Successful Treatment of Ascites using a Denver® Peritoneovenous Shunt in a Patient with Paroxysmal Nocturnal Hemoglobinuria and Budd-Chiari syndrome

Tomomi Kogiso¹, Etsuko Hashimoto¹, Taito Ito¹, Toshifumi Hara¹, Yuichi Ikarashi¹, Kazuhiro Kodama¹, Makiko Tanai¹, Nobuyuki Torii¹, Kentaro Yoshinaga², Satoru Morita³, Yutaka Takahashi⁴, Junji Tanaka², Shuji Sakai³, Masakazu Yamamoto⁴ and Katsutoshi Tokushige¹

Abstract

A 56-year-old man was diagnosed with aplastic anemia and paroxysmal nocturnal hemoglobinuria at 43 years of age and treatment with cyclosporin A was started. Liver cirrhosis, ascites, and thrombus in the hepatic veins were found at 56 years of age and Budd-Chiari syndrome (BCS) was diagnosed according to angiography findings. He was treated with diuretics and paracentesis was performed several times, but with limited efficacy. A Denver® peritoneovenous shunt (PVS) was inserted into the right jugular vein; his ascites and renal function improved immediately and his general condition has remained good for 12 months since starting the above treatment regimen. A PVS is a treatment option for ascites due to BCS.

Key words: Denver peritoneovenous shunt (PVS), Budd-Chiari syndrome (BCS), paroxysmal nocturnal hemoglobinuria (PNH)

(Intern Med 55: 2957-2963, 2016) (DOI: 10.2169/internalmedicine.55.7087)

Introduction

A case of aplastic anemia-paroxysmal nocturnal hemoglobinuria (AA-PNH) syndrome was initially reported as AA presenting with symptoms characteristic of PNH during the course of the disease (1-3). PNH is a rare acquired disorder of pluripotent hematopoietic stem cells that is characterized by intravascular hemolysis and venous thrombosis (4, 5). It is caused by a somatic mutation in the X-linked phosphatidylinositol glycan class A (PIG-A) gene, which is required for the synthesis of the glycosyl phosphatidylinositol (GPI) anchor. The mutation results in the absence of key complement regulatory proteins CD55 and CD59 (6-9). On erythrocytes, CD55 and CD59 deficiency leads to intravascular hemolysis upon complement activation. Intravascular complement-mediated lysis results in anemia, hemoglobinuria, and venous thrombosis (4). Thrombotic events occur in 40% of PNH patients and hepatic vein thrombosis (Budd-Chiari syndrome; BCS) is the most frequent manifestation (40.7%) (10-12).

Thrombosis in a hepatic vein results in abdominal pain, hepatomegaly, and ascites, which are the characteristic findings in BCS (11, 13). The management of ascites involves treating thrombosis and thrombolysis (14-16). Percutaneous hepatic vein balloon angioplasty (17, 18) should be considered in early thrombosis. Anticoagulants are selected for long-term management (5, 19). Patients with thrombosis have a high risk of recurrence and anticoagulant treatment is necessary, although the duration of treatment is controversial because these patients also have a high risk of bleeding (5). The accumulation of ascites is a common complication in...
BCS and medically intractable ascites can be treated with a peritoneovenous shunt (PVS) (18, 20), surgical portosystemic shunt (13, 21), transjugular intrahepatic portosystemic shunt (TIPS) (22-24), liver transplantation (13, 21), or paracentesis (20). Since Levene et al. first reported the treatment of refractory ascites using a PVS (25), several modifications have been made. The Denver® PVS transfers fluid from the peritoneal space to the circulatory system and can be used to treat ascites (20).

We herein report the successful treatment of ascites using a Denver® PVS in a patient with PNH and BCS.

Case Report

A 56-year-old man was diagnosed with AA at 34 years of age and treated with cyclosporin A. He developed PNH at 43 years of age and was thought to have AA-PNH syndrome. At 56 years of age, his abdomen became distended and his weight increased from 66 to 72 kg in 2 weeks. He was admitted to our hospital to evaluate the weight increase (Fig. 1a). Biochemical data showed liver dysfunction and pancytopenia (Table 1). Computed tomography (CT) revealed liver cirrhosis, ascites, and thrombus formation in the left hepatic vein (LHV) and hepatic inferior vena cava with stenosis (Fig. 1b and c). The cause of thrombosis was thought to be AA-PNH. No other risk factors for BCS were found, such as JAK-V617F mutations (26) (Table 1).

Angiography showed stenosis of the hepatic inferior vena cava and hepatic veins due to thrombosis, with collateral formation (Fig. 1d and e). According to these findings, the patient was diagnosed with BCS. The right and middle hepatic veins were obstructed by thromboses. The thrombosis in the inferior vena cava was extremely large. Urokinase injection and balloon dilation of the LHV were performed several times. Heparin was administered for 2 weeks and then switched to warfarin at day 40. Although there was no change in the thrombosis, his weight and the ascites decreased and he was discharged on day 97.

He was re-admitted to our hospital for variceal bleeding on day 165 and endoscopic variceal ligation (EVL) was performed (Fig. 2a). After EVL, the ascites increased and was not controllable with diuretics. The increased ascites led to compartment syndrome and an altered renal function. In addition to paracentesis, cell-free and concentrated ascites reinfusion therapy (CART) was performed on days 200, 218, and 234. CART therapy was temporarily effective, however, the ascites re-accumulated rapidly a few days after drainage. The ascites was transudative, caused by cirrhosis and there was no evidence of infection. Because the right and middle hepatic veins and the hepatic inferior vena cava were obstructed by thrombosis, TIPS would have been ineffective. Therefore, we considered inserting a Denver® PVS. His heart function was normal according to echocardiography and he could tolerate the intravenous return of ascites. The day before the procedure (day 248), he weighed 67.8 kg and 3 L of ascites were drained to reduce the returned-volume of ascites. On day 249, a percutaneous Denver® PVS was inserted by a surgeon from the right upper quadrant of the abdomen, subcutaneously through the thorax, and placed via the right internal jugular vein (Fig. 2b). During PVS insertion, warfarin was replaced by heparin. After the procedure was completed, warfarin was re-started. The urine flow increased to 4 L/day soon after transferring the ascites intravascularly. His weight decreased from 65.4 to 63.1 kg the next day. His renal function improved and the use of diuretics could be reduced (Table 1). His weight did not increase after inserting the PVS and he was discharged on day 259. His weight had decreased to 50 kg 1 month after discharge and his distended abdomen was obviously improved with reduced ascites (Fig. 2c). Although his weight had increased slightly 4 months after shunt insertion because his appetite had improved, the ascites was controlled according to abdominal and pelvic CT 4 months after discharge (Fig. 2d and e). While the thrombosis remained, it was found to have slightly diminished in size. His general condition was good, his quality of life had improved and he could finally return to work. Six months after inserting the Denver® PVS, the renal and liver function tests improved markedly (serum creatinine, 0.69 mg/dL; estimated glomerular filtration rate (eGFR), 92.7 mL/min/1.73 m²; total bilirubin (T-BIL), 2.0 mg/dL; aspartate aminotransferase (AST), 21 U/L; and alanine aminotransferase (ALT), 15 U/L). Although his weight had increased, an estimation of the body components using an impedance assay showed that this was because his muscle mass had increased (Table 2). His esophageal varices became slightly enlarged at 10 months after PVS insertion.

Discussion

Our patient with AA-PNH syndrome who developed BCS and ascites was successfully treated using a Denver® PVS. Prior to treatment, urokinase injection, percutaneous transluminal balloon angioplasty (PTA) of the LHV, fibrinolytic therapy, and anticoagulation all failed to resolve thrombosis caused by AA-PNH. The PVS dramatically improved the patient’s quality of life and his general condition was good at the 12-month follow-up.

Thrombosis results in a high morbidity and mortality. Overall, 40-67% of PNH patients will die of thrombotic complications and an initial thrombotic event increases the relative risk of death by 5- to 10-fold (27). Differences have been reported in the incidence of thrombosis in PNH (28). Thrombosis was observed at the diagnosis/follow-up in 19.3/31.8% of Western patients versus only 6.2/4.3% of Japanese patients (28). Significantly more Western patients died from thrombosis. Retrospective studies have suggested that the risk of thrombosis is correlated with the size of the PNH granulocyte clone (29, 30). A lower risk was reported in Chinese and Japanese patients, which is likely explained by a significantly lower PNH granulocyte size in these patients compared with Western patients (28). A survival analysis re-
Figure 1. (a) Clinical course during the first admission. (b, c) Abdominal computed tomography (CT) on admission. (b) A transverse CT view through the middle abdomen shows liver cirrhosis, enlargement of the caudate lobe of the liver, and ascites (arrows: thrombi). (c) A coronal view of the middle abdomen shows thrombosis in the left hepatic vein (LHV) and stenotic inferior vena cava (IVC) with a thrombus. (d, e) Angiography of the abdominal veins. (d) The IVC was stenotic; the pressure in the IVC was 17 mmHg, and that in the right atrium was 1 mmHg (arrows: thrombi, triangle: IVC stenosis). (e) The LHV was obstructed with spider-like collateral formation and thrombosis; Budd-Chiari syndrome was diagnosed (arrows: thrombus). CyA: cyclosporin A, ALB: albumin, PLT: platelets, RCC: red cell concentrates stored in mannitol-adenine-phosphate solution, BW: body weight
Table 1. The Patient’s Biochemical Data.

|                      | On 1st admission | Day 178 | After PVS insertion | Six months after PVS insertion |
|----------------------|------------------|---------|---------------------|-------------------------------|
| WBC (×10⁹/L)        | 4,960            | 4,870   | 2,550               | 2,120                         |
| RBC (×10⁹/L)        | 375              | 351     | 266                 | 302                           |
| Hb (g/dL)           | 10.2             | 10.2    | 8.0                 | 9.0                           |
| Ht (%)              | 30.7             | 30.1    | 24.9               | 27.7                          |
| PLT (×10⁹/μL)       | 3.4              | 2.3     | 2.5                 | 3.7                           |
| Ret (%)             | 2.6              |          |                     |                               |
| TP (g/dL)           | 6.5              | 6.5     | 7.2                 | 6.9                           |
| ALB (g/dL)          | 3.7              | 3.2     | 3.3                 | 3.4                           |
| T-BIL (mg/dL)       | 2.3              | 5.2     | 2.0                 | 1.9                           |
| D-BIL (mg/dL)       | 0.5              | 3.0     | 0.5                 | 0.3                           |
| AST (U/L)           | 160              | 171     | 21                 | 24                            |
| ALT (U/L)           | 160              | 114     | 15                 | 12                            |
| LD (U/L)            | 452              | 487     | 340               | 294                           |
| ALP (U/L)           | 461              | 351     | 547               | 398                           |
| γ-GTP (U/L)         | 53               | 55      | 101               | 110                           |
| CRP (mg/dL)         | 0.76             | 3.62    | 3.40               | 0.30                          |
| Na (mEq/L)          | 141              | 132     | 140                | 143                           |
| K (mEq/L)           | 4.4              | 4.8     | 4.2               | 3.6                           |
| Cl (mEq/L)          | 105              | 98      | 106                | 108                           |
| BUN (mg/dL)         | 14.9             | 62.9    | 17.2               | 14.4                          |
| Cr (mg/dL)          | 0.92             | 3.73    | 0.69               | 0.81                          |
| eGFR (mL/min/1.73m²) | 14.7             | 92.7    | 72.7               |                               |
| TC (mg/dL)          | 125              |         |                     |                               |
| TG (mg/dL)          | 92               |         |                     |                               |
| FBS (mg/dL)         | 108              |         | 154                |                               |
| HbA1c (%)           | 5.7              |         |                     |                               |
| PT (%)              | 51               | 42.1    | 34.2               | 21.9                          |
| PT-INR              | 1.39             | 1.61    | 1.82               | 2.51                          |
| APTT (sec)          | 39.2             |         |                     |                               |
| AT-III (%)          | 85               |         |                     |                               |
| Fibrinogen (mg/dL)  | 174              |         | 341                |                               |
| FDP (μg/mL)         | 15.7             |         | 4.5                |                               |
| D-dimer (μg/mL)     | 7.9              |         | 1.4                |                               |
| IgG (mg/dL)         | 1,168            |         |                     |                               |
| IgA (mg/dL)         | 244              |         |                     |                               |
| IgM (mg/dL)         | 94               |         |                     |                               |
| RF (-)              |                  |         |                     |                               |
| ANA <20             |                  |         |                     |                               |
| AMA M2 <1.5         |                  |         |                     |                               |
| HbAsAg (-)          |                  |         |                     |                               |
| Anti-HBc (-)        |                  |         |                     |                               |
| Anti-HCV (-)        |                  |         |                     |                               |
| Protein C activity (%) | 45              |         |                     |                               |
| Protein S activity (%) | 83              |         |                     |                               |
| Lupus anticoagulant | 1.2              |         |                     |                               |
| Anti-CL-IgG Ab (U/mL) | <5±           |         |                     |                               |
| Jak2 mutation (+)   |                  |         |                     |                               |
| CyA (ng/mL)         | 116              | 180     |                     |                               |

WBC: white blood cell, RBC: red blood cell, Hb: hemoglobin, Ht: hematocrit, PLT: platelets, Ret: reticulocytes, ALB: albumin, T-BIL: total bilirubin, D-BIL: direct bilirubin, LD: lactate dehydrogenase, ALP: alkaline phosphatase, γ-GTP: γ-glutamyl transpeptidase, CRP: C-reactive protein, Na: sodium, K: potassium, Cl: chloride, BUN: blood urea nitrogen, Cr: creatinine, eGFR: estimated glomerular filtration rate, TC: total cholesterol, TG: triglycerides, FBS: fasting glucose, HbA1c: hemoglobin A1c, NGSP: national glycohemoglobin standardization program, PT: prothrombin time, INR: international normalized ratio, APTT: activated partial thromboplastin time, FDP: fibrinogen degradation product, RF: rheumatoid factor, ANA: antinuclear antibody, AMA: anti-mitochondrial antibody, Anti-CL-IgG Ab: anti-cardiolipin antibodies, JAK2: Janus kinase 2, CyA: cyclosporin A.

A poor survival was associated with an age over 50 years, and showed a similar death rate, however, Japanese patients had a longer mean survival time (32.1 vs. 19.4 years) (28). A poor survival was associated with an age over 50 years, and showed a similar death rate, however, Japanese patients had a longer mean survival time (32.1 vs. 19.4 years) (28).
Figure 2. (a) Clinical course of the second admission. The abdomen (b) before and (c) 1 month after peritoneovenous shunt (PVS) insertion. (d, e) Abdominal and pelvic CT 4 months after discharge. Some ascites remained 1 month after PVS insertion; however, his distended abdomen was obviously improved. CyA: cyclosporin A, ALB: albumin, PLT: platelets, RCC: red cell concentrates stored in mannitol-adenine-phosphate solution, CT: computed tomography, BW: body weight
exhausted thereafter. Thus, PVS-treated patients are able to eat well, resulting in a better nutritional status. Following insertion, our patient’s anticoagulant therapy was switched from warfarin to heparin; warfarin was re-started after the procedure. Warfarin administration was responsible for the decrease in the PT%; however, there was no reduction in his liver function.

Major prognostic factors for BCS are the prothrombin time, serum bilirubin level, creatinine, and presence of hepatic encephalopathy and ascites (18, 40). Control of ascites might be important for improving the prognosis. In our institution, five cases of BCS have been seen in the last 15 years, including the present case. The cause of BCS was unknown in the other cases. One case was treated with PTA and remained alive for 14 years. In three cases, PTA and thrombolysis were performed; however, two of these cases needed liver transplantation. In our patient, liver transplantation was contraindicated due to the complication of PNH, the future medical treatment of which is currently under consideration. In the interim, the Denver® PVS has been a useful treatment.

In conclusion, ascites control is important to improve the patient’s quality of life and the prognosis of BCS. Although an improvement in the prognosis following PVS insertion remains to be confirmed formally, prior to treatment our patient was dying, whereas afterwards his nutrition improved and he was able to return to work. The Denver® PVS is one treatment option if paracentesis is effective, but is required multiple times for intractable ascites.

The authors state that they have no Conflict of Interest (COI).

Financial Support
This study was supported by a Takako Satake Award from Tokyo Women’s Medical University and a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science, and Technology, Japan (#26461024-0001) to T.K.

References
1. Lewis SM, Dacie JV. The aplastic anaemia–paroxysmal nocturnal haemoglobinuria syndrome. Br J Haematol 13: 236-251, 1967.
2. Griscelli-Bennaceur A, Gluckman E, Scrobhacili ML, et al. Aplastic anemia and paroxysmal nocturnal hemoglobinuria: search for a pathogenetic link. Blood 85: 1354-1363, 1995.
3. Marsh JC, Elebute MO. Stem cells in paroxysmal nocturnal hemoglobinuria and aplastic anemia: increasing evidence for overlap of haemopoietic defect. Transfus Med 13: 377-386, 2003.
4. Hillmen P, Lewis SM, Bessler M, Luzzato L, Dacie JV. Natural history of paroxysmal nocturnal hemoglobinuria. N Engl J Med 333: 1253-1258, 1995.
5. Leebeck FW, Smalberg JH, Janssen HL. Prothrombotic disorders in abdominal vein thrombosis. Neth J Med 70: 400-405, 2012.
6. Miyata T, Takeda J, Iida Y, et al. The cloning of PIG-A, a component in the early step of GPI-anchor biosynthesis. Science 259: 1318-1320, 1993.
7. Takeda J, Miyata T, Kawagoe K, et al. Deficiency of the GPI anchor caused by a somatic mutation of the PIG-A gene in paroxysmal nocturnal hemoglobinuria. Cell 73: 703-711, 1993.
8. Bessler M, Mason P, Hillmen P, Luzzato L. Somatic mutations and cellular selection in paroxysmal nocturnal haemoglobinuria. Lancet 343: 951-953, 1994.
9. Brodsky RA, Vala MS, Barber JP, Medof ME, Jones RJ. Resistance to apoptosis caused by PIG-A gene mutations in paroxysmal nocturnal hemoglobinuria. Proc Natl Acad Sci U S A 94: 8756-8760, 1997.
10. Hoeckstra J, Leebeck FW, Plessier A, et al. Paroxysmal nocturnal hemoglobinuria in Budd-Chiari syndrome: findings from a cohort study. J Hepatol 51: 696-706, 2009.
11. Menon KV, Shah V, Kamath PS. The Budd-Chiari syndrome. N Engl J Med 350: 578-585, 2004.
12. Ziakas PD, Poulou LS, Rekas GI, Bartzoudis D, Voulgarelis M. Thrombosis in paroxysmal nocturnal hemoglobinuria: sites, risks, outcome. An overview. J Thromb Haemost 5: 642-645, 2007.
13. Hemming AW, Langer B, Greig P, Taylor BR, Adams R, Heathcote EJ. Treatment of Budd-Chiari syndrome with porto-systemic shunt or liver transplantation. Am J Surg 171: 176-180; discussion 80-81, 1996.
14. McMullin MF, Hillmen P, Jackson J, Ganly P, Luzzato L. Tissue plasminogen activator for hepatic vein thrombosis in paroxysmal nocturnal haemoglobinuria. J Intern Med 235: 85-89, 1994.
15. Hauser AC, Bricta A, Pabinger-Fasching I, Jäger U. Fibrinolytic therapy with rt-PA in a patient with aroxysmal nocturnal hemoglobinuria and Budd-Chiari syndrome. Ann Hematol 82: 299-302, 2003.
16. Kuo GP, Brodsky RA, Kim HS. Catheter-directed thrombolysis and thrombectomy for the Budd-Chiari syndrome in paroxysmal nocturnal hemoglobinuria in three patients. J Vasc Interv Radiol 17: 383-387, 2006.
17. Orloff MJ, Daily PO, Orloff SL, Girard B, Orloff MS. A 27-year experience with surgical treatment of Budd-Chiari syndrome. Ann Surg 232: 340-352, 2000.
18. Darwin Murad S, Valla DC, de Groen PC, et al. Determinants of survival and the effect of portosystemic shunting in patients with Budd-Chiari syndrome. Hepatology 39: 500-508, 2004.
19. Hall C, Richards S, Hillmen P. Primary prophylaxis with warfarin prevents thrombosis in paroxysmal nocturnal hemoglobinuria (PNH). Blood 102: 3587-3591, 2003.
20. Gines P, Arroyo V, Vargas V, et al. Paracentesis with intravenous infusion of albumin as compared with peritoneovenous shunting in cirrhosis with refractory ascites. N Engl J Med 325: 829-835, 1991.
21. Bismuth H, Sherlock DJ. Portasystemic shunting versus liver transplantation for the Budd-Chiari syndrome. Ann Surg 214: 581-589, 1991.
22. Ganger DR, Klapman JB, McDonald V, et al. Transjugular intraperi- hepatocitary portosystemic shunt (TIPS) for Budd-Chiari syndrome or portal vein thrombosis: review of indications and problems. Am J Gastroenterol 94: 603-608, 1999.
23. Rosemurgy AS, Zervos EM, Clark WC, et al. TIPS versus peritoneovenous shunt in the treatment of medically intractable ascites: a prospective randomized trial. Ann Surg 239: 883-889; discussion 9-91, 2004.
24. Sharma A, Itha S, Baijal SS, Gupta R, Sonkar A, Aggarwal R. Superior sagittal sinus thrombosis and Budd-Chiari syndrome due to paroxysmal nocturnal hemoglobinuria managed with transjugular intrahepatic portosystemic shunt: a case report. Trop Gastroenterol...
25. Leveen HH, Christoudias G, Ip M, et al. Peritoneovenous shunting for ascites. Ann Surg 180: 580-591, 1974.
26. Shen W, Clemente MJ, Hosono N, et al. Deep sequencing reveals stepwise mutation acquisition in paroxysmal nocturnal hemoglobinuria. J Clin Invest 124: 4529-4538, 2014.
27. Malato A, Saccullo G, Coco LL, et al. Thrombotic complications in paroxysmal nocturnal haemoglobinuria: a literature review. Blood Transfus 10: 428-435, 2012.
28. Nishimura J, Kanakura Y, Ware RE, et al. Clinical course and flow cytometric analysis of paroxysmal nocturnal hemoglobinuria in the United States and Japan. Medicine (Baltimore) 83: 193-207, 2004.
29. Moyo VM, Mukhina GL, Garrett ES, Brodsky RA. Natural history of paroxysmal nocturnal haemoglobinuria using modern diagnostic assays. Br J Haematol 126: 133-138, 2004.
30. Darnige L, Peffault de Latour R, Zemori L, et al. Antiphospholipid antibodies in patients with paroxysmal nocturnal haemoglobinuria receiving eculizumab. Br J Haematol 153: 789-791, 2011.
31. Scheinberg P, Marte M, Nunez O, Young NS. Paroxysmal nocturnal hemoglobinuria clones in severe aplastic anemia patients treated with horse anti-thymocyte globulin plus cyclosporine. Haematologica 95: 1075-1080, 2010.
32. Hillmen P, Hall C, Marsh JC, et al. Effect of eculizumab on hemolysis and transfusion requirements in patients with paroxysmal nocturnal hemoglobinuria. N Engl J Med 350: 552-559, 2004.
33. Helley D, de Latour RP, Porcher R, et al. Evaluation of hemostasis and endothelial function in patients with paroxysmal nocturnal hemoglobinuria receiving eculizumab. Haematologica 95: 574-581, 2010.
34. Brodsky A, Mazzocchi O, Sánchez F, Khursigara G, Malhotra S, Volpacchio M. Eculizumab in paroxysmal nocturnal hemoglobinuria with Budd-Chiari syndrome progressing despite anticoagulation. Exp Hematol Oncol 1: 26, 2012.
35. Schattenfroh N, Bechstein WO, Blumhardt G, et al. Liver transplantation for PNH with Budd-Chiari syndrome. A case report. Transpl Int 6: 354-358, 1993.
36. Bahr MJ, Schubert J, Bleck JS, et al. Recurrence of Budd-Chiari syndrome after liver transplantation in paroxysmal nocturnal hemoglobinuria. Transpl Int 16: 890-894, 2003.
37. Singer AL, Locke JE, Stewart ZA, et al. Successful liver transplantation for Budd-Chiari syndrome in a patient with paroxysmal nocturnal hemoglobinuria treated with the anti-complement antibody eculizumab. Liver Transpl 15: 540-543, 2009.
38. Lund RH, Moritz MW. Complications of Denver peritoneovenous shunting. Arch Surg 117: 924-928, 1982.
39. Tawes RL Jr, Sydorak GR, Kennedy PA, et al. Coagulopathy associated with peritoneovenous shunting. Am J Surg 42: 51-55, 1981.
40. Qi X, Ren W, Wang Y, Guo X, Fan D. Survival and prognostic indicators of Budd-Chiari syndrome: a systematic review of 79 studies. Expert Rev Gastroenterol Hepatol 9: 865-875, 2015.

The Internal Medicine is an Open Access article distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (https://creativecommons.org/licenses/by-nc-nd/4.0/).