Eur J Clin Microbiol Infect Dis
DOI 10.1007/s10096-011-1308-9

ARTICLE

Healthcare costs of methicillin resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa* infections in veterans: role of vitamin D deficiency

D. Youssef · B. Bailey · A. El-Abbassi · M. Vannoy · T. Manning · J. P. Moorman · A. N. Peiris

Received: 2 March 2011 / Accepted: 23 May 2011

Abstract Methicillin resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa* (*P. aeruginosa*) infections are frequently associated with hospitalization and increased healthcare costs. Vitamin D deficiency may contribute to increased costs for patients with these infections and there is evidence that vitamin D may have an antimicrobial role. To evaluate the role of vitamin D deficiency in the costs incurred with these infections, we studied the relationship of serum 25(OH)D levels to healthcare costs in veterans in the southeastern United States. Patients with both infections were vitamin D deficient to a similar extent and so were combined for further analysis. Vitamin D deficient patients had higher costs and service utilization than those who were not vitamin D deficient. Those with vitamin D deficiency had higher inpatient costs compared to the non-deficient group, and this difference was across most categories except for the number of inpatient hospitalizations or total number of days as an inpatient. Vitamin D deficiency was not significantly related to outpatient cost or service utilization parameters. We conclude that vitamin D deficiency is intimately linked to adverse healthcare costs in veterans with MRSA and *P. aeruginosa* infections. Vitamin D status should be assayed in patients with these infections.

D. Youssef · J. P. Moorman
Department of Internal Medicine, Division of Infectious Diseases,
East Tennessee State University,
Johnson City, TN, USA

D. Youssef
e-mail: estecina@hotmail.com

B. Bailey
Department of Family Medicine, East Tennessee State University,
Johnson City, TN, USA

A. El-Abbassi
Department of Internal Medicine,
Division of Pulmonary/Critical Care,
East Tennessee State University,
Johnson City, TN, USA

M. Vannoy · T. Manning · J. P. Moorman · A. N. Peiris (✉)
Medicine Service 111, Mountain Home VAMC,
Mountain Home 37684 TN, USA
e-mail: Alan.peiris@va.gov

A. N. Peiris
Department of Internal Medicine, Division of Endocrinology,
East Tennessee State University,
Johnson City, TN, USA

Introduction

Vitamin D deficiency has reached pandemic proportions [1] and is linked to increased health expenditures [2]. Vitamin D has potential benefits on innate immunity [3] and it appears to potentiate antimicrobial actions through a variety of mechanisms, including expression of potent antimicrobial peptides, such as beta defensin 2 and cathelicidin [4, 5]. Moreover, the antimicrobial actions of vitamin D cover a wide range of organisms, such as bacteria (including *Mycobacterium tuberculosis*) [6], viruses [7], and fungi [8]. Vitamin D deficiency is also associated with an increased risk of MRSA nasal carriage [9].

Methicillin resistant *Staphylococcus aureus* (MRSA) is endemic in many hospitals, with prevalence rates approaching 30% of all *Staphylococcus aureus* (*S. aureus*) infections [10]. Eradication has been difficult, with inappropriate antibiotic use contributing to its prevalence [11]. In New York City, the attributable infection cost of a patient with MRSA was approximately $2,500 higher than the attributable cost of a patient with methicillin sensitive *Staphylococcus aureus*

Published online: 22 June 2011

(MSSA) [12]. The higher cost of MRSA infections versus MSSA infections appears to be due to the higher cost of vancomycin, longer hospital stay, cost of patient isolation procedures, enteral feeding and intensive care [12, 13]. Increased mortality associated with MRSA infection has been documented globally across all age groups [14]. The costs associated with MRSA in Canadian hospitals have been estimated to be $42 to $59 million annually [15].

Similarly, *P. aeruginosa* is also associated with higher mortality, morbidity and cost of care, and could be community or nosocomially acquired [16]. Pseudomonas septicemia is a significant contributor to mortality in patients with burns [17]. *P. aeruginosa* is among the most common contributors to intravenous catheter sepsis [18] and a significant contributor to urinary tract infections [19]. Cystic fibrosis patients are susceptible to this pathogen [20], which also contributes frequently to ventilator-associated pneumonia [21]. Patients involved in an outbreak of *P. aeruginosa* in an intensive care unit had 66% higher adjusted hospital costs than non-affected patients, and had 70 days excess length of ICU stay [22]. Multidrug resistance complicates effective treatment of *P. aeruginosa* and contributes to increased mortality and costs [23–25]. In one prospective study, bloodstream infections due to *P. aeruginosa* had a greater risk of hospital mortality compared to bloodstream infections due to *S. aureus* despite adequate antibiotic treatment [26]. In the 2001 SENTRY Surveillance Program report, *P. aeruginosa* was the second most common pathogen isolated from ICU patients, trailing only *S. aureus* [27].

Given the economic burden of the infections related to *S. aureus*, and *P. Aeruginosa*, and the emerging evidence of the antimicrobial role of vitamin D, the present study was conducted to determine if vitamin D status is related to increased healthcare costs associated with infections with these two organisms.

Methods

This study was conducted at James H. Quillen Veterans Medical Facility in the southeastern United States. The Research and Development Committee at the Veterans Affairs Medical Center (VAMC) and the Institutional Review Board at the affiliated university approved the study. Data were obtained electronically through retrospective review after personal information was removed. The sample included all patients within the veterans integrated service network-9 (VISN 9) diagnosed with either methicillin resistant *Staphylococcus aureus* (MRSA) or *P. aeruginosa* infections from 2000 to 2008, and that also had serum 25-hydroxyvitamin D [25(OH)D] analysis run within 3 months of the initial diagnosis. VISN-9 comprises six VA hospitals in the southeast, including sites in Huntington, WV, Lexington, KY, Louisville, KY, Memphis, TN, Mountain Home, TN and Tennessee Valley, TN. The 25(OH)D assay was peformed by immunochemiluminometric assay (Labcorp, USA).

Patient healthcare costs incurred within one year of diagnosis were estimated. They were estimated by the technical guidelines via the Decision Support System and clinical National Data Extracts standardized by the VA [28]. Costs in the year following diagnosis were broken down into separate inpatient and outpatient categories (i.e. laboratory, pharmacy, radiology, surgery, primary care, emergency room, etc.). For each of the cost categories, a total amount (US$) was analyzed. Fees refer to costs incurred by the VA as a result of consultation and/or procedures performed in the private sector utilizing diagnosis and procedure codes specified in the International Classification of Diseases, Ninth Revision, and Clinical Modification (ICD-9) [29]. Additionally, the total number of inpatient stays, and the number of days of each inpatient stay, represented service utilization and were also recorded for each patient. The database was queried for patients with a discharge diagnosis code of 008.42 reflecting *Pseudomonas enteritis*, 038.43 for *Pseudomonas septicemia*, 041.7 for Pseudomonas infections, and 482.1 for *Pseudomonal pneumonia*; patients with MRSA infections were identified using the ICD-9 code of 038.12 for MRSA septicemia, and 041.12 for other MRSA infections.

Statistical analysis

The 25(OH)D level was analyzed as a dichotomous variable, with vitamin D deficiency defined as 25(OH)D <20 ng/ml [1]. Statistical analyses were performed using SPSS software, version 14.0 (SPSS Inc., USA). All variables were checked for outliers and normality of distribution before analyses were performed. Correlations and χ^2 analysis were used to examine associations between type of infection and 25(OH)D level and deficiency status. Student *t*-tests were used to examine associations between vitamin D status and cost and service utilization.

Results

The final sample contained 58 patients, and as described above, included all patients diagnosed with either MRSA or Pseudomonas infections that had a 25(OH) D within 3 months of the diagnosis, and had at least one year of cost data available. There were 510 MRSA patients and 2,482 *Pseudomonas* patients without a 25(OH) D level checked within 3 months of diagnosis. Of the 58 patients that had a 25(OH)D level, 14 were diagnosed with MRSA and 44 with *Pseudomonas*. Of the total sample, 31 were vitamin D deficient (25(OH)D<20 ng/ml).

Sample background characteristics, in total and by vitamin D status, are presented in Table 1. As can be seen, there were no demographic differences by vitamin D status. In addition, vitamin D status was not significantly different between the MRSA (57.1% deficient) and the *Pseudomonas* (52.3%) groups ($p>0.05$). Since the two diagnosis groups did not differ significantly in vitamin D levels, all analyses were run for the combined group of 58 patients.

As shown in Table 2, the vitamin D deficient group as a whole (i.e. regardless of diagnosis) had higher costs and service utilization. Those that were vitamin D deficient had significantly higher inpatient costs across most categories, despite the fact that those with vitamin D deficiency did not have significantly more inpatient stays or total number of inpatient days (there was a non-significant trend for total number of days). Interestingly, vitamin D deficiency status was not significantly associated with any of the outpatient costs or service utilization variables. In fact, the trend was for those who were deficient to have lower costs and to have fewer visits compared with those who were not deficient.

Discussion

Veterans with vitamin D deficiency and either *P. aeruginosa* or MRSA infections have increased healthcare utilization and expenses. The expenses associated with these infections were significantly higher in hospitalized patients. This report is, to the best of our knowledge, the first to indicate that vitamin D deficiency may be an important and under-recognized contributor to increased hospitalization costs incurred among patients with these two costly infections. Given the increased morbidity and mortality of these infections and the presence of significant vitamin D deficiency among many veterans [2], vitamin D may have a potential role in assisting standard antimicrobial therapies.

Increasing evidence indicates that vitamin D may have an important antimicrobial role. For example, rickets was found to be a significant predictor of reduced success in the treatment of very severe pneumonia, as seen in a prospective cohort study conducted in Yemen [30]. In this Yemeni study, vitamin D deficiency also predicted reduced neutrophil counts and 5-day hypoxemia. In one double-blind, randomized, placebo-controlled study in inner city children in Kabul, a single high dose treatment (100,000 IU) of vitamin D3 along with antibiotic treatment reduced repeated pneumonia episodes by approximately 22% [31]. This is possibly secondary to the fact that vitamin D3 proved inhibitory to *S. aureus*, *Streptococcus pyogenes*, *Klebsiella pneumoniae*, *Escherichia coli*, and other bacteria in vitro studies [32]. Similarly, in an experimental model of turkey osteomyelitis, vitamin D treatment resulted in reduced bacterial presence in tissue and improved mortality [33]. In addition, vitamin D may reduce the risk of caries and periodontal disease by anti-bacterial action against *Streptococcus mutans* [34].

The antimicrobial effects of vitamin D are not confined solely to bacterial infections. There is evidence that vitamin D may have a protective role in influenza [7] and other viral diseases, such as AIDS in HIV [35], hepatitis infection [36, 37], Avian flu [38] and other viruses. Recent discoveries indicate the importance of vitamin D-dependent generation of antimicrobial peptides in human host defense against *Mycobacterium tuberculosis* [6]. Low vitamin D levels were associated with a 5-fold increased risk for progression to tuberculosis [39]. Vitamin D may also play a role in the control of fungal infections such as candidiasis [40], chromoblastomycosis [8] and histoplasmosis [41]. In addition, studies on parasitic infections revealed that enriched vitamin D supplements hinder growth of *P. falciparum* [42], decrease the rate of reinfection with *Schistosoma mansoni* [43], and exert a toxic effect on *Hymenolepis microstoma* [44].

The antimicrobial effects of vitamin D may work through a multitude of complex mechanisms which are becoming better delineated. The vitamin D receptor is ubiquitous, including a presence on B and T lymphocytes, monocytes and dendritic cells [45]. Circulating vitamin D levels have a direct influence on macrophages, increasing their oxidative burst potential [7]. It also facilitates neutrophil motility and phagocytic function [46]. Vitamin D stimulates the expression of potent antimicrobial peptides, such as beta defensin and cathelicidin [4], which exist in neutrophils, natural killer cells, and in epithelial cells lining the respiratory tract [5]. Schauber et al. revealed that vitamin D3 induced cathelicidin expression in keratinocytes and monocytes, and enhanced antimicrobial activity against *S. aureus* [47]. Human cathelicidin has antimicrobial as well as anti-endotoxin activity [48]. The potential boost in innate immunity by vitamin D may also help recovery from acute illness such as the case of patients in intensive care units

Table 1 Sample characteristics by vitamin D status

None of the differences between the groups were statistically significant

Characteristic	Full sample	Vitamin D deficient	Vitamin D non-deficient
Age (mean; range)	70.0 (40–107)	69.8 (48–107)	70.2 (40–92)
Gender (% male)	96.6%	100%	92.6%
Race (% Caucasian)	79.3%	74.2%	85.2%
State of residence (% TN)	46.6%	51.6%	40.7%

Table 2 Associations between vitamin D status and cost/service parameters in veterans (N=58) with MRSA or Pseudomonas infections

Cost/care parameter	Vitamin D level <20 ng/ml	Vitamin D level >20 ng/ml	p
Out patient			
Primary care costs	$296	$321	0.41
Pharmacy costs	$1,617	$2,126	0.28
Laboratory costs	$578	$772	0.24
Radiology costs	$626	$551	0.38
Surgery costs	$173	$383	0.19
Emergency room costs	$87	$172	0.25
Total outpatient costs	$12,665	$15,869	0.23
Total number of clinic visits	29.6	37.5	0.18
Inpatient			
Pharmacy costs	$3,384	$1,337	0.05
Laboratory costs	$1,870	$553	0.03
Radiology costs	$1,756	$626	0.06
Surgery costs	$1,750	$374	0.05
Total inpatient costs	$39,640	$15,205	0.04
Total number of stays	1.3	1.3	0.95
Total number of inpatient days	18.5	10.2	0.14

[49]. In patients with cystic fibrosis, an inverse relationship between vitamin D and serum immunoglobulin G has been reported [50]. Vitamin D also reduces both local and systemic inflammatory responses as a result of modulating cytokine responses and reducing toll-like receptor activation [4]. Clinical evidence from ICU studies indicates that lower vitamin D levels may be associated with an approximate doubling of length of stay and mortality in intensive care units [51].

The current study does have certain inherent limitations. Given the retrospective nature of our investigation, not all factors which could have influenced outcomes could be controlled. Our sample size is small and we believe this reflects inadequate testing in veteran populations, as has been noted previously [52]. Only about 1% of patients with MRSA and *Pseudomonas aeruginosa* had 25(OH)D levels done. We could not assess the extent to which vitamin D was replaced; however, we do not believe this would have significant impact on our study since prior studies were consistent with inadequate monitoring and replacement of vitamin D in veterans [52, 53].

It is also possible that because the patients with the infections of interest were acutely ill, this in itself could have resulted in lower vitamin D levels. We do not believe this likely, however, since the levels of 25(OH)D observed in this study are comparable to 25(OH)D values previously reported in many different populations [54–56]. More importantly, acute infections such as falciparum malaria infection do not appear to lower vitamin D levels [57].

Underlying conditions could be responsible for the findings, and a selection bias could be present in that testing was done in sicker patients or patients more likely to be vitamin D deficient. However, the sample size was too small to statistically control for underlying conditions. It is also possible that underlying illness rather than vitamin D deficiency could have contributed to costs. However, preadmission vitamin D levels were linked to adverse outcomes [58], and potentially increased costs. Data for BMI, age and comorbidities were available, and while they may confound the findings, the sample size was just too small to control for them statistically. Future studies should include larger study groups and factors that could account for vitamin D deficiency including co-morbid conditions, seasonality, race and obesity. Large study populations may enable a greater in-depth look at specific infections; we were unable to do this on account of our sample size.

In conclusion, we believe that achieving a vitamin D replete state should be given high priority when treating *P. aeruginosa* and MRSA infections. The present study confirms and extends similar findings found in veterans with *Clostridium difficile* and Methicillin sensitive *staphylococcus aureus* (MSSA) infections. This suggests that vitamin D deficiency may be a significant factor in increasing costs not only in MSSA and *Clostridium difficile*, but also in MRSA and Pseudomonas infections, and possibly other bacterial infections [59]. Inappropriate antibiotic therapy along with overzealous antibiotic use enhances the development of such pathogens as MRSA, with concomitant increases in mortality, length of stay and hospital costs [60–62]. Higher doses of vitamin D than currently recommended may be needed to achieve and maintain 25(OH)D levels in the therapeutic range [55] and

have the benefit of negligible costs compared to many antibiotics. An exciting area for further exploration is the potential for brief, very high dose therapy in acute infectious illness. In any event, these potential antimicrobial benefits may be added to the long list of health benefits associated with adequate vitamin D reserves, including improved well-being and enhanced longevity [63], with a projected significant savings in global healthcare costs [64]. Our findings in this current study should provide an impetus to initiate additional prospective controlled studies to evaluate the important antibacterial benefits of vitamin D supplementation.

Acknowledgements We thank the Mountain Home VAMC library staff and staff at affiliated VA libraries for their excellent assistance. This material is the result of work supported with resources and the use of facilities at the Mountain Home VAMC. The contents of this paper do not reflect the position of the US Government and the Department of Veterans Affairs.

Conflict of interest None to declare.

References

1. Holick MF (2008) The vitamin D deficiency pandemic and consequences for nonskeletal health: mechanisms of action. Mol Aspects Med 29:361–368
2. Peiris AN, Bailey BA, Manning T (2008) The relationship of vitamin D deficiency to health care costs in veterans. Mil Med 173:1214–1218
3. Kamen DL, Tangpricha V (2010) Vitamin D and molecular actions on the immune system: modulation of innate and autoimmunity. J Mol Med 88:441–450
4. Jeng L, Yamshchikov AV, Judd SE, Blumberg HM, Martin GS, Ziegler TR, Tangpricha V (2009) Alterations in vitamin D status and anti-microbial peptide levels in patients in the intensive care unit with sepsis. J Transl Med 7:28
5. Ginde AA, Mansbach JM, Camargo CA Jr (2009) Association between serum 25-hydroxyvitamin D level and upper respiratory tract infection in the Third National Health and Nutrition Examination Survey. Arch Intern Med 169:384–390
6. Shapira Y, Agmon-Levin N, Shoenfeld Y (2010) Mycobacterium tuberculosis, autoimmunity, and vitamin D. Clin Rev Allergy Immunol 38:169–177
7. Cannell JJ, Vieth R, Umhau JC, Holick MF, Grant WB, Madronich S, Garland CF, Giovannucci E (2006) Epidemic influenza and vitamin D. Epidemiol Infect 134:1129–1140
8. Bonilla E (1954) Treatment of chromoblastomycosis with calciferol; report of three cases. AMA Arch Derm Syphilol 70:666–667
9. Matheson EM, Mainous AG III, Hueston WJ, Diaz VA, Everett CJ (2010) Vitamin D and methicillin-resistant *Staphylococcus aureus* nasal carriage. Scand J Infect Dis 42:455–460
10. Panlilio AL, Culver DH, Gaynes RP, Banerjee S, Henderson TS, Tolson JS, Martone WJ (1992) Methicillin-resistant *Staphylococcus aureus* in U.S. hospitals, 1975–1991. Infect Control Hosp Epidemiol 13:582–586
11. Shorr AF, Micek ST, Kollef MH (2008) Inappropriate therapy for methicillin-resistant *Staphylococcus aureus*: resource utilization and cost implications. Crit Care Med 36:2335–2340
12. Rubin RJ, Harrington CA, Poon A, Dietrich K, Greene JA, Moiduddin A (1999) The economic impact of *Staphylococcus aureus* infection in New York City hospitals. Emerg Infect Dis 5:9–17
13. Graffunder EM, Venezia RA (2002) Risk factors associated with nosocomial methicillin-resistant *Staphylococcus aureus* (MRSA) infection including previous use of antimicrobials. J Antimicrob Chemother 49:999–1005
14. Madani TA (2002) Epidemiology and clinical features of methicillin-resistant *Staphylococcus aureus* in the University Hospital, Jeddah, Saudi Arabia. Can J Infect Dis 13:245–250
15. Kim T, Oh PI, Simor AE (2001) The economic impact of methicillin-resistant *Staphylococcus aureus* in Canadian hospitals. Infect Control Hosp Epidemiol 22:99–104
16. Micek ST, Lloyd AE, Ritchie DJ, Reichley RM, Fraser VJ, Kollef MH (2005) *Pseudomonas aeruginosa* bloodstream infection: importance of appropriate initial antimicrobial treatment. Antimicrob Agents Chemother 49:1306–1311
17. Armour AD, Shankowsky HA, Swanson T, Lee J, Tredget EE (2007) The impact of nosocomially-acquired resistant *Pseudomonas aeruginosa* infection in a burn unit. J Trauma 63:164–171
18. Arnow PM, Quimosing EM, Beach M (1993) Consequences of intravascular catheter sepsis. Clin Infect Dis 16:778–784
19. Talbot GH, Bradley J, Edwards JE Jr, Gilbert D, Scheld M, Bartlett JG (2006) Bad bugs need drugs: an update on the development pipeline from the Antimicrobial Availability Task Force of the Infectious Diseases Society of America. Clin Infect Dis 42:657–668
20. Braccini G, Festini F, Boni V, Neri AS, Galici V, Campana S, Zavataro L, Trevisan F, Braggion C, Taccetti G (2009) The costs of treatment of early and chronic *Pseudomonas aeruginosa* infection in cystic fibrosis patients. J Chemother 21:188–192
21. Eagye KJ, Nicolau DP, Kuti JL (2009) Impact of superinfection on hospital length of stay and costs in patients with ventilator-associated pneumonia. Semin Respir Crit Care Med 30:116–123
22. Bou R, Lorente L, Aguilar A, Perpiñán J, Ramos P, Peris M, Gonzalez D (2009) Hospital economic impact of an outbreak of *Pseudomonas aeruginosa* infections. J Hosp Infect 71:138–142
23. Tacconelli E, Tumbarello M, Bertagnolio S, Citton R, Spanu T, Fadda G, Cauda R (2002) Multidrug-resistant *Pseudomonas aeruginosa* bloodstream infections: analysis of trends in prevalence and epidemiology. Emerg Infect Dis 8:220–221
24. Harris A, Torres-Viera C, Venkataraman L, DeGirolami P, Samore M, Carmeli Y (1999) Epidemiology and clinical outcomes of patients with multiresistant *Pseudomonas aeruginosa*. Clin Infect Dis 28:1128–1133
25. Carmeli Y, Troillet N, Karchmer AW, Samore MH (1999) Health and economic outcomes of antibiotic resistance in *Pseudomonas aeruginosa*. Arch Intern Med 159:1127–1132
26. Osmon S, Ward S, Fraser VJ, Kollef MH (2004) Hospital mortality for patients with bacteremia due to *Staphylococcus aureus* or *Pseudomonas aeruginosa*. Chest 125:607–616
27. Streit JM, Jones RN, Sader HS, Fritsche TR (2004) Assessment of pathogen occurrences and resistance profiles among infected patients in the intensive care unit: report from the SENTRY Antimicrobial Surveillance Program (North America, 2001). Int J Antimicrob Agents 24:111–118
28. VIReC Research User Guide (2004) VHA DSS clinical national data extracts FY2000-FY2004. Veterans Affairs Information Resource Center, Hines, IL, revised August 2005
29. Napier RH, Bruelheide LS, Demann ET, Haug RH (2008) Insurance billing and coding. Dent Clin North Am 52:507–527, viii
30. Banajeh SM (2009) Nutritional rickets and vitamin D deficiency—association with the outcomes of childhood very severe pneumonia: a prospective cohort study. Pediatr Pulmonol 44:1207–1215
31. Manaseki-Holland S, Qader G, Isaq Masher M, Bruce J, Zulf Mughal M, Chandramohan D, Walraven G (2010) Effects of vitamin D supplementation to children diagnosed with pneumonia in Kabul: a randomised controlled trial. Trop Med Int Health 15:1148–1155

32. Feindt E, Stroder J (1977) Studies on the antimicrobial effect of vitamin D (author's transl). Klin Wochenschr 55:507–508
33. Huff GR, Huff WE, Balog JM, Rath NC, Xie H, Horst RL (2002) Effect of dietary supplementation with vitamin D metabolites in an experimental model of turkey osteomyelitis complex. Poult Sci 81:958–965
34. Islam B, Khan SN, Khan AU (2007) Dental caries: from infection to prevention. Med Sci Monit 13:RA196–RA203
35. de la Torre MS, Torres C, Nieto G, Vergara S, Carrero AJ, Macías J, Pineda JA, Caruz A, Fibla J (2008) Vitamin D receptor gene haplotypes and susceptibility to HIV-1 infection in injection drug users. J Infect Dis 197:405–410
36. Li JH, Chen DM, Li Z, Liu Y, Gao JR, Zeng XJ, Zhong CF, Zhu XL, Gou CY, Pan L, Shan J, Guo XH, Li H (2006) Study on association between vitamin D receptor gene polymorphisms and the outcomes of HBV infection. Zhonghua Yi Xue Yi Chuan Xue Za Zhi 23:402–405
37. Yano M, Ikeda M, Abe K, Dansako H, Ohkoshi S, Aoyagi Y, Kato N (2007) Comprehensive analysis of the effects of ordinary nutrients on hepatitis C virus RNA replication in cell culture. Antimicrob Agents Chemother 51:2016–2027
38. Beigel JH, Farrar J, Han AM, Hayden FG, Hyer R, de Jong MD, Lochindarat S, Nguyen TK, Nguyen TH, Tran TH, Nicoll A, Touch S, Yuen KY, Writing Committee of the World Health Organization (WHO) (2005) Consultation on human influenza A/H5: Avian influenza A (H5N1) infection in humans. N Engl J Med 353:1374–1385
39. Talat N, Perry S, Parsonnet J, Dawood G, Hussain R (2010) Vitamin d deficiency and tuberculosis progression. Emerg Infect Dis 16:853–855
40. Cantorna MT, Yu S, Bruce D (2008) The paradoxical effects of vitamin D on type 1 mediated immunity. Mol Aspects Med 29:369–375
41. Murray JJ, Heim CR (1985) Hypercalcemia in disseminated histoplasmosis. Aggravation by vitamin D. Am J Med 78:881–884
42. Vial HJ, Thuet MJ, Philippot JR (1982) Inhibition of the in vitro growth of *Plasmodium falciparum* by D vitamins and vitamin D-3 derivatives. Mol Biochem Parasitol 5:189–198
43. Olsen A, Thiong'o FW, Ouma JH, Mwaniki D, Magnussen P, Michaelsen KF, Friis H, Geissler PW (2003) Effects of multi-micronutrient supplementation on helminth reinfection: a randomized, controlled trial in Kenyan schoolchildren. Trans R Soc Trop Med Hyg 97:109–114
44. Chowdhury N (1978) Effects of fat soluble vitamins (vitamin A, D3 and E) on axenically in vitro growth of *Hymenolepis microstoma*. Z Parasitenkd 56:29–38
45. Veldman CM, Cantorna MT, DeLuca HF (2000) Expression of 1,25-dihydroxyvitamin D(3) receptor in the immune system. Arch Biochem Biophys 374:334–338
46. Lorente F, Fontan G, Jara P, Casas C, Garcia-Rodriguez MC, Ojeda JA (1976) Defective neutrophil motility in hypovitaminosis D rickets. Acta Paediatr Scand 65:695–699
47. Schauber J, Dorschner RA, Yamasaki K, Brouha B, Gallo RL (2006) Control of the innate epithelial antimicrobial response is cell-type specific and dependent on relevant microenvironmental stimuli. Immunology 118:509–519
48. Gombart AF, Borregaard N, Koeffler HP (2005) Human cathelicidin antimicrobial peptide (CAMP) gene is a direct target of the vitamin D receptor and is strongly up-regulated in myeloid cells by 1,25-dihydroxyvitamin D3. FASEB J 19:1067–1077
49. Mata-Granados JM, Vargas-Vasserot J, Ferreiro-Vera C, de Castro MD Luque, Pavón RG, Quesada Gómez JM (2010) Evaluation of vitamin D endocrine system (VDES) status and response to treatment of patients in intensive care units (ICUs) using an on-line SPE-LC-MS/MS method. J Steroid Biochem Mol Biol 121:452–455
50. Pincikova T, Nilsson K, Moen IE, Karpati F, Fluge G, Hollsing A, Knudsen PK, Lindblad A, Mared L, Pressler T, Hjelte L (2011) Scandinavian cystic fibrosis study consortium: inverse relation between vitamin D and serum total immunoglobulin G in the Scandinavian Cystic Fibrosis Nutritional study. Eur J Clin Nutr 65:102–109
51. McKinney JD, Bailey B, Garrett L, Peiris P, Manning T, Peiris AN (2011) Relationship between vitamin D Status and ICU outcomes in veterans. J Am Med Dir Assoc 12:208–211
52. Braddy KK, Imam SN, Palla KR, Lee TA (2009) Vitamin D deficiency/insufficiency practice patterns in a veterans health administration long-term care population: a retrospective analysis. J Am Med Dir Assoc 10:653–657
53. Peiris AN, Bailey BA, Manning T, Adebonojo L (2010) Are 25-hydroxyvitamin D levels adequately monitored following evidence of vitamin D insufficiency in veterans? Mil Med 175:453–456
54. Grant WB, Giovannucci E (2009) The possible roles of solar ultraviolet-B radiation and vitamin D in reducing case-fatality rates from the 1918–1919 influenza pandemic in the United States. Dermatoendocrinol 1:215–219
55. Grant WB, Schuitemaker GE (2010) Health benefits of higher serum 25-hydroxyvitamin D levels in The Netherlands. J Steroid Biochem Mol Biol 121:456–458
56. Roth DE, Shah R, Black RE, Baqui AH (2010) Vitamin D status and acute lower respiratory infection in early childhood in Sylhet, Bangladesh. Acta Paediatr 99:389–393
57. Newens K, Filteau S, Tomkins A (2006) Plasma 25-hydroxyvitamin D does not vary over the course of a malarial infection. Trans R Soc Trop Med Hyg 100:41–44
58. Braun A, Chang D, Mahadevappa K, Gibbons FK, Liu Y, Giovannucci E, Christopher KB (2011) Association of low serum 25-hydroxyvitamin D levels and mortality in the critically ill. Crit Care Med 39:671–677
59. Youssef D, Bailey B, El Abbassi A, Copeland R, Adebonojo L, Manning T, Peiris AN (2010) Healthcare costs of *Staphylococcus aureus* and *Clostridium difficile* infections in veterans: role of vitamin D deficiency. Epidemiol Infect 138:1322–1327
60. Jones RN (2001) Resistance patterns among nosocomial pathogens: trends over the past few years. Chest 119:397S–404S
61. Patterson JE (2001) Antibiotic utilization: is there an effect on antimicrobial resistance? Chest 119:426S–430S
62. Kollef MH, Sherman G, Ward S, Fraser VJ (1999) Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. Chest 115:462–474
63. Autier P, Gandini S (2007) Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. Arch Intern Med 167:1730–1737
64. Grant WB, Cross HS, Garland CF, Gorham ED, Moan J, Peterlik M, Porojnicu AC, Reichrath J, Zittermann A (2009) Estimated benefit of increased vitamin D status in reducing the economic burden of disease in western Europe. Prog Biophys Mol Biol 99:104–113