World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
wjg@wjgnet.com
doi:10.3748/wjg.v19.i9.1349

World J Gastroenterol 2013 March 7; 19(9): 1349-1353
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

Juan-Ramón Larrubia, PhD, *Series Editor*

Efficacy of the vaccination in inflammatory bowel disease

Elisa Carrera, Rebeca Manzano, Elena Garrido

Elisa Carrera, Department of Gastroenterology, University Hospital of Guadalajara, 19002 Guadalajara, Spain
Rebeca Manzano, Department of Gastroenterology, Sureste Hospital, Arganda, 28500 Madrid, Spain
Elena Garrido, Inflammatory Bowel Disease Clinic, Department of Gastroenterology, University Hospital Ramón y Cajal, 28034 Madrid, Spain
Author contributions: Carrera E, Manzano R and Garrido E contributed equally to this work; all authors approved the final version of the manuscript.
Correspondence to: Elisa Carrera, MD, Department of Gastroenterology, University Hospital of Guadalajara, Av. Donantes de sangre sn, 19002 Guadalajara, Spain. ecarreraa@hotmail.com
Telephone: +34-94-9209200 Fax: +34-94-9209259
Received: May 29, 2012 Revised: August 21, 2012
Accepted: August 25, 2012
Published online: March 7, 2013

Abstract

Inflammatory bowel disease (IBD) is associated with conditions that may predispose to infections, such as the lack of an appropriate innate immune response to infectious agents, malnutrition, surgery, and immunosuppressive and biological drugs. Some of these infections may be preventable by vaccination. Therefore, for this particular patient population, the benefits of implementing a well-established immunization protocol in daily clinical practice are potentially even greater than for the general population. In recent years international consensus guidelines have been published, but in spite of theses recommendations, studies have shown that a significant number of patients with IBD remain inadequately immunized. Another important issue regarding immunization in this population is that vaccine efficacy among patients receiving immunosuppressive therapies has been variable. In a healthy population, a humoral immune response to hepatitis B vaccination (HBV) is expected in > 90%, whereas a much lower rate is achieved in the IBD patients. Immunosuppressive, anti-tumor necrosis factor therapy and disease activity have been implicated in the impaired efficacy of the vaccination. The serological response to HBV should be confirmed and patients with an inadequate response should receive a second full series of vaccine. Modified dosing regimens, including doubling the standard antigen dose, might increase the effectiveness. Response to influenza, pneumococcal and tetanus immunization is still not clear, as there are studies that show a normal response to the vaccination while others demonstrate a lack of efficacy. We pose a series of questions on the efficacy of the different vaccinations recommended for IBD patients and attempt to answer them using scientific evidence.

Key words: Vaccination; Efficacy; Infections; Immunization; Inflammatory bowel disease; Immunosuppressive medications; Hepatitis B vaccines; Influenza vaccines; Pneumococcal vaccines; Tetanus vaccines

Carrera E, Manzano R, Garrido E. Efficacy of the vaccination in inflammatory bowel disease. *World J Gastroenterol* 2013; 19(9): 1349-1353 Available from: URL: http://www.wjgnet.com/1007-9327/full/v19/i9/1349.htm DOI: http://dx.doi.org/10.3748/wjg.v19.i9.1349

INTRODUCTION

Current therapy for inflammatory bowel disease (IBD) patients often involves agents that suppress the immune system, placing them at an increased risk for developing infections. In recent years the scientific community has made an effort toward promoting preventative and prophylactic strategies against some of these infections[1-5]. Several guidelines have been published specifically for the vaccination and immunization of patients with IBD[6-9]. Although a consensus exists on the need to vaccinate these patients, it seems to be underused in clinical practice, and the response to immunizations in this group of patients and the factors influencing this efficacy is unknown.

ARE IBD PATIENTS CORRECTLY VACCINATED IN CLINICAL PRACTICE?

When we try to elucidate the real efficacy of vaccinations in IBD patients, the first question we have to answer is if physicians are following the immunization and vaccination recommendations provided by the guidelines. Several studies have reported on apparent knowledge deficiencies among gastroenterologists, and show that a significant number of patients remain inadequately immunized. Yeung *et al*[10] assessed 167 patients and 43 gastroenterologists for immunization attitudes, knowledge and practice. Only 14% of the gastroenterologists surveyed reported taking an immunization history from most of their patients, and the majority of patients felt they did not have enough information about immunizations. Similar data were highlighted in another study, where around a half of the gastroenterologists surveyed remembered asking their patients about their immunization history[11]. Melmed *et al*[12] assessed risk of exposure and immunization status among patients receiving care in an IBD specialty clinic. While about 44% of patients had at least one risk factor for hepatitis B, only 28% had been vaccinated against the infection. Only 45% of the patients in this study recalled receiving a tetanus immunization within the past 10 years, 28% reported regular flu shots and 9% reported having received the pneumococcal vaccine. A Spanish multicenter study detected vaccination against hepatitis B in only 12% of IBD patients[13].

About 20% of the gastroenterologists surveyed reported that they did not know how important it was for their IBD patients to be up to date on specific immunizations before starting immunomodulating or biological therapy[10].

In summary, the lack of awareness of vaccination recommendations puts IBD patients at risk of infections which might easily be avoided through a more intensive vaccination program[14].

HOW EFFECTIVE ARE VACCINATIONS IN IBD PATIENTS?

Vaccine efficacy is defined as percent risk reduction for clinically significant infection in a vaccinated group versus a control group[15].

Vaccination is a proven and well-established strategy for preventing infectious diseases in the general population. However, immunosuppressive illnesses in general are associated with reduced immunogenicity following vaccination[16,17]. Moreover, patients receiving immunosuppressive therapy may have a suboptimal serological response after a variety of vaccinations[18-22].

Hepatitis B virus

A standard 3-dose hepatitis B virus (HBV) vaccination induces protective antibody concentrations in approximately 95% of healthy individuals[16,23,24]. However the response rate to HBV is lower in patients with IBD, especially in those receiving immunosuppressive or biological therapies. In a study published by Vida *et al*[25], where 43% were on immunosuppressive therapy, only 36% of patients achieved adequate hepatitis B surface antibody (HBsAb) levels (defined as > 10 IU/L). Melmed *et al*[12] report similar data in a study where only 33% of the subgroup of patients who were immunized had detectable antibodies to hepatitis B surface antigen (anti-HBs) titers.

According to the World Health Organization, an HBsAb concentration ≥ 10 IU/L is considered a reliable marker of protection against infection[23,24,26-28].

As time passes, HBsAb titers frequently diminish and become undetectable[29]. Among immunocompromised patients who respond to the vaccine, clinical HBV infection has been documented in those who do not maintain a HBsAb concentration of ≥ 10 IU/L. Based on this evidence, in the United Kingdom seroprotection against hepatitis B was redefined at ≥ 100 IU/mL, especially in those with chronic diseases or with immunosuppressive therapies[16,28,30,31]. A recent study published by Altunöz *et al*[30] defined the effective immune response as an antibody level > 100 IU/L after comparing the efficacy of the standard 3-dose vaccine in a group of IBD patients and comparing it to a control group. The effective immune response was significantly higher in the control group compared to the IBD group (89% *vs* 53%).

The response rate to the HBV vaccine seems to be quite low in IBD patients. Modified dosing regimens, including doubling the standard antigen dose, might increase response rates in immunocompromised patients[28,32-35]. Chaparro *et al*[36] assessed the efficacy of the HBV vaccine at a double dosage (0, 1 and 2 mo) in IBD patients and found that 60% of the IBD patients had adequate HBsAb titers (≥ 10 IU/mL), but only 34% achieved adequate immunity (≥ 100 IU/mL).

Influenza

Since influenza infection may result in serious illness in immunocompromised individuals, the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention recommends influenza vaccination for all immunosuppressed patients[37]. Several studies have concluded that the influenza vaccine is safe and effective in both children and adults with various chronic diseases[38-41]. However, the immune response in immunocompromised patients varies. Most studies attempting to identify the efficacy of the influenza vaccine in IBD patients have been carried out in the pediatric population. Mamula *et al*[42] compared response to influenza vaccine in children with IBD and observed that the IBD group mounted less effective responses to one-third of antigens compared to controls, while patients on a combination of biologics and immunomodulators had an impaired response to two-thirds of antigens. In contrast, Lu *et al*[43] assessed the response rates to influenza vaccinations in IBD children and reported similar responses among IBD patients, regardless of their immunosuppressive status. A recent study performed in adults came to

similar conclusions and demonstrated that IBD patients on immunosuppressive treatment are able to mount an effective immune response[44].

Pneumococcal

Melmed *et al*[45] assessed response to pneumococcal vaccine in IBD adults compared to controls. Patients treated with a combination of biologics and immunosuppressants presented with an impaired response to the pneumococcal vaccine compared to controls and patients not receiving immunosuppressive therapy. Dotan *et al*[44] reported contradictory results in a recent study where they concluded that IBD patients do not have an intrinsic immunodeficiency and display a significant increase in titers for all pneumococcal serotypes.

Tetanus

Response to tetanus immunization in IBD patients is not clear, as there are studies[44,46] that demonstrate that IBD patients have a normal response to the tetanus vaccine, while others[47] suggest an impaired anti-tetanus response.

WHAT ARE THE FACTORS THAT AFFECT THE EFFICACY OF VACCINATION IN IBD PATIENTS?

In healthy individuals, several risk factors for non-response to hepatitis B vaccination have been described, such as smoking, older age, male gender and a high body mass index[24]. Influenza immunization may be less effective for those in the general population with certain medical conditions, such as systemic lupus erythematosus[48] or patients receiving immunosuppressive treatments[49].

The lack of response to vaccines by IBD patients may be due to associated immunosuppressive and anti-tumor necrosis factor (TNF) treatments rather than IBD *per se*. In this sense, some authors have demonstrated a suboptimal response to pneumococcal vaccination in patients with IBD under combination therapy with anti-TNF drugs and immunosuppressants[42], while IBD patients who received non-immunosuppressive therapy exhibited a good response to the vaccine[45].

Patients on anti-TNF agents have demonstrated a decreased immune response to influenza vaccine in IBD and non-IBD populations[22,42,43]. HBV vaccination is also influenced by the medication administered. In a study by Chaparro *et al*[36], 40% of patients had an adequate response to immunization (> 100 IU/L), while the response was much lower in patients undergoing biological therapy (10%), although this difference did not achieve statistical significance, probably due to the small size sample. Altunoz *et al*[30] assessed immune response to HBV vaccination, and demonstrated in their subgroup analysis that the group of patients not under immunosuppressive treatment achieved an adequate immune response (> 10 IU/L) in 91% and an effective immune response (> 100 IU/L) in 73%, whereas only 61% and 29% of patients under immunosuppressive therapy, respectively, acquired an adequate and effective immune response. There are contradictory results by Vida *et al*[25] that could not demonstrate the effect of immunomodulators on the efficacy of the HBV vaccine. The small sample size and corresponding low statistical power may explain the lack of statistically significant differences. In fact, a tendency towards a lower rate of response to vaccine was found in the immunosuppressed group[28].

Disease activity has also been implicated in impaired responses to vaccination. In this respect, a subanalysis in the study by Altunoz *et al*[30] concluded that active IBD patients achieved a significantly lower response to vaccination compared to patients in remission (41% *vs* 63%). Thus, these authors recommend HBV vaccination during remission periods.

In summary, patients receiving anti-TNF therapy, immunosuppressants, or with active disease, are at risk of developing an inadequate serologic response. Future studies should attempt to determine if booster immunizations are needed in this group of patients[43]. Further studies should determine if other factors such as genetics, gender or age could affect the response to immunization in IBD patients.

WHAT CAN WE DO IF REGULAR VACCINATION IS NOT EFFECTIVE?

Although routine serology testing for immunity is not recommended after HBV vaccination in adults, post-vaccination serology is advisable for high-risk individuals such as the immunocompromised, including IBD patients[16,24,28,50]. Recommended seroprotection against HBV in immunosuppressed patients is defined as HBsAb ⩾ 100 IU/mL[16]. In HBV immunization studies, 25%-50% of the patients that do not respond to a primary three-dose vaccine responded to an additional dose, and 44%-100% respond to a second three-dose course. Therefore, those patients that do not achieve an adequate immune response after the primary immunization should be revaccinated with three additional doses[51]. Moreover, revaccination with a three-dose regimen using a double dose has also been suggested[52].

Mamula *et al*[42] propose a second booster dose of influenza vaccine in IBD patients with concomitant immunomodulatory and anti-TNF treatment. There are no other recommendations for the remaining vaccinations.

In conclusion, IBD patients are considered to be at risk for several infections and should therefore be immunized. Response to immunization in this group of patients is still a controversial issue. Further studies are necessary in order to clarify the true efficacy of these vaccinations and to provide recommendations on specific situations such as failure to respond. In spite of the aforementioned recommendations, several studies demonstrate that vaccines are under-prescribed and that intensive educational efforts are required in order to ensure correct adherence to the set guidelines by gastroenterolo-

gists and primary care physicians.

REFERENCES

1 **Deutsch DE**, Olson AD, Kraker S, Dickinson CJ. Overwhelming varicella pneumonia in a patient with Crohn's disease treated with 6-mercaptopurine. *J Pediatr Gastroenterol Nutr* 1995; **20**: 351-353 [PMID: 7608833 DOI: 10.1097/00005176-199504000-00016]

2 **Leung VS**, Nguyen MT, Bush TM. Disseminated primary varicella after initiation of infliximab for Crohn's disease. *Am J Gastroenterol* 2004; **99**: 2503-2504 [PMID: 15571606 DOI: 10.1111/j.1572-0241.2004.41389_7.x]

3 **Ritz MA**, Jost R. Severe pneumococcal pneumonia following treatment with infliximab for Crohn's disease. *Inflamm Bowel Dis* 2001; **7**: 327 [PMID: 11720324]

4 **Foster KJ**, Devitt N, Gallagher PJ, Abbott RM. Overwhelming pneumococcal septicaemia in a patient with ulcerative colitis and splenic atrophy. *Gut* 1982; **23**: 630-632 [PMID: 7084807]

5 **Esteve M**, Saro C, González-Huix F, Suarez F, Forné M, Viver JM. Chronic hepatitis B reactivation following infliximab therapy in Crohn's disease patients: need for primary prophylaxis. *Gut* 2004; **53**: 1363-1365 [PMID: 15306601]

6 Recommendations of the Advisory Committee on Immunization Practices (ACIP): use of vaccines and immune globulins for persons with altered immunocompetence. *MMWR Recomm Rep* 1993; **42**: 1-18 [PMID: 8474421]

7 **Sands BE**, Cuffari C, Katz J, Kugathasan S, Onken J, Vitek C, Orenstein W. Guidelines for immunizations in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2004; **10**: 677-692 [PMID: 15472534 DOI: 10.1097/00054725-200409000-00028]

8 **Rahier JF**, Ben-Horin S, Chowers Y, Conlon C, De Munter P, D'Haens G, Domènech E, Eliakim R, Eser A, Frater J, Gassull M, Giladi M, Kaser A, Lémann M, Moreels T, Moschen A, Pollok R, Reinisch W, Schunter M, Stange EF, Tilg H, Van Assche G, Viget N, Vucelic B, Walsh A, Weiss G, Yazdanpanah Y, Zabana Y, Travis SP, Colombel JF. European evidence-based Consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis* 2009; **3**: 47-91 [PMID: 21172250 DOI: 10.1016/j.crohns.2009.02.01]

9 **Esteve M**, Loras C, García-Planella E. Inflammatory bowel disease in travelers: choosing the right vaccines and check-ups. *World J Gastroenterol* 2011; **17**: 2708-2714 [PMID: 21734778 DOI: 10.3748/wjg.v17.i22.2708]

10 **Yeung JH**, Goodman KJ, Fedorak RN. Inadequate knowledge of immunization guidelines: a missed opportunity for preventing infection in immunocompromised IBD patients. *Inflamm Bowel Dis* 2012; **18**: 34-40 [PMID: 21337671 DOI: 10.1002/ibd.21668)]

11 **Wasan SK**, Coukos JA, Farraye FA. Vaccinating the inflammatory bowel disease patient: deficiencies in gastroenterologists knowledge. *Inflamm Bowel Dis* 2011; **17**: 2536-2540 [PMID: 21538710]

12 **Melmed GY**, Ippoliti AF, Papadakis KA, Tran TT, Birt JL, Lee SK, Frenck RW, Targan SR, Vasiliauskas EA. Patients with inflammatory bowel disease are at risk for vaccine-preventable illnesses. *Am J Gastroenterol* 2006; **101**: 1834-1840 [PMID: 16817843 DOI: 10.1111/j.1572-0241.2006.00646.x]

13 **Loras C**, Saro C, Gonzalez-Huix F, Mínguez M, Merino O, Gisbert JP, Barrio J, Bernal A, Gutiérrez A, Piqueras M, Calvet X, Andreu M, Abad A, Ginard D, Bujanda L, Panés J, Torres M, Fernández-Bañares F, Viver JM, Esteve M. Prevalence and factors related to hepatitis B and C in inflammatory bowel disease patients in Spain: a nationwide, multicenter study. *Am J Gastroenterol* 2009; **104**: 57-63 [PMID: 19098850 DOI: 10.1038/ajg.2008.4]

14 **Wasan SK**, Baker SE, Skolnik PR, Farraye FA. A practical guide to vaccinating the inflammatory bowel disease patient. *Am J Gastroenterol* 2010; **105**: 1231-1238 [PMID: 20104218 DOI: 10.1038/ajg.2009.733]

15 **Qin L**, Gilbert PB, Corey L, McElrath MJ, Self SG. A framework for assessing immunological correlates of protection in vaccine trials. *J Infect Dis* 2007; **196**: 1304-1312 [PMID: 17922394 DOI: 10.1086/522428]

16 **WHO Publication**. Hepatitis B vaccines: WHO position paper--recommendations. *Vaccine* 2010; **28**: 589-590 [PMID: 19896455 DOI: 10.1016/j.vaccine.2009.10.110]

17 **Elkayam O**, Yaron M, Caspi D. Safety and efficacy of vaccination against hepatitis B in patients with rheumatoid arthritis. *Ann Rheum Dis* 2002; **61**: 623-625 [PMID: 12079904 DOI: 10.1136/ard.61.7.623]

18 **Wagner D**, Wagenbreth I, Stachan-Kunstyr R, Flik J. Failure of vaccination against hepatitis B with Gen H-B-Vax-D in immunosuppressed heart transplant recipients. *Clin Investig* 1992; **70**: 585-587 [PMID: 1392427]

19 **Moses J**, Alkhouri N, Shannon A, Raig K, Lopez R, Danziger-Isakov L, Feldstein AE, Zein NN, Wyllie R, Carter-Kent C. Hepatitis B immunity and response to booster vaccination in children with inflammatory bowel disease treated with infliximab. *Am J Gastroenterol* 2012; **107**: 133-138 [PMID: 21876562 DOI: 10.1038/ajg.2011.295.]

20 **Melmed GY**. Vaccination strategies for patients with inflammatory bowel disease on immunomodulators and biologics. *Inflamm Bowel Dis* 2009; **15**: 1410-1416 [PMID: 19462435 DOI: 10.1002/ibd.20943]

21 **Bruguera M**, Cremades M, Salinas R, Costa J, Grau M, Sans J. Impaired response to recombinant hepatitis B vaccine in HIV-infected persons. *J Clin Gastroenterol* 1992; **14**: 27-30 [PMID: 1532609]

22 **Gelinck LB**, van der Bijl AE, Beyer WE, Visser LG, Huizinga TW, van Hogezand RA, Rimmelzwaan GF, Kroon FP. The effect of anti-tumour necrosis factor alpha treatment on the antibody response to influenza vaccination. *Ann Rheum Dis* 2008; **67**: 713-716 [PMID: 17965123]

23 **Coates T**, Wilson R, Patrick G, André F, Watson V. Hepatitis B vaccines: assessment of the seroprotective efficacy of two recombinant DNA vaccines. *Clin Ther* 2001; **23**: 392-403 [PMID: 11318074]

24 **Mast EE**, Weinbaum CM, Fiore AE, Alter MJ, Bell BP, Finelli L, Rodewald LE, Douglas JM, Janssen RS, Ward JW. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) Part II: immunization of adults. *MMWR Recomm Rep* 2006; **55**: 1-33; quiz CE1-4 [PMID: 17159833]

25 **Vida Pérez L**, Gómez Camacho F, García Sánchez V, Iglesias Flores EM, Castillo Molina L, Cerezo Ruiz A, Casáis Juanena L, De Dios Vega JF. Adequate rate of response to hepatitis B virus vaccination in patients with inflammatory bowel disease. *Med Clin* (Barc) 2009; **132**: 331-335 [PMID: 19268981 DOI: 10.1016/j.medcli.2008.07.013]

26 **Chevaux JB**, Bigard MA, Bensenane M, Oussalah A, Jarlot S, Belle A, Nani A, Bronowicki JP, Peyrin-Biroulet L. Inflammatory bowel disease and hepatitis B and C. *Gastroenterol Clin Biol* 2009; **33**: 1082-1093 [PMID: 19896313 DOI: 10.1016/j.gcb.2009.03.021]

27 **Shouval D**. Hepatitis B vaccines. *J Hepatol* 2003; **39** Suppl 1: S70-S76 [PMID: 14708681 DOI: 10.1016/S0168-8278(03)00152-1]

28 **Gisbert JP**, Chaparro M, Esteve M. Review article: prevention and management of hepatitis B and C infection in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2011; **33**: 619-633 [PMID: 21416659 DOI: 10.1111/j.1365-2036.2010.04570.x]

29 **Hall AJ**. Boosters for hepatitis B vaccination? Need for an evidence-based policy. *Hepatology* 2010; **51**: 1485-1486 [PMID: 20432250 DOI: 10.1002/hep.23674]

30 **Altunöz ME**, Senateş E, Yeşil A, Calhan T, Ovünç AO. Patients with inflammatory bowel disease have a lower response rate to HBV vaccination compared to controls. *Dig Dis Sci* 2012; **57**: 1039-1044 [PMID: 22147248 DOI: 10.1007/s10620-011-1980-8]

31 **Lemon SM**, Thomas DL. Vaccines to prevent viral hepatitis. *N Engl J Med* 1997; **336**: 196-204 [PMID: 8988900]

32 **Advisory Committee on Immunization Practices**. Recommended adult immunization schedule: United States, 2010. *Ann Intern Med* 2010; **152**: 36-39 [PMID: 20048270 DOI: 10.1059/0003-4819-152-1-201001050-00008]

33 **Choudhury SA**, Peters VB. Responses to hepatitis B vaccine boosters in human immunodeficiency virus-infected children. *Pediatr Infect Dis J* 1995; **14**: 65-67 [PMID: 7715995]

34 **Fonseca MO**, Pang LW, de Paula Cavalheiro N, Barone AA, Heloisa Lopes M. Randomized trial of recombinant hepatitis B vaccine in HIV-infected adult patients comparing a standard dose to a double dose. *Vaccine* 2005; **23**: 2902-2908 [PMID: 15780739 DOI: 10.1016/j.vaccine.2004.11.057]

35 **Rey D**, Krantz V, Partisani M, Schmitt MP, Meyer P, Libbrecht E, Wendling MJ, Vetter D, Nicolle M, Kempf-Durepaire G, Lang JM. Increasing the number of hepatitis B vaccine injections augments anti-HBs response rate in HIV-infected patients. Effects on HIV-1 viral load. *Vaccine* 2000; **18**: 1161-1165 [PMID: 10649616]

36 **Chaparro M**, Villagrasa JR, Rodriguez Nogueiras A, Gisbert JP. Immune response to hepatitis B vaccination in patients with inflammatory bowel disease. *Gastroenterology* 2010; **138**: S197 [DOI: 10.1016/S0016-5085(10)60891-8]

37 **Harper SA**, Fukuda K, Uyeki TM, Cox NJ, Bridges CB. Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2005; **54**: 1-40 [PMID: 16086456]

38 **Chalmers A**, Scheifele D, Patterson C, Williams D, Weber J, Shuckett R, Teufel A. Immunization of patients with rheumatoid arthritis against influenza: a study of vaccine safety and immunogenicity. *J Rheumatol* 1994; **21**: 1203-1206 [PMID: 7966058]

39 **Malleson PN**, Tekano JL, Scheifele DW, Weber JM. Influenza immunization in children with chronic arthritis: a prospective study. *J Rheumatol* 1993; **20**: 1769-1773 [PMID: 7848389]

40 **Brydak LB**, Roszkowska-Blaim M, Machala M, Leszczyńska B, Sieniawska M. Antibody response to influenza immunization in two consecutive epidemic seasons in patients with renal diseases. *Vaccine* 2000; **18**: 3280-3286 [PMID: 10869773]

41 **Agarwal N**, Ollington K, Kaneshiro M, Frenck R, Melmed GY. Are immunosuppressive medications associated with decreased responses to routine immunizations? A systematic review. *Vaccine* 2012; **30**: 1413-1424 [PMID: 22197580]

42 **Mamula P**, Markowitz JE, Piccoli DA, Klimov A, Cohen L, Baldassano RN. Immune response to influenza vaccine in pediatric patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2007; **5**: 851-856 [PMID: 17544875 DOI: 10.1016/j.cgh.2007.02.035]

43 **Lu Y**, Jacobson DL, Ashworth LA, Grand RJ, Meyer AL, McNeal MM, Gregas MC, Burchett SK, Bousvaros A. Immune response to influenza vaccine in children with inflammatory bowel disease. *Am J Gastroenterol* 2009; **104**: 444-453 [PMID: 19174786 DOI: 10.1038/ajg.2008.120]

44 **Dotan I**, Werner L, Vigodman S, Agarwal S, Pfeffer J, Horowitz N, Malter L, Abreu M, Ullman T, Guzner-Gur H, Halpern Z, Mayer L. Normal response to vaccines in inflammatory bowel disease patients treated with thiopurines. *Inflamm Bowel Dis* 2012; **18**: 261-268 [PMID: 21438101 DOI: 10.1002/ibd.21688)]

45 **Melmed GY**, Agarwal N, Frenck RW, Ippoliti AF, Ibanez P, Papadakis KA, Simpson P, Barolet-Garcia C, Ward J, Targan SR, Vasiliauskas EA. Immunosuppression impairs response to pneumococcal polysaccharide vaccination in patients with inflammatory bowel disease. *Am J Gastroenterol* 2010; **105**: 148-154 [PMID: 19755964 DOI: 10.1038/ajg.2009.523]

46 **Nielsen HJ**, Mortensen T, Holten-Andersen M, Brünner N, Sørensen S, Rask-Madsen J. Increased levels of specific leukocyte- and platelet-derived substances during normal anti-tetanus antibody synthesis in patients with inactive Crohn disease. *Scand J Gastroenterol* 2001; **36**: 265-269 [PMID: 11305513]

47 **Brogan MD**, Shanahan F, Oliver M, Stevens RH, Targan SR. Defective memory B cell formation in patients with inflammatory bowel disease following tetanus toxoid booster immunization. *J Clin Lab Immunol* 1987; **24**: 69-74 [PMID: 3437440]

48 **Abu-Shakra M**, Press J, Varsano N, Levy V, Mendelson E, Sukenik S, Buskila D. Specific antibody response after influenza immunization in systemic lupus erythematosus. *J Rheumatol* 2002; **29**: 2555-2557 [PMID: 12465151]

49 **Matsuzaki A**, Suminoe A, Koga Y, Kinukawa N, Kusuhara K, Hara T. Immune response after influenza vaccination in children with cancer. *Pediatr Blood Cancer* 2005; **45**: 831-837 [PMID: 16007602 DOI: 10.1002/pbc.20470]

50 **Lok AS**, McMahon BJ. Chronic hepatitis B. *Hepatology* 2007; **45**: 507-539 [PMID: 17256718 DOI: 10.1002/hep.21513]

51 **Bertino JS**, Tirrell P, Greenberg RN, Keyserling HL, Poland GA, Gump D, Kumar ML, Ramsey K. A comparative trial of standard or high-dose S subunit recombinant hepatitis B vaccine versus a vaccine containing S subunit, pre-S1, and pre-S2 particles for revaccination of healthy adult nonresponders. *J Infect Dis* 1997; **175**: 678-681 [PMID: 9041342]

52 **Cardell K**, Akerlind B, Sällberg M, Frydén A. Excellent response rate to a double dose of the combined hepatitis A and B vaccine in previous nonresponders to hepatitis B vaccine. *J Infect Dis* 2008; **198**: 299-304 [PMID: 18544037 DOI: 10.1086/589722]

P- Reviewer Bian ZX **S- Editor** Gou SX
L- Editor Rutherford A **E- Editor** Zhang DN