

SPECIAL ARTICLE

Changing Nomenclature for PBC: From ‘Cirrhosis’ to ‘Cholangitis’

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The disease entity today widely called ‘primary biliary cirrhosis’ was first described by Addison & Gull in 1851¹ and Hanot in 1876.² One hundred years after its first description, MacMahon & Thannhauser proposed the term ‘xanthomatous biliary cirrhosis’ for this disease based on the typical xanthoma formation with accumulation of cholesterol esters in the skin around the eyes in association with inflammatory destruction of small intrahepatic bile ductules leading to a biliary type cirrhosis.³ Xanthoma formation, however, is not a very common sign in this disorder. This may be the reason why the term ‘primary biliary cirrhosis,’ proposed one year later for the same disorder by Ahrens et al.,⁴ gained wider acceptance when most patients were presenting with advanced liver disease.

Dame Sheila Sherlock, already in 1959, opposed the term ‘primary biliary cirrhosis’ as many of her patients were free of cirrhosis at the time of diagnosis and the mean survival was 5 and a half years (3-11) even for the fatal cases, whereas many asymptomatic patients would survive more than 10 years.⁵ The term ‘primary biliary cirrhosis’ remained an issue of concern as reflected by the name change proposal of Rubin, Schaffner and Popper in 1965 with their paper “Primary Biliary Cirrhosis—Chronic Nonsuppurative Destructive Cholangitis.”⁶ S. Sherlock wisely commented on this new name: “. . . a

better one, although it is unlikely that it will replace the more popular, although inaccurate, one of primary biliary cirrhosis.”⁷ She was right, again. And even 40 years later, the European⁸ and American⁹ Clinical Practice Guidelines still used the term ‘primary biliary cirrhosis’ even though it was an anachronism and did not accurately reflect the natural history of disease in the vast majority of patients as it is today.

The early diagnosis of primary biliary cirrhosis has dramatically improved with the more accurate measurements of markers of cholestasis and improvements in the detection of the classic serologic hallmark, anti-mitochondrial antibodies. Furthermore, the prognosis has dramatically improved with the introduction of orthotopic liver transplantation in the 1970s and 1980s, and of ursodeoxycholic acid (UDCA, 13-15 mg/kg daily) treatment in the 1980s and 1990s. Today, two out of three patients diagnosed with primary biliary cirrhosis and treated with UDCA have an expected survival not different from the general population and only a minority will ever develop cirrhosis.

The pathogenesis of primary biliary cirrhosis remains enigmatic although enormous progress has been made in unravelling genetic, immunological and pathophysiological molecular mechanisms involved.¹⁰⁻¹³ This has also led to new therapeutic approaches which are now under evaluation.^{14,15}

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On 23–24 May, 2014, the 2nd European Association for the Study of the Liver (EASL) Monothematic Conference on Primary Biliary Cirrhosis took place in Milan, Italy. On this occasion, patient representatives from the UK and Germany, Robert Mitchell-Thain and Ingo van Thiel, representing numerous national patient groups from different parts of the world requested to change the name of ‘primary biliary cirrhosis’ to “correct the inaccuracy” and “remove the cirrhosis stigma” as well as all the misunderstanding, disadvantages and discriminations emanating from this misnomer in daily life of the patients. This initiative was based on former discussions at a meeting with international patient advocates and medical experts led by Raoul Poupon of France during the EASL International Liver Congress 2014 in London, and based in part on worldwide survey by patient support groups performed among >1200 patients with primary biliary cirrhosis.

E-mail discussions among experts in the field before the meeting, as well as intense discussions during the EASL Monothematic Conference in Milan with continual e-mail exchanges after the meeting has led to the widespread view among the vast majority of worldwide experts that; (1) the name ‘primary biliary cirrhosis’ should be changed (as advocated by Dame Sheila Sherlock in 1959). In addition, the following proposals found broad support among the discussants; (2) the acronym ‘PBC’ should be kept if possible; (3) a simple and short term should be used (imperfection acceptable) as long as the exact pathogenesis of primary biliary cirrhosis remained undefined and, therefore, an ‘ideal’ replacement is not available.

In parallel with the growing patient support from Europe and the U.S., several surveys were performed among international experts in the field. Among EASL-selected committee members and senior reviewers of the EASL Guidelines for management of cholestatic liver diseases (n = 15), 100% agreed to a name change for primary biliary cirrhosis and 100% voted to keep the abbreviation ‘PBC.’ 60% preferred ‘primary biliary cholangitis,’ 20% ‘primary biliary cholangiopathy,’ and 20% various other names. Among international experts from the American Association for the Study of Liver Disease (AASLD), Asian Pacific Association for the Study of the Liver (APASL) and EASL [outside the EASL committees] (n = 16), 88% agreed to a name change for primary biliary cirrhosis and 88% voted to keep the abbreviation ‘PBC.’ 56% preferred ‘primary biliary cholangitis,’ 13% ‘primary biliary cholangiopathy,’ and 38% various other names. Among Japanese experts (n = 18), 100% agreed to a name change for primary biliary cirrhosis and 78% voted to keep the abbreviation

PBC. 61% preferred ‘primary biliary cholangitis,’ 28% ‘primary biliary cholangiopathy,’ and 11% various other names. Thus, considering that imperfection was acceptable in name finding, ‘primary biliary cholangitis’ found the broadest support as the new name for PBC among experts worldwide.

Our goal, as physicians, is to help and heal our patients both actively at the bedside but also passively in everyday social challenges as patients balance their personal lives with their clinical needs. Our misuse of the name ‘cirrhosis’ is counterproductive to our support and our role as physicians. We should also note that the change of name for an autoimmune disease is not without precedence: Wegener’s granulomatosis for example is now known as granulomatous polyangiitis.

The proposal for a name change of primary biliary cirrhosis to ‘primary biliary cholangitis’ was approved by the EASL Governing Board in November 2014, by the AASLD Governing Board in April 2015 and by the American Gastroenterological Association (AGA) Governing Board in July 2015. A vote of the APASL Governing Board and the United European Gastroenterology (UEG) Governing Board was pending at the moment this article was written, whereas support by respected Governing Board members from both associations was provided beforehand.

What are the next steps? The World Health Organization (WHO) is asking medical professionals for the first time to help in the revision process of the diagnosis and symptom codes (International Classification of Diseases 11th Revision, ICD-11). The medical representatives of the “Name Change Initiative for PBC”—with support of the international primary biliary cirrhosis patient groups—will take responsibility to submit the joint proposal of international experts around the world for the name ‘primary biliary cholangitis.’

We are aware of the imperfection of the new simple name and agree that alternative proposals like primary small bile duct cholangitis, primary intrahepatic cholangitis, primary small bile duct cholangiopathy, primary biliary/peripheral (destructive) cholangitis, or primary cholangiohepatitis may come somewhat closer to what we think this inflammatory liver disorder is about. However, we would kindly remind all critics of the fate of Hans Popper’s carefully chosen ‘chronic non-suppurative destructive cholangitis’—too difficult according to the late Dame Sheila Sherlock. It failed to reach sufficient support.

‘Primary biliary cholangitis’ is a tautology (“saying the same thing twice”), some critics say. But is that true? ‘Cholangitis’ adequately describes the dense inflammatory infiltrates around small damaged interlobular bile

ductules. Recent experimental evidence suggests that hydrophobic bile acids in bile, the major biliary organic solutes, may play a crucial role in the initiation of inflammation in primary biliary cirrhosis.¹⁶⁻²¹ Future research will teach us whether we have chosen a simple and, beyond that, reasonable name.

The new term 'primary biliary cholangitis' will lead to confusion in daily clinical practice with other forms of immune-mediated cholangitis such as primary sclerosing cholangitis (PSC), some critics say. Indeed, the term 'cholangitis' is a general description of an inflammatory disorder of the intra- and/or extrahepatic bile ducts as is 'cirrhosis' for the description of replacement of normal liver tissue by scar tissue. The name change for primary biliary cirrhosis offers the unique opportunity for new awareness campaigns among medical professionals as well as patient groups to draw more attention to immune-mediated biliary diseases like PBC or PSC and, ultimately, their early correct diagnosis and treatment.

From 'cirrhosis' to 'cholangitis'—the change has critical implications for patients. It removes the stigmata of cirrhosis and its implications of alcohol abuse. It removes the stigmata of a poor prognosis. Its removal reminds patients that they are living with this syndrome, not dying of it. Its removal improves their opportunities in the workplace and in their everyday social lives. Thus, we sincerely call on all medical professionals and all patients and their families and friends worldwide to use from this moment on the name 'primary biliary cholangitis' for the disease known by its abbreviation PBC! We owe this to our patients and to further our role as caring physicians.

References

- Addison T, Gull W. On a certain affection of the skin—vitiligoidea a plana, b tuberosa. *Guy's Hosp Rep* 1851;7:265-276.
- Hanot V. Study on a form of hypertrophic liver cirrhosis [hypertrophic cirrhosis with chronic jaundice]. Paris: JBBaillière; 1876.
- MacMahon HE, Thannhauser SJ. Xanthomatous biliary cirrhosis: a clinical syndrome. *Ann Intern Med* 1949;30:121-179.
- Ahrens EH, Jr., Payne MA, Kunkel HG, Eisenmenger WJ, Blondheim SH. Primary biliary cirrhosis. *Medicine* 1950;29:299-364.
- Sherlock S. Primary biliary cirrhosis (chronic intrahepatic obstructive jaundice). *Gastroenterology* 1959;37:574-586.
- Rubin E, Schaffner F, Popper H. Primary biliary cirrhosis chronic non-suppurative destructive cholangitis. *Am J Pathol* 1965;46:387-407.
- Sherlock S. *Diseases of the Liver and Biliary System*. Oxford, UK: Blackwell Scientific; 1968.
- European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of cholestatic liver diseases. *J Hepatol* 2009; 51:237-267.
- Lindor KD, Gershwin ME, Poupon R, Kaplan M, Bergasa NV, Heathcote EJ. Primary biliary cirrhosis. *HEPATOLOGY* 2009;50:291-308.
- Gershwin ME, Mackay IR. The causes of primary biliary cirrhosis: convenient and inconvenient truths. *HEPATOLOGY* 2008;47:737-745.
- Bianchi I, Carbone M, Lleo A, Invernizzi P. Genetics and epigenetics of primary biliary cirrhosis. *Semin Liver Dis* 2014;34:255-264.
- Hirschfield GM, Gershwin ME. The immunobiology and pathophysiology of primary biliary cirrhosis. *Ann Rev Pathol* 2013;8:303-330.
- Lleo A, Maroni L, Glaser S, Alpini G, Marziani M. Role of cholangiocytes in primary biliary cirrhosis. *Semin Liver Dis* 2014;34:273-284.
- Beuers U, Trauner M, Jansen PL, Poupon R. New paradigms in the treatment of hepatic cholestasis: from UDCA to FXR, PXR and beyond. *J Hepatol* 2015;62(1 Suppl):S25-S37.
- Dyson JK, Hirschfield GM, Adams DH, Beuers U, Mann DA, Lindor KD, Jones DE. Novel therapeutic targets in primary biliary cirrhosis. *Nat Rev Gastroenterol Hepatol* 2015;12:147-158.
- Odin JA, Huebert RC, Casciola-Rosen L, LaRusso NF, Rosen A. Bcl-2-dependent oxidation of pyruvate dehydrogenase-E2, a primary biliary cirrhosis autoantigen, during apoptosis. *J Clin Invest* 2001;108:223-232.
- Beuers U, Hohenester S, Maillette de Buy Wenniger L, Kremer AE, Jansen PL, Oude Elferink RP. The biliary HCO₃ umbrella—a unifying hypothesis on pathogenetic and therapeutic aspects of fibrosing cholangiopathies. *HEPATOLOGY* 2010;52:1489-1496.
- Hohenester S, Wenniger LM**, Paulusma CC, van Vliet SJ, Jefferson DM, Elferink RP, Beuers U. A biliary HCO₃- umbrella constitutes a protective mechanism against bile acid-induced injury in human cholangiocytes. *HEPATOLOGY* 2012;55:173-183.
- Banales JM, Sáez E, Uriz M, Sarvide S, Urribarri AD, Splinter P, et al. Up-regulation of microRNA 506 leads to decreased Cl-/HCO₃- anion exchanger 2 expression in biliary epithelium of patients with primary biliary cirrhosis. *HEPATOLOGY* 2012;56:687-697.
- Lleo A, Bowlus CL, Yang GX, Invernizzi P, Podda M, Van de Water J, et al. Biliary apoptoses and anti-mitochondrial antibodies activate innate immune responses in primary biliary cirrhosis. *HEPATOLOGY* 2010;52: 987-998.
- Sasaki M, Miyakoshi M, Sato Y, Nakanuma Y. Increased expression of mitochondrial proteins associated with autophagy in biliary epithelial lesions in primary biliary cirrhosis. *Liver Int* 2013;33:312-320.

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