[1]

[1] Университетская детская больница, Медицинский университет Софии, педиатрическое отделение, София, Болгария
[2] Институт микробиологии им. Стефана Ангелова Болгарской академии наук, София, Болгария
[3]Александровская больница, Центральная клиническая лаборатория, Софийский медицинский университет, София, Болгария
[4] Университетская больница неотложной медицины "Пирогов", София, Клиника детской хирургии, София, Болгария

AN ASSOCIATION BETWEEN LOW VITAMIN D STATUS AND CHILDHOOD PNEUMONIA SEVERITY IN HOSPITALIZED BULGARIAN PATIENTS

Rimpova N.[a],
Valcheva V.[b],
Tsakova A.[c],
Shivachev H.[d],
Iliev D.[a]

[a] University Children's Hospital, Medical University of Sofia, Department of Paediatrics, Sofia, Bulgaria

[b] The Stephan Angeloff Institute of Microbiology, Bulgarian Academy of Sciences, Sofia, Bulgaria

[c] Aleksandrovska Hospital, Central Clinical Laboratory, Medical University of Sofia, Bulgaria

[d] University Hospital for Emergency Medicine "Pirogov," Sofia, Clinic of Pediatric Surgery, Sofia, Bulgaria

Резюме: Инфекции нижних дыхательных путей являются одной из наиболее важных причин заболеваемости и детской смертности во всем мире. Несмотря на успехи в лечении и профилактике, детская пневмония является основной причиной госпитализации и остается основной причиной смерти, унеся примерно 800 000 жизней детей в 2018 году. Во всем мире более 1,23 миллиона детей умерли от пневмонии, не дожив до своего 5-летия, что эквивалентно более 3.400 смертей в день во всем мире. Появляется все больше свидетельств того, что витамин D играет важную роль в иммунной системе, модулируя как врожденный, так и адаптивный иммунитет. Витамин D является дополнительным фактором регуляции воспалительной реакции. Его действие опосредуется рецептором витамина D (VDR), который присутствует практически во всех типах иммунных клеток, включая активированные клетки CD4 + и CD8 +, B-клетки, макрофаги, нейтрофилы и дендритные клетки. Дефицит витамина D связан со снижением защиты хозяина от инфекций. Целью был анализ низкого уровня витамина D как фактора риска осложнений пневмонии, использования нескольких антибиотиков и длительного пребывания в больнице среди госпитализированных педиатрических пациентов с внебольничной пневмонией. Всего в исследование были включены 200 детей (102 здоровых контроля и 98 с тяжелой пневмонией) в возрасте от 11 дней до 17 лет. Электрохемилюминесцентный иммуноанализ использовали для измерения уровней 25-гидроксивитамина D. Средние уровни витамина D у всех обследованных детей находились в недостаточном диапазоне 51,4-68,9 нмоль / л. Контрольная группа показала более низкие значения, чем основная. группа. Больные случаи с осложненной пневмониех имели значительно более низкие уровни в диапазоне 29,7-68,0 нмоль / л по сравнению с больными без осложнений в диапазоне 49,1-88,6 нмоль / л. Была обнаружена значимая отрицательная корреляция между концентрацией витамина D и продолжительностью пребывания в больнице, количеством антибиотиков,

используемых для лечения, и уровнями маркеров воспаления в сыворотке крови. Низкий уровень витамина D связан с тяжестью заболевания, но не связан с заболеваемостью / частотой заболевания. Дети с низким уровнем витамина D могут подвергаться более высокому риску развития опасных для жизни осложнений, госпитализации с реанимацией и более выраженной воспалительной реакции.

Ключевые слова: тяжелая пневмония, сыворотка 25-гидроксивитамин D, дети, добавки витамина D, маркеры воспаления

Abstract: Lower respiratory tract infections are among the most important causes of morbidity and mortality in the pediatric population worldwide. Despite advances in treatment and prevention, childhood pneumonia is a major reason for hospital admissions and remains a leading cause of death, claiming an estimated 800,000 children's lives in 2018. Globally, over 1.23 million children died of pneumonia before reaching their 5th birthday - the equivalent of over 3.400 deaths per day worldwide. There is growing evidence that vitamin D plays an important role in the immune system by modulating both innate and adaptive immunity. Vitamin D is an additional factor in the inflammatory response regulation. Its action is mediated via the vitamin D receptor (VDR), which is present in almost all types of immune cells, including activated CD4+ and CD8+ cells, B cells, macrophages, neutrophils and dendritic cells. Vitamin D deficiency is associated with decreased host defenses against infections. Therefore, our aim was to investigate whether low vitamin D status was a risk factor for pneumonia complications, usage of multiple antibiotics and prolonged hospital stay among hospitalized pediatric patients with community-aquired pneumonia. Total of 200 children (102 healthy controls and 98 with severe pneumonia) from 11 days to 17 years old were included in the study. Cases with severe pneumonia were subdivided into groups with and without complications (36 and 62, respectively).

Electro-chemiluminescence immunoassay was used to measure the serum 25-hydroxyvitamin D levels. The control group showed lower values than the study group. Cases with complicated pneumonia had significantly lower levels 29.7-68.0 nmol/l, compared with 49.1-88.6 nmol/l in cases without complications. A significant negative correlation was found between vitamin D concentrations and duration of hospital stay, the number of antibiotics used for treatment, and serum levels of inflammatory markers. The low status of vitamin D is related to the severity of the disease, but has not been associated with the incidence/frequency of the disease. Children with low vitamin D levels may be at higher risk of developing life-threatening complications, intensive care *admissions* and a higher inflammatory response.

Keywords: severe pneumonia, serum 25-hydroxyvitamin D, children, vitamin D supplementation, inflammatory markers

Abstract: Lower respiratory tract infections are among the most important causes of morbidity and mortality in the pediatric population worldwide. Despite advances in treatment and prevention, childhood pneumonia is a major cause for hospital admissions that remains a lead cause of death, claiming an estimated 800,000 children's lives in 2018. Globally, over 1.23 million children died from pneumonia before reaching their 5th birthday - the equivalent of over 3.400 deaths per day worldwide. There is growing evidence that vitamin D plays an important role in the immune system by modulating both innate and adaptive immunity. Vitamin D is an additional factor in the inflammatory response regulation. Its action is mediated via the vitamin D receptor (VDR), which is present in almost all types of immune cells, including activated CD4+ and CD8+ cells, B cells, macrophages, neutrophils and dendritic cells. Vitamin D deficiency is associated with decreased host defenses against infections. Therefore, our aim was to investigate whether a low vitamin D status was a risk factor for pneumonia complications, usage of

multiple antibiotics and prolonged hospital stay among hospitalized pediatric patients with community-acquired pneumonia. **Total of 200 children (**102 healthy controls and 98 with severe pneumonia) **aged** 11 days to 17 years old were enrolled to the study. Cases with severe pneumonia were subdivided into groups with and without complications (36 and 62, respectively). Electro-chemiluminescence immunoassay was used to measure the serum 25-hydroxyvitamin D levels. The control group showed lower magnitude than in the study group. Cases with complicated pneumonia had significantly lower levels of vitamin D reaching 29.7-68.0 nmol/l, compared with 49.1-88.6 nmol/l in uncomplicated cases. A significant negative correlation was found between vitamin D concentrations and duration of hospital stay, the number of antibiotics used for treatment, and serum levels of inflammatory markers. The low status of vitamin D is related to the disease severity, but has not been associated with the incidence/frequency of the disease. Children with low vitamin D levels may be at higher risk of developing life-threatening complications, intensive care *admissions* and a higher inflammatory response.

Introduction

Lower respiratory tract infections are among the most important causes of morbidity and mortality in the pediatric population worldwide. Despite advances in treatment and prevention, childhood pneumonia is a major reason for hospital admissions and remains a leading cause of death, claiming an estimated 800,000 children's lives in 2018. Globally, over 1.23 million children died of pneumonia before reaching their 5th birthday - the equivalent of over 3.400 deaths per day worldwide. [1, 2]

There is growing evidence that vitamin D plays an important role in the immune system by modulating both innate and adaptive immunity. Vitamin D is an additional factor in the inflammatory response regulation [3]. Its action is mediated via the vitamin D receptor (VDR), which is present in almost all types of immune cells, including activated CD4+ and CD8+ cells, B cells, macrophages, neutrophils and dendritic cells. Vitamin D deficiency is associated with decreased host defenses against infections [4].

The relationship between vitamin D deficiency and the susceptibility to infections was investigated initially for tuberculosis patients [5]. Human alveolar macrophages stimulate the Toll-like receptors (TLR) in the presence of M. tuberculosis. TLR-activation upregulates VDR expression and vitamin D- 1-α-hydroxylase gene, thus increasing the local levels of $1,25(OH)_2D_3$ [6]. A positive correlation between vitamin D levels in respiratory epithelial cells and antimicrobial peptide mRNA production has been reported [7]. Cathelicidine and beta-defensins are important components of the innate immunity in the lower respiratory tract. They inhibit pneumococcal, meningococcal, and group A streptococcal disease-causing agents [8]. These local vitamin D effects suggest the role of its deficiency in the development of acute lower respiratory tract infections. Some studies report that low vitamin D status is a risk factor for more severe disease among hospitalized pneumonia patients [9].Recent reviews also supported

the possible role of vitamin D in decreasing the risk of COVID19 infections and mortality [10]. Adequate vitamin D concentrations can be a beneficial factor in preventing serious illness, faster recovery, and reduced hospital stays [11].

The relationship between serum vitamin D levels and the incidence and severity of pneumonia in hospitalized children has not been analyzed yet in Bulgaria. The aim of this study was to examine whether a low vitamin D status was a risk factor for complications of the disease, the use of multiple antibiotics and a long hospital stay in children with pneumonia. We hypothesized that lower levels of vitamin D contributed to a more severe clinical course of the disease.

Materials and methods

Patients characteristics

The study collection included 200 **children aged** 11 days to 17 years old from Pulmonology clinic with ICU at the University Children's Hospital, Sofia from January 2015 to January 2019. A written informed consent was signed by each participant's parent upon enrollment. Ninety-eight children (48 male and 50 female) with severe pneumonia were chosen as study (pneumonia) group. Patients who developed complications, required admission to the ICU and/or surgical treatment were grouped into "complicated pneumonia". All other patients were subgrouped to the "non-complicated-pneumonia". One hundred and two healthy children (54 male and 48 female) selected in an outpatient setting were chosen as the control group. They were compared with the study group by sex and sampling season.

Immunoassay

Serum vitamin D levels were measured using Electro-chemiluminescence immunoassay (ECLIA) for the *in-vitro* determination of 25-hydroxyvitamin D. Information for vitamin D intake prior to measurement was obtained for all the

patients. All of them underwent venous puncture and withdrawal of 2-3 ml of blood. Serum was separated and immediately frozen at -20 ˚C until measurement. For determination of the vitamin D status, the following cutoffs were set: > 75 nmol/l - sufficiency; 50 – 75 nmol/l - insufficiency; 25-50 nmol/l - deficiency and < 25 nmol/l - severe deficiency. These cutoff values were set in accordance with the data, published by the Institute of Medicine (IOM) [12].

Statistical analysis

The Spearman correlation coefficient was calculated as described previously using SPSS v.23.0 software [13]. and was used to indicate the direction of association. Testing for normality of variables was performed, using Kolmogorov-Smirnov and Shapiro-Wilk tests. The Mann-Whitney U-test and the Kruskal-Wallis test were used to evaluate quantitative data. Range values are presented in brackets.

Results

Patients characteristics

Cases with severe pneumonia were subdivided into groups with and without complications (36 and 62, respectively). Only 6 children in the complicated pneumonia subgroup were found to be vitamin D supplemented. The proportion of supplemented children in the non-complicated pneumonia subgroup was much higher - 44. Complications were mainly pulmonary with parapneumonic effusion **(Table 1).**

Table 1. Types of Complications in pneumonia subgroup

Only 19,6% (n=20) of the healthy children and 32.6% (n=32) of pneumonia patients were found to be vitamin D supplemented. Median vitamin D intake in the

healthy children group was 200 IU/day, whereas patients in both subgroups were receiving 500 IU – a significantly higher dose than controls by the time of study measurement (p=0.013).

However, the study and control groups differed in age. The average age of the pneumonia group was 4 (2-8) years and the median age of the healthy controls was 7 (4 –8) years, p=0.002. Exclusion criteria for the children in the control group were history of respiratory symptoms one month prior to enrollment as well as any accompanying chronic disease.

We evaluated the relationship between the inflammatory markers (CRP, erythrocyte sedimentation rate, white blood count) and vitamin D levels in the pneumonia group. We also evaluated the length of hospital stay and duration of antibiotic treatment and looked for correlations with vitamin D status.

Overall vitamin D status

All children, included in the study had a median vitamin D level of 52.4 (36.7 – 72.7) nmol/l, typically in the insufficient range. In the control group, half of the children had deficiency. Only 16.7% of the children had sufficient vitamin D concentrations and 33.3% had insufficiency. Surprisingly, sufficient levels were more frequent for children with pneumonia, accounting 33.8%. In the pneumonia group, 31.7% had insufficiency and 34.5% had deficiency.

In the pneumonia subgroups, the larger proportion of the non-complicated pneumonia patients had sufficiency – 40.3 %; deficiency was found in 27.4% and insufficiency was present in 32.3%. In the complicated pneumonia group 47.2% had deficiency, 30.6% had insufficiency and 22.2 had sufficiency.

No gender relationship between vitamin D levels in the pneumonia and control groups was found in this study.

Vitamin D levels

The pneumonia subgroup median 25-hydroxyvitamin D level was 61.3 (40.9-82.0) nmol/l, whereas in the control subgroup it was 49.5 (33.1 – 65.8) **(Fig. 1).** Using the Mann-Whitney's U test we found significantly lower vitamin D levels in the control group (mean ranks: 111.75 and 98.6, U = 9147.5, Z = -2.269, p = 0.007, r = 0.19).

Fig. 1. 25-hydroxyvitamin D level comparison between pneumonia and control group

Pneumonia subgroups comparison

Vitamin D levels in the non-complicated and complicated pneumonia subgroups were 63.8 (49.1-88.6) nmol/l and 50.8 (29.7-68.0) nmol/l, respectively **(Fig. 2).** Patients, who developed complications showed significantly lower levels, than patients with no complications (mean ranks 57.02 and 36.54, U = 649.5, Z= -3.43, p = 0.001, r = 0.32).

Fig. 2. 25-hydroxyvitamin D levels comparison in pneumonia subgroups

All complicated pneumonia patients were treated in an intensive care setting. Patients with surgical complications and mechanical ventilation were found to have significantly lower vitamin D concentrations in comparison to non-complicated pneumonia patients **(Table 2**).

Table 2. Comparison between vitamin D serum levels in children, receiving (yes) and not receiving (no) ICU procedures

Median vitamin D levels in all types of complications, found in the study group are shown on **Fig. 3.**

Fig. 3. Vitamin D levels (median values) related to pneumonia complications

OR for developing complicated pneumonia if 25-hydroxyvitamin D level was below 51 nmol/l was 1.925 times higher (CI 95% 1.15 – 3.20). Mortality rate due to pulmonary complications in the complicated pneumonia subgroup was 8.3%, accounting for 3 cases. Their vitamin D levels were within the deficiency and severe deficiency state - 9.0 nmol/l, 9.2 nmol/l and 35.3 nmol/l.

This study was not conducted to evaluate seasonal vitamin D variations. However, we compared vitamin D levels in different seasons for the main groups – pneumonia and control, but not for pneumonia subgroups. Statistically, there was no significant difference between vitamin D levels in pneumonia and cotrol groups across seasons (not shown). However, this might be due to the small sample sizes.

Inflammatory markers

Significant negative correlation between serum vitamin D values and levels of the inflammatory markers – CRP and erythrocyte sedimentation rate (ESR) was found. White blood count (WBC) did not correlate with vitamin D concentrations, though there was a tendency towards higher leucocyte number at lower 25-hydroxyvitamin D level **(Table 3).**

Table 3. Correlation between vitamin D concentrations and inflammatory markers in all pneumonia patients

Hospital stay and duration of antibiotic treatment

In the study group, significant negative correlation between serum vitamin D levels and lenght of hospital stay, as well as duration of intravenous antibiotic treatment was established **(Table 4).**

Table 4. Vitamin D levels and duration of hospital stay and intravenous antibiotic therapy in all pneumonia patients

Complicated pneumonia patients had significantly longer hospital stay, thus longer antibiotic therapy than non-complicated pneumonia cases.

Patients in the complicated pneumonia subgroup had significantly longer hospital stay of 12 days (8-20), compared to non-complicated pneumonia patients, who were hospitalized for 5 days (5-7.5), p=0.0001.

Median duration of antibiotic treatment in non-complicated pneumonia patients was 5 days (5-6), whereas complicated pneumonia patients were treated significantly longer – 10 days (7-15), p=0.0001.

Number of antibiotics

In the pneumonia group, 56% (n=55) received 1 intravenous antibiotic for treatment, whereas 44% (n=43) needed multiple antibiotic treatment**.**

In the non-complicated pneumonia subgroup, 76% (n=47) were treated with monotherapy, whereas 24% (n=15) received multiple antibiotic therapy. In the complicated pneumonia subgroup, 22% (n=8) were treated with monotherapy and 78% (n=28) received multiple antibiotic therapy.

Median vitamin D levels were significantly lower in children, receiving multiple intravenous antibiotic therapy at 51.6 nmol/l, compared to those requiring monotherapy at 64.0 nmol/l (p=0.004).

Frequent respiratory illness was reported for 45% (n=44) of the study group and for 21% (n=21) of the control group.

Discussion

All 200 children who participated in this study had overall deficient and insufficient vitamin D levels. This result confirms previously published data by

Holick and Palacios on the high prevalence of inadequate vitamin D status among children and adolescents worldwide [14, 15, 16]. Since subjects of this study were chosen not to have underlying conditions known to affect vitamin D production, we assume limited sun exposure and reduced dietary intake and supplementation to be the main causes of this result. It has been recognized hat using sunscreen with SPF 30 might inhibit up to 95% of vitamin D skin production [17.

It has been found that pneumonia occurs throughout the year with a peak frequency in winter, when serum vitamin D concentrations are naturally depleted. In comparison with other studies, vitamin D levels in our healthy subjects are generally low [18, 19, 20]. This might be explained with the fact, that determination of vitamin D status was based mainly on winter serum concentrations. Much of our studied controls, higher than 50%, showed deficient levels. Different studies estimated large variation of vitamin D status within different European countries. In details, Lips et al. concluded that deficiency of vitamin D levels in healthy children in Europe were present in almost as high proportion in Germany (44.5%), Greece (40.5%) and UK (56.4%), but not in Romania (29%) may be due to the low age range of the examined children (0-3y), where supplementation was wide spread and a major factor for maintaining adequate levels. [21, 22].

Supplemented children in the study group were a larger number, than supplemented controls. Thus vitamin D levels in patients were significantly higher than healthy controls'. Median vitamin D intake was 500 IU/day for the pneumonia patients vs only 200 IU/day for controls. The latter doses are lower than recommended by the IOM [12].This result highlights the importance of supplementation in elevating and maintaining adequate vitamin D status. In this study, however, supplementation proves not to be sufficient.

Since vitamin D serum levels were higher in patients, compared to controls, we assumed that vitamin D status was not a major factor for pneumonia incidence. Vitamin D status, however might be a factor for disease severity, since cases with

pneumonia complications had significantly lower vitamin D levels, than non-complicated pneumonia patients. Complicated pneumonia patients had insufficient vitamin D levels along with significantly elevated inflammatory markers, causing usage of multiple antibiotics and prolonged length of hospital stay for adequate treatment and observation.

In terms of laboratory tests, the most important for assessing the severity of pneumonia are C-reactive protein (CRP) and the parallel leukocyte count, DCC and ESR. CRP is one of the generally accepted markers in clinical practice, reflecting the magnitude of the activity of inflammatory processes and tissue damage. According to the Van den Berghe, the inflammatory markers, among which CRP, ESR and WBC levels were negatively correlated with vitamin D concentrations. In the conditions of active inflammation, vitamin depletion, as well as increase or decrease of the inflammatory response parallel processes are completely possible [23].

High dose supplementation in the course of treatment of pneumonia did not lower inflammatory markers, but reduced disease relapses. Although the degree of inflammatory response is known to vary individually due to factors unrelated to vitamin D status, we hypothesize that our results are consistent with the immunomodulatory role of vitamin D in infectious diseases. 25-hydroxyvitamin D increases the antimicrobial peptide synthesis in lungs. In addition, it induces the switch of Th1 to a more regulatory Th2 type of immune response (5). Thus, adequate 25-hydroxyvitamin D concentration could be protective against the adverse physiologic effects that occur in excessive inflammatory areas. [6, 23, 24, 25]

Our *observational study* has indicated that there is an association between low serum vitamin D levels and elevated markers of inflammation at presentation of the disease acute pneumonia but we cannot answer the question of whether decreased vitamin D levels lead to or cause increased inflammatory activity.

We also found high incidence of life-threatening complications, requiring ICU-treatments, surgical interventions and mechanical ventilation to be significantly correlated to vitamin D insufficient levels. Patients with pulmonary complications – parapneumonic effusion, hydrothorax, pneumothorax and necrotizing pneumonia had profound vitamin D deficiency, suggesting that there might be association between low vitamin D status and impairment of the local immune defense in lung parenchyma. Patients developed respiratory failure did not show lower vitamin D levels. This might be due to other factors, such as anatomical features of pediatric patients, including low chest wall compliance – important factor in the development of respiratory failure. Correlation between vitamin D deficiency and severity in hospitalized pneumonia patients was found by Sakka, Oliuvera and Inamo, showing similar results [26, 27, 28]

The chances of developing complicated pneumonia when serum levels are below 51 nmol / l are quite small in this study. However, complications were major and associated with multiple use of antibiotics, longer therapy, and prolonged hospital stay.

Pneumonia is widely recognized as a leading cause of death among the pediatric population under the age of 5, especially in developing countries. Vitamin D may be important for an adequate immune response in developing lungs, especially in in the setting of infection. Children with low levels of vitamin D were likely to have higher inflammatory markers and might be at higher risk of developing life-threatening complications. Whether vitamin D supplementation is helpful in preventing complications of pneumonia or in reducing inflammatory markers in children is a matter of further large scale studies.

We found high rates of insufficient and deficient vitamin D levels in all participants. Attention should be paid to supplementation of healthy children. Serum 25-hydroxyvitamin D concentrations were not related to pneumonia incidence. However, low vitamin D levels were associated with disease severity. Children with low levels of vitamin D might be at higher risk for developing life-

threatening complications, higher inflammatory response at presentation, ICU-admission, usage of more than one antibiotics and prolonged hospital stay.

Acknowledgements

The authors thank the Health insurance fund Doverie and Medcross outpatient care centers for providing the controls group. We are grateful to the medical personnel at the University Children's Hospital, Pediatric Surgery Clinic at the University Hospital for Emergency Medicine "Pirogov".

This work was supported by Medical University of Sofia, grant (Grant 335/15.01.2015).

FIGURES

Fig. 1. 25-hydroxyvitamin D level comparison between pneumonia and control group

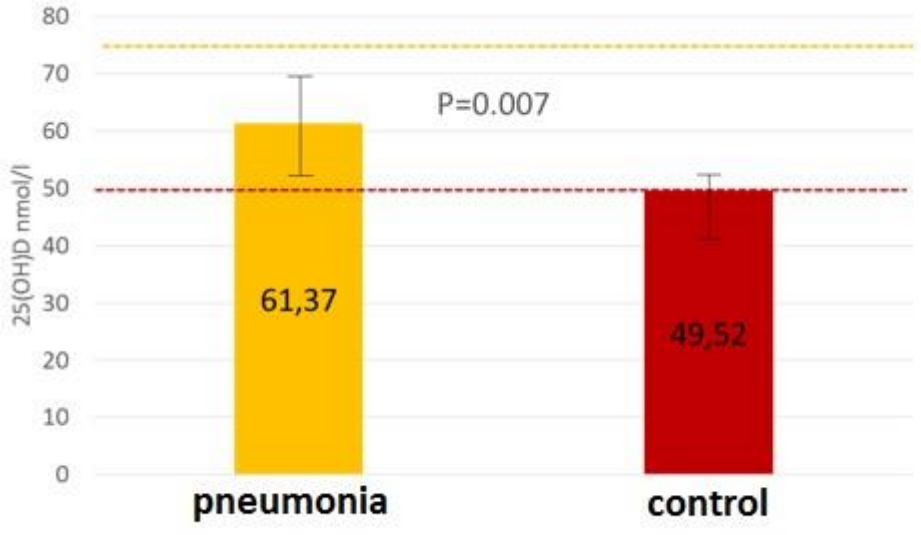
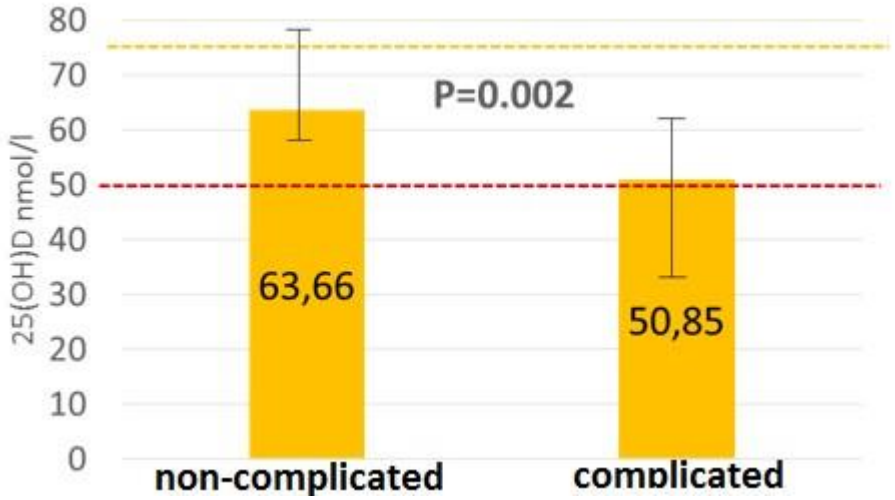
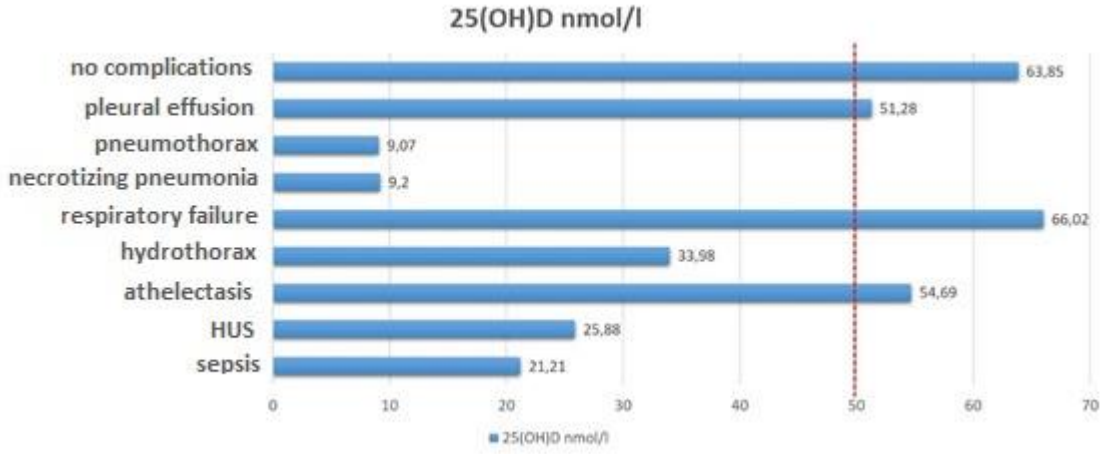


Fig. 2. 25-hydroxyvitamin D levels comparison in pneumonia subgroups



 10.15789/2220-7619-AAB-1765

Fig. 3. Vitamin D levels (median values) related to pneumonia complications



 10.15789/2220-7619-AAB-1765

TABLES

Table 1. Types of Complications in pneumonia subgroup

Complication		n of cases	%
Pulmonary	Parapneumonic effusion	24	66.7
	Respiratory failure	6	16.7
	Pneumothorax	1	2.7
	Hydrothorax	1	2.7
	Atelectasis	1	2.7
	Necrotizing pneumonia	1	2.7
Extrapulmonary	Sepsis	1	2.7
	Hemolytic uremic syndrome (HUS)	1	2.7
Total		36	100

Table 2. Comparison between vitamin D serum levels in children, receiving (yes) and not receiving (no) ICU procedures

Procedure		**n**	**Median vitamin D nmol/l**	**P**
ICU admission	Yes	36	50.85	**0.001**
	No	62	63.85	
Oxygen supplementation	Yes	21	50.90	0.066
	No	77	62.15	
Mechanical ventilation	Yes	6	21.16	**0.0002**
	No	92	62.27	
Surgery	Yes	11	48.19	**0.029**
	no	87	62.43	

 10.15789/2220-7619-AAB-1765

Table 3. Correlation between vitamin D concentrations and inflammatory markers in all pneumonia patients

value	**CRP mg/L**	**ESR mm/h**	**WBC, nx10^9/l**
median	32.1	32.0	11.2
range	0.38 – 390.0	2 - 115	0.8 – 40.5
Spearman correlation coefficient	-0.357	-0.237	-0.045
p-value	**0.001**	**0.047**	0.674

 10.15789/2220-7619-AAB-1765

Table 4. Vitamin D levels and duration of hospital stay and intravenous antibiotic therapy in all pneumonia patients

correlation Between Vitamin D Levels	**Hospital stay (days)**	**AB-treatment i.v. (days)**
median	7.00	5.50
range	5-30	0-21
Spearman Correlation Coefficient	-0.238	-0.254
p	**0.018**	**0.013**

 10.15789/2220-7619-AAB-1765

METADATA

Association of low vitamin D status with Childhood Pneumonia Severity in Hospitalized Bulgarian Patients

Rimpova N., MD, Assistant Professor, University Children's Hospital, Medical University of Sofia, Department of Paediatrics, Sofia, Bulgaria

Valcheva V., PhD, Associate Professor, Department of Infectious Microbiology, The Stephan Angeloff Institute of Microbiology, Bulgarian Academy of Sciences, 26, Acad. Georgi Bonchev str., Sofia 1113, Bulgaria

Tsakova A., Chief Assistant Professor, Aleksandrovska Hospital, Central Clinical Laboratory, Medical University of Sofia, Bulgaria

Shivachev H., PhD, Associate Professor, University Hospital for Emergency Medicine "Pirogov," Sofia, Clinic of Pediatric Surgery, Sofia, Bulgaria

Iliev D., PhD, Associate Professor, University Children's Hospital, Medical University of Sofia, Department of Paediatrics, Sofia, Bulgaria

Number of text pages: 20
Number of figures: 3
Number of tables: 4

Suggested section of the journal: *original article*

Date: 10.07.2021

 10.15789/2220-7619-AAB-1765

Связь низкого статуса витамина D с тяжестью детской пневмонии у госпитализированных болгарских пациентов

Римпова Н., научный сотрудник, Педиатрическое отделение, Университетская детская больница, Медицинский университет Софии, София, Болгария

Вылчева В., кандидат наук, доцент, отдел инфекционной микробиологии, Институт микробиологии им. Стефана Ангелова, Болгарская академия наук, 26, ул. Акад. Георги Бончев, София 1113, Болгария

Цакова А., научный сотрудник, Центральная клиническая лаборатория, Александровская больница, Софийский медицинский университет, София, Болгария

Шивачев Х., кандидат наук, доцент, Университетская больница неотложной медицины им. Пирогова и Клиника детской хирургии, София, Болгария

Илиев Д., кандидат наук, доцент, Педиатрическое отделение, Университетская детская больница, Медицинский университет Софии, София, Болгария

Количество страниц: 20
Количество рисунков: 3
Количество таблиц: 4

Раздел журнала: оригинальная статья

Дата: 10.07.2021

TITLE PAGE

Association of low vitamin D status with Childhood Pneumonia Severity in Hospitalized Bulgarian Patients

Rimpova N.[a], Valcheva V.[b] , Tsakova A.[c], Shivachev H.[d], Iliev D.[a]

[a] University Children's Hospital, Medical University of Sofia, Department of Paediatrics, Sofia, Bulgaria

[b] The Stephan Angeloff Institute of Microbiology, Bulgarian Academy of Sciences, Sofia, Bulgaria

[c] Aleksandrovska Hospital, Central Clinical Laboratory, Medical University of Sofia, Bulgaria

[d] University Hospital for Emergency Medicine "Pirogov," Sofia, Clinic of Pediatric Surgery, Sofia, Bulgaria

Short title: vitamin D and childhood pneumonia severity

Keywords: pneumonia, serum 25-hydroxyvitamin D, children, vitamin D supplementation

* **Corresponding authors:**
Violeta Valcheva, PhD
Department of Infectious Microbiology,
The Stephan Angeloff Institute of Microbiology,
Bulgarian Academy of Sciences,
26, Acad. Georgi Bonchev str., Sofia 1113, Bulgaria;
Phone:+3592 979 31 57; e-mail: violeta_valcheva@mail.bg

 10.15789/2220-7619-AAB-1765

Связь низкого статуса витамина D с тяжестью детской пневмонии у госпитализированных болгарских пациентов

Римпова Н.[1], Вылчева В.[2 *,] Цакова А.[3], Шивачев Х.[4], Илиев Д.[1]

[1]Университетская детская больница, Медицинский университет Софии, педиатрическое отделение, София, Болгария
[2]Институт микробиологии им. Стефана Ангелова Болгарской академии наук, София, Болгария
[3]Александровская больница, Центральная клиническая лаборатория, Софийский медицинский университет, София, Болгария
[4] Университетская больница неотложной медицины "Пирогов", София, Клиника детской хирургии, София, Болгария

Краткое название статьи: витамин D и тяжесть детской пневмонии

Ключевые слова: пневмония, сыворотка 25-гидроксивитамин D, дети, добавки витамина D

***Автор для переписки:**

Виолета Вылчева, кандидат биологических наук
Кафедра инфекционной микробиологии,
Институт микробиологии им. Стефана Ангелова,
Болгарская академия наук,
26, ул. Акад. Георги Бончев, София 1113, Болгария;
Телефон: +3592 979 31 57; e-mail: violeta_valcheva@mail.bg

REFERENCES

Порядковый номер ссылки	Авторы, название публикации и источника, где она опубликована, выходные данные	ФИО, название публикации и источника на английском	Полный интернет-адрес (URL) цитируемой статьи и/или doi
1.	World Health Organisation (August 2, 2019). Pneumonia and diarrhea progress report	World Health Organisation (August 2, 2019). Pneumonia and diarrhea progress report	https://www.who.int/news-room/fact-sheets/detail/pneumonia
2.	WHO-UNICEF Estimates of National Immunization Coverage (WUENIC), 1980-2019. (July, 2020) report	WHO-UNICEF Estimates of National Immunization Coverage (WUENIC), 1980-2019. (July, 2020) report	https://apps.who.int/immunization_monitoring/globalsummary/timeseries/tswucoveragedtp3.html
3.	Martens P-J, Gysemans C, Verstuyf A, Mathieu C. Vitamin D's Effect on Immune Function. *Nutrients.* 2020; vol 12 no 5, pp1248.	Martens P-J, Gysemans C, Verstuyf A, Mathieu C. Vitamin D's Effect on Immune Function. *Nutrients.* 2020; vol 12 no 5, pp1248.	doi:10.3390/nu12051248
4.	Gois PHF, Ferreira D, Olenski S, Seguro AC. Vitamin D and Infectious Diseases: Simple Bystander or Contributing Factor? Nutrients. 2017 vol 9 no 7, pp 651.	Gois PHF, Ferreira D, Olenski S, Seguro AC. Vitamin D and Infectious Diseases: Simple Bystander or Contributing Factor? Nutrients. 2017 vol 9 no 7, pp 651.	doi: 10.3390/nu9070651
5.	Nnoaham KE, Clarke A. Low serum vitamin D levels and tuberculosis: a systematic review and meta-analysis. Int J Epidemiol. 2008, vol 37 no	Nnoaham KE, Clarke A. Low serum vitamin D levels and tuberculosis: a systematic review	doi: 10.1093/ije/dym247

1, pp 13-19. and meta-analysis. Int J Epidemiol. 2008, vol 37 no 1, pp 13-19.

6. Rolf L, Muris AH, Hupperts R, Damoiseaux J. Vitamin D effects on B cell function in autoimmunity. Ann N Y Acad Sci. 2014, vol 1317, pp 84-91. Rolf L, Muris AH, Hupperts R, Damoiseaux J. Vitamin D effects on B cell function in autoimmunity. Ann N Y Acad Sci. 2014, vol 1317, pp 84-91. doi: 10.1111/nyas.12440.

7. Liu PT, Stenger S, Li H, Wenzel L, Tan BH, Krutzik SR, Ochoa MT, Schauber J, Wu K, Meinken C, Kamen DL, Wagner M, Bals R, Steinmeyer A, Zügel U, Gallo RL, Eisenberg D, Hewison M, Hollis BW, Adams JS, Bloom BR, Modlin RL. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. Science. 2006, vol. 24, pp 1770-1773. Liu PT, Stenger S, Li H, Wenzel L, Tan BH, Krutzik SR, Ochoa MT, Schauber J, Wu K, Meinken C, Kamen DL, Wagner M, Bals R, Steinmeyer A, Zügel U, Gallo RL, Eisenberg D, Hewison M, Hollis BW, Adams JS, Bloom BR, Modlin RL. Toll-like receptor triggering of a doi: 10.1126/science.1123933.

vitamin D-mediated human antimicrobial response. Science. 2006, vol. 24, pp 1770-1773.

8. De Smet K, Contreras R. Human antimicrobial peptides: defensins, cathelicidins and histatins. Biotechnol Lett. 2005, vol 27, no18, pp 1337-1347.

De Smet K, Contreras R. Human antimicrobial peptides: defensins, cathelicidins and histatins. Biotechnol Lett. 2005, vol 27, no18, pp 1337-1347. doi: 10.1007/s10529-005-0936-5.

9. Mamani M, Muceli N, Ghasemi Basir HR, Vasheghani M, Poorolajal J. Association between serum concentration of 25-hydroxyvitamin D and community-acquired pneumonia: a case-control study. Int J Gen Med. 2017, vol 10, pp 423-429.

Mamani M, Muceli N, Ghasemi Basir HR, Vasheghani M, Poorolajal J. Association between serum concentration of 25-hydroxyvitamin D and community-acquired pneumonia: a case-control study. Int J Gen Med. 2017, vol 10, pp 423-429. doi: 10.2147/IJGM.S149049.

10. Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB, Aliano JL, Bhattoa HP. Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths. Nutrients. 2020, vol 12, no 4, pp 988.

Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB, Aliano JL, Bhattoa HP. Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths. Nutrients. 2020, vol 12, no 4, pp 988.

doi: 10.3390/nu12040988.

11. Pletz MW, Terkamp C, Schumacher U, Rohde G, Schütte H, Welte T, Bals R; CAPNETZ-Study Group. Vitamin D deficiency in community-acquired pneumonia: low levels of 1,25(OH)2 D are associated with disease severity. Respir Res. 2014, vol 15, no 1, pp 53.

Pletz MW, Terkamp C, Schumacher U, Rohde G, Schütte H, Welte T, Bals R; CAPNETZ-Study Group. Vitamin D deficiency in community-acquired pneumonia: low levels of 1,25(OH)2 D are associated with

doi: 10.1186/1465-9921-15-53.

disease severity. Respir Res. 2014, vol 15, no 1, pp 53.

12. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, Durazo-Arvizu RA, Gallagher JC, Gallo RL, Jones G, Kovacs CS, Mayne ST, Rosen CJ, Shapses SA. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metab. 2011, vol 96, no 1, pp 53-58.

Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, Durazo-Arvizu RA, Gallagher JC, Gallo RL, Jones G, Kovacs CS, Mayne ST, Rosen CJ, Shapses SA. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metab. 2011, vol 96, no 1, pp 53-58. doi: 10.1210/jc.2010-2704.

13. Mukaka MM. Statistics corner: A guide to appropriate

Mukaka MM. Statistics corner: A guide to appropriate PMID: 23638278

use of correlation coefficient in medical research. Malawi Med J. 2012, vol 24, no 3, pp 69-71. | use of correlation coefficient in medical research. Malawi Med J. 2012, vol 24, no 3, pp 69-71. |

14. Holick MF. Vitamin D: extraskeletal health. Rheum Dis Clin North Am. 2012, vol 38, no 1, pp 141-160. | Holick MF. Vitamin D: extraskeletal health. Rheum Dis Clin North Am. 2012, vol 38, no 1, pp 141-160. | doi: 10.1016/j.rdc.2012.03.013.

15. Hossein-nezhad A, Holick MF. Optimize dietary intake of vitamin D: an epigenetic perspective. Curr Opin Clin Nutr Metab Care. 2012, vol 15, no 6, pp 567-579. | Hossein-nezhad A, Holick MF. Optimize dietary intake of vitamin D: an epigenetic perspective. Curr Opin Clin Nutr Metab Care. 2012, vol 15, no 6, pp 567-579. | doi: 10.1097/MCO.0b013e3283594978.

16. Palacios C, Gonzalez L. Is | Palacios C, Gonzalez L. Is vitamin D | doi: 10.1016/j.jsbmb.2013.11.003.

vitamin D deficiency a major global public health problem? J Steroid Biochem Mol Biol. 2014, vol 144, pp 38-45. | deficiency a major global public health problem? J Steroid Biochem Mol Biol. 2014, vol 144, pp 38-45. |

17. Holick MF. Vitamin D deficiency. N Engl J Med. 2007, vol 357, no 3, pp 266-281. | Holick MF. Vitamin D deficiency. N Engl J Med. 2007, vol 357, no 3, pp 266-281. | doi: 10.1056/NEJMra070553

18. Şişmanlar T, Aslan AT, Gülbahar Ö, Özkan S. The effect of vitamin D on lower respiratory tract infections in children. Turk Pediatri Ars. 2016, vol 51, no 2, pp 94-99. | Şişmanlar T, Aslan AT, Gülbahar Ö, Özkan S. The effect of vitamin D on lower respiratory tract infections in children. Turk Pediatri Ars. 2016, vol 51, no 2, pp 94-99. | doi: 10.5152/TurkPediatriArs.2016.3383.

19. Pilz S, Rutters F, Dekker JM. Disease prevention: vitamin D | Pilz S, Rutters F, Dekker JM. Disease prevention: vitamin D | doi: 10.1126/science.338.6109.883-c.

trials. Science. 2012, vol 338, no 6109, pp 883.

20. Esposito S, Lelii M. Vitamin D and respiratory tract infections in childhood. BMC Infect Dis. 2015, vol 15, pp 487.

21. Lips P, Cashman KD, Lamberg-Allardt C, Bischoff-Ferrari HA, Obermayer-Pietsch B, Bianchi ML, Stepan J, El-Hajj Fuleihan G, Bouillon R. Current vitamin D status in European and Middle East countries and strategies to prevent vitamin D deficiency: a position statement of the European Calcified Tissue Society. Eur J Endocrinol. 2019, vol 180, no 4, pp 23-54.

trials. Science. 2012, vol 338, no 6109, pp 883.

Esposito S, Lelii M. Vitamin D and respiratory tract infections in childhood. BMC Infect Dis. 2015, vol 15, pp 487.

Lips P, Cashman KD, Lamberg-Allardt C, Bischoff-Ferrari HA, Obermayer-Pietsch B, Bianchi ML, Stepan J, El-Hajj Fuleihan G, Bouillon R. Current vitamin D status in European and Middle East countries and strategies to prevent vitamin D deficiency: a position statement of the European

doi: 10.1186/s12879-015-1196-1.

doi: 10.1530/EJE-18-0736.

		Calcified Tissue Society. Eur J Endocrinol. 2019, vol 180, no 4, pp 23-54.	
22.	Ene MC., Tertiu O., Vrancianu O. , Chifiriuc M. Vitamin D status in adult and pediatric Romanian population. 2018, Roumanian Archives of Microbiology and Immunology, vol 77 no 3 pp. 198-212.	Ene MC., Tertiu O., Vrancianu O. , Chifiriuc M. Vitamin D status in adult and pediatric Romanian population. 2018, Roumanian Archives of Microbiology and Immunology, vol 77 no 3 pp. 198-212	doi: 10.1371/journal.pone.0128010
23.	Van den Berghe G, Van Roosbroeck D, Vanhove P, Wouters PJ, De Pourcq L, Bouillon R. Bone turnover in prolonged critical illness: effect of vitamin D. J Clin Endocrinol Metab. 2003, vol 88, no 10, pp 4623-4632.	Van den Berghe G, Van Roosbroeck D, Vanhove P, Wouters PJ, De Pourcq L, Bouillon R. Bone turnover in prolonged critical illness: effect of vitamin D. J Clin Endocrinol Metab. 2003, vol 88, no 10, pp 4623-4632.	doi: 10.1210/jc.2003-030358.

24. Dhungel, A., Alam, M. Efficacy of vitamin D in children with pneumonia: a randomized control trial study. Janaki Medical College Journal of Medical Science, 2016, vol 3, no 1, 5-13. doi:10.3126/jmcjms.v3i1.15369.

25. Landry, A., Docherty, P., Ouellette, S., & Cartier, L. J. Causes and outcomes of markedly elevated C-reactive protein levels. Canadian family physician Medecin de famille canadien, 2017,vol 63, no 6, e316–e323. PMCID: PMC5471098

26. Sakka ASE, Iman SS, doi:10.1016/j.epag.2013.12.001.

Sakka ASE, Iman SS, Amer HA, Moustafa SA. Vitamin D deficiency and low hemoglobin level as risk factors for severity of acute lower respiratory tract infections in Egyptian children: a case-control study. Egypt Pediatr Assoc Gaz. 2014, vol 62, pp 1–7.

Amer HA, Moustafa SA. Vitamin D deficiency and low hemoglobin level as risk factors for severity of acute lower respiratory tract infections in Egyptian children: a case-control study. Egypt Pediatr Assoc Gaz. 2014, vol 62, pp 1–7.

27. de Oliveira C, Biddulph JP, Hirani V, Schneider IJC. Vitamin D and inflammatory markers: cross-sectional analyses using data from the English Longitudinal Study of Ageing (ELSA). *J Nutr Sci*. 2017, vol 6, e1.

de Oliveira C, Biddulph JP, Hirani V, Schneider IJC. Vitamin D and inflammatory markers: cross-sectional analyses using data from the English Longitudinal Study of Ageing (ELSA). *J Nutr Sci*. 2017, vol 6, e1. doi:10.1017/jns.2016.37.

28. doi: 10.1111/j.1442-200x.2010.03224.x.

Inamo Y, Hasegawa M, Saito K, Hayashi R, Ishikawa T, Yoshino Y, Hashimoto K, Fuchigami T. Serum vitamin D concentrations and associated severity of acute lower respiratory tract infections in Japanese hospitalized children. Pediatr Int. 2011, vol 53, no 2, pp 199-201

Inamo Y, Hasegawa M, Saito K, Hayashi R, Ishikawa T, Yoshino Y, Hashimoto K, Fuchigami T. Serum vitamin D concentrations and associated severity of acute lower respiratory tract infections in Japanese hospitalized children. Pediatr Int. 2011, vol 53, no 2, pp 199-201.