Autoimmune Diseases of the Liver

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Abstracts of Invited Lectures
Poster Abstracts

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AUTOIMMUNE DISEASES OF THE LIVER

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Scientific Organization:
U. Beuers, Amsterdam (The Netherlands)
H. Cortez-Pinto, Lisbon (Portugal)
P. Ginès, Barcelona (Spain)
A.W. Lohse, Hamburg (Germany)
A. Parés, Barcelona (Spain)
Session I

Introduction

Chair:
H. Cortez-Pinto, Lisbon
P. Ginès, Barcelona

Worldwide incidence of autoimmune liver diseases
P. Jepsen, L. Grønbæk, H.A. Vilstrup, Aarhus 17

Are there common genetic factors among the three autoimmune liver diseases?
T.H. Karlsen, Oslo 18

Extrahepatic manifestations associated with autoimmune hepatitis
M.A. Heneghan, London 19

Pediatric autoimmune liver diseases
R. Liberal, London 20

Session II

Autoimmune hepatitis

Chair:
A.W. Lohse, Hamburg
A. Parés, Barcelona

Diagnostic criteria: Scores and more
A.W. Lohse, Hamburg 23

Role of histopathology: What is typical for, what is compatible with AIH?
D.G. Tiniakos, Newcastle upon Tyne 24

Autoantibodies in autoimmune hepatitis: Which ones, with what tests, how often?
Autoimmune hepatitis: From pathogenesis to novel immune therapies
J. Herkel, Hamburg

Session II (cont)

Autoimmune hepatitis/Primary biliary cirrhosis

Chair:
A.W. Lohse, Hamburg
A. Parés, Barcelona

Standard treatment in adults: Which steroids? Or without steroids?
D.C. Gleeson, Sheffield

AIH: Which alternative for difficult to treat patients?
C. Schramm, Hamburg

Geoepidemiology, genetic and environmental risk factors for PBC
P. Invernizzi, Rozzano

The immunobiology and pathophysiology of PBC
G. Hirschfield, Birmingham

Treatment of autoimmune hepatitis: Should we ever stop?
G. Bouma, Amsterdam

Session III

Primary biliary cirrhosis

Chair:
U. Beuers, Amsterdam
A. Parés, Barcelona

Fatigue in PBC. Prevalence, pathogenesis and management
D.E.J. Jones, Newcastle upon Tyne

Non-invasive assessment of liver fibrosis progression and prognosis in PBC
R. Poupon, Paris

Surrogate markers for optimal therapeutic response to UDCA
H.R. van Buuren, W.J. Lammers, M.H. Harms,
B.E. Hansen, Rotterdam
Novel approaches for patients with suboptimal response to UDCA
A. Parés, Barcelona

Session IV

Primary sclerosing cholangitis

Chair:
U. Beuers, Amsterdam
H. Cortez-Pinto, Lisbon

Diagnosis, differential diagnosis, and epidemiology of primary sclerosing cholangitis
C.Y. Ponsioen, Amsterdam

Genetic factors: Their role in pathogenesis of PSC
A. Franke, Kiel

Immunopathology of PSC
D.H. Adams, P.J. Trivedi, Birmingham

Malignancies in primary sclerosing cholangitis – A continuing threat
L. Fabris, Padova

Presentation of poster prizes
P. Ginès, Barcelona; U. Beuers, Amsterdam

Session IV (cont)

Primary sclerosing cholangitis

Chair:
U. Beuers, Amsterdam
P. Ginès, Barcelona

Therapy of PSC today and tomorrow
M. Trauner, Vienna

Pathogenesis and management of pruritus in PBC and PSC
A.E. Kremer, Erlangen
IgG4-associated cholangitis: A mimic of primary sclerosing cholangitis

U. Beuers, L. Hubers, M. Doorenspleet, L. Maillette de Buy Wenniger, S. van de Graaf, N. de Vries, Amsterdam

55 – 57

Overlap syndromes

O. Chazouillères, Paris

58 – 59

List of Chairpersons, Speakers and Scientific Organizers

61 – 63
Poster Abstracts

PBC

1. Non-invasive assessment of disease stage in patients with primary biliary cirrhosis
   N. Ben Mustapha, M. Mahmoudi, M. Amri, R. Ben Jemaa, M. Fekih, L. Kallel, M. Serghini, S. Matri, J. Boubaker, A. Filali (Tunis, TN)

2. The UK-PBC Risk Score: Derivation and validation of a risk score to predict liver events in PBC

3. The role of peripheral blood Treg and Th17 cells in primary biliary cirrhosis

4. Primary biliary cirrhosis: Clinical characteristics and treatment response
   D. Dukova, I. Ivanova, I.A. Kotzev (Varna, BG)

5. The impact of age at presentation on symptoms in primary biliary cirrhosis

6. Age at presentation and gender are predictors of increased mortality over long-term follow-up in primary biliary cirrhosis
   J. Dyson, L. Jopson, S. Ducker, D.E.J. Jones (Newcastle upon Tyne, GB)

7. Alternative to liver biopsy in primary biliary cirrhosis: Non-invasive serum markers of liver fibrosis
   E. Gravito-Soares, M. Gravito-Soares, C. Lerias, S. Lopes, C.M.R. Sofia (Coimbra, PT)

8. Is primary biliary cirrhosis a systemic disease? Cardiovascular risk assessment
   M. Gravito-Soares, E. Gravito-Soares, C. Agostinho, D. Gomes, P. Figueiredo, L. Tome, C.M.R. Sofia (Coimbra, PT)

9. Antimitochondrial antibody-negative primary biliary cirrhosis: A different entity?
   M. Gravito-Soares, E. Gravito-Soares, S. Lopes, C. Agostinho, D. Gomes, P. Figueiredo, L. Tome, C. Sofia (Coimbra, PT)

10. Expression of IL-17 and IgG4 in portal tracts in primary biliary cirrhosis
    M.V. Gulubova, K. Ivanova, J. Ananiev, M.M. Iganatova (Stara Zagora, BG)


16. Enhanced expression of hepatic fibroblast growth factor 19 (FGF19) is associated with suppression CYP7A1 and correlates with severity of the disease in primary biliary cirrhosis M. Milkiewicz, E. Wunsch, U. Wasik, J. Trottier, A. Kępinska-Podhorodecka, E. Elias, O. Barbier, P. Milkiewicz (Szczecin, Warsaw, PL; Quebec, CA; Birmingham, GB)

17. CTLA-4 and TNF-α polymorphisms and concomitant autoimmune diseases in Slovenian patients with primary biliary cirrhosis K. Novak, M. Ribnikar, A. Markovic-Predan, K. Zaletel, A. Bicek, V. Dolzan (Ljubljana, SI)

18. GP210 and/or SP100 autoantibodies in primary biliary cirrhosis: Predictors of cirrhosis/autoimmune (AIH) overlap syndrome? O. Taiwo, S. Mathew, J. Van Vlymen, A. Correa, J. Deacock, P. Berry, K. Cheent, H. Lewis, A. Ala (Guildford, Frimley, GB)
PSC

19. Clinical features and outcome of CSP patients with IBD: A comparative single center experience

20. The bile acid intermediate c4 and serum bile acid levels are potential mechanistic endpoints in human cholestatic trials: The ATRA + UDCA pilot in PSC
D.N. Assis, K.D.R. Setchell, J.L. Boyer (New Haven, Cincinnati, US)

21. Changing pattern of indications and results of endoscopic retrograde cholangiopancreatography in patients with primary sclerosing cholangitis

22. Transplant-free survival is PSC is influenced by azathioprine, steroids and the presence of inflammatory bowel disease

23. Primary sclerosing cholangitis: A review of clinical cases
M. Stambolyiska, K. Ivanov, D. Gancheva, I.A. Kotzev (Varna, BG)

24. VAP-1 is elevated in PSC, correlates with clinical outcome and exhibits amine oxidase activity in a substrate-dependent manner

25. Connecting liver and gut in PSC: CCL25 expression is upregulated in colitis, correlates with inflammatory activity and facilitates effector CCR9+ lymphocyte recruitment

26. Sulphotransferase2A1 (SULT2A1) is not adequately induced in patients with primary sclerosing cholangitis
U. Wasik, E. Wunsch, M. Milkiewicz, A. Kempinska-Podhorodecka, E. Elias, P. Milkiewicz (Szczecin, Warsaw, PL; Birmingham, GB)

27. Serum autotaxin is associated with pruritus and severity of liver disease in primary sclerosing cholangitis
E. Wunsch, A. Kremer, J. Trottier, M. Krawczyk, O. Barbier, F. Lammert, P. Milkiewicz (Szczecin, PL; Erlangen, DE; Quebec, CA; Homburg, DE)
AIH

28. Celiac disease, cryptogenic hypertransaminasemia and autoimmune hepatitis

29. Impact of age on natural history and response to treatment of autoimmune hepatitis
   M. Amri, L. Kallel, M. Mahmoudi, M. Serghini, N. Ben Mustapha, M. Fekih,
   S. Matri, J. Boubaker, A. Filali (Tunis, TN)

30. Autoimmune hepatitis: A challenging disease deserving of specialist care
   G.D. Appanna, M.A. Czajkowski, A.D. Yeoman (Newport, GB)

31. Autoimmune hepatitis and the polyglandular autoimmune syndrome type 1 in 12-year-old girl
   K. Bak-Drabik, J. Porebska, A. Chobot, A. Krzywicka (Zabrze, PL)

32. Celiac disease-associated autoimmune liver and thyroid diseases in a pediatric population from Western Romania
   O.-A. Belei, L. Olariu, M. Pop, O. Gradinaru-Tascau, T. Marcovici, O. Marginian
   (Timisoara, RO)

33. Autoimmune hepatitis and cryptogenic hypertransaminasemia among Romanian children with celiac disease
   O.-A. Belei, L. Olariu, A. Craciun, T. Marcovici, O. Gradinaru-Tascau,
   I. Simedrea, O. Marginian (Timisoara, RO)

34. Prevalence of hepatitis B virus infection in patients with autoimmune hepatitis in a Tunisian patient population
   R. Ben Jemaa, M. Fekih, W. Ben Ameur, S. Matri, M. Serghini, J. Boubaker,
   L. Kallel, A. Filali (Tunis, TN)

35. Biomarkers of oxidative stress and their implication in autoimmune hepatitis
   M.C. Bezna, C. Deliu, M. Bezna, O. Diaconu, N. Gard, M. Balasoiu
   (Craiova, RO)

36. Celiac disease with autoimmune hepatitis; a case report
   (Antalya, TR)

37. A 20-year experience in the treatment of autoimmune hepatitis
   V. Chaloska-Ivanova, V. Serafimoski, M. Miloshevska, M. Genadieva-Dimitrova,
   B. Todorovska (Skopje, MK)

38. Bone mineral density in Tunisian patients with autoimmune hepatitis
   M. Cheikh, H. Romdhane, R. Ennaifer, H. Ben Nejma, W. Bougassas,
   N. Bel Hadj (Tunis, TN)
39. Clinical features of autoimmune hepatitis in the elderly. Results of a Tunisian study
   M. Cheikh, H. Romdhane, R. Ennaifer, H. Ben Nejma, W. Bougassas, N. Bel Hadj (Tunis, TN)

40. Concurrent autoimmune diseases in patients with autoimmune hepatitis. Results of a Tunisian survey
   M. Cheikh, H. Romdhane, R. Ennaifer, H. Ben Nejma, W. Bougassas, N. Bel Hadj (Tunis, TN)

41. Etanercept-induced fever in autoimmune hepatitis
   E. Ergin (Manisa, TR)

42. Autoimmune and cholestatic liver disorders
   E. Ergin (Manisa, TR)

43. Autoimmune diseases are common in patients with autoimmune hepatitis
   F. Gundling, T. Leimbach, A. Nerlich, W. Schepp (Munich, DE)

44. The primary biliary cirrhosis (PBC)-autoimmune hepatitis (AIH) overlap syndrome - A single center Tunisian experience

45. Efficacy of alternative immunosuppressive strategy to induce and maintain remission in patients with autoimmune hepatitis
   V. Hejda, J. Kozeluhova, K. Balihar, H. Mirka, O. Daum (Pilsen, CZ)

46. Upper gastrointestinal mucosal lesions and Helicobacter pylori infection in autoimmune liver disease
   E. Kasap, U. Demirci, T. Buran, H. Yüceyar (Manisa, TR)

47. Combined liver injury (overlap syndrome), particular qualities of flow
   N.V. Kharchenko, G. Anokhina, V. Kharchenko, D. Janelidze (Kiev, UA)

48. Epidemiological and clinical characteristics of autoimmune hepatitis in Albania
   B. Kraja, I. Akshija, D. Vathi, F. Kraja, A. Babameto (Tirana, AL)

49. Epidemiological, clinical and therapeutic characteristics of autoimmune hepatitis. Results of a Tunisian study
   M. Labbane, K. Torjmane, S. Zarrouk, Y. Bouteraa, S. Ouerdiane (Bizerta, TN)

50. Ultrastructural features of hepatic fibrogenesis in children with autoimmune hepatitis
   J.M. Lotowska, M.E. Sobaniec-Lotowska, D.M. Lebensztejn, S. Sulkowski (Bialystok, PL)
51. Myeloid-derived suppressor cells and the liver microenvironment in autoimmune liver disease  
X. Ma, H. Zhang, Z. Bian, Q. Wang, P. Invernizzi, M.E. Gershwin  
(Shanghai, CN; Rozzano, IT; Davis, US)

52. The most common rheumatic diseases in patients with autoimmune liver disease in a Tunisian center  
M. Mahmoudi, N. Ben Mustapha, M. Amri, R. Ben Jemaa, M. Fekih, L. Kallel,  
M. Serghini, S. Matri, J. Boubaker, A. Filali (Tunis, TN)

53. The role of repeat liver biopsies in autoimmune hepatitis: Clinical practice and outcomes  
S. Mathew, R. Narang, M. Pericleous, A. Ramu, P. Berry, K. Cheent, H. Lewis,  
G. Kousparos, A. Ala (Frimley, GB)

54. Correlations between serologic markers, clinical presentation and response to treatment in patients with autoimmune hepatitis at a tertiary referral center  
R. Maxim, A. Chelaru, E. Sarca, A. Plesa (Iasi, RO)

55. Aspartate aminotransferase to platelet ratio index for fibrosis and cirrhosis evaluation in autoimmune liver diseases  
R. Maxim, A. Trifan, O. Stoica, A. Plesa, C. Stanciu (Iasi, RO)

56. Autoimmune hepatitis/primary biliary cirrhosis (AIH/PBC)-overlap syndrome (OS) and hepatic carcinogenesis  
K. Pavlov, J. Genov, R. Mitova, D. Sotirov, I. Terziev, B. Vladimirov, D. Dimitrov,  
M. Spasov, G. Taneva, E. Pophristova (Sofia, BG)

57. Angiotensin converting enzyme for non-invasive assessment of liver fibrosis in autoimmune hepatitis  
T. Pürnak, C. Efe, Y. Beyazit, E. Özaslan (Ankara, Batman, Canakkale, TR)

58. Ultrastructural characteristics of sinusoidal Kupffer cells/macrophages in pediatric autoimmune hepatitis – The analysis of 17 cases  
M.E. Sobaniec-Lotowska, J.M. Lotowska, D.M. Lebensztejn, S.B. Lotowska (Bialystok, PL)

59. Therapeutic strategies in autoimmune hepatitis: Results from daily practice  
C. Teixeira, D. Trabulo, S. Ribeiro, C. Martins, C. Cardoso, I. Cremers,  
A.L. Alves, A.P. Oliveira (Setubal, PT)

60. Use of tacrolimus in patients with treatment resistant type 1 autoimmune hepatitis  
N.N. Than, C. Wiegard, K. Fussel, J. Mann, G. Hirschfield, A.W. Lohse,  
D.H. Adams, C. Schramm, Y.H. Oo (Birmingham, GB; Hamburg, DE)
61. Serological differential diagnosis of autoimmune liver diseases by line immunoassay for parallel detection of 9 different autoantibodies
T. Velikova, E. Ivanova-Todorova, K. Toumangelova-Yuzeir, L. Kancheva, D. Kyurkchiev, B. Tomov, A. Aleksiev, R. Nikolov, L. Mateva-Vladimirova (Sofia, BG)

62. Infliximab leading to autoimmune hepatitis: An increasingly recognized side effect

63. The use of azathioprine metabolites in monitoring patients with autoimmune hepatitis
F. Yousuf, P. Richardson, T. Cross, I. Patanwala (Liverpool, GB)

64. Diagnostic value of autoantibodies to asialoglycoprotein receptor (ASGPR) in children with autoimmune hepatitis
O. Zaja, A. Tesija Kuna, A. Jaklin Kekez, I. Vukasovic, N. Vrkić (Zagreb, HR)

MISCELLANEOUS

65. Perioperative and long-term morbi-mortality associated with surgery for ileocecal Crohn's disease

66. Liver abnormalities in patients with primary Sjögren's syndrome

67. Assessment of coagulation status in cirrhotic patients
M. Fekih, A. Laabidi, H. Baccouche, K. Agar, J. Boubaker, N. Ben Romdhane, L. Kallel, A. Filali (Nabeul, Tunis, TN)

68. Anomalies of bone tissue metabolism during cirrhosis

69. Hepatobiliary manifestations in Tunisian inflammatory bowel disease patients
L. Hamzaoui, M. Mahmoudi, S. Elbouchtili, M. Medhioub, H. Ezzine, M.M. Azouz (Tunis, Nabeul, TN)

70. Does the implementation of a new research-focussed clinical care model improve research activity in autoimmune liver disease?
K. Houghton, S. Ducker, L. Jopson, D. Jones (Newcastle upon Tyne, GB)
71. Epidemological and clinic-pathological survey of patients with autoimmune diseases of the liver in the Austrian Federal State Salzburg: Experience of a single center
   (Salzburg, AT)

72. Impact of viral etiology on hemostatic state in cirrhotic patients

73. Autoimmune disorders in celiac disease
   M. Mahmoudi, N. Ben Mustapha, M. Amri, M. Serghini, L. Kallel, M. Fekih, S. Matri, J. Boubaker, A. Filali (Tunis, TN)

74. The role of ultraviolet phototherapy in treatment of cholestasis-induced pruritus
   D. Neagoe, S. Ianosi, A. Farmazon, D. Toma, A. Fetoiu, T. Ciurea (Craiova, RO)

75. Presepsin as a new biomarker for old expectations in the diagnosis and prognosis of bacterial infection in cirrhosis
   M. Papp, T. Tornai, D. Tornai, Z. Vitalis, I. Tornai, P.L. Lakatos, P. Antal-Szalmas (Debrecen, Budapest, HU)

76. Hypereosinophilic autoimmune liver disease: A report of three unusual cases
   M. Pericleous, S. Mathew, M. Lloyd, P. Berry, H. Lewis, K. Cheent, A. Ramu, A. Ala (Frimley, Guildford, GB)

77. Soluble CD163 (sCD163) is a marker of infection in patients with cirrhosis and acute decompensation and an independent predictor of the short-term mortality
   T. Tornai, D. Tornai, N. Sipeki, I. Foldi, T. Dinya, Z. Vitalis, P. Antal-Szalmas, I. Tornai, M. Papp (Debrecen, HU)

78. Attitude to and practice of diagnostic paracentesis on the general medical take: Room for improvement?
   L. Tyson, K. Patel, S. Mann (London, GB)

* = Posters of Distinction
Session I

Introduction
Worldwide incidence of autoimmune liver diseases

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Background: Variation in the incidence of autoimmune liver diseases may provide insight into risk factors for developing the diseases. We systematically reviewed studies of the incidence of autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), and immunoglobulin G4-associated cholangitis (IAC) in general populations.

Methods: We found relevant articles through Medline and Scopus.

Results: The identified studies varied greatly in their case-finding methods, and few used a standard population. Reported incidence rates of AIH were around 1 per 100,000 population per year, but they were higher in Scandinavia, and a Danish study of the 1994–2012 period found an increasing incidence. Most PBC studies found incidence rates of 1–2 per 100,000 population per year and an increasing time trend, but incidence was lower in the Netherlands and New Zealand and higher in Northeast England. Most studies of PSC found incidence rates around 1 per 100,000 population per year, but there were no incident cases among Alaska natives in 1984–2000. The incidence of IAC remains unknown.

Conclusion: The incidence of the autoimmune liver diseases is around 1–2 per 100,000 population per year for each disease. The variation in incidence over time and place suggests that there are differences in the prevalence of risk factors for the diseases, but the studies used different methods so it is difficult to draw firm conclusions. We recommend that groups of investigators conduct multisite studies with identical case-finding methods, and that they use a standard population to account for differences in demographics.
Are there common genetic factors among the three autoimmune liver diseases?

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Following a series of genetic discoveries in Mendelian liver traits throughout the 1990’s and the first years after 2000, a shift occurred with the application of genome-wide association studies (GWAS) in complex liver traits from 2007 onward. The study design has been applied to primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC) and more recently autoimmune hepatitis (AIH). For all these liver diseases, the defining genetic feature is that of strong associations within the major histocompatibility complex (MHC) on chromosome 6p21. The MHC associations are superimposed onto a background architecture of weaker associations in dozens of genes representing to some extent pathways apparently involving in immune regulation.

As genetic knowledge is accumulating, several features emerge that will be elaborated in the presentation. First, a genetic overlap between the conditions does exist, consistent with the clinical co-occurrence of AIH in patients with PBC and PSC. Examples include SH2B3 and MMEL1/TNFRSF14 (PSC, PBC and AIH); IRF5, STAT4, IL12A and IL12RB (PBC and AIH); CTLA4/CD28 and BACH2 (PSC and AIH). Second, the fraction of the disease liability explained by the genetic findings is less than 10% and not likely to exceed 30–40%, highlighting a major role for interacting environmental factors in the pathophysiology. Third, the gene findings show considerable overlap with prototypical autoimmune diseases like type 1 diabetes and celiac disease, pointing to similar mechanisms involving in the development of autoimmune manifestations in the liver as a generally perceived tolerogenic environment as in other tissues. Finally, in light of the autoimmune genetic architecture, the efficacy of immunosuppressive treatment in PBC and PSC in particular, appears paradoxically poor.

The gene findings collectively represent a major new resource for studies aimed at exploring pathways of tissue injury in autoimmune biliary and liver diseases, with the aim of understanding how the autoreactivity arises, how broadly its targets ranges, and how to effectively treat it.
Extrahepatic manifestations associated with autoimmune hepatitis

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For many patients with autoimmune hepatitis (AIH), the presence of extrahepatic features is well recognised both at presentation and during long-term follow-up. Concomitant “autoimmune disorders” have been described in 30–50% of patients with AIH and moreover, has been described in both adults and children. Indeed, the presence of these associated phenomena has been incorporated into both the original and revised International AIH group scoring systems as an aid to codifying the diagnosis.

In acute index presentations, non-specific joint pains sometimes flitting in nature have been reported in 30–60% of patients, and whilst joint swelling is uncommon, Rheumatoid arthritis and Mixed connective tissue disease have been reported in 2–5% of patients with AIH. For the majority of patients, these joint symptoms resolve within days of the introduction of immunosuppressive therapy. Rarer features at index presentation include a maculopapular skin rash and unexplained fever, again, features that tend to resolve quickly with treatment. Interestingly, joint pain and stiffness is also well recognised in the context of steroid withdrawal and cessation in AIH.

The occasional co-presentation of AIH with coeliac disease is clinically important (1–2%), since for some patients, there is a risk of immunosuppression malabsorption, thus delaying effective treatment. Similarly, the co-existence of selective IgA deficiency can occur in patients with coeliac disease or in isolation. Selective IgA deficiency as a co-existing extrahepatic feature seems to be more common in paediatric patients with AIH. For these patients, they are at increased risk of respiratory and sinus infections. Although, typically associated with primary sclerosing cholangitis (PSC), the presence of inflammatory bowel disease (both Crohn’s disease and Ulcerative Colitis) has been described in between 2 and 8% of patients with AIH. Interestingly, for patients with autoimmune sclerosing cholangitis (AISC) a distinct pattern of inflammatory bowel disease has been recently described. Other conditions have been reported at lower frequency including Sjögren’s syndrome 1–4%, Systemic lupus erythematosus 1–2%, glomerulonephritis 1%. Rarer still and at a frequency of < 1% include fibrosing alveolitis, haemolytic anaemia, vitiligo, glomerulonephritis, uveitis, mononeuritis multiplex, polymyositis and multiple sclerosis. In contrast the reported associations between AIH and thyroiditis 10–23%, diabetes 7–9% and psoriasis 3% are commonly seen and notable in clinical practice.
Pediatric autoimmune liver diseases

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In pediatrics, there are two liver disorders in which liver damage most likely stems from an autoimmune attack: “classical” autoimmune hepatitis (AIH) and the AIH/sclerosing cholangitis overlap syndrome (also known as autoimmune sclerosing cholangitis, ASC). Autoimmunity has also been implicated in the pathogenesis of de-novo AIH arising after liver transplantation.

The presentation of childhood autoimmune liver disease is non-specific and can mimic most other liver disorders. AIH is exquisitely responsive to immunosuppressive treatment, which should be instituted promptly to prevent rapid deterioration and promote remission and long-term survival. Difficult-to-treat or non-responsive patients should be treated with mycophenolate mofetil or, failing that, calcineurin inhibitors. Persistent failure to respond or lack of adherence to treatment result in end-stage liver disease. These patients, and those with fulminant liver failure at diagnosis, will require liver transplantation. ASC responds to the same immunosuppressive treatment used for AIH when treatment is initiated early. Abnormal liver function tests often resolve within few months of treatment, although medium- to long-term prognosis is worse than that of AIH because bile duct disease continues to progress despite treatment in approximately 50% of patients. Ursodeoxycholic acid is usually added to conventional treatment regimen in ASC, but whether this actually helps arrest the progression of bile duct disease remains to be established.

The pathogenesis of pediatric-onset autoimmune liver disease is not fully understood, although there is mounting evidence that genetic susceptibility, molecular mimicry and impaired immunoregulatory networks contribute to the initiation and perpetuation of the autoimmune attack. Liver damage is thought to be mediated primarily by CD4+ T-cells: while Th1 effector cells are associated with hepatocyte damage in both AIH and ASC, Th17 immune responses predominate in the latter where they correlate with biochemical indices of cholestasis, indicating that IL-17 is involved in the bile duct damage characteristic of this condition. Since a substantial difference between these two pathologies is the frequent association of ASC with IBD, it can be speculated that lymphocytes of intestinal origin are present in patients with a diagnosis of ASC rather than those suffering from AIH. Animal models faithfully representing the human condition are needed to unravel the contribution of innate and adaptive, effector and regulatory immune responses. A deeper understanding of the pathogenesis of AIH is likely to contribute to the development of novel treatments, such as the adoptive transfer of autologous expanded antigen-specific regulatory T-cells, which ultimately aim to restore tolerance to liver-derived antigens.
Session II

Autoimmune hepatitis
Diagnostic criteria: Scores and more

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The diagnosis of autoimmune hepatitis is often not easy, and rests on a combination of clinical, laboratory and serological criteria in combination with liver biopsy. Diagnostic difficulties can particularly arise due to the wide heterogeneity of the disease’s spectrum ranging from a very mild sub-clinical smoldering disease up to acute and even fulminant hepatic failure. Diagnostic difficulties can furthermore arise due to co-existence of two conditions. In particular, in Western countries co-existence of fatty liver and NASH with autoimmune hepatitis is observed in up to 10% of cases. Diagnostic scores can help in making the diagnosis, and have an accuracy of about 90%. In untreated patients, the simplified diagnostic score combining the features of raised IgG, presence of autoantibodies (ANA, SMA, SLA/LP, LKM) and absence of viral hepatitis in the patient showing histological features compatible with autoimmune hepatitis is easy to use in everyday practice and detects the majority of cases reliably. The score may miss patients with atypical presentation and in particular patients with very acute disease. In these cases, in whom drug-induced immunoallergic liver injury is the most important differential diagnosis, a trial of corticosteroid treatment is warranted, and the prompt response supports the diagnosis of an immune-mediated liver injury. Whether or not in these cases the immune-mediated injury is autoimmune or drug-induced should be tested by withdrawal of the drug and slow tapering of steroids. In drug-induced liver injury, the inflammation does not recur, while in autoimmune hepatitis recurrence is almost universal. However, it needs to be considered that this recurrence may be delayed up to a year after withdrawal of steroids, and therefore patients with suspected drug-induced liver injury should be followed up regularly. In acute hepatitis, the histological features of autoimmune hepatitis may mimic drug-induced disease with central lobular necrosis rather than periportal interface hepatitis. In these patients, the characteristic histological features only develop a few months later. It would be a mistake not to give immunosuppression in these suspicious cases.

The prompt response to corticosteroids and the almost universal recurrence of the disease after withdrawal of corticosteroids are a reliable feature of autoimmune hepatitis. Patients with suspected autoimmune hepatitis, either on the basis of the simplified score or on the basis of clinical suspicion, should be followed up by these criteria, allowing a reliable diagnosis in almost all cases within the first year of initial presentation.
Role of histopathology: What is typical for, what is compatible with AIH?

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The diagnosis of autoimmune hepatitis (AIH) is clinico-pathological and is based on a combination of biochemical, immunological and histological features and exclusion of other causes of liver disease. Typical histological features include a chronic hepatitis pattern of injury with portal inflammation and interface activity (present in most cases), predominance of plasma cells in the portal infiltrate (present in only 2/3 of biopsies), emperipolesis, and hepatocellular rosette formation. Liver biopsy histology compatible with AIH is one of the four necessary elements for AIH diagnosis according to the recently updated and simplified clinic-pathological criteria. Histopathological criteria for AIH fall into three categories: typical when interface hepatitis, rosettes and emperipolesis are all present, compatible when not all three features are seen, and atypical when an alternative diagnosis is suggested. Centrilobular injury with prominent hepatocellular necrosis and mononuclear inflammation is included in the histological spectrum of AIH and probably represents an early disease stage that may later undergo transition to the classical pattern of interface hepatitis. Current guidelines recommend liver biopsy at presentation to establish diagnosis and guide treatment in all patients with suspected autoimmune hepatitis. However, using the simplified criteria, even in the absence of liver biopsy or of compatible AIH histology, it is possible to reach a probable diagnosis of AIH. At least compatible AIH liver histology is necessary for a definite diagnosis. In the absence of positive autoantibodies in repeated tests, liver biopsy is essential to diagnose “autoantibody-negative” AIH, a variant that responds equally well to corticosteroid therapy. In acute-onset AIH, liver biopsy may exclude other etiology, and support AIH diagnosis by identifying centrilobular necrosis, with or without interface hepatitis, and other typical features. Histological criteria of a probable autoimmune etiology have recently been proposed in acute liver failure patients. These include a distinctive pattern of massive hepatic necrosis with centrilobular accentuation, lymphoid follicles, a plasma cell-rich inflammatory infiltrate and central perivenulitis. Liver histopathology in addition to its role in diagnosis and differential diagnosis of AIH, is also important to assess for possible concurrent disease, to identify cases with overlapping features within the spectrum of autoimmune liver diseases, and to give prognostic information. Communication between clinicians and pathologists and clinico-pathological correlation are essential for getting the most out of a liver biopsy in a patient with suspected AIH and are indispensable for optimal patient management.
Autoantibodies in autoimmune hepatitis: Which ones, with what tests, how often?

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Autoimmune hepatitis is a chronic inflammation of the liver of unknown cause characterized by interface hepatitis on liver biopsy, hypergammaglobulinemia, and serum autoantibodies, the most important of which being anti-nuclear (ANA), anti-smooth muscle (SMA), anti-liver kidney microsomal type 1 (anti-LKM1), anti-liver cytosol type 1 (anti-LC1) and anti-soluble liver antigen (anti-SLA). The precise molecular target(s) of ANA have not been identified as yet: SMA binds to filamentous actin, anti-LKM1 recognizes linear and conformational epitopes of cytochrome P4502D6, anti-LC1 is directed to linear and conformational epitopes of formiminotransferase-cyclodeaminase, anti-SLA reacts with linear and conformational epitopes of O-phosphoseryl-tRNA:selenocysteinyl-tRNA synthese. The detection of at least one of these autoantibodies is considered of particular relevance to corroborate the diagnosis of autoimmune hepatitis.

ANA, SMA, anti-LKM1 and anti-LC1 are usually detected by indirect immunofluorescence on rodent substrate and human epithelial cell lines, whereas anti-SLA is revealed with an immunochemical test with the recombinant protein.

At onset/diagnosis the following hierarchy of frequency was observed in 335 patients with autoimmune hepatitis (female sex 79%, mean age 38 ± 19 years): ANA 61%, SMA 56%, anti-LKM1 16%, anti-SLA 14%, anti-LC1 12%; only 8 patients (2.3%) were seronegative. Two or even three autoantibodies are sometimes detected in the same patient, the most common associations being ANA with SMA, LKM1 with LC1, ANA and/or SMA with anti-SLA. Anti-LKM1 and anti-LC1 were significantly more frequent in children, whereas ANA were more often present in adults; SMA and anti-SLA were not age-dependent.

No correlation was noticed between the autoantibody profile at diagnosis and the features of the disease or the clinical outcome. Over time and in concomitance with the immunosuppressive treatment the diagnostic autoantibodies may change, sometimes remarkably, and even disappear.

In conclusion, the detection of the conventional serological markers of autoimmune hepatitis are essential during the diagnostic process, but these autoantibodies do not possess any prognostic significance, therefore they play no role in the guidance of the clinical and therapeutic decisions.
Autoimmune hepatitis: From pathogenesis to novel immune therapies

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The pathogenesis of autoimmune hepatitis is not clear. It is believed that the disease is driven by an inflammatory immune response to hepatic autoantigens. However, the reasons for the loss of immune tolerance to these autoantigens are not known. The loss of tolerance to liver antigens observed in autoimmune hepatitis is all the more astounding, because the liver is actually known for its peculiar ability to induce tolerance. A common assumption is that a generalized imbalance between pro- and anti-inflammatory mechanisms might account for the loss of tolerance in autoimmune hepatitis. In particular, a defective regulatory T (Treg) cell compartment, marked by reduced frequency and function of Foxp3+ Tregs, was held responsible for the occurrence of autoimmune hepatitis.

As we could not detect a generalized Treg defect in our autoimmune hepatitis patients, we aimed to clarify in mice whether Treg impairment as such might cause loss of tolerance and precipitate autoimmune liver inflammation. To that end, we used a model, which is characterized by ectopic expression of the neural autoantigen myelin basic protein (MBP) in the liver and by abundance of autoreactive MBP-specific T cells, due to a transgenic T cell receptor. As a result of MBP expression in the liver, these mice were tolerant and completely resistant to autoimmune inflammation both in the CNS and the liver. We found that MBP-specific Tregs that were induced in the liver were instrumental for disease resistance. However, even upon severe impairment of the Treg compartment, either by antibody-mediated Treg depletion or prevention of peripheral Treg induction through a T cell-specific dominant-negative TGFβ receptor, complete disease resistance was not abrogated. These findings indicated that Treg impairment alone is not a sufficient cause of autoimmune liver inflammation.

Yet these findings also indicated that the liver might be utilized for the induction of tolerance to non-hepatic autoantigens, such as MBP, provided effective autoantigen delivery to tolerogenic liver cells. As we have previously shown that antigen-presenting LSECs are particularly effective inducers of Tregs, we now have developed a nanoparticle-based method to selectively deliver autoantigen peptides to LSECs in vivo. Indeed, only a single administration of MBP peptide-loaded nanoparticles to mice enabled MBP-specific Treg induction by LSECs and effective treatment of autoimmune neuroinflammation. Our findings provide proof-of-principle that the selective delivery of autoantigen peptides to LSECs by nanoparticles can provide effective treatment of autoimmune diseases. One might speculate that a defective tolerance induction by LSECs and other liver cells might predispose for the development of autoimmune liver inflammation.
Session II (cont)

Autoimmune hepatitis/
Primary biliary cirrhosis
Standard treatment in adults: Which steroids? Or without steroids?

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Standard treatment of autoimmune hepatitis (AIH) in adults is steroid-based. In early trials, prednisolone (Pred) ± azathioprine (AZA) was superior to AZA monotherapy (not significantly better than placebo). There is little evidence for efficacy of cyclosporine and tacrolimus as first-line agents.

Pred (30 reducing to 10 mg/day) plus azathioprine 50 mg/day has similar efficacy to but is better tolerated than Pred alone (60 reducing to 20 mg/day) and so, is the most commonly used regime. Usually, AZA is started 2–4 weeks later (to await exclusion of TPMT deficiency and for serum bilirubin to fall, if initially > 100 µmol/l).

In 90% of so-treated patients, serum transaminases and globulin/IgG fall, with 11–90% achieving normal values after 6–12 months. Patients failing to do so are more likely to develop cirrhosis and liver failure. A higher initial Pred dose (1 mg/kg/day) + AZA achieved 90% serum transaminase normalisation after 6 months but needs longer-term evaluation.

Histological remission (minimal hepatitis on repeat biopsy) lags behind transaminase normalisation by 6–12 months and is achieved in 60–70% of patients after 24–36 months Pred. This lag and the inefficacy of AZA mono-therapy justifies continuing Pred (5–10 mg/day), even after transaminase normalisation, for a total period of > 2 years. Repeat biopsy should be considered then because 40% of patients still have (usually mild) persisting inflammation, despite normal transaminases and IgG. In such patients, fibrosis is less likely to regress and long term mortality may be higher. Optimal treatment for these patients is not defined.

Pred-treated patients need calcium and vitamin D, 1–2 yearly DEXA scans, and bisphosphonates if osteopenia develops. Osteoporosis can usually be prevented. Weight gain should be minimised. Steatosis may develop or worsen on repeat biopsy.

In a large trial, non-cirrhotic treatment-naive patients receiving Budesonide (9 mg/day) + AZA, were more likely to achieve normal serum ALT (not IgG) after 6 months than those receiving Pred (30 mg/day reducing to 10 mg/day) + AZA and had less side effects. This study was short-term, lacked of follow-up histology and rate of transaminase normalisation was low in the Pred group. However, Budesonide may be considered in non-cirrhotic patients in whom there are serious (actual or anticipated) Pred-related side effects.

In an open study of mycophenolate (MMP), with Pred, 88% of treatment-naive patients achieved normal transaminases within 12 months. However, only one of 8 re-biopsied patients achieved histological remission. MMP (unlike AZA) is teratogenic, limiting its use in younger women.
AIH: Which alternative for difficult to treat patients?

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Patients with autoimmune hepatitis (AIH) may confront us with difficult treatment decisions. Among these cases, advanced liver cirrhosis, fulminant AIH with hepatic failure, or pregnancy with highly active AIH will pose challenges on their own. Risk of disease progression including liver transplantation has to be weighed against the risk of drug related side effects, including infectious complications.

Standard treatment of AIH consists of corticosteroids and usually azathioprine. However, up to 15% of patients will require second line treatment. There are no prospective studies evaluating second or third line treatment regimens in AIH. In our opinion it is essential to differentiate between those patients intolerant to standard treatment and those who don’t respond sufficiently to standard treatment. For patients intolerant to prednisolone due to steroid induced side effects, budesonide may be a feasible alternative, unless liver cirrhosis forbids its use. Our experience indicates that 6-mercaptopurine (6MP) may be given as an alternative to azathioprine, especially in cases of gastrointestinal side effects, with good tolerance and response rates of up to 70%. As a more costly alternative mycophenolate mofetil (MMF) has been shown to effectively suppress disease activity in the majority of patients intolerant to azathioprine. Of note, MMF is contraindicated in pregnancy. In patients with insufficient response to azathioprine, dose should be increased up to 2.5 mg/kg of body weight and measurement of azathioprine metabolites (6TGN and MMP) may aid the optimal dosage. Several other immunosuppressive treatment strategies have been tested and published in small case series. These include the calcineurin inhibitors cyclosporine A and tacrolimus, mTOR inhibitors, anti-TNFalpha treatment with infliximab, rituximab as well as cyclophosphamide. It is difficult to tell whether one strategy is superior to another and the choice of second and third line treatment will depend on the patient’s comorbidity, patient’s choice after informed consent and also local expertise.
Primary biliary cirrhosis (PBC) is the most paradigmatic autoimmune liver disease, with still several controversial issues in epidemiology, diagnosis, causation, and therapy. Although we are witnessing an enormous increase in our basic knowledge of the disease with an initial translation in clinical practice, there are still a number of key open questions in PBC. Among them, why there are large geographical variations in disease frequency, the reasons for female preponderance, why only small-size bile ducts are affected, and the real role of genetics and epigenetics in its development. In particular, the prevalence of PBC is known to vary both on an international and a regional level, suggesting the existence of substantive geographical differences in terms of genetic susceptibility and environmental factors. New theories on potential environmental triggers, such as chemical xenobiotics, which leads to the breaking of self-tolerance within a unique immunological milieu of the liver, have been suggested. On the other hands, new and solid data on the genetic architecture of PBC are now coming from recent high-throughput studies, together with data on sex chromosomes defects, and epigenetic abnormalities, thus strongly suggesting a role of genetic and epigenetic factors in the triggering and perpetuation of the autoimmune aggression in PBC. Based on these evidences, a number of novel drugs directed against specific immune-related molecules are currently under development.
Primary biliary cirrhosis is the most common of the autoimmune liver diseases. Clinical, serologic and genetic features of disease confirm that autoimmunity is key to pathogenesis. Insights from human and murine studies have ensured a better understanding of the immune mechanisms that lead to the characteristic chronic granulomatous lymphocytic cholangitis that is evident microscopically, and which is accompanied serologically by highly specific anti-mitochondrial and anti-nuclear antibodies. Disease course is however unlike other classical autoimmune diseases because of the nature of the target of the immune system, namely the biliary epithelial cell. Chronic and persistent injury to biliary epithelium inevitably leads to cholestasis and disturbance of bile acid signalling which adds a second layer to disease pathophysiology. Finally the response to liver injury and bile duct loss is in high risk patients, evident as a progressive biliary fibrosis. Our insights into PBC are therefore focused to date on characterising the basis for, and nature of, the loss of immunoregulation, secondly on the consequences to the liver of cholestasis, and finally on the balance of liver injury, repair and fibrosis. With these three disease components it is possible to understand the opportunities for new therapies for patients failing current standard-of-care with ursodeoxycholic acid.
Treatment of autoimmune hepatitis: Should we ever stop?

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Autoimmune hepatitis (AIH) is a chronic inflammatory liver disorder of unknown etiology, which when left untreated can lead to liver cirrhosis and hepatic failure. AIH is observed in all age groups and predominantly affects women.

Current treatment strategies in AIH include long-term treatment with corticosteroids and/or azathioprine. Corticosteroid therapy induces clinical, laboratory and histological improvement in 80% of patients with AIH. The combination of corticosteroids and azathioprine is associated with lower occurrence of corticosteroid related side effects than prednisolone treatment alone, and combination treatment is the preferred therapeutic strategy for patients with active disease. Nevertheless, both drugs are associated with serious side effects that can sometimes be severe and may necessitate drug withdrawal. In addition, most patients respond well to immune-suppressive therapy and treatment usually results in an asymptomatic course of AIH in remission, which makes it all the more tempting to try and withdraw treatment. A major unresolved dilemma relates to the question as to whether treatment in patients who are in longstanding remission can be safely discontinued. Available data rely on retrospective data sets and are not conclusive. Some studies indicate that these patients can achieve a sustained remission after treatment withdrawal whereas other studies have found relapse rates up to 90%, even in patients with established histological remission. A higher IgG and combined immunosuppression at the time of drug withdrawal, a younger age at onset and the presence of concomitant autoimmune diseases have been suggested as risk factors for early relapse. Successive attempts for drug withdrawal in patients who relapse after drug withdrawal are associated with a high probability for a re-relapse. Life-long maintenance therapy should be strongly considered in these patients, since patients who have multiple relapses are more likely to progress to cirrhosis, liver transplantation and death from liver failure.

Several important questions regarding the optimal treatment schedule and duration of AIH remain unanswered. Therefore, prospective studies in well-defined groups of AIH patients are urgently needed.
Session III

Primary biliary cirrhosis
Fatigue in PBC. Prevalence, pathogenesis and management

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Fatigue is a significant problem in approximately 50% of PBC patients, with 20% experiencing significant or life-altering fatigue. In the absence of effective therapy it is stable over time, with non-fatigued patients tending to remain so. Large scale population studies have suggested that fatigue has a major impact on life quality in PBC, and that it disproportionately affects younger patients. The presence of social dysfunction accompanying fatigue appears to be a major factor in determining whether fatigue of a particular severity impacts on life quality; a factor which can be born in mind in developing management approaches. The pathogenesis of fatigue in PBC remains unclear, although it appears to be unrelated to the severity of underlying disease (with the exception of a small group of people with very advanced disease in whom fatigue and quality of life impairment are significant). Perhaps unsurprisingly it appears to be complex in origin with a number of underlying factors which should be considered when approaching management. In the first instance the presence of confounding conditions (potentially linked to PBC through autoimmune etiology or alternatively associated demographically; the former category includes thyroid disease and anaemia and the latter diabetes) should be screened for and managed in all patients. Fatigue in PBC is also associated with depression, autonomic dysfunction (manifest as dizziness on standing) and sleep disorder (manifest in particular as daytime somnolence) all of which again can be specifically managed. Clinically fatigue in PBC has both central and peripheral components. The central component is associated with significant cognitive impairment and sleep disturbance and is characterised by neurophysiological abnormalities of activation and facilitation, together with CNS changes on novel MR methodologies. Peripheral fatigue is associated with muscle dysfunction and an inability to sustain exercise. One hypothesis is that the central processes result directly from cholestasis in inflammation (a process modelled quite well in animal models of cholestasis) which impacts on autonomic centres in the brain which then regulate peripheral muscle perfusion leading to systemic peripheral effects. At present there is no specific drug therapy for fatigue for PBC and transplantation is contraindicated as the benefits appear limited. Neither UDCA nor emerging second line therapies appear to have any benefit. Current management paradigms are around identifying and treating co-existent conditions, targeting daytime somnolence and autonomic dysfunction, and exploring optimisation of peripheral muscle function through, potentially, exercise and other interventions. In managing patients with fatigue, understanding is critical and advice regarding pacing life and maintaining social interactions is critical. Most important of all is an understanding of the impact this symptom has on patients’ lives and an empathetic clinical interaction.
Non-invasive assessment of liver fibrosis progression and prognosis in PBC

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PBC is a disease with a wide range of severity and variable rate of progression. The diagnosis of advanced liver fibrosis/cirrhosis portends an increased risk of liver related morbidity and mortality. In addition, PBC patients with advanced fibrosis/cirrhosis usually fail to respond to any medical therapy.

Nowadays, PBC is frequently diagnosed in an early stage of disease. Most of these patients currently received UDCA as a mainstay treatment. However, about 35% of the patients do not achieve a satisfactory response to UDCA. In particular, half of the patients with liver fibrosis (Metavir F3 score) at onset of UDCA therapy develops cirrhosis within five years of follow-up. These patients are thus candidates to complementary/ investigative therapeutic approaches. Because of its invasiveness, liver biopsy tends to be replaced by non-invasive tools for prognosis making and optimizing risk stratification for selection of patients requiring new medical approaches.

To assess liver fibrosis three main radiologic approaches are proposed: vibration controlled transient elastography (VCTE), acoustic radiation force impulse and magnetic resonance elastography. In this talk I will review the advantage and limits of VCTE for detection, longitudinal evaluation of liver fibrosis and prognosis.

Many direct or indirect serum biomarkers are also available. Among them serum bilirubin, aspartate aminotransferase (AST) and alkaline phosphatase activities as part (alone or combined) of the UDCA response criteria have been shown to have robust prognostic capacity. More recently, evidence has been provided in a large cohort of patients that the simple and widely used AST-platelet index could further add prognostic information to existing UDCA response criteria.

None of the radiologic and serum markers have a perfect/excellent accuracy in studies so far published. Moreover, routine use of VCTE and serum biomarkers includes acknowledging confounding factors that may influence the results. Accordingly, concordance between VCTE and serum biomarkers is a prerequisite for a correct prognosis assessment in individuals in clinical practice.
Surrogate markers for optimal therapeutic response to UDCA

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Ursodeoxycholic acid (UDCA) is the standard treatment in primary biliary cirrhosis (PBC) as it can delay histological progression and improve long-term outcome. However, UDCA is not an uniformly effective drug and the prognosis of patients insufficiently responding to treatment is worse compared with the general population. Reliable identification of non-responders is of key importance, not only for selecting patients who could benefit from additional, second-line therapy, but also for identifying those individuals who are at low risk of developing end-stage disease and in whom UDCA mono-therapy can be safely continued. Potential surrogate markers of outcome are liver histology and elastography. However, liver biopsy is an unattractive tool given its invasive character and data supporting elastography are still limited.

Several laboratory predictors have been proposed as surrogate markers for the long term response to UDCA, including the Barcelona, Paris I and II, Toronto and Rotterdam criteria. These criteria have all limitations and the superiority of one over the other has not been firmly established. Therefore it remains unclear which criteria should be preferred in clinical practice.

Recently the Global PBC Study Group aimed to develop a superior prognostic tool by studying a large, representative and multinational cohort of 4119 UDCA treated patients. In a random sample of 2488 cases a risk score predicting transplantation-free survival was developed based on variables obtained after 1 year therapy. Age, bilirubin, albumin, alkaline phosphatase and platelet count were all independently associated with survival. Using these variables a risk score for death or liver transplantation was constructed. The prognostic performance of this score (C statistic 0.81, 95% CI: 0.79–0.83) was markedly better than that of previously proposed response criteria: Barcelona (0.58, 0.55–0.60), Paris-1 (0.69, 0.66–0.71), Rotterdam (0.69, 0.66–0.71), Toronto (0.61, 0.58–0.63) and Paris-2 criteria (0.63, 0.61–0.65). The C statistic in an independent validation cohort of 1632 cases was 0.82, 95% CI: 0.79–0.84. A computer app will allow easy application of the score in clinical practice.

In conclusion, prognosis in UDCA treated PBC can be predicted accurately with a new score comprising objective and easy obtainable clinical and laboratory variables. The performance of the score was validated and was superior to that of previously reported criteria. This score will likely improve the quality of patient management and, in particular, allow more reliable identification of individuals responding (in)sufficiently to UDCA.
Novel approaches for patients with suboptimal response to UDCA

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Primary biliary cirrhosis (PBC) is a chronic cholestatic disease of presumed autoimmune pathogenesis, characterized by inflammation and damage of the intrahepatic intermediate and small bile ducts, which eventually results in cirrhosis. A number of randomized and observational and pilot studies using several agents were carried out in the eighties, but no clear results or even harmful effects were reported. Over the past two decades, increasing evidence indicates that ursodeoxycholic acid (UDCA) – 13 to 16 mg/kg/day – is the treatment of choice for patients with PBC. Biochemical response to UDCA, assessed at one year, clearly predict the long-term outcome, since in UDCA responders the survival is similar to that estimated for the matched control population. However, about 40% of patients have incomplete biochemical response, and therefore resulting in an increased risk of progression and decreased survival free of transplantation. Patients with suboptimal biochemical response to UDCA outline the group in whom further single or combined treatments with UDCA are needed. Accordingly, data on the effect of fibrates alone or in combination with UDCA, and budesonide in combination with UDCA have been reported. The combined treatment of UDCA and fibrates in patients without optimal biochemical response to UDCA improves the degree of cholestasis and may minimize the long-term management of these patients. The results of the combined therapy of UDCA with budesonide are appealing but they should be established in large randomized trials. The effect of new agents such obeticholic acid are promising since the addition of this FXR agonist bile acid in patients with stable UDCA dosage and increased alkaline phosphatase levels results in an improvement of cholestasis as compared to placebo, with a parallel decrease of aminotransferases and IgM, as well as one surrogate marker of bile acid synthesis. Apart from these agents, antiretroviral treatments have been proposed but the results are meager. Furthermore, new molecular therapies are currently being investigated.
Session IV

Primary sclerosing cholangitis
Diagnosis, differential diagnosis, and epidemiology of primary sclerosing cholangitis

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According to recent guidelines from EASL and AASLD a diagnosis of primary sclerosing cholangitis (PSC) is made when a patient has a cholestatic liver enzyme profile (e.g. elevated alkaline phosphatase), characteristic bile duct changes on imaging (e.g. magnetic resonance cholangiography or endoscopic retrograde or percutaneous transhepatic cholangiography, and secondary causes of sclerosing cholangitis are excluded. In patients with a clinical suspicion but normal cholangiography a liver biopsy is indicated to establish a diagnosis of small duct PSC. Several other disease entities such as IgG4-associated cholangitis (IAC), cholangiocarcinoma (CCA), and secondary causes of sclerosing cholangitis such as choledocholithiasis, AIDS-cholangiopathy, ischemia, surgical bile duct trauma, or mast cell cholangiopathy can mimic PSC. IAC can be differentiated from PSC by applying the HISORt criteria including serum IgG4 level. In cases where serum IgG4 is less than 2x ULN, the ratio of IgG4/IgG1 > 0.24 is indicative for IAC. A diagnosis of CCA, either sporadic or as a complication of PSC, is established by biliary brushing or by intraductal biopsy. However, the sensitivity of brush cytology for CCA is limited. Including FISH can augment the positive predictive value of brush cytology. Recently, endoscopic ultrasound guided fine needle aspiration showed improved sensitivity for malignant biliary strictures. Choledocholithiasis with recurrent cholangitis as a cause of sclerosing cholangitis can pose a conundrum, since PSC itself is associated with an increased prevalence of gallstones.

The epidemiology of PSC worldwide has been poorly described. Incidence and prevalence rates vary from 0–1.3 and 0–16.2 per 100,000 inhabitants respectively. However, these figures are not based on population-based cohorts. A recent large population-based cohort from the Netherlands reported an incidence of 0.5 and a prevalence of 6/100,000. Approximately 10% fulfill the criteria for small duct PSC. At diagnosis of PSC, concurrent inflammatory bowel disease (IBD), primarily ulcerative colitis or Crohn’s colitis is present in 50%, mounting to 80% ten years or more after diagnosis. Conversely, 3% of IBD patients will develop PSC.

PSC predisposes to malignancy. The estimated cumulative risk of developing CCA after 30 years is 20%. For colorectal carcinoma in PSC/colitis patients the estimated cumulative risk at 30 years is 13%.

In summary: Despite established diagnostic criteria the diagnosis of PSC can be difficult. Recent population-based data provide a clearer view on the epidemiology of PSC.
Past genome-wide association studies (GWAS) have revealed a remarkable genetic overlap between distinct human diseases, even if different organs are affected. The latter applies in particular to the overlap of the distinct chronic inflammatory conditions ankylosing spondylitis (AS), Crohn’s disease (CD), psoriasis (PS), primary sclerosing cholangitis (PSC) and ulcerative colitis (UC). Increased comorbidity rates in individual patients and families of patients, i.e. patients having at least two of the afore-mentioned diseases, have been reported before. However, whether the same or different causal alleles are involved in the seemingly distinct diseases remains elusive and key molecular aspects of the suggested shared and distinct etiology are mostly unknown. Recently, cross-disease studies were proposed as a valuable means to address this need and to sort associations into discrete pathways. In the talk I will present an ongoing study where we simultaneously investigate the genetic landscape of AS, CD, PS, PSC and UC, using high-density SNP genotype data of > 86,000 cases and controls with European-ancestry from 26 different countries. Employing novel statistical cross-phenotype analysis methodologies, we identified 29 shared and 38 novel disease loci, respectively, with genome-wide significance (gws) and revealed 250 independent multi-disease signals at overall 171 distinct gws susceptibility loci. Most “shared” loci exhibit complex patterns of multi-disease association (sometimes pointing to different alleles), suggesting that the common practice in GWAS studies to define genetic sharing just by positional overlap is inaccurate. Genetic risk score correlation analyses across patients show that genetic sharing is attributable to pleiotropic effects rather than excessive comorbidity, e.g supporting the hypothesis that PSC patients with concomitant IBD-like syndromes likely have a genetically distinct bowel disease compared to CD or UC. The state-of-the-art on IBD and PSC genetics will be presented.
Autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) are autoimmune liver diseases characterised by immune-mediated hepatocellular or hepatobiliary injury. Recent GWAS studies demonstrate strong associations between PSC and immune regulatory genes confirming the autoimmune nature of PSC. PSC and AIH are strongly linked to inflammatory bowel disease (IBD) and this clinical observation has stimulated novel pathogenic concepts in which gut commensals, pathogens and intestinal antigens are implicated in driving liver injury. The intestine is a key regulator of both immune regulatory pathways and immunopathogenic Th17 responses suggesting that dysregulated mucosal immunity may provide a common disease mechanism that suggests novel treatments based on targeting of gut-associated immune pathways. For example, the discovery that mucosal effector T-cells are recruited to the liver in response to aberrantly expressed endothelial cell adhesion molecules and chemokines which are normally ‘gut-restricted,’ could explain the tissue distributions of these diseases and pave the way for therapeutic strategies based on modulating organ specific lymphocyte homing. The emerging data showing an association between gene-polymorphisms that determine the composition of the microbiome and PSC susceptibility underscores the fundamental role of the microbiome and mucosal immunogenicity in disease pathogenesis.
Malignancies in primary sclerosing cholangitis – A continuing threat

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**Background**: Primary sclerosing cholangitis (PSC) is a chronic inflammatory liver disease, of unknown etiology but likely of immune-mediated origin, primarily targeting the biliary epithelium. PSC is characterized by portal inflammation and peribiliary fibrosis leading to strictures in any portion (intra- and/or extrahepatic) of the bile duct system. No effective medical treatments are hitherto available. A unique feature of PSC is the close association (about 80%) with inflammatory bowel disease (IBD), mainly ulcerative colitis (UC), often diagnosed before PSC (PSC/UC). As observed in other chronic inflammatory diseases, development of malignancies is a feared complication of PSC. Previous studies showed that more than 40% of deaths in PSC patients were cancer-related, not only hepatobiliary. Cholangiocarcinoma (CCA), gallbladder carcinoma (GBC) and colorectal carcinoma (CRC) in subjects with concomitant IBD, have been variably reported, with a prevalence up to 13–14% for hepatobiliary malignancies. Cancer development is one of the most challenging issues in the management of PSC, as it raises several still unanswered questions about cancer surveillance, early diagnosis, prevention and treatment.

**Key messages**: Among the different cancer types complicating PSC, CCA is the most relevant, as either epidemiological burden (incidence of 0.5–1.5%) or poor prognosis (5-year survival < 10%). Early diagnosis of CCA in PSC can be difficult because lesions are morphologically similar at radiological studies, especially in the case of dominant strictures. Furthermore, detection of high-grade dysplasia on brush cytology is not rare in PSC patients; however, its management is controversial since it can regress with resolution of acute biliary infections. Nevertheless, HGD may involve multiple segments of the biliary tree and associate with CCA in liver parenchyma. Given the disappointing results with surgical resection (3-year survival < 20%), liver transplantation combined with neoadjuvant chemotherapy is currently considered the best approach, although only to highly selected groups and in limited specialized centers.

Although gallbladder abnormalities are a frequent finding in PSC (about 40%), risk of GBC deserves specific attention. Ultrasound examination is an appropriate tool for surveillance. In PSC, GBC affects younger individuals (< 60 years) than GBC not associated to PSC, and carries a very bad prognosis, similar to CCA. Therefore, cholecystectomy is recommended in all gallbladder lesions detected in PSC, regardless of their size, if liver function is preserved.

**CRC**, mostly arising in the right colon, is a frequent complication of PSC/UC, with an incidence steadily increasing with time of colitis, from 8–10% after 10 years to 20–30% after 20 years, much higher than that reported in UC alone (2% and 5% respectively). Colonoscopy at an annual/biannual interval is an effective surveillance strategy. Since the risk of progression of dysplastic lesions is increased in PSC/UC, preemptive proctocolectomy may be considered even in cases of low-grade dysplasia in non-cirrhotic patients.
Conclusions: PSC may be regarded as paradigmatic of the sequence from a chronic inflammatory epithelial damage to a neoplastic transformation; however, strategies of disease surveillance and cancer prevention and treatment are still debated likely reflecting deep uncertainties on the mechanisms regulating this pathogenetic sequence. Understanding the molecular players involved might provide important clues for facing this sword of damocles.
Session IV (cont)

Primary sclerosing cholangitis
Therapy of PSC today and tomorrow

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Primary sclerosing cholangitis (PSC) is a chronic inflammatory bile duct disease of unknown etiology, frequently associated with inflammatory bowel disease (IBD) and leading to end stage liver disease requiring liver transplantation. Moreover, PSC is a premalignant condition associated with an increased risk for hepatobiliary and/or colorectal malignancy. Since effective medical therapy for PSC is still lacking, this disorder represents a potentially fatal disease with poor prognosis. Liver transplantation so far represents the only established treatment of PSC with excellent long-term survival rates of 70–80% over 10 years, but PSC recurrence can occur in up to 20%. In contrast to PSC, secondary sclerosing cholangitis has sometimes potentially treatable causes such as in IgG4-associated cholangitis. Such other causes of (secondary) sclerosing cholangitis and overlap syndromes with autoimmune hepatitis always need to be considered in the differential diagnosis, since (in contrast to PSC) steroids are a therapeutic option.

A major challenge in the management of PSC is the lack of an effective and established medical treatment which may reflect our limited understanding of the pathomechanisms underlying the disease. Immunosuppressive treatment strategies targeting immunological factors, treatment of associated IBD or targeting gut-derived factors by antibiotics had so far no major therapeutic effects. Similarly, conventional anti-fibrotic strategies cannot be recommended. Ursodeoxycholic acid (UDCA) is frequently used in daily clinical practice in many centers, although a role of UDCA in slowing PSC progression and prolonging survival has not been demonstrated. Conventional dose UDCA (15–20 mg/kg/day) is safe, but its efficacy is unclear and high dose UDCA (28 mg/kg/day to 30 mg/kg/day) in PSC has been shown to be even harmful. There is controversial information to support UDCA as a chemo-preventive drug against colorectal or cholangiocellular cancer. As such, the American Association for the Study of Liver Disease (AASLD) recommendations advise against the use of UDCA in PSC, while the European Association for the Study of the Liver (EASL) recommendations are more open for its use (especially in early stage disease), however emphasizing that the limited data do not allow a specific recommendation for the general use of UDCA in PSC. Nevertheless, in daily clinical practice of many centers across Europe, UDCA is combined with endoscopic therapy of dominant strictures, an approach shown to improve predicted patient survival in retrospective trials. Given these limitations, there is an urgent need for novel therapeutic approaches in PSC.

24-nor-ursodeoxycholic acid (norUDCA) is a side-chain shortened derivate of ursodeoxycholic acid (UDCA). Since norUDCA is only ineffectively conjugated with glycine or taurine, it has specific physicochemical and therapeutic properties distinct from UDCA. As such, non-amidated norUDCA undergoes cholehepatic shunting allowing ‘ductular targeting’ and inducing a bicarbonate-rich hypercholeresis, with cholangio-protective effects. At the same time norUDCA has direct anti-inflammatory, anti-lipotoxic, anti-fibrotic and anti-proliferative properties. norUDCA reversed sclerosing cholangitis in the experimental Mdr2/Abcb4-/- cholangiopathy model of PSC,
while the mother compound UDCA even aggravated bile infarcts in cholestatic conditions with (complete or partial) biliary obstruction. Notably, neither norUDCA nor its mother compound UDCA have relevant affinities for the nuclear bile acid receptor/farnesoid X receptor (FXR) or G-protein-coupled plasma membrane receptor for bile acids TGR5, which are targets for some of the new therapeutic approaches discussed below. Based on these encouraging preclinical data in, norUDCA is currently undergoing further clinical development by Dr. Falk Pharma GmbH. Phase I clinical trials have been successfully completed and a double-blind, randomized, multicenter, placebo-controlled, comparative, exploratory phase II dose-finding trial comparing three different doses of norUDCA with placebo in the treatment of PSC (with more than 160 patients) has been initiated in several centers across Europe. The results of this study are expected for the secon half of 2015.

Apart from norUDCA other currently emerging bile acid-targeted therapies include FXR/TGR5 ligands and ASBT inhibitors, the latter blocking the enterohepatic circulation of bile acids and also improving cholestasis sclerosing cholangitis in preclinical models (e.g. Mdr2⁻/⁻ mouse). The FXR ligand obeticholic acid (OCA), a 6α-ethyl derivative of the naturally occurring bile acid chenodexycholic acid, had beneficial effects in mouse models of cholestatic liver injury and PBC. FXR ligands have not yet been tested in patients with PSC, but planning of clinical trials is already under way. FXR-induced fibroblast growth factor 19 from the ileum supresses hepatic bile acid synthesis and is currently emerging as novel therapeutic approach to cholestatic and metabolic liver diseases. Fibrates (PPAR alpha ligands) may also modify intrinsic toxicity of bile by supressing bile acid synthesis and promoting biliary phospholipid excretion in addition to their more general anti-inflammatory effects, but experiences in PSC are limited to smaller case series.

Although therapeutic strategies against tumor necrosis factor-alpha (e.g., infliximab, pentoxifylline) have been disappointing in PSC, the potential of newer biological agents targeting the inflamed gut still deserves further evaluation. As such emerging novel treatment strategies for PSC may target intestinal inflammation as well as homing of gut primed T-lymphocytes from the inflamed gut to the liver/bile ducts (vedolizumab). Potential changes in microbiota (dysbiosis) may be targeted by pre-/probiotics and antibiotics (metronidazole, tetracycline, azithromycin; more recently vancomycin, and rifaximin) some of which have shown promising results (vancomycin). The tyrosine kinase/janus kinase inhibitor tofacitinib has been shown to have beneficial effects in ulcerative colitis and inhibits pro-inflammatory cytokine signaling and T-cell differentiation which are also involved in PSC pathogenesis.

Direct inhibition of fibrosis remains an attractive target in PSC as paradigm fibrosing cholangiopathy. Simtuzumab, a monoclonal antibody against lysyl oxidase homolog 2 (an extracellular matrix protein/enzyme) is currently under evaluation in clinical studies. Notably, norUDCA (but not UDCA) reduces hepatic fibrosis in a mouse model of Schistosoma mansoni infection as world-leading cause of liver fibrosis and portal hypertension, pointing towards more general anti.fibrotic effects. Other potential future therapeutic approaches may consider docosahexanoic acid (a fatty acid metabolite reduced in cystic fibrosis and used for treatment of cystic fibrosis), as well as modulation of the renin-angiotensin system to reduce fibrosis.
Selected references (reviews):


Pathogenesis and management of pruritus in PBC and PSC

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Chronic Pruritus is a preeminent symptom in patients with chronic cholestatic liver disorders such as primary biliary cirrhosis and primary sclerosing cholangitis. More than two-thirds of these patients experience itching during the course of their disease. This symptom is also frequently observed in patients with other causes of cholestasis such as cholangiocarcinoma, inherited forms of cholestasis and intrahepatic cholestasis of pregnancy, but may accompany almost any other liver disease. The pathogenesis of pruritus of cholestasis remains largely elusive. Increased concentrations of bile salts, histamine, serotonin, progesterone metabolites and endogenous opioids have been controversially discussed as potential pruritogens. However, for these molecules neither a correlation with itch intensity nor a causative link could be established. The G protein-coupled receptor for bile salts, TGR5, has been shown to be expressed in dorsal root ganglia, albeit supraphathological concentrations of bile salts were required to activate this receptor. The potent neuronal activator lysophosphatidic acid (LPA) and its forming enzyme, autotaxin (ATX), could be identified in serum of patients suffering from cholestatic pruritus. Autotaxin activity correlated with itch severity and effectiveness of several anti-pruritic therapeutic interventions in cholestatic patients. Thus, the ATX-LPA-axis may represent a key element in the pathogenesis of this agonizing symptom.

Treatment options for pruritus of cholestasis remain limited to a few evidence-based and several experimental medical and interventional therapies. The current guideline-based recommendations include the anion exchange resins colestyramine, the PXR-agonist and enzyme inducer rifampicin, the μ-opioid antagonist naltrexone, and the selective serotonin reuptake inhibitors sertraline. Still, a considerable part of patients is unresponsive to these drugs and requires experimental approaches including phototherapy, plasmapheresis, albumin dialysis or nasobiliary drainage. This review outlines the current knowledge on pathogenesis of cholestatic pruritus and summarizes evidence-based and experimental therapeutic interventions for cholestatic patients suffering from itch.
IgG4-associated cholangitis: A mimic of primary sclerosing cholangitis

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IgG4-associated cholangitis (IAC) is the hepatobiliary manifestation of Immunoglobulin G4-related disease (IgG4-RD), an increasingly recognized systemic fibroinflammatory disorder with a wide variety of clinical presentations and organ manifestations which predominantly affects the hepatobiliary tract (IAC) and pancreas (autoimmune pancreatitis, AIP)\(^1\)\(^-\)\(^5\). IgG4-RD is characterized by fibrosing inflammation of the affected organs, tissue infiltration of IgG4-loaded plasma/B cells and often elevated serum levels of IgG4. A large number of medical conditions fall within the spectrum of IgG4-RD and the list of organ manifestations (pancreas (AIP); biliary tree (IAC), gallbladder and liver; salivary, parotid and lacrimal glands; retroperitoneum; kidney; lungs; lymphatic system (especially hilus); stomach, intestine including ileal pouch; vascular system (aortitis); nervous system, eye (uveitis); prostate, testis; thyroid; pseudotumor) is still expanding.

**Diagnosis of IAC and IgG4-RD**

In clinical practice, it is difficult to make a clear-cut diagnosis of IgG4-RD as an accurate diagnostic marker is lacking. Patients often present with painless obstructive jaundice and tumor-like swelling of involved organs that can be easily mistaken for pancreatic or bile duct cancer, as well as primary sclerosing cholangitis (PSC) or other forms of secondary sclerosing cholangitis. In up to one of three patients, extensive surgery for presumed malignant hepatobiliary or pancreatic malignancy has taken place prior to diagnosis of IAC and IgG4-RD\(^6\). For these reasons, consensus criteria have been developed first for AIP\(^7\) and subsequently for IAC\(^2\) to improve the accuracy of diagnosis of IgG4-RD including clinical, biochemical, radiological and histomorphological features.

**Serum levels of IgG4 (sIgG4)** are often elevated in IAC and IgG4-RD, but not diagnostic at moderately elevated levels (< 4 x ULN) as other conditions such as primary sclerosing cholangitis (PSC), cholangiocarcinoma or pancreatic carcinoma are also associated with elevated sIgG4\(^8\)\(^-\)\(^10\). In addition, up to 20% of patients with IAC and AIP do not show elevated sIgG4 levels upon presentation\(^5\)\(^,\)\(^11\). We recently reported that the ratio sIgG4/sIgG1 may better distinguish IAC from PSC than sIgG4 alone, particularly when sIgG4 is only slightly elevated\(^12\). In conclusion, the use of serum IgG4 as a biomarker has limitations due to its limited sensitivity and specificity when only moderately elevated.

**Histopathological examination** discloses infiltration with IgG4+ plasma cells and storiform fibrosis, regardless of the affected organ\(^2\). However, such infiltrates are also observed in other diseases.

**Radiologic studies** commonly show diffuse swelling of the affected organ\(^1\)\(^,\)\(^13\), e.g. pancreas, salivary glands, lymph nodes. However, swelling is a nonspecific feature of inflammation or neoplasia. Cholangiography discloses alterations compatible with sclerosing cholangitis or cholangiocarcinoma.
We recently identified dominant IgG4+ B cell receptor (BCR) clones in blood and tissue of all patients with active IAC under study, but in no single healthy or disease control including patients with PSC and hepatobiliary/pancreatic malignancy and elevated serum IgG4\textsuperscript{14}. More studies based on these findings are underway in order to establish a highly accurate diagnostic test for the diagnosis of IAC and AIP as well as other organ manifestations of IgG4-RD.

**Pathogenesis of IgG4-RD**

Pathophysiological mechanisms underlying IAC and IgG4-RD are poorly understood. Whether IgG4 antibodies behave as tissue-destructive immunoglobulins or as an anti-inflammatory antibody to dampen the immune system in reaction to an unknown stimulus remains to be clarified. IgG4 normally form the smallest fraction of total IgG in serum\textsuperscript{15}, are upregulated in chronic immune stimulation\textsuperscript{15}, are unable to bind C1q and have a low Fc affinity thereby barely initiating a complement response\textsuperscript{16, 17}, and exchange their Fab arms\textsuperscript{18}.

The recent finding of dominant IgG4+ BCR clones in blood and tissue of patients with active IAC (and other organ manifestations of IgG4-RD), but not in controls, shed a new light on development of IgG4-RD and may suggest that specific B-cell responses are pivotal to the pathogenesis of IAC possibly under chronic immune stimulation. These findings support the hypothesis that the abundant production of IgG4 antibodies is part of an antigen-driven immune response.

Remarkably, the majority of patients with IAC is over 60 years old and 80–85% are of male sex\textsuperscript{19}. These findings contrast strongly with comparable autoimmune diseases such as primary biliary cirrhosis or Sjögren’s syndrome, which predominantly affect middle-aged female patients\textsuperscript{20}, raising the question whether IgG4-RD is really an autoimmune disease. Thus far, no specific antigen has convincingly been identified in IgG4-RD patients. Our observation that the vast majority of our patients with IgG4-related cholangiopathy and other organ manifestations of IgG4-RD (but not a disease control cohort with PSC) have experienced prolonged exposure to occupational potentially hazardous antigens recently led us to publish the ‘blue collar worker hypothesis’: chronic stimulation to toxic dusts, industrial oils, paints or other pathogens associated with ‘blue collar’ jobs could be the environmental trigger that lays at the basis of the uncontrolled immune reaction in IgG4-RD\textsuperscript{21}.

**Treatment of IgG4-RD**

Most patients with IAC or AIP have an excellent response to initial high to moderate dose corticosteroid therapy, typically with diminution of symptoms, of organ enlargement and of serum levels of IgG4\textsuperscript{5, 22}. Notably, dominant IgG4+ clones in blood disappeared upon successful corticosteroid therapy within a month. Long-term low dose maintenance immunosuppressive therapy is needed in the majority of patients to prevent symptom recurrence\textsuperscript{23}.
References:

Overlap syndromes

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Patients presenting with clinical, biochemical, serological, and/or histological features reminiscent of both primary biliary cirrhosis (PBC) or primary sclerosing cholangitis (PSC) on one hand and autoimmune hepatitis (AIH) on the other hand, either simultaneously or consecutively, have been repeatedly recognised. The term overlap syndrome (OS) is used to describe these settings. Unfortunately, lack of universal agreement on what precisely constitutes an OS has generated considerable confusion in the literature and the clinical phenotypes of patients with the same OS designation exhibit considerable heterogeneity (1). The IAIHG criteria are an attractive tool for making the diagnosis of OS in patients with an existing diagnosis of PBC or PSC. However, their diagnosis performance appears low and their use is not recommended for the diagnosis of OS (2). Nevertheless, interface hepatitis is a fundamental component and histology is vital in evaluating patients with overlap presentation. The pathogenesis of OS is debated and it remains unclear whether this syndrome forms a distinct entity or a variant of PBC, PSC or AIH. In this regard, the name overlap that strongly suggests the presence of 2 distinct diseases could be a misnomer. It should be kept in mind that OS should not be over-diagnosed in order not to expose unnecessarily PBC or PSC patients to the risk of steroid side effects. The low prevalence of OS has made it impracticable to perform randomized controlled trials.

PBC-AIH Overlap syndrome
It is generally assumed that OS prevalence is approximately 8–10% in adult patients with PBC or AIH. The “Paris criteria” are currently the most commonly used tool for diagnosing PBC-AIH OS and require the presence of at least 2 of the 3 accepted key (biochemical, serological, and histological) criteria of each disease (3). The 2009 EASL guidelines endorsed these diagnostic criteria but specified that histologic evidence of moderate to severe lymphocytic piecemeal necrosis (interface hepatitis) was mandatory (4). In most cases, it is possible to define one primary disorder (“dominant” disease), usually PBC. Patients with OS seem to have a more severe disease compared to conventional PBC. Despite the lack of controlled trials, EASL guidelines have recommended adding steroids (eventually budesonide) either at the time of diagnosis of OS or in case of inadequate biochemical response after 3 months of UDCA (4). The results of a recent large study strongly support the use of a combination of UDCA and immunosuppression as first-line therapy in OS patients with severe interface hepatitis (5). Interestingly, in responders, doses of immunosuppressors in the long term could be lower and rate of successful withdrawal higher than in classical AIH. In UDCA treated PBC developing AIH (“sequential” OS), use of immunosuppressive treatment is mandatory.

PSC-AIH Overlap syndrome
PSC-AIH OS has been described in both children and adults and is assumed to exist in a considerable part of mainly young patients with autoimmune liver disease. Unfortunately, diagnosis criteria are even less well defined than in PBC-AIH OS. As a result, reported prevalence figures vary greatly but an approximate prevalence of 7–14% is generally assumed in adult patients (2). In children, the hepatic feature can
be very dominant and up to 50% of pediatric AIH have cholangiographic abnormalities suggestive of PSC including some without any histological features of bile duct injury (6). This condition has been named autoimmune sclerosing cholangitis (AiSC). AIH and PSC may be sequential in their occurrence in children but also in adults. Various results of therapy (usually prednisolone and azathioprine with or without UDCA) have been reported. It is difficult to draw any firm conclusions because of the small number of patients, the usually retrospective nature of the studies and the heterogeneity of the regimens. In the pediatric AiSC form treated with immunosuppressors, liver biopsies may show improvement in inflammation but cholangiographic appearances may progress and transplant-free survival at 10 years (65%) is lower than in AIH (100%) (6). The combination of UDCA and immunosuppressive therapy may improve liver biochemistry and this approach has been advocated by EASL guidelines (4). However, in the long term (> 10 years), long-term progression toward cirrhosis seems to occur in the majority of patients (7).

References:


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POSTER ABSTRACTS

Poster Numbers 1 – 78
(∗ = Posters of Distinction)

Author Index to Poster Abstracts
Non-invasive assessment of disease stage in patients with primary biliary cirrhosis

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Introduction: Primary biliary cirrhosis (PBC) is a chronic, progressive cholestatic liver disease of unknown cause that usually affects middle-aged women and eventually leads to liver failure and the need for liver transplantation. Biopsy is the gold standard for assessing of disease progression and presence of cirrhosis, but an alternative non-invasive, simple and non-expensive method to predict cirrhosis would be highly desirable.

Aim: To evaluate different non-invasive methods in the assessment of PBC stages.

Methods: This study included 49 patients with PBC who underwent a complete clinical investigation. We analyzed the correlation (Spearman's test) between aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio, aspartate aminotransferase/platelet ratio index (APRI), and Fib-4 with different stages of PBC. The discriminative values were compared using areas under receiver operating characteristic (ROC) curves.

Results: The mean age of patients included in the study was 53.13 years, including 48 females and 1 male. We found a statistically significant correlation between PBC stage and aspartate aminotransferase/alanine aminotransferase ratio, alanine aminotransferase (ALT) to platelet ratio (APRI), ALT/cholesterol ratio, and Fib-4 with the values of Spearman's rank correlation coefficient of 0.328, 0.336, 0.401, and 0.348, respectively.

We also analyzed correlation between the results of non-invasive methods and two grades of primary biliary cirrhosis (stage I and II-mild disease, stage III and IV advanced disease). There was statistically significant correlation as well, with the results of Spearman's correlation 0.421, 0.331 and 0.325, respectively. Despite the statistically significant correlation, the best sensitivity and specificity was shown for APRI, with an area under ROC of only 0.6.

Discussion/Conclusion: Non-invasive methods do correlate with different sensitivity to and specificity of PBC disease stage. But, because of limited sensitivity and specificity, the use of non-invasive methods in clinical evaluation of PBC patients may reduce, but not eliminate, the need for liver biopsy.
The UK-PBC Risk Score: Derivation and validation of a risk score to predict liver events in PBC


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Introduction: Outcomes in primary biliary cirrhosis (PBC) can be predicted by biochemical response to ursodeoxycholic acid (UDCA). However, stratification based on UDCA response does not take the stage of the liver disease into account. Furthermore, existing definitions dichotomise UDCA response and long-term risk, whereas both are a continuum. We analysed the UK-PBC Research Cohort to develop and validate a risk score that includes markers of disease stage, as well as the post-treatment liver biochemistries modelled as continuous variables.

Methods: We constructed a PBC risk score for LT and liver-related death at 15 years in a derivation cohort (n = 2422) and evaluated it in a validation cohort (n = 1600). We used multivariable fractional polynomials (MFP) to model non-linear risk relations with continuous variables, and multiple imputation (20 imputations) to replace missing values in the derivation cohort. We fit a Cox proportional hazards model in each imputed dataset, and used Rubin’s rules to combine the results. The resulting coefficients were used together with the baseline survivor function to derive an equation for absolute risk at 15 years. Net reclassification improvement (NRI) was calculated to compare the predictive performance of this risk score compared with other published prognostic scores.

Results: Median follow up time was 6.6 years (IQR, 3.3–11.1) years and 537 patients reached the endpoint. The following variables were independently associated with a liver event: albumin and platelet count at baseline, and ALP, bilirubin and transaminases after twelve months of UDCA. The PBC risk score incorporated these five variables, appropriately transformed using MFP. When applied to the validation cohort, the score was highly predictive (c-statistic = 0.90). The NRI showed that the risk score had greater ability to identify individuals with and without events compared to other risk scores (NRI of PBC risk score vs. Paris1 = 90% [95% CI: 84–96%]; Paris2 = 64% [95% CI: 58–70%]; Barcelona = 38 [95% CI: 32–43%]; Toronto = 71% [95% CI: 65–76%]).
**Discussion/Conclusion:** Prognosis of UK patients with PBC can be accurately assessed with the PBC risk score by using readily available objective clinical measures. This may be used to identify high-risk patients for closer monitoring and second-line therapies, as well as low-risk patients who require infrequent monitoring and might even be followed-up in primary care. However, validation of the score in an external independent cohort and identification of thresholds to inform clinical decision-making is required.
The role of peripheral blood Treg and Th17 cells in primary biliaris cirrhosis

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Introduction: Primary biliary cirrhosis (PBC) is a chronic cholestatic liver disease characterized by progressive destruction of small size intrahepatic bile ducts leading to cirrhosis. Among genetic, environmental, also immunological factors have conclusively been shown to contribute to the pathogenesis of PBC. The role of peripheral blood cell subpopulations, particularly Treg and Th17 in PBC pathogenesis remains still uncertain.

The aim of this research was to describe the percentages and absolute counts of Th17, Treg in patients with newly diagnosed PBC and the relationships between analyzed cell subsets and selected clinical parameters (itching and the degree of PBC severity).

Methods: The frequencies of Treg and Th17 were measured by flow cytometry in 40 previously untreated female patients with PBC. The control group consisted of 20 healthy age- and sex-matched volunteers.

The diagnosis of PBC was based on the common known criteria. The degree of severity of PBC was evaluated in each patient by histologic examination.

Results: Significantly lower frequencies and absolute counts of CD4(+) CD25(+) FoxP3(+) Treg cells were found in the study group in comparison with controls (p < 0.0001).

Higher percentages and absolute counts of IL-17A(+) CD3(+) CD4(+) Th17 lymphocytes were found in the PB of PBC patients than in the control group (p < 0.0001).

Among 40 patients with PBC, 7 showed the I stage of severity – portal stage, 16 patients the II stage – periportal stage, 11 the III – septal stage, and 6 patients the IV stage – cirrhosis. Itching of the skin was observed in 18 patients with PBC.

The frequencies and absolute counts of CD4(+) CD25(+) FoxP3(+) Treg cells correlated with the degree of severity of PBC however not with itching. The higher value of this parameter (0.090133 x 10³/ul) was observed in the more advanced stage of PBC (stage III) compared to the II stage of PBC (0.034990 x 10³/ul). The correlation between frequencies and absolute counts of IL-17A(+) CD3(+) CD4(+) Th17 lymphocytes and histological stage of PBC and/or presence of itching was not observed.

Discussion/Conclusion: The study demonstrates that both Treg and Th17 cells might play an important role in the pathogenesis of PBC. The reduced number of Treg cells and higher levels of Th17 cells in PBC could be responsible for the loss of immune tolerance and development of inflammatory and autoimmune process in PBC. The counts of Treg cells correlates with the degree of severity of PBC.
Primary biliary cirrhosis: Clinical characteristics and treatment response

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Introduction: Primary biliary cirrhosis (PBC) is a chronic cholestatic liver disease characterized by destruction of interlobular bile ducts, which if untreated, leads to fibrosis, cirrhosis and liver failure. It is more frequent among females and is usually diagnosed in the fifth decade of life. Ursodeoxycholic acid (UDCA) is the only approved drug, but up to 40% of PBC patients failed to respond adequately. This study aims to determine the demographic, clinical, biochemical and serological characteristics, histological stage and treatment response of patients with PBC.

Methods: Retrospective analysis of the adult patients admitted to our clinic for PBC from January 2005 to December 2014 was performed. Data collection included demographics, clinical features, biochemical and serological markers, histological stage and treatment response. Treatment included UDCA 13–15 mg/kg/day with the addition of azathioprine and/or corticosteroids at the treating physician's discretion.

Results: 84 patients were diagnosed with PBC (mean age: 55 ± 12 years, range: 19–78), of whom 90.5% were women. 76.2% were symptomatic at diagnosis in the form of pruritus, jaundice, fatigue, bleeding esophageal varices, ascites. 47.6% of patients had cirrhosis at presentation. Positive anti-mitochondrial antibodies were found in 94.0% of cases. 31.6% of the patients were positive for antinuclear antibodies (ANA). Eleven of 16 (68.7%) PBC patients had PBC specific ANA (sp100 and/or gp210). Overlap syndromes were present in 10.7% (8 patients with autoimmune hepatitis, based on Paris criteria and 1 with primary sclerosing cholangitis). Liver biopsy was performed in 42.9% of the patients. 53.2% of patients had suboptimal response (abnormal bilirubin or alkaline phosphatase more than three-fold ULN) after at least one year of treatment.

Discussion/Conclusion: Most of our patients were symptomatic and had clinically advanced disease when they presented. More than half of patients had suboptimal response to therapy. These patients are candidates for adjuvant therapy.
The impact of age at presentation on symptoms in primary biliary cirrhosis

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Introduction: Primary biliary cirrhosis (PBC) causes clinical impact both through progression to advanced liver disease and increasingly well-characterised symptoms. The UK-PBC Study has shown that a significant proportion of patients present before age 50 and disease characteristics appear to be different in younger patients.


Results: The study cohort includes 2353 patients; 90.6% females, median age at diagnosis 55 years (range 16–86). For analysis, the cohort was divided into younger (< 50 years) and older (> 60 years) patients. Frequency of very poor or poor perceived overall QoL was significantly higher in younger than older presenting patients (41% vs. 26%, Chi-Square (CS) 54.2, p < 0.0001). All symptom severity scores were significantly higher in young presenting than old presenting patients. Younger patients with poor QoL had significantly more symptom domains showing clinically significant abnormality (CS 18.1, p < 0.0005). In terms of extreme symptom load, 27% of < 50 year old patients with poor QoL had between 8 and 10 (the maximum possible) significant symptom domain scores compared with 16% of the over 60s with poor QoL. Social dysfunction symptoms were a particularly discriminating feature in young patients with poor QoL compared to good QoL (OR = 423 [95% CI: 58–3078], p < 0.0001). Amongst younger patients with poor QoL, social dysfunction symptoms correlated particularly strongly with depression, fatigue and cognitive symptoms (r = 0.67, 0.56, and 0.8 respectively, all p < 0.0001).

Discussion: There are marked phenotypic differences in PBC patients presenting at a younger age with worse perceived QoL and increased symptom burden. Social dysfunction symptoms are a specific feature of younger patients. Offering psychological support and targeting specific symptoms in young PBC patients offer a potential approach to life quality improvement.

References:


Age at presentation and gender are predictors of increased mortality over long-term follow-up in primary biliary cirrhosis

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Introduction: Recent findings from the UK-PBC study have shown that non-response to ursodeoxycholic acid (UDCA) therapy is associated with increased risk of death or need for transplant in primary biliary cirrhosis (PBC). Younger age at presentation and male gender were associated with increased risk of UDCA non-response.

Methods: To utilise a comprehensive, geographically-defined, long-term follow-up cohort of PBC patients and matched community controls to explore the impact of age at presentation and gender on actual outcome in PBC. Kaplan-Meier survival analysis in the North-East England PBC patient cohort of 588 patients (529 female) incident between 1979 and 2003, prior to the widespread use of UDCA in Newcastle. Cohort participants were followed up to death or transplant, or the end of 2010 (whichever was latest). Full outcome data were available for all participants.

Results: The 588 patients were followed up for a total of 5900 patient years. 41% of female patients had died or been transplanted compared with 51% males. Survival to death or transplant was significantly reduced in PBC patients compared to controls (p < 0.0001, HR 2.8 [95% CI: 1.7–2.9]), with impairment in both female and male patients compared to controls (p < 0.0001 and p < 0.05, respectively). Survival to death or transplant was significantly better in female than male PBC patients (p = 0.01, HR = 0.6 [95% CI: 0.3–0.9]). Age at presentation had a significant and stepwise impact on survival (p < 0.0001, Chi-Square 123.1). Amongst PBC patients presenting under 60 years, survival was substantially reduced compared with controls matched for age at diagnosis (p < 0.0001, HR = 13.1 [95% CI: 1.7–26.6]).

Conclusions: Younger age at presentation and male gender are important factors in determining risk of death or need for transplant in PBC and should be included for models of stratified disease management.
Alternative to liver biopsy in primary biliary cirrhosis: Non-invasive serum markers of liver fibrosis

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Introduction: Although expensive and invasive, liver biopsy is still the gold-standard to fibrosis evaluation in Primary biliary cirrhosis (PBC). Alternatively, several non-invasive serum markers of liver fibrosis have been evaluated with unclear histology correlation.

Objective: To evaluate indirect serum markers as predictors of liver fibrosis in PBC.

Methods: Retrospective study of 89 patients with PBC admitted in a gastroenterology service, between 2000–2013. Histological staging was performed using Metavir score, categorized in significant (F2–4) and extensive (F3–4) fibrosis. The evaluated non-invasive serum markers of liver fibrosis were liver function tests (AST, ALT and total bilirubin), albumin/globulin ratio, MELD score, MELD-Na score, PBC Mayo risk score, AST/ALT ratio (AAR), ALT/AST ratio, APRI (AST to platelet ratio index), API (Age to platelet index), CDC (Bonacini cirrhosis discriminant score), Forns index, GUCI (Gottenberg university cirrhosis index), Pohl score, FIB-4, FibroQ, Lok score and King score.

Results: Liver fibrosis was significant in 73.0% of cases, and CDS (rs 0.472; p < 0.001), King (rs 0.470; p < 0.001), GUCI (rs 0.460; p < 0.001), APRI (rs 0.454; p < 0.001), total bilirubin (rs 0.450; p < 0.001) and FIB-4 (rs 0.448; p < 0.001) showed highest positive correlations. The best scores in significant fibrosis prediction were King (Area under the ROC [AUROC]: 0.806, p < 0.001), CDS (AUROC: 0.803, p < 0.001), APRI (AUROC: 0.796, p < 0.001), FIB-4 and total bilirubin (both with AUROC: 0.792, p < 0.001). Extensive fibrosis was presented in 43.8% of cases, with highest positive correlation for CDS (rs 0.647, p < 0.001), Lok (rs 0.596, p < 0.001), FibroQ (rs 0.524, p < 0.001), FIB-4 (rs 0.524, p < 0.001), and Mayo risk score (rs 0.508, p < 0.001). The CDS (AUROC: 0.872, p < 0.001), Lok (AUROC: 0.847, p < 0.001), FibroQ and FIB-4 (both with AUROC: 0.805, p < 0.001) showed higher diagnostic accuracy. Fibrosis was associated with worse outcomes, relatively to the development of cirrhosis complications (F2–4: OR = 5.02, p = 0.002 and F3–F4: OR = 13.74, p < 0.001) and liver transplantation necessity (F2–4: OR = 6.31, p = 0.042 and F3–4: OR = 4.52, p = 0.012).

Discussion/Conclusion: King, CDS, APRI, FIB-4, and total bilirubin for significant fibrosis and CDS, Lok, FibroQ and Fib-4 for extensive fibrosis, are useful, rapid and accurate alternative diagnostic methods to liver biopsy in the evaluation of liver fibrosis in PBC.
Is primary biliary cirrhosis a systemic disease? Cardiovascular risk assessment

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Introduction: Like other cholestatic liver diseases, there is hypercholesterolemia in primary biliary cirrhosis (PBC), due to the suppression of bile acids secretion, mainly in advanced stage. Despite frequent, the dyslipidemia impact at cardiovascular level remains unclear.

Objective: Frequency of dyslipidemia before ursodeoxycholic acid treatment in PBC and its impact on cardiovascular risk (clinically relevant non-fatal/fatal heart and cerebrovascular events).

Methods: Case-control retrospective study of the inpatient gastroenterology service, between 2000–2013, with PBC diagnosis (G1-cases: 93 patients) and diverticular colic disease (DCD) without autoimmune diseases (G2-controls: 101 patients), and between PBC without cardiovascular risk factors (G3-cases: 22 patients) and DCD without cardiovascular risk factors (G4-controls: 23 patients).

Results: PBC patients were mostly middle-aged women (women: 75 vs. 56, p < 0.001; age: 54 ± 15 vs. 73 ± 14 years old, p < 0.001). Dyslipidemia was more frequent in cases (51.6% vs. 19.8%, p < 0.001), with total-cholesterol 223 ± 76, LDL-cholesterol 115.8 ± 83.8, HDL-cholesterol 50 ± 18 and triglycerides 141 ± 102; however hypertension (38.7% vs. 60.4%; p = 0.003) and diabetes mellitus (16.1% vs. 28.7%; p = 0.027) were more frequent in controls. Vascular events occurred in 22.6% of patients (vs. 24.8%; p = 0.722), 11.8% of which were cardiovascular events (vs. 20.8%; p = 0.093): 5-acute myocardial infarction and 6-ischaemic heart disease; and 15.0% cerebrovascular events (vs. 5.9%; p = 0.037): 7-transient ischemic accident, 6-ischemic stroke and 1-hemorrhagic stroke. Of cases, 11.8% died due to no cardiovascular causes. Relatively to Mayo risk score at the diagnosis, the majority of cases presented low risk (54.8%), with more dyslipidemia (60.8% vs. 40.5%; p = 0.043) and cardio/cerebrovascular events (27.4% vs. 16.7%; p = 0.174), comparatively to the intermediate/high risk. In relation to the histological stage at the diagnosis, there were more cases in stage I (31.1%) and II (31.1%), with more dyslipidemia (stage I: 52.2%; stage II: 56.5%) and cardio/cerebrovascular events (stage I: 39.1%; stage II: 17.4%). After cardiovascular risk factors exclusion (G3 vs. G4), there was no significant statistical differences in the frequency of cardiovascular (4.5% vs. 21.7%; p = 0.090) or cerebrovascular events (4.5% vs. 4.3%; p = 0.974).

Discussion/Conclusion: PBC patients have more dyslipidemia, however without more non-fatal/fatal cardiovascular risk comparatively to the patients without PBC. Therefore, preventive strategies of vascular events should be the same of those for the general population.
Antimitochondrial antibody-negative primary biliary cirrhosis: A different entity?

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Introduction: Antimitochondrial antibody (AMA) is a diagnostic marker in primary biliary cirrhosis (PBC), due to high sensitivity and specificity. However, 5–10% of patients with clinical, biochemical and histological findings consistent with PBC are seronegative. The characterization and clinical significance of this subgroup of patients remains unclear.

Objective: Determine at the diagnosis, the clinical, biochemical, serological and histological profiles and the prognosis of patients with seronegative PBC.

Methods: Case-control retrospective study of the inpatient gastroenterology service, between 2000–2013, with PBC diagnosis negative-AMA (cases) and positive-AMA (controls).

Results: Of the total of 93 patients with PBC, 13 (14.0%) were seronegative. In cases, there was lower proportion of women (69.2% vs. 78.8%; p = 0.001), but similar age at the diagnosis (54 ± 18 vs. 54 ± 14 years old; p = 0.071) and follow-up of disease (9 ± 5 vs. 8 ± 5 years old; p = 0.818). Relatively to the clinic, the most cases were symptomatic (92.3% vs. 72.5%; p = 0.049), mainly jaundice (53.8% vs. 7.9%; p = 0.001), fatigue (69.2% vs. 42.5%; p = 0.256), pruritus (53.8% vs. 36.2%; p = 0.577) and portal hypertension complications (15.4% vs. 8.8%; p = 0.508). Dyslipidemia was more frequent in cases (61.5% vs. 48.8%; p = 0.026), but there were no significant statistical differences in the biochemical and immunological findings. In respect to serological/autoimmune characterization, cases had more circulating antibodies: antinuclear (76.9% vs. 55.4%; p < 0.001), anti-smooth muscle (15.4% vs. 1.2%; p < 0.001), anti-Ro/SSA (7.7% vs. 0.0%; p < 0.001) and anti-parietal cells (46.2% vs. 38.0%; p < 0.001); and higher prevalence of other autoimmune diseases (69.2% vs. 23.8%; p = 0.001): Raynaud's phenomenon (23.1% vs. 5.0%; p = 0.049), type 1 diabetes mellitus (23.1% vs. 2.5%; p = 0.008), autoimmune hepatitis (23.1% vs. 1.25%; p = 0.001) and idiopathic thrombocytopenic purpura (7.7% vs. 0.0%; p = 0.043). At histological level, there was a predominance in cases of stage I (44.4% vs. 30.8%; p = 0.451), stage IV (33.3% vs. 21.5%; p = 0.462), severe hepatocellular and piecemeal lymphocytic necrosis (25.0% vs. 1.7%; p = 0.007) and lobular necrosis (25.4% vs. 1.7%; p = 0.013). There were no significant statistical differences in the Mayo risk score, mortality, death causes and need/time of disease to liver transplantation.

Discussion/Conclusion: At the diagnosis, patients with seronegative PBC have more symptoms, dyslipidemia, other autoimmune diseases and hepatocellular necrosis in the histology. However, there was no prognostic implications relatively to the developing of portal hypertension complications, mortality or liver transplantation necessity.
Expression of IL-17 and IgG4 in portal tracts in primary biliary cirrhosis

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Introduction: Primary biliary cirrhosis (PBC) is an organ-specific autoimmune liver disease characterized by progressive loss of intrahepatic small biliary ducts epitheloid granuloma formation, and presence of plasmatic cells in granulomas. IL-17 contributes to the inflammation of many autoimmune diseases including PBC. We aimed to characterize immunohistochemically the inflammatory infiltrate in portal tract granulomas in PBC and to compare it with chronic active hepatitis, active cirrhosis and secondary biliary cirrhosis.

Methods: We investigated group of patients with primary biliary cirrhosis immunohistochemically with antibodies against CD3, CD4, CD8, CD56, CD57, GranzymeB, FOXP3, IgG4, IL-10, IL-17 and TGFβ cytokines.

Results: In portal tract (PT) CD56 and CD57 were significantly lower as compared to CD8+ (p < 0.001). IL-17 in granulomas was moderately expressed in inflammatory infiltrate as compared to IL-10. IL-17 was positive biliary epithelial cells in portal tracts. IgG4 cells prevailed in the periphery of PT granulomas in comparison IgG4 was absent in PT of chronic active hepatitis, secondary biliary cirrhosis and active cirrhosis.

Discussion/Conclusion: IgG4 is a hallmark of autoimmune granulomas in PBC and IL-17 it is involves in autoimmune inflammatory process there.
Risk factors for hepatic decompensation in primary biliary cirrhosis – Results of an international follow-up study of 2326 patients

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Introduction: Hepatic decompensation is an important complication in primary biliary cirrhosis (PBC). However, it remains unclear which factors best predict decompensation. Therefore we aimed to identify baseline factors predicting decompensation.

Methods: Long-term follow-up (FU) data of ursodeoxycholic acid (UDCA) treated patients was derived from 11 North American and European centers. Decompensation was defined as a first event of ascites, variceal bleeding, or encephalopathy. Patients decompensated prior to baseline or within the first year of FU were excluded. Risk factor analysis was performed using Cox proportional hazard models. Biochemical non-response was defined by the Paris-I-criteria. Survival was defined as liver transplantation-free survival.

Results: The population consisted of 2326 UDCA-treated PBC patients. 413 patients (18%) were excluded because of missing data, and 78 (3%) because of decompensation before baseline or within first year of FU. Of 1835 included patients (median FU 9.1 years, IQR 5.0–14.3), 163 developed decompensation (ascites: 70 (42.9%), variceal bleeding: 25 (15.3%), encephalopathy: 11 (6.7%), multiple events:...
57 (35%)). On multivariable analysis, the following baseline factors were independently predictive of occurrence of decompensation: calendar year of diagnosis ($p = 0.007$), moderate disease stage (abnormal bilirubin and/or albumin) ($p < 0.001$), advanced disease stage (abnormal bilirubin & albumin) ($p = 0.013$), higher serum alkaline phosphatase ($p < 0.001$), lower platelet count ($p < 0.001$), higher AST/ALT-ratio ($p < 0.001$) and biochemical non-response after one year ($p < 0.001$). Among biochemical non-responders 3-, 5-, and 10-year decompensation rates were 8.2%, 15.1% and 24.8%, versus 0.7%, 1.3%, and 3.8% in biochemical responders. One-year survival of decompensated vs. non-decompensated patients was 65.6% vs. 99.7% respectively and 5-year survival was 26.2% vs. 93.6% (time dependent HR = 33.9; 95% CI: 22.3–51.7). Survival after decompensation did not significantly differ between ascites, variceal bleeding and encephalopathy.

**Discussion/Conclusion:** Earlier year of diagnosis, later stage of disease, higher alkaline phosphatase, lower platelet count, higher AST/ALT ratio, and biochemical non-response are independently associated with hepatic decompensation in PBC.
A comparative study of cholestatic pruritus in primary biliary cirrhosis cohorts from USA, UK and Italy

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Introduction: Pruritus is a common problem in cholestatic liver diseases such as Primary Biliary Cirrhosis (PBC). There are limited studies of 'real-life' experience of cholestatic itch and its treatment in international cohorts. We aimed to compare pruritus experienced by PBC patients from UK, USA and Italy to: 1) understand the prevalence of pruritus in PBC in each cohort, 2) report the frequency of anti-pruritic treatments received by PBC patients from their local health care, 3) study any differences in the frequency and intensity of pruritus between the cohorts and 4) assess the correlation between measures of itch intensity in each cohort.

Methods: This was a cross-sectional study of experience of itch reported by PBC patients without a liver transplant from UK, Mayo clinic (USA) and Italy. Data were collected on frequency of itch (never, rarely, occasionally, frequently, all the time), PBC-40 itch score, intensity of worst itch measured using a 0-10 visual analogue scale (VAS) and treatment received for their itch since diagnosis of PBC. We defined persistent itch as pruritus occurring ‘frequently’ or ‘all the time’ and severe itch as persistent itch with a combination of itch score of more than 8 on VAS.

Results: Data were available for 2977 PBC patients from UK, 655 patients from USA and 75 patients from Italy.
1) 2076 (70%) UK, 445 (68%) USA and 45 (60%) Italy patients had experienced itch at some point in their illness. Of these, persistent itch was reported by 32% (UK), 34% (USA) and 27% (Italy) patients and severe itch by 15% of UK & USA and 13% of Italy patients. 2) Patients with severe itch in UK, USA and Italy reported to have received treatment with cholestyramine in 50%, 35% and 30% cases and rifampicin in 16%, 18% and 20% cases respectively. 3) There was no significant difference in the distribution of frequency of itch or PBC-40 itch scores between groups (Figure 1). However intensity of worst itch since development of PBC measured in VAS was significantly higher in UK cohort (Figure 2). 4) PBC-40 itch score and VAS, the two measures of itch intensity correlated significantly in all three cohorts (Figures 3a-c).
Discussion/Conclusion: This comparative study of three independent PBC cohorts suggests prevalence of pruritus in PBC is 60–70% of which nearly a third experience persistent itch and up to 15% endure severe itch. Overall, the characteristics of pruritus were similar in three cohorts but UK patients had higher scores for severity of worst itch since development of PBC. Treatment of itch in PBC appeared unsatisfactory in all three cohorts as more than half of patients with severe itch had not received first line therapy (colestyramine) suggesting a need for improvement in the awareness and management of itch in PBC.
Are gastroenterologists and hepatologists ready for stratified therapy in primary biliary cirrhosis? A study of educational awareness

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Introduction: Primary biliary cirrhosis is a chronic cholestatic liver disease that has only one licensed therapy, ursodeoxycholic acid. Approximately 20% of patients do not respond to ursodeoxycholic acid and are at risk of progressing to end stage liver disease, transplantation or death. A new era of stratified medicine with second-line therapies to treat high risk disease is emerging however it is unclear whether clinicians are confident at managing primary biliary cirrhosis using current therapies and whether they have the knowledge to implement second-line therapies appropriately when they become available.

Methods: Online questionnaires were sent to gastroenterologists and hepatologists in the US; the first 100 completed questionnaires from each group used for analysis.

Results: 80% of hepatologists felt they were highly competent in their understanding of the importance of early diagnosis and early therapy compared with 65% of gastroenterologists. However, only 36% of hepatologists and 30% of gastroenterologists felt competent at assessing response to treatment. Competence in knowledge (mode of action, efficacy and side effects) of second-line therapies and enrolment into clinical trials was low amongst both groups.

Discussion/Conclusion: The significant knowledge gaps in clinicians managing Primary Biliary Cirrhosis presents a problem in optimising care for patients and particularly in moving forward towards an era of stratified medicine. It is perhaps not surprising that knowledge of emerging second-line therapies is low as they are not yet FDA approved however more concerning is the suboptimal use of ursodeoxycholic acid and the lack of confidence at assessing response to treatment which should be a routine part of clinical practice. Assessing disease response will be key in delivering stratified medicine and ensuring that second-line therapies are utilised appropriately. This study highlights the need for improved educational awareness in primary biliary cirrhosis, particularly in the area of therapeutics and assessing response to treatment.
Assessment of metabolic syndrome in patients with primary biliary cirrhosis

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Introduction: Metabolic syndrome (MS) is associated with abdominal obesity, blood lipid disorders, inflammation, insulin resistance or diabetes, and increased risk for cardiovascular disease. Primary biliary cirrhosis (PBC) is a chronic, progressive cholestatic liver disease of unknown etiology that usually affects middle-aged women. Despite the high prevalence of hypercholesterolemia, patients with PBC are not exposed to a higher risk of cardiovascular events comparing to the general population. We aimed to analyze variables of MS in patients with PBC.

Methods: Data were collected for 49 patients with PBC (mean age 53.13 years) and 50 age and sex matched viral hepatitis patients (mean age 49 years). An assessment for MS has been made according to the third report of the National Cholesterol Education Program Adult Treatment Panel criteria. Measurements included body mass index (BMI), waist circumference, and blood pressure. Blood analyses were performed to assess liver function, lipid profile, fasting blood sugar and CRP.

Results: No difference in MS occurrence has been detected between study and control group (14/49 vs. 15/50; p > 0.05). No differences were observed in BMI, waist circumference, and blood pressure. Patients with PBC have higher values of cholesterol (3.23 vs. 2.01 g/l, respectively; p < 0.05), while fasting blood sugar, LDL, HDL and triglycerides were alike (p > 0.05, respectively). Liver function tests were, significantly elevated in patients with PBC (bilirubin 21.13 vs. 11.01 mol/l; AST 53.27 vs. 25.07 U/l; ALT 48.53 vs. 36.01 U/l, alkaline phosphatase 474 vs. 63.93 U/l; GT 261 vs. 19.0 U/l). The level of CRP was lower in patients with PBC (3.09 vs. 4.62 mg/l).

Discussion/Conclusion: Patients with PBC despite dyslipidemia, does not have higher risk for developing MS and increased risk for cardiovascular disease.
Autoantibody status and histological variables influence biochemical response to treatment and long-term outcomes in Tunisian patients with primary biliary cirrhosis

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Introduction: The aim of the present study is to evaluate the factors influencing biochemical response to treatment and the value of biochemical response for predicting long-term outcomes in Tunisian patients with primary biliary cirrhosis (PBC).

Methods: Biochemical response to ursodeoxycholic acid (UDCA) was defined as good (≤ upper limit of normal [ULN]), fair (≤ 1.5 × ULN) or poor (> 1.5 × ULN) at 1 years after initiation of UDCA treatment. Associations between various factors (including age, sex, autoantibody status and histological variables at baseline), biochemical response to treatment and long-term outcomes were evaluated in 49 Tunisian PBC patients.

Results: Anti-gp210 positivity was significant risk factor for worse alkaline phosphatase (ALP) response (odds ratios [OR], 2.11). Age, and anti-gp210 positivity were significant risk factors for worse alanine aminotransferase (ALT) response (OR = 1.5, 1.8, respectively). Anti-gp210 positivity and a higher hepatitis score were significant risk factors for worse immunoglobulin (Ig)M response (OR = 2.2 and 1.71, respectively). Worse ALP, ALT and IgM response were significant risk factors for progression to late-stage disease with persistent jaundice (OR = 2.4; 2.06; 1.98, respectively).

Discussion/Conclusion: Biochemical response to treatment at 1 year, which is influenced by autoantibody status and histological variables at baseline, can predict long-term outcomes in Tunisian patients with PBC.
Enhanced expression of hepatic fibroblast growth factor 19 (FGF19) is associated with suppression CYP7A1 and correlates with severity of the disease in primary biliary cirrhosis

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Introduction: Bile acids (BA) synthesis is primarily controlled by cholesterol 7α-hydroxylase (CYP7A1) which expression is regulated by FGF19 and farnesoid X receptor (FXR). Activated FGF receptor 4 (FGFR4) represses CYP7A1 either via c-Jun kinases pathway or in extracellular signal-regulated kinase (ERK1/2) dependent manner. As the FXR/FGF-19/CYP7A1 axis has not been studied in PBC we analyzed expression of proteins engaged in this pathway and searched for potential relationship with laboratory findings.

Methods: Concentration of FGF19 (ELISA), liver biochemistry, and 29 BAs metabolites (LCMS/MS) were analyzed in serum samples of patients with PBC (n = 51). Liver specimens from non-cirrhotic (n = 24) and cirrhotic (n = 21) PBC along with control tissues (n = 21) were used for analysis of mRNA (real-time PCR) and protein (Western Blots) expression.

Results: Serum concentration of FGF19 was higher in UDCA non-responders than in UDCA responders (167 ± 240 vs. 67 ± 42 pg/ml; p = 0.04) and was associated with worse liver biochemistry. Furthermore, it positively correlated with total BA concentration and glycine or taurine conjugates of cholic and chenodeoxycholic acid. The elevated expression of liver FGF19 mRNA in non-cirrhotic and cirrhotic tissues (9-fold and 69-fold, respectively) was associated with a stage of liver fibrosis. Considerable reduction of CYP7A1 in cirrhotic livers (p=0.006) was accompanied by enhanced hepatic expressions of FGF19, FGFR4, FXR and short heterodimer partner (SHP), (9-fold; 3.5-fold; 2.4-fold; 2.8-fold vs. controls, respectively). The levels of activated ERK1/2 or c-Jun kinase were not altered in PBC.

Discussion/Conclusion: In chronic cholestasis FGF19 is additionally produced in hepatocytes yet, the precise role of hepatic FGF19 expression requires further investigation. Insufficient response to UDCA-treatment is characterized by the elevated level of serum FGF19. Absence of activation of FGFR-dependent MAPK may imply further inhibition of CYP7A1 through FXR-induced hepatic expression of SHP.
**CTLA-4 and TNF-α polymorphisms and concomitant autoimmune diseases in Slovenian patients with primary biliary cirrhosis**

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**Introduction:** Patients with primary biliary cirrhosis (PBC) are frequently affected with concomitant autoimmune disease (AID), such as Sjögren’s syndrome (SS), autoimmune thyroid disease (AITD), Raynaud phenomenon (RP), CREST syndrome and rheumatoid arthritis (RA). The reason for that association is unknown. Genetic polymorphisms of cytotoxic T lymphocyte associated molecule 4 (CTLA-4) and tumor necrosis factor alpha (TNF-α) may be involved in pathogenesis of different AID. We investigated the influence of common CTLA-4 and TNF-α polymorphisms on AID in Slovenian PBC patients.

**Methods:** In total 92 PBC patients (91 females, 1 male) and 92 age matched healthy controls (HC) were genotyped for CTLA-4 49A/G (rs231775), CTLA-4 6230A/G (CT60) (rs3087243) and TNF-α -308G/A (rs1800629). Dominant genetic models were applied in statistical analysis using SPSS 20.0.

**Results:** Concomitant AID was confirmed in 37 (40%) PBC patients: AITD affected 32 (34%), SS 20 (21%), RP 13 (14%), CREST 10 (10%), and RA 4 (4%) patients. The minor allele frequencies (MAF) of tested SNPs did not differ between PBC and HC, nor between PBC patients with or without RP, CREST or RA. Significant differences in CTLA-4 6230A MAF were detected between PBC with or without AITD (12% vs. 31%; Pearson p ≤ 0.0001; Fisher p = 0.0000193; OR = 3.24, 95% CI: 1.87–5.60). CTLA-4 49G MAF differed significantly between PBC patients with or without SS (9.6% vs. 28.4%; Pearson p ≤ 0.00001; Fisher p = 0.00001; OR = 3.71, 95% CI: 1.87–5.60), while TNF-α -308A MAF differed significantly between PBC patients with or without any concomitant AID (50% vs. 35%; Pearson p = 0.005; Fisher p = 0.007; OR = 0.54, 95% CI: 0.35–0.83). These differences remained significant after multiple testing correction.

**Discussion/Conclusion:** The observed differences in CTLA-4 49A/G, CTLA-4 6230A/G (CT60) and TNF-α -308G/A polymorphisms between PBC patients with concomitant AID vs without concomitant AID, suggest different genetic background of PBC.
GP210 and/or SP100 autoantibodies in primary biliary cirrhosis: Predictors of cirrhosis/autoimmune (AIH) overlap syndrome?

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Introduction: GP210 and SP100 anti-nuclear antibodies are suggested as possible markers for primary biliary cirrhosis (PBC) in AASLD guidance. However, the role and benefit of anti-GP210/SP100 testing in routine practice is unclear.

Methods: We conducted a retrospective study of PBC patients (AASLD criteria), across 3 hospitals in Surrey, England; population 1.1 million. Prospective ELISA testing for GP210 and SP100 antibodies were undertaken on all PBC-patients in active follow-up. Baseline characteristics and progression were analysed between both groups.

Results: 51 PBC patients were identified, with anti-GP210/SP100 demonstrated in 14 patients (27%); 9 with anti-SP100, 5 with GP210. Demographic characteristics were similar (age 64 vs. 61 years; females 80% vs. 70% in the PBC and GP210/SP100 groups). 1 (1/51) patient was AMA negative (M2-ive), also ANA, SP100, GP210 negative. Baseline cirrhosis (imaging/biopsy) was present in 3/27 patients (11%) in the PBC group vs. 3/12 (25%) in the GP210/SP100 group. Quantitative mean M2 values were similar (100 vs.96), as were baseline mean laboratory values (Bili, ALT, ALK P, GGT, IGM). Cirrhosis was present at follow up (range 0.5–10 years) in 5/37 patients (13.5%) vs. 4/13 (31%) in the GP210/SP100 group. Treatment response to UDCA (Barcelona criteria) was similar: 10/24 (42%) vs. 5/13 (38%) in the GP210/SP100 group. Post-treatment mean alkaline phosphatase levels were higher in the GP210/SP100 group 231 vs.174 (p = 0.84). 8/51 PBC patients (16%) had diagnosed autoimmune hepatitis (AIH)/PBC overlap syndrome (OS) (histological/serological features). OS cases were seen in 2/37 (5%) in the non-ANA group vs. 6/14 (43%) of those in the GP210/SP100 group, reaching statistical significance (p = 0.05); with no significant difference in ALT levels between groups.

Discussion/Conclusion: Although a small sample, our findings support the role of anti-GP210/SP100 as possible markers of severity (cirrhosis), and suggest a role for these auto-antibodies in identifying those patients with PBC/AIH overlap syndromes; even in the absence of a significant transaminitis.
Clinical features and outcome of CSP patients with IBD: A comparative single center experience

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Introduction: Primary sclerosing cholangitis (PSC) is a chronic, cholestatic liver disease caused by diffuse inflammation and fibrosis of the biliary tree that may ultimately lead to cirrhosis. It has been associated with inflammatory bowel disease (IBD). It's assumed that PSC patients with IBD have distinct disease features and worse outcome than those without IBD. Our aim was to compare clinical features and outcome between CSP patients with and without IBD as a single center experience.

Methods: All cases of CSP admitted to our unit between 2000 and 2014 were retrospectively enrolled. Twenty-three patients with CSP were included and then separated in two groups: Group A: 7 patients with IBD (5 with Crohn's disease and 2 with ulcerative colitis) and Group B: 16 patients without IBD.

Results: Patients from Group A were significantly younger at CSP diagnosis than those in Group B with a mean age of 30.5 (± 15 years) vs. 47.3 (± 12 years) respectively (p < 0.1). Whereas sex-ratio was comparable between both groups with male predominance (7H/0F vs. 14H/2F vs. respectively in Group A and B, p = 0.76; n.s.). Patients with IBD had lower BMI compared to those without IBD although the difference was not statistically significant (16.5 kg/m² vs. 20.2 kg/m² p = 0.34; n.s.). Jaundice was less present in the inaugural presentation in IBD patients than in the others (35% vs. 87.5% p < 0.01). Cirrhosis was less frequent at CSP onset among IBD patients than in those without IBD (14 % vs. 43% p = 0.05). However, IBD patients with CSP had less clinical and biological response rate to AUDC compared to the others (28% vs. 47%; p = 0.05). During follow up period, risk of cholangiocarcinoma was not statistically different between both groups (14% vs. 6% p = 0.52; n.s.) whereas occurrence of colonic cancer was exclusively observed in IBD patients (14% vs. 0% p = 0.03).

Discussion/Conclusion: This study shows that CSP was discovered earlier in IBD patients through the systematic screening of extra-intestinal manifestations but the global clinical outcome of these patients is still poor.
The bile acid intermediate c4 and serum bile acid levels are potential mechanistic endpoints in human cholestatic trials: The ATRA + UDCA pilot in PSC

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Introduction: The search for new therapies for PSC is limited by the lack of validated and mechanistically-based surrogate endpoints. We recently undertook a small human pilot study to evaluate combination therapy with all-trans retinoic acid (ATRA) and ursodeoxycholic acid (UDCA) in PSC. Pre-clinical studies indicated that ATRA inhibits CYP7A1 and reduced the bile acid pool. We thus analysed bile acid intermediate 7α-hydroxy-4-cholest-3-one (c4) and bile acid levels as measures of efficacy.

Methods: Adults with PSC and elevated alkaline phosphatase (AP) > 1.5 x normal despite UDCA monotherapy were enrolled. ATRA (45 mg/m²/day divided twice daily) was added to moderate-dose UDCA for 12 weeks, followed by a 12 week washout with UDCA alone. Baseline levels were compared to week 12 and week 24 (washout).

Results: Fifteen subjects completed 12 weeks of combination therapy. Mean serum c4 level significantly decreased at week 12 (17 ± 19 vs. 9 ± 11 ng/ml, p = 0.04). A subset (n = 7) of patients had serum bile acid measurements, with a significant decrease at week 12 (41 ± 52 vs. 28 ± 45 umol/l, p = 0.04). The reduced bile acid pool resulted in a marked decline of serum ALT (94 ± 55 vs. 56 ± 32 U/L, p = 0.007). Interestingly, c4 and bile acid levels did all return to baseline after washout, suggesting a lasting effect of ATRA on CYP7A1.

Discussion/Conclusion: Combination therapy with ATRA+UDCA significantly reduced serum c4 and bile acid levels in PSC patients with cholestasis despite UDCA monotherapy. These parameters are intimately related to ATRA’s mechanism of action and thus are candidates to serve as surrogate endpoints in future human studies of PSC.
Changing pattern of indications and results of endoscopic retrograde cholangiopancreatography in patients with primary sclerosing cholangitis

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Introduction: Primary sclerosing cholangitis (PSC) is a chronic cholestatic disease, characterized by progressive fibrosing obliteration of the biliary tract. In recent years, magnetic resonance cholangiography (MRC) as a non-invasive technique has increasingly been used in the diagnosis of PSC. However, in unclear cases, diagnostic endoscopic retrograde cholangiography (ERCP) remains necessary. Patients with dominant stenoses may be treated by endoscopic dilatation with or without concomitant endoprotheses placement.

The current study presents an endoscopy centre’s 20-year experience using ERCP in the diagnosis and treatment of patients with PSC.

Methods: All patients with PSC who underwent ERCP during the study period were identified. Patients with suspected secondary sclerosing cholangitis were excluded. Data on demographics, presenting symptoms, liver enzymes, indication of ERCP, cholangiographic features, endoscopic treatment and follow-up were recorded.

Success was defined as resolution of the presenting symptoms as well as resolution of cholestasis.

Results: A total of 21 patients (30 ERCP) with PSC were collected (sex-ratio 2; mean age 45.28 years). A marked change in the indications of ERCP was found, with predominance of therapeutic procedures during recent years. Fourteen (67%) patients had dominant bile duct stenosis. The overall rate of early procedure-related complications was 10% (1 case of cholangitis, 1 case of post-ERCP pancreatitis and 1 case of acute cholecystitis after stent placement). Complications were mild and there was no mortality related to the procedure. A subset of 11 patients received endoscopic therapy for treatment of dominant strictures. This treatment consisted on biliary dilation in 6 cases followed by stent insertion in all cases, and have shown favorable results in 91% of the cases. A mean of 2.5 [1–5] treatment sessions was required to obtain satisfactory reopening of major biliary strictures.

Discussion/Conclusion: Complications requiring hospitalisations occurred in 10% of PSC patients undergoing ERCP confirming the emerging role of MRC as a first choice diagnostic test. Endoscopic therapy, indicated in selected patients, is safe and effective.
Transplant-free survival in PSC is influenced by azathioprine, steroids and the presence of inflammatory bowel disease


Introduction: Liver transplantation (LT) is the only effective therapeutic option for Primary Sclerosing Cholangitis (PSC). We assessed potential factors affecting the severity of PSC, comparing patients not needing LT and those who died or were transplanted.

Methods: 370 consecutive patients were diagnosed for PSC between 1990–2013. Follow-up was censored at LT, death or last follow-up. Cox-regression analysis was used to evaluate factors known to affect disease severity: Inflammatory Bowel Diseases (IBD) duration/colonic extent, disease activity in the last 5 years, IBD treatment (steroids, azathioprine (AZA), anti-TNF, surgery), disease severity at last colonoscopy (before last FUP or LT), prevalence of colorectal dysplasia/cancer, PSC severity at last FUP before LT (serum albumin, bilirubin and decompensation), UDCA treatment, cholangiocarcinoma, outcome.

Results: 333 patients were diagnosed with PSC, 16 with small-duct PSC, 21 with autoimmune overlap. 234 (63%) were male, median age at diagnosis 41 years. 138 (41%) were transplanted and 62 (17%) died at a median of 40 and 94 months from the diagnosis, respectively. 246 (67%) had concomitant IBD: 208 ulcerative colitis, 30 Crohn’s disease, 8 indeterminate colitis. 20 had colon cancer, 13 dysplasia, 66 underwent colectomy. Factors associated with transplant-free survival at Cox analysis were: AZA treatment (p = 0.012, OR = 2.3, 95% CI: 1.2–4.4), steroids (p = 0.001, OR = 4.7, 95% CI: 2.2–10.1) and concomitant IBD (p = 0.023, OR = 2.11, 95% CI: 1.11–3.4). 53 patients were on AZA pre-LT: 7 were transplanted at a median of 62 m and 5 died at a median of 105 m from diagnosis. Of 318 not on AZA: 131 underwent LT and 57 died at a median of 44 m and 82 m after the diagnosis. The only factors associated with survival were age at diagnosis < 40 years (p = 0.01, OR = 1.03, 95% CI: 1.01–0.03) and the absence of hepatobiliary malignancy (p = 0.03, OR = 0.7, 95% CI: 0.5–0.99).

Discussion/Conclusion: Concomitant IBD and treatment with AZA and steroids had a transplant-free survival benefit in this big cohort of PSC patients.
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Primary sclerosing cholangitis: A review of clinical cases

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Introduction: Primary sclerosing cholangitis (PSC) is a rare, cholestatic liver disease, characterized by fibro-obliterative inflammation of the entire biliary tree.

Methods: In our study 10 patients were diagnosed with PSC and followed up for a 5-years period (6 females and 4 males), with the median age of 53.1 years. Female predominated in ratio 1.5:1. Eight of the patients with PSC were associated with IBD (inflammatory bowel diseases), two of them with a liver cirrhosis. At presentation- liver function tests, serum autoantibodies and imaging technique – ultrasonography and MRCP were estimated.

Results: All of the patients were with cholestatic hepatitis, 8 of them were asymptomatic – presenting with a raised serum alkaline phosphatase and gamma-glutamyl transpeptidase (GGT). Two patients had a liver cirrhosis and one had developed liver cirrhosis with cholangiocarcinoma. They all had a clinical symptoms, demonstrated with abdominal pain, jaundice and pruritus. Eight of the patients with PSC were associated with IBD. By the immunological tests – pANCA was positive by 4 patients. In 3 of the patients – serum transaminase activity was presented, combined with a cholestatic activity. Liver disease was determinated as fatty liver, by 3 of the patients, hepatitis in 3 patients and liver cirrhosis in 2 of them. By the MRCP imaging technique – 3 of the patients were presented with a features of large bile ducts diseases, dilatated choledochus and intrahepatic bile ducts. In 2 of our patients, the diagnose was histologically proved. In our 5-years period of studying, 1 patient with PSC – liver cirrhosis progressed to a cholangiocarcinoma and died in hepatic failure. The treatment with Ursofalk® was successfully in all of the patients with PSC associated with IBD.

Discussion/Conclusion: PSC is diagnosed as strongly associated with IBD. PSC tends to arise in IBD patients. The first and leading symptom is a diarrhea. We observed correlation between involvement and severity of IBD and progression of PSC.
VAP-1 is elevated in PSC, correlates with clinical outcome and exhibits amine oxidase activity in a substrate-dependent manner

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Introduction: Vascular adhesion protein (VAP)-1 is an adhesion molecule possessing potent amine-oxidase activity. Activation on hepatic sinusoidal endothelium (HSEC) leads to H₂O₂ production, NFκB activation and expression of the gut-homing receptor MAdCAM-1, which promotes homing of gut-tropic lymphocytes to the liver. Given the proposed role this pathway has in hepatic disorders complicating inflammatory bowel disease (IBD), our aim was to quantify circulating soluble (sVAP-1) titre and determine intrahepatic/colonic enzyme activity in patients with primary sclerosing cholangitis (PSC)/IBD, and investigate consequences of activating VAP-1 with variant amine substrates.

Methods: Circulating sVAP-1 was quantified by ELISA from patients with PSC (n = 105); primary biliary cirrhosis/PBC (n = 90); autoimmune hepatitis/AIH (n = 99); IBD-alone (n = 50) and healthy controls (n = 21). Correlations with clinical outcome were assessed using Cox proportional hazards assumption and KM-estimates. Protein lysates were extracted from (a) explanted liver (PSC = 9; PBC = 10, AIH = 5, normal donor, n = 10); and (b) colonic resections (ulcerative colitis = 7) and VAP-1 activity quantified using the Amplex red assay. Putative VAP-1 substrates were selected based on their inclusion in the human metabolome database (www.hmdb.ca) and induced kinetic rates measured via Michaelis-Menton analysis. The induction of MAdCAM-1 was evaluated quantitatively by HSEC-ELISA, and functionally in flow-adhesion assays.

Results: PSC patients had higher sVAP-1 concentrations (median 517 ng/ml) than those with AIH (475), PBC (472), IBD-alone (413) and healthy controls (425) (p < 0.001). sVAP-1 levels ≥ 530 ng/ml in PSC were associated with significantly worse transplant-free survival (unadj. HR = 2.94, p = 0.008), and retained independent predictive value when controlling for other significant risk factors (disease stage, ascending cholangitis and biochemical parameters; adj. HR = 3.85, p = 0.003). Intrahepatic VAP-1 enzyme activity was significantly greater in PSC (227 pmol H₂O₂/min/mg protein) compared with PBC (124), AIH (128) and donor liver (109) (p < 0.001), yet comparable to activity in colonic tissue (220; p = n.s.). The substrate associated with highest VAP-1 enzymatic efficiency was cysteamine (kcatapp/Kmapp: 5.4 x 10⁷); an amine secreted by Escherichia spp. which induces colitis in the murine colon. Cysteamine+TNFα provision resulted in greater MAdCAM-1 expression by HSEC ELISA than that with other substrates or TNFα alone (p < 0.01), with increased α4β7-dependent adhesion under flow (p < 0.01).
Conclusion: Elevated levels of circulating sVAP-1 exist in PSC and predictive of poor outcome. Intrahepatic VAP-1 enzyme activity is also increased in PSC akin to that seen in the colon. The ability of VAP-1 to catabolise amine substrates secreted by gut commensals/enteric pathogens, provides a theoretical link between altered colonic microbiota and mucosal immunity in the pathogenesis of PSC.
Connecting liver and gut in PSC: CCL25 expression is upregulated in colitis, correlates with inflammatory activity and facilitates effector CCR9+ lymphocyte recruitment

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Introduction: Recruitment of mucosal T-cells to the liver in response to aberrantly expressed homing signals drives hepatobiliary inflammation in primary sclerosing cholangitis (PSC). This is exemplified by the ‘gut-homing’ chemokine CCL25, which recruits intestinal CCR9+ effector cells to the PSC liver. However, previous studies report CCL25 expression as being confined to the small bowel whereas PSC is typically associated with colonic inflammation. Our aim was to determine whether CCL25 and CCR9 are expressed in the inflamed human colon in patients with colitis.

Methods: Mucosal biopsies were obtained during surveillance colonoscopy (n = 40) and colonic tissue from patients undergoing surgical resection for colitis (n = 6), or non-colitis-associated cancer (n = 5). CCL25 mRNA was evaluated by qRT-PCR (relative to GUSβ) and protein expression confirmed using western blotting and tissue-ELISA. Lymphocyte CCR9 expression was quantified by flow cytometry, and the ability of sorted α4β7+CCR9+ and α4β7+CCR9- T-cells to transmigrate across hepatic sinusoidal endothelium (HSEC) investigated in flow-based adhesion assays.

Results: CCL25 mRNA and protein were absent from normal colon but present in colitis. CCL25 mRNA expression correlated with endoscopic Mayo score (p < 0.0001) and tissue levels of TNFα (Spearman’s rho = 0.811; p < 0.0001) as indices of inflammatory activity. In colitis, > 90% of CD3+CD4+ and > 15% of CD8+ T-cells expressed CCR9 (6% and 2% in normal colon; p = 0.01 and 0.03) and were predominantly CD127+ effector lymphocytes. α4β7CCR9+ T-cells showed enhanced adhesion and transendothelial migration across HSEC compared with α4βCCR9- T-cells (p < 0.05).

Conclusion: CCL25 is expressed in the inflamed human colon, correlates with inflammatory activity and is associated with high frequencies of CCR9+ tissue-infiltrating lymphocytes. These findings lend further support to the mucosal lymphocyte homing hypothesis of PSC and show how it can be applied to patients with colitis.
Sulphotransferase2A1 (SULT2A1) is not adequately induced in patients with primary sclerosing cholangitis

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Background and aim: The activity of sulphotransferase2A1 (SULT2A1) plays an essential part in the defense machinery against the cholestatic effects of toxic bile acid (BA). The enzyme transforms BA into more hydrophilic water-soluble sulfate conjugates. Transcription of SULT2A1 gene is mainly induced by pregnane-X-receptor (PXR) activated by BA intermediates and can be translationally repressed by miR-378a-5p. Decreased sulphation of lithocholic acid in PSC was reported (Trottier et al. Dig Liver Dis. 2012). PXR/ SULT2A1 axis has not been studied in context of chronic cholestasis therefore we investigated the regulation of SULT2A1 expression in patients with PSC and PBC.

Materials and methods: Western blot analysis for SULT2A1 and PXR was performed on explanted livers from patients with PSC (n = 11), PBC (n = 19) and control tissue (n = 19). Total RNA was isolated and miRNA expression was evaluated using the Affymetrix GeneChip miRNA4.0. Genomic DNA was isolated from blood samples of PSC patients (n = 120) and healthy volunteers (n = 120).

Results: Increased level of PXR protein was observed in both PSC and PBC (2.7- fold and 5.9- fold, respectively, both p < 0.0001). The enhanced PXR expression was accompanied by the increased level of SULT2A1 in PBC (1.5-fold, p = 0.001 vs. controls) but not in PSC. Therefore, the genomic analysis of SULT2A1 promoter was performed. The examination of two SNPs localized near/within the PXR binding (rs11569683, rs112433193) and total promoter sequencing detected no changes in nucleotides sequence. However, miRNA analysis has shown a substantial increase in liver miR-378a-5p in PSC, a negative regulator of SULT2A1gene (3.6-fold, p = 0,005 vs. PBC).

Conclusions: The SULT2A1-modulated defense is impaired in PSC where regardless of PXR stimulation SULT2A1 expression remained unchanged. The results of miRNA analysis imply that SULT2A1 expression in PSC may be regulated by miR-378a-5p.

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Serum autotaxin is associated with pruritus and severity of liver disease in primary sclerosing cholangitis

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Background/Aim: Autotaxin (ATX) is involved in the synthesis of lysophosphatidic acid (LPA), a strong neuronal activator. They were both recently linked with pruritus of cholestasis (Hepatology. 2012;56:1391–1400) and it was hypothesized that ATX inhibitors could be of use in the treatment of cholestatic itching. Potential associations between ATX and relevant clinical factors in primary sclerosing cholangitis (PSC) have not yet been studied.

Methods: This study involved a group of 115 well characterized patients with PSC (M/F-75/40; mean age 35 ± 13). PBC-40 and SF-36 questionnaires were used to assess the health related quality of life (HRQoL). Twenty-nine patients had liver cirrhosis on histology or imaging. Total serum bile acids (BA) levels were analyzed in 42 patients.

Results: Serum ATX showed a significant correlation with pruritus assessed with the itch specific domain of the PBC-40 questionnaire (r = 0.376; p < 0.0001). ATX did not correlate with HRQoL domains of generic SF-36. It also correlated with serum AST (r = 0.306; p = 0.002) and ALP (r = 0.362; p < 0.0001) and was significantly higher in patients with cirrhosis (9.2 ± 3.8/6.6 ± 3.04; p = 0.0003). Furthermore, ATX correlated with Mayo Risk Score (r = 0.371; p = 0.016) and total serum BA levels (r = 0.379; p = 0.013).

Conclusions: This study demonstrates that in patients with PSC serum ATX is associated with pruritus and is an indicator for the severity of liver disease.

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Celiac disease, cryptogenic hypertransaminasemia and autoimmune hepatitis

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Introduction: Celiac disease (CD) is an autoimmune enteropathy due to food gluten intolerance in genetically predisposed people. Celiac disease, which affects nearly 1 percent world’s population, is a gluten-sensitive enteropathy that resolves with gluten-free diet (GFD). The clinical spectrum of CD is remarkably varied, and the disease can affect many extraintestinal organs and systems, including the liver. CD can accompany with other autoimmune diseases. Occurrence of autoimmune diseases with CD is related with the time of disease onset and gluten exposure interval. CD and other autoimmune diseases share the same HLA haplotypes (HLA DR3-DQ2 or DR3-DQ8 etc.). We investigated transaminase levels and autoimmune hepatitis presence in CD patients before gluten free diet administration in this study.

Methods: 31 CD patients were enrolled in the study. Patient demographics were 28 female, 3 male patients. Mean age was 39.96 ± 16.5, between 20–69 years old. Diagnosis was made by positive marker of antitissue transglutaminase antibodies (IgA-tTG) and/or antiendomysial antibodies (EMA-IgA). In case of seropositivity, a small bowel histological evaluation was performed. The modified Marsh grading system was used for grading mucosal changes. Patients’ serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were recorded at diagnosis before gluten free diet intake. Other liver pathologies like autoimmune hepatitis, viral hepatitis, metabolic liver diseases were investigated in patients with high levels of transaminase.

Results: High transaminase levels were revealed in 6 of 31 patients (19.15%). 5 patients diagnosed with cryptogenic hypertransaminasemia and gluten free diet had begun. 8–14 months after gluten free diet, transaminase levels came down to normal levels in these 5 patients. 1 (3.2%) patient (49 years/female) diagnosed with autoimmune hepatitis. Laboratory results were as follows: AST 95 U/l (N: 0–35), ALT 85 U/l (N: 0–35), alkaline phosphatase 158 U/l (N: 40–150), γ-glutamyl transferase 61 U/l (N: 0–64), total bilirubin 0.8 mg/dl (N: 0.6–1.2). Anti-nuclear antibody was 3+, whereas antismooth muscle antibody, liver kidney microsomal-1, anti-DNA, AMA-M2, SLA, and hepatitis serologies were negative. Serum IgG was 18.9 g/l (N: 7–16) and IgM was 2.4 g/l (N: 0.4–2.3). Human leukocyte antigen typing was reported as HLA-A26, B8, DR17, and DR52. There were no alcohol consumption and drug usage history. Liver biopsy was performed to investigate autoimmune hepatitis. Autoimmune hepatitis was diagnosed by presence of interface hepatitis, mononuclear portal inflammation, fibrous enlargement in portal spaces, portoportal fibrosis in liver biopsy. Gluten free diet was given. Corticosteroid treatment was avoided in osteoporotic patient. 100 mg/day Azathioprine had begun. Liver function tests were decreased by 2 months and normal after 1 year.
Conclusions: Liver abnormalities are a common extraintestinal manifestation in celiac disease patients ranging from mild hepatic dysfunction to severe liver disease. Isolated hypertransaminasemia with non-specific histologic changes, which normalizes with a gluten free diet, is the most common hepatic presentation of CD. Liver involvement with CD also includes severe forms of AIH, and, much more rarely, other autoimmune liver diseases such as autoimmune cholangitis and PSC. Early diagnosis and dietary treatment with a gluten-free diet might slow down the progression of associated autoimmune diseases in celiac disease, but the data are contradictory.
Impact of age on natural history and response to treatment of autoimmune hepatitis

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Introduction: The impact of age on inaugural symptoms, response to treatment and outcome of autoimmune hepatitis (AIH) is controversial. The aim of this retrospective study was to compare clinical, biological and histological features and treatment response in patients with AIH according to age at the time of presentation.

Methods: Consecutive patients with type AIH followed between 2000 and 2014, were included. Patients were matched in 3 groups, group A: age < 40 years old (n = 10), Group B: between 40 and 59 (n = 15) and group C: > 60 (n = 10).

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<th>Groups</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Age&lt;40</td>
<td>Age 40-59</td>
<td>Age&gt;60</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>10</td>
<td>15</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>% females</td>
<td>90</td>
<td>100</td>
<td>90</td>
<td>ns</td>
</tr>
<tr>
<td>Inaugural symptoms: jaundice%</td>
<td>60%</td>
<td>50%</td>
<td>60%</td>
<td>ns</td>
</tr>
<tr>
<td>ALAT(xN)</td>
<td>17</td>
<td>18</td>
<td>4</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Total bilirubin(mg/l)</td>
<td>38.5</td>
<td>13.5</td>
<td>14.7</td>
<td>ns</td>
</tr>
<tr>
<td>Serum albumin(g/l)</td>
<td>38.8</td>
<td>39.6</td>
<td>30.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Gammaglobulin(g/l)</td>
<td>18.5</td>
<td>20.2</td>
<td>23.1</td>
<td>ns</td>
</tr>
<tr>
<td>Positive antibodies</td>
<td>90%</td>
<td>93%</td>
<td>100%</td>
<td>ns</td>
</tr>
<tr>
<td>Severe fibrosis F3F4 of Metavir</td>
<td>30%</td>
<td>20%</td>
<td>60%</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Results: Thirty-five patients were included. The characteristics at the time of diagnosis were analyzed according to 3 groups of age. The majority of patients in the 3 groups (A, B, C) were treated with steroids (90 vs. 86 vs. 80%, n.s.) and azathioprine (80 vs. 69 vs. 70%, n.s.) without significant difference of dose, duration of treatment or side effects. Only one non responder patient to steroids/azathioprine was treated with MMF. Complete response was respectively achieved in 90, 97 and 70% of the patients treated with immunosuppressors (p < 0.01). During follow-up (median 50 months),
there were 5 relapses (Group A: n = 1, Group B: n = 1, Group C: n = 3, p < 0.01),
4 ascites (Group A: n = 0, Group B: n = 1, Group C n = 2, n.s.), and 1 liver-related
death in the elderly group by hepatic encephalopathy.

**Discussion/Conclusion:** The occurrence of AIH after 60 years is not rare,
representing 28.5% of cases in our series. The degree of hepatic fibrosis increases
with age without significant impact on prognosis. Treatment with steroids/azathioprine
was well tolerated and effective in elderly patients.
Autoimmune hepatitis: A challenging disease deserving of specialist care

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Introduction: Recent reports have suggested that the outcome of AIH is not as benign as previously thought and failure to normalise LFTs within one year may be associated with poorer outcomes. A multicentre survey of UK clinical practice has also demonstrated wide variations in care for patients with AIH.

Methods: We set out to evaluate whether there are any differences in how AIH is managed between Hepatologists and Gastroenterologists within our organisation (ABUHB).

Results: 146 patients currently attend ABUHB with a diagnosis of AIH, 120 F, 26 M. The median age at diagnosis was 47 years (M) and 58 years (F). Almost 1/3rd of patients (31%) presented acutely with jaundice.

In total 59 patients were initially managed by a Hepatologist and 87 by a Gastroenterologist. 25 patients were subsequently referred on to Hepatology by Gastroenterologists because of non-response.

Patients under a Hepatologist are more likely to be on treatment (98% vs. 82% p = 0.001) and 88% managed initially by Hepatologists underwent remission as opposed to 58% managed by Gastroenterologists (p = 0.03). The median time to remission under Hepatology was 133 days (range 14–1058) versus 277 days (range 31–3211) for those initially managed by Gastroenterology (p = 0.011).

Among 25 patients subsequently referred on to Hepatology, 24/25 (96%) underwent remission at a median time of 123 days (range 65–1998) from transfer of care.

Discussion/Conclusion: AIH is a challenging disorder to manage with a third presenting with significant liver disease (jaundice). Patients under Hepatology care are more likely to be on treatment and remission
Autoimmune hepatitis and the polyglandular autoimmune syndrome type 1 in 12-year-old girl

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Introduction: Autoimmune polyglandular syndrome type 1 (APS 1), also known as Blizzard syndrome is a rare autosomal recessive disease caused by mutation in the autoimmune regulator (AIRE) gene. The prevalence of APS 1 in Poland was estimated to be about 1:129,000 individuals. Two diseases of classic triad of hypoparathyreoidism, adrenocortical failure and mucocutaneous candidiasis are required for the diagnosis. There are other autoimmune diseases coexisting with APS 1. Here we present a case report of a 12-year-old girl who complained of progressive weakness and vomiting during treatment for autoimmune hepatitis. The reported case illustrates a rare form of APS-1 failure, in which the diagnosed autoimmune hepatitis was only the first symptom.

Case report: A 12-year-old girl was admitted to the Clinical Hospital in Zabrze for progressive weakness and vomitus. The girl was treated for autoimmune hepatitis type 2 for 10 years (steroids, azathioprine). There were no abnormalities of liver function since 4 years. The recurring oral candidosis was observed since 8 years. On admission to hospital laboratory studies revealed a decrease in sodium concentration and a serum calcium concentration, a high phosphorus concentration, decreased parathormone concentration, increased titre of anti-adrenal cortex antibodies. Due to identified calcium phosphate metabolism disorders, adrenocortical failure and presence of oral candidosis we could recognize autoimmune polyglandular syndrome type 1. The applied treatment was multidirectional (hydrocortisone substitution, calcium agents, vitamin D, dietary education). We look forward to the outcome of genetic testing (AIRE gene).

Conclusion: Autoimmune hepatitis may be first symptom of APS-1 and may preceded by several years other symptoms of polyglandular failure. Careful long-lasting follow-up since onset of the first symptoms seems to be necessary to prevent from other acute complications.
Celiac disease-associated autoimmune liver and thyroid diseases in a pediatric population from Western Romania

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Introduction: Recent researches proved that classical definition of celiac disease (CD) comprises only 30% of cases with genetic predisposition, the vast majority of patients being pauci-symptomatic. Active-case finding in groups at risk for CD is a cost/effective strategy. The association of CD with several autoimmune conditions is well-known.

Objectives: The aim was to determine the prevalence of CD in a pediatric population from the Western part of Romania with autoimmune hepatitis (AIH) and autoimmune thyroid disorders (AITD) and in a control lot and to assess the clinical forms of presentation and the HLA polymorphism in all cases.

Methods: Between Jan 2005 and Dec 2014 there were screened for CD 74 children with AITD (lot 1), 62 children with AIH – 17 type1/45 type 2 (lot 2) and 60 healthy children (control lot). In patients with at least one positive autoantibody for CD, intestinal biopsy was performed. All children underwent HLA typing for DQ2/DQ8.

Results: CD prevalence after screening in lot 1 was 7% (5 patients) and in lot 2–6% (4 patients). In the control lot there there weren't any CD cases. There weren't significant differences between the frequency of CD cases among children with AITD and AIH (p > 0.05). Most of the cases presented as silent CD (78%). All children diagnosed with CD presented DQ2/DQ8 haplotype. 20% of the control subjects associated heterozygous DQ2 alleles. From 69 children with AITD without CD, only 3 patients (4%) presented predisposing haplotype for CD-heterozygous DQ2. From 58 children with AIH and negative results for CD screening, 37 patients (64%) associated homo or heterozygous DQ2/DQ8 alleles.

Discussion/Conclusion: Recommending AITD and AIH as selection parameters for CD screening in asymptomatic children is justified by the high frequency of gluten enteropathy obtained in this study (7% and 6% respectively). CD and AIH share selected combinations of genes coding for class II HLA, which could explain their coexistence. Besides immunosuppressives, early detection and dietetic treatment of CD in AIH children may prevent progression to end-stage liver failure.
Autoimmune hepatitis and cryptogenic hypertransaminasemia among Romanian children with celiac disease

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²Gastroenterology Department, University of Medicine and Pharmacy Victor Babes Timisoara, Romania

Introduction: Celiac disease (CD) is an immune-mediated enteropathy caused by exposure to gluten in genetically susceptible individuals. CD can be associated with autoimmune liver diseases.

Objectives: The aim of this study was to assess the prevalence of cryptogenic persistent hypertransaminasemia (CPHT) and autoimmune hepatitis (AIH) among children with CD and to evaluate the response to treatment.

Methods: We performed a retrospective study analyzing the medical files of all children diagnosed with CD over a period of 10 years (Jan 2005–Dec 2014) in a Pediatric reference Center from Western Romania.

Results: From 258 CD patients, 72 cases (28%) presented elevated transaminases levels. We excluded from analyze children with CD and hypertransaminasemia due to viral/drug induced hepatitis or other associated metabolic conditions. From 72 cases with elevated TGP and TGO levels, 65 cases had CPHT due to gluten-dependent non-specific mild hepatitis and 7 cases had AIH. For AIH diagnosis, liver examinations, specific antibodies and liver biopsy were performed. CPHT normalized on gluten-free diet (GFD) in all patients. Clinical and biochemical parameters improved on immunosuppressive treatment and GFD in all 7 AIH patients (mean follow-up period: 5 years). After treatment withdrawal, 5 AIH cases relapsed only on GFD.

Discussion/Conclusion: CD is associated with elevated transaminases levels in about one-third of cases. The prevalence of CPHT among CD children was 24%. The prevalence of AIH among CD children was 2.7%. CPHT resolved after 2–3 month of GFD in all cases. In CD children with AIH, GFD and immunosuppressants determined a high remission rate. The impact of GFD alone on the outcome of AIH is ineffective in the treatment of children with comorbidity CD/AIH.
Prevalence of hepatitis B virus infection in patients with autoimmune hepatitis in a Tunisian patient population

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Introduction: Hepatitis B is a very common communicable disease in Tunisia but the prevalence of hepatitis B virus (HBV) infection in patients with autoimmune hepatitis is unknown.

Patient and methods: We retrospectively investigated the prevalence of HBV infection in patients with autoimmune hepatitis. Autoimmune hepatitis included autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis and overlap syndrome. A positive test result for hepatitis B surface antigen (HBsAg) was used to indicate the presence of HBV infection.

Results: The medical records of 53 patients with autoimmune hepatitis were reviewed. The proportion of autoimmune disease patients who were HBsAg positive was 5.66% and those who were HBsAg negative with Hepatitis B core antibody (Anti HBc) positive was 3.77%. Regarding hepatic autoimmune diseases, the positivity rates for HBsAg in autoimmune hepatitis patients (9.01%) and primary biliary cirrhosis patients (6.06%). Patients with autoimmune diseases, especially those with primary biliary cirrhosis patients, may more efficiently clear HBV than patients with no autoimmune diseases. The management of both diseases was made according to the nature of liver disease and the HBV DNA rate at the time of the support.
Biomarkers of oxidative stress and their implication in autoimmune hepatitis

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Introduction: Complex biochemical perturbations due to liver autoimmune aggression play an important role in diagnosis and management of patients with autoimmune hepatitis.

Aim: Estimation of oxidative stress biomarkers involvement in the investigation and orientation for additional dietary measures in the autoimmune liver disease evolution and treatment.

Methods: There were determined oxidative stress enzymes (malondialdehyde as marker for lipids peroxidation, nitric oxide) and the level of antioxidative enzymes (glutathion peroxidase and superoxide dismutase) to a total of 14 patients with autoimmune hepatitis (aged 20–55). Specific methods were used in determining the oxidative stress existence and level, as well as the relationship between oxidants and antioxidants balance existing in these patients.

Results: It was observed an increased level of oxidative stress enzymes (malondialdehyde, nitric oxide) and a decreased level of antioxidants (glutathion peroxidase and superoxide dismutase) in 13 of the 14 patients with autoimmune hepatitis, demonstrating the existence of an imbalance between oxidants and antioxidants. Autoimmune aggression over target antigen represented by mono-oxygenase enzyme of the P450 II D6 (CYP 2D6) cytochrome in autoimmune hepatitis can lead to the appearance of oxidative stress, a condition that can be influenced by immunosuppressive therapy (decreasing immune aggression), concomitant with the use of antioxidant supplements or food which may carry benefits.

Conclusion:
1. Determination of oxidative stress biomarkers plays an important role in the evolution control and long-term adapted treatment of autoimmune hepatitis.
2. The increased oxidative stress level involves also the use of antioxidants in diet or medication, in order to improve oxidant-antioxidant balance.
3. The decreasing of oxidative stress marker enzymes can be the expression of autoimmune aggression reduction and of a favorable prognosis undergoing therapy.
Celiac disease with autoimmune hepatitis; a case report

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Introduction: Celiac disease is a proximal small intestine disease described as persistent intolerance to gluten or gluten like proteins found in grains such as wheat, barley and rye. Celiac disease is named as gluten sensitive enteropathy, celiac sprue and non-tropical sprue also. Celiac disease develops with autoimmune mechanisms and is related with other autoimmune disorders.

Autoimmune hepatitis is a progressive, chronic necroinflammatory liver disease characterized with chronic inflammation, interphase hepatitis, serum autoantibodies and hypergammaglobulinemia. During the course of disease; cirrhosis, portal hypertension, liver failure and even death can be seen. Autoimmune hepatitis is a relatively rare cause of chronic liver disease in Turkey.

Case presentation: 26-year-old male patient working as labourer in a private company; admitted to our hospital with complaints of pruritus and weight loss. Laboratory tests revealed that; AST 63 u/l, alt 79 u/l, ALP and GGT had been in normal range. Patient had been forwarded to our gastroenterology out patient clinic. In his medical history; levosetirizine and desloratadine usage, iron deficiency anemia were present. Patient were followed up during 6 months. Laboratory tests performed in our outpatient clinic were concluded as; AST: 53 u/l, alt 79 u/l, albumin: 4.2, ALP: 110 u/l, total billirubine: 0.9 mg/dl, direct billirubine: 0.40 mg/dl, sedimentation rate: 5 mm/h, CRP: 3 mg/dl, wbc:8200, hgb:13.8 g/dl, plt: 196000, INR:1.16, acute and chronic viral markers: negative. IgA, IgM, IgG levels were normal. ANA, ASMA, ANCA, AMA, AMA-M2, Anti-LKM-1, Anti-LC-1 antibodies were detected negative, whereas anti Ro-52, anti SLA/LP were positive. Abdominal ultrasonographic examination was normal also.

During follow up period of 6 months, elevation in liver enzymes had continued, so liver biopsy was planned. Tdp transfusion was done because INR was still higher than normal. In pathologic evaluation of liver biopsy specimen; portal inflammation, interface hepatitis, confluent necrosis around of central vein, mononuclear inflammation of parenchyma, hydropic degeneration of hepatocytes, vacuolar changes, rosette formation were present. During his hospitalization, because he had history of iron deficiency anemia and being enable to gain weight we thought celiac disease as preliminary diagnosis. Ferritin level of the patient was detected lower (5 ng/ml) than normal. Anti-endomysium and anti-gliadin antibodies were detected as positive also. We performed upper gastrointestinal endoscopy and atrophic appearance, scalloping of intestinal folds were seen in second part of duodenum. multiple duodenal biopsies were performed. In pathological evaluation; blunting of villi, cript hyperplasia were detected and patient was diagnosed as celiac sprue.
Autoimmune hepatitis scoring of the patient was made and calculated as 17. (ALP/ALT < 1.5, viral markers were negative, presence of another autoimmune disease, no alcohol or drug usage, antibody positivity were present, interface hepatitis, lymphocytic infiltration and rosette formation was present whereas biliary changes were absent in pathological examination) the patient was evaluated for steroid treatment of autoimmune hepatitis. Because he had no indication, steroid treatment was not started. Gluten free diet was suggested to the patient and outpatient clinic follow up was planned. After 6 months, AST and ALT levels were decreased to normal ranges, hemoglobin level was increased and anti endomysium, antigliadin antibodies were detected as negative. also the patient had gained 5 kg weight.

Discussion: Celiac disease is a common autoimmune disorder induced by the intake of gluten proteins present in wheat, barley and rye. Celiac disease is named as gluten sensitive enteropathy, celiac sprue and non-tropical sprue also. CD is associated with increased rates of several diseases, such as iron deficiency anemia, osteoporosis, dermatitis herpetiformis, several neurologic and endocrine diseases, persistent chronic hypertransaminasemia of unknown origin, various types of cancer and other autoimmune disorders. CD is diagnosed by findings such as intraepithelial lymphocyte increase, cript hyperplasia, villus atrophy in small intestinal mucosa. Before duodenal biopsy, detection of anti-gliadin, anti-tissue transglutaminase, anti endomysium antibodies is important. In 30% of celiac patients; transient elevation of liver enzymes can be seen. Autoimmune hepatitis, primary biliary cirrhosis, primary sclerosan cholangitis may develop also. Liver failure and liver transplantation are seen it these patients more common. Causes of accompanying liver disease in celiac sprue patients have not been understood yet. But it is been put forward that some immunological mechanisms may play a role in etiology. Chronic hepatitis can be detected in first admission.

Autoimmune hepatitis is a necroinflammatory liver disease of unknown etiology that occurs in adults of all ages. Characteristics are its autoimmune features, hyperglobulinemia (IgG), and the presence of circulating autoantibodies, as well as a response to immunosuppressant drugs. During the follow up of the disease; cirrhosis, portal hypertension, liver failure and even death may be seen. Autoimmune hepatitis is a relatively rare cause of chronic liver disease in Turkey. According to autoantibody pattern, a subclassification has been proposed. AIH-1 accounts for about 75–80% of all cases. AIH-1 is characterized by the presence of ANA and/or smooth muscle autoantibodies (SMA), which may associate in 60–90% of patients with perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA). Most of the patients are below age of 40. HLA DR3 and HLA DR4 positivity can be seen. AIH-2 is characterized by the detection of specific anti-LKM1 or infrequently anti-LKM type 3 (anti-LKM3) antibodies and/or anti-LC1 antibody. AIH-2 is seen in younger ages than AIH-1. AIH-3 is characterized by presence of specific Anti-SLA and/or Anti-LP antibodies.

Conclusion: In our patient, because of anti-SLA/LP positivity and clinical improvement with gluten free diet, we diagnosed him as OIH-3 and celiac disease. In patients with any autoimmune disorders, autoimmune hepatitis can be kept in mind in case of liver enzymes elevation.
A 20-year experience in the treatment of autoimmune hepatitis

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Introduction: Autoimmune hepatitis is a chronic disease characterized by hyperglobulinemia, the presence of circulating autoantibodies, continuing hepatocellular inflammation and necrosis and has a tendency to progress to cirrhosis. The aim of the study is to evaluate clinical course of patients with AIH treated with immunosuppressant therapy.

Methods: 39 patients with AIH (13 male and 26 female) have been diagnosed and treated in our Department for the last 20 years. The average age at the time of diagnosis was 26 years (range 16–45). The diagnosis was established using biochemistry, ultrasound examination, liver biopsy and routine histology, immunofluorescent examinations, HLA phenotypisation, as well as ultra-structural analysis in 8 cases. The follow-up period ranged from 6 months to 14 years (mean time 8 years).

Results: The disease started as clinically apparent acute hepatitis in 9 cases, as a chronic hepatic diseases in 23 cases whereas in 7 cases the disease was accidentally revealed. Four patients had autoimmune extra hepatic phenomenons. According the presence of autoantibodies, the patients were classified on the following way: 19 cases as AIH type 1; 11 pts. as AIH type 2; 5 patients had coexistence of HCV infection and 4 female patients had manifestations of coexisting PBC (overlap syndrome). All patients had increased values of aminotransferase activity (mean value 568 ± 134 U/l), as well as hypergammaglobulinemia. Histopathologic examination showed: Lymphocyte inflammatory infiltration as a dominant sign, partial scarring in two cases that developed cirrhosis during the follow-up and a clear signs of cirrhosis in 3 cases. The combination therapy with prednisolone or budesonide and azathioprine was administrated in 15 cases and 24 cases have received prednisolone of budesonide alone. The duration of treatment ranged from 6 months in 1 case, to 12 years. Evolution to cirrhosis was established in 6 cases (one of them died because of end-stage liver disease). The majority of patients (32/39) have good control of the disease, with evident improvement of biological findings (decrease of aminotransferase activity and hypergammaglobulinemia).

Discussion/Conclusion: Our experience in the long-term control of activity of autoimmune hepatitis using the immunosuppressive drugs (combined therapy or prednisolone/budesonide alone) is very satisfactory in the case of early diagnosis and absence of overlap syndrome.
Bone mineral density in Tunisian patients with autoimmune hepatitis

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Introduction: Bone loss in autoimmune hepatitis (AIH) scanty and conflicting. The pathogenic mechanisms are not completely elucidated. We aimed to assess the prevalence and risk factors for bone loss in patients with AIH.

Methods: Bone mineral density (BMD) using X-ray absorptiometry at both lumbar spine and femoral neck sites was measured in patients with AIH. Were excluded patients with diseases disturbing the bone density. Osteopenia was considered if T-score < -1.5 DS and osteoporosis if T-score < -2.5 DS.

Results: Twenty patients were enrolled in the study. They were women (66%), with a mean age of 53 years [extremes: 13–73]. Sixty-one percent of cases were at stage of cirrhosis. Fifty-five percent of patients were on steroid treatment with or without azathioprine. BMD was low in 9 patients (45%) as fellow: osteopenia in 6 cases (30%) and osteoporosis in 3 cases (15%). There was a correlation between bone loss and use of steroid treatment but it wasn't statistically significant (p = 0.07).

Discussion/Conclusion: In our series, the prevalence of bone loss in AIH is high (45%). This data suggests that bone status should be assessed routinely in patients with AIH, especially in those on steroid treatment.
Clinical features of autoimmune hepatitis in the elderly. Results of a Tunisian study

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Introduction: Autoimmune hepatitis (AIH) affects all ages, and it is probably under-diagnosed in the elderly. The aim of this study was to assess the clinical features of AIH in elderly Tunisian patients.

Methods: We reviewed retrospectively features of 26 patients with AIH seen in our department between January 2011 and December 2014. Two groups were individualized: patients with AIH diagnosed at age ≥ 60 years (n = 12) and those at age < 60 years (n = 14). Clinical features were compared between elderly and younger patients.

Results: The clinical presentation was similar in both groups. Cirrhosis was more frequent in elderly without statistically significant difference. There was no difference between the 2 groups in biological and immunological features. Regarding the frequency of concurrent autoimmune diseases, no significant difference was observed. Treatment outcomes were identical in both group.

Discussion/Conclusion: Our series revealed a great similarity in clinical characteristics between elderly and younger Tunisian patients with AIH, except a higher frequency of cirrhosis at presentation in elderly than younger patients.
Concurrent autoimmune diseases in patients with autoimmune hepatitis. Results of a Tunisian survey

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Introduction: Although the pathogenesis of autoimmune diseases in various organs remain unclear, an accumulation of autoimmune diseases in individual patients has been observed. An overlap of autoimmune hepatitis (AIH) and primary biliary cirrhosis (PBC) or primary sclerosing cirrhosis (PSC) has been well documented. Autoimmune diseases, other than PBC or PSC had been reported in patients with AIH. We aimed to investigate the prevalence of concurrent autoimmune diseases in patients with AIH.

Methods: Retrospective study including 26 patients with AIH admitted in our department between January 2011 and December 2014. We analyzed our cohort for concurrent autoimmune diseases.

Results: A total of eleven patients (42.3%) were diagnosed with additional autoimmune diseases besides overlap syndrome for PBC (5 patients). The most common concurrent disease was type I diabetes (4 patients, 15.3%). Other concurrent autoimmune diseases comprised systemic lupus erythematodes (2 patients, 7.7%) and autoimmune thyroiditis (2 patients). One patient each was diagnosed with Dupuytren's contracture, linear Ig A deratosis and autoimmune gastritis.

Discussion/Conclusion: Concurrent autoimmune diseases are common in patients with AIH and mirror the full range of known autoimmune diseases. Therefore, an extended diagnosis screening for accumulating autoimmune diseases seems reasonable in patients with AIH.
Etanercept-induced fever in autoimmune hepatitis

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Etanercept is a recombinant soluble tumor necrosis factor (TNF) fusion protein, which inhibits biological activity of TNF. In this report, we describe autoimmune hepatitis (AIH) exacerbated by the administration of rheumatoid arthritis.

Case: A 50-year-old woman was admitted for active rheumatoid arthritis (RA). She was found to have RA 1 year prior to this admission. Past history was unremarkable and she had no family for rheumatic diseases. As methotrexate were not effective, etanercept was started (25 mg, twice a week). Mild elevation of alanine transaminase (ALT) and aspartate transaminase (AST) was found as an outpatient, and it was considered to be NSAID-induced liver injury. Two weeks after the first dose of etanercept, she developed progressive elevation of AST and ALT with right upper quadrant tenderness and hepatomegaly. Etanercept was discontinued and liver biopsy was performed, which demonstrated portal-area-dominant lymphoplasmacytic inflammatory cell infiltration. She was diagnosed as autoimmune hepatitis. Glucocorticoid was started with normalized liver function and stable joint symptoms. AIH was thought to be acutely aggravated by the administration of etanercept.
Autoimmune and cholestatic liver disorders

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Objective: Autoimmune and cholestatic liver disorders account for a significant part of end-stage liver disease and are leading indications for liver transplantation. They represent a small proportion of hepatobiliary disorders and results from diverse etiologies. It’s a prevalent disease observed in adults and children and it’s frequently seen in women. Their management is very challenging but there is a wide variety of drugs that have been assessed for the treatment of this condition: Ursodeoxycholic acid, corticosteroids, cyclosporine and azathioprine.

Methods: All cases of autoimmune and cholestatic liver disorders were collected from February 2014 to January 2015. Clinical and laboratory features, immunological data, radiological and liver biopsy findings were studied.

Results: 16 cases of cholestatic and autoimmune liver disorders were diagnosed. 14 were female (87.5%) and 2 were male (12.5%). The mean age was 57.2 years old (27–70). There were 8 primary biliary cirrhosis, 1 overlap syndromes, 6 autoimmune hepatitis and 1 primary sclerosing cholangitis. Jaundice was present in 4 cases. In all cases high levels of gamma glutamyl transpeptidase and alkaline phosphatase were found. Cirrhosis was notified in 2 patients. Treatment based on ursodeoxycholic acid for at least 1 year, but had not achieved complete disease remission in seven patients. In these patients were given to additional prednisone (30 mg per day initially, tapered to 10 mg daily after 8 weeks) and azathioprine (50 mg daily). Complete or partial remission in majority of patient was observed.

Conclusions: We recommend that patients diagnosed with the presymptomatic or symptomatic stages of PBC with features of AIH undertake early therapy combining UDCA and corticosteroids, even though there is currently no cure for the disease. These results strongly encourage the evaluation of this triple treatment regimen in long-term controlled trials of adequate size to document its effect on clinical events.
Autoimmune diseases are common in patients with autoimmune hepatitis

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²Department of Pathology, Academic Teaching Hospital Bogenhausen, Technical University of Munich, Munich, Germany

Introduction: An association of autoimmune diseases in patients with autoimmune hepatitis (AIH) other than primary biliary cirrhosis (PBC) or primary sclerosing cirrhosis (PSC) has been observed. However, the incidence and the spectrum of concurrent autoimmune disorders is not fully understood.

Methods and study population: Retrospectively, the data from hospitalized patients with AIH during a 6-year period (January 2009 to December 2014) were evaluated. 60 patients satisfied clearly the international criteria for the diagnosis of AIH. The majority of our study population was referred to our hospital because of an acute manifestation of AIH. Of these 60 patients, 47 (78.3%) were women and 13 (21.7%) were men. Median age was 58 years, ranging between 22 and 90 years. On the basis of immunoserologic assessment for autoantibodies, 52 patients (86.7%) were classified as type-1 AIH. All patient records were manually searched for indications of concurrent autoimmune diseases. Diagnosis of overlap syndrome was made according to the international diagnostic criteria of the involved diseases.

Results: Additional autoimmune diseases could be diagnosed in 32 patients (53.3%). Interestingly, 5 patients were suffering from more than one autoimmune disease. Besides overlap syndromes for PBC (8 patients) and PSC (4 patients), rheumatologic autoimmune disorders such as Sjögren syndrome were the most common concurrent disease (13 patients, 21.7%). Other associated autoimmune diseases included Crohn's disease (2 patients), autoimmune thyroiditis (3 patients), type I diabetes (2 patients) and autoimmune hemolytic anemia (2 patients). One patient each was diagnosed with sarcoidosis and purpura Schönlein-Henoch. Apart from hepatic overlap syndroms, AIH was diagnosed after initial diagnosis of non-hepatic autoimmune disease while the majority of patients with concurrent diseases were females (30 patients, 85.7%).

Conclusion: An association of non-hepatic autoimmune diseases in patients with AIH such as rheumatologic autoimmune disorders is a common phenomenon. Therefore, regular diagnostic screening for associated diseases is mandatory.
The primary biliary cirrhosis (PBC)-autoimmune hepatitis (AIH) overlap syndrome – A single center Tunisian experience

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Introduction: The primary biliary cirrhosis (PBC)-autoimmune hepatitis (AIH) overlap syndrome is defined by the simultaneous or consecutive association of at least two of three diagnostic criteria usually recognized in both pathologies. The prevalence of this syndrome is unknown, but it may vary between 5% and 20%.

Patients and methods: We retrospectively reviewed all cases of PBC and AIH between 2012 and 2013. We included all patients that suffered from overlap syndrome.

Results: We reviewed 53 cases of dysimmune liver disease: PBC and AIH. Among them, 9 cases of overlap syndrome (PBC-AIH) were diagnosed (16%) with mean age of 52 years. The diagnosis was made mainly at presentation, in 8 patients. One patient, who was ranked CBP has developed cytolysis during follow up, that we have later referred to as caused by an overlap syndrome. Five patients had extra-hepatic autoimmune manifestations: Goujerot Sjögren's syndrome, arthritis, erythema noeux, hypothyroidism. Clinically, 7 patients had jaundice and 6 pruritus, none was decompensated at the time of inclusion. Mean follow-up time was 66.82 months. 5 patients had a liver biopsy with only one that met histological criteria for both PBC and AIH; three those of PBC and one those of AIH. Thus, the diagnosis was focused on biological criteria: cholestasis and anti-M2 for PBC and cytolysis and hyper IgG for AIH. Regarding treatment three had at least one cure by steroids. three underwent UDCA alone and 3 had both azathioprine and UDCA. Patients on UDCA alone have all progressed to cirrhosis and one among them decompensated. For those under combination two did not develop cirrhosis and one has evolved into compensated cirrhosis.

Conclusion: This study shows that overlap syndrome isn’t rare among patients with dysimmunitary hepatopathy. More than half these patients had important other extra hepatic dysimmunitary diseases.
Efficacy of alternative immunosuppressive strategy to induce and maintain remission in patients with autoimmune hepatitis

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Introduction: AIH is chronic and progressive inflammatory disease of the liver. Immunosuppressive treatment (IST) leads in most patients to disease remission and improvement of prognosis. Reduction of IS therapy can often lead to relapses of the disease and the necessity of new course of induction therapy.

Methods: Prospective longitudinal study designed to find out the average dose of IST needed to induce remission as well as needed for long-term remission maintenance and the average dose of IS treatment necessary for a long-term remission in a subgroup of patients with history of relapses after first dose reduction. We tried to identify individual risk factors increasing probability of the relapses. Prospectively we followed a group of AIH patients between 2005 and 2014 and we evaluated (every 3 months) the given criteria of the treatment efficacy and the risk factors of the disease relapses.

Results: 55 patients (15 men and 40 women), average age of the 46 years (17–72) entered the study. 45 patients with AIH of type 1 and 10 patient with AIH of type 2. 26 patients had a cirrhosis (Metavir F4) at the time of diagnosis, 11 patients F3, 9 patient F2, 6 patients F1 and 3 patients F0. All patients achieved initial remission under corticosteroid (CS) therapy (average dosage was 0.55 mg of prednisone/kg of weight). 15 patients (27%), (older patients with comorbidities including osteoporosis) were treated with combination therapy (CS + AZA) from the time of diagnosis. Average time to reach the initial remission (ALT normalization) of the disease was 12.2 weeks (6–36 weeks). We reached the long-term remission with permanent termination of therapy in 5 patients. (9%). The long-term remission with stable IST without relapses we reached in 22 patients (40%) and 28 patients (51%) experienced a relapse after the IST reduction. The average maintaining dosage of CS in monotherapy was 7.12 mg/day and in combination therapy it was 7.2 mg/day CS and 90 mg AZA/day. 28 patients had a relapse of the disease. Significant differences between both groups (remission vs. relaps) was initial level of gamaglobulins (38% vs. 31%, p < 0.05), presence of LKM2 (8 vs. 2, p < 0.05), more advanced initial histological stage (F3,5 vs. F2,96, p < 0.05) and the time needed for normalization of liver tests after starting IS therapy (16 vs. 10 weeks, p < 0.05) and less frequent presence of jaundice at the time of diagnosis (10 vs. 19 patients, p < 0.05) in the remission group.

Discussion/Conclusion: We reached initial response to IS therapy in all patients with less aggressive dosage of IST in a reasonable time. Permanent discontinuation of IST is rare. By frequent following AIH patients. is possible to identify pts. with high risk of relapse and promptly modify dosage of IST.
Upper gastrointestinal mucosal lesions and Helicobacter pylori infection in autoimmune liver disease

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Introduction: Helicobacter pylori (H. pylori) is the main cause of gastric lesions especially chronic gastritis, autoimmune gastritis, peptic ulcer disease and gastric cancer. Autoimmune liver disease can be associated with various upper gastrointestinal mucosal lesions with or without severity of the disease. The aim of this study was to retrospectively investigate upper gastrointestinal mucosal lesions in relation to the prevalence of H. pylori infection in autoimmune liver disease (autoimmune hepatitis [AH] and primary biliary cirrhosis [PBC]).

Methods: This study was carried out in 99 patients with autoimmune liver disease (71 patients with AH and 28 patients with PBC) and 110 control dyspeptic patients. In all research subjects, upper gastrointestinal endoscopy was performed, and two biopsy specimens were taken from the antrum and gastric body for histological examination and H. pylori detection. Patients were excluded if they had a history of acid suppression therapy, antibiotic or non-steroidal anti-inflammatory drug treatment and the patients they can not be taken biopsy specimen from antrum and gastric body (platelet under 70,000, INR > 1.5).

Results: Helicobacter pylori was positive in 60% of AH, 57% of PBC and 63% of control groups and there was no significant difference between the three groups. 45% of AH, 52% of PBC and 43% of dyspeptic control groups were found to have abnormal findings during upper gastrointestinal endoscopy, including esophagitis, endoscopic antral and pangastritis gastric ulcer, bulbar ulcer and esophageus varices. Endoscopic antral gastritis were more prevalent in AH than PBC. Esophageus varices were more prevalent in autoimmune hepatitis and primary biliary cirrhosis than control groups.

Discussion/Conclusion: H. pylori rate among cases with in autoimmune liver disease was similar to values than control groups. Endoscopic antral gastritis were more prevalent in AH than PBC but autoimmune liver disease are not significantly characterized by upper gastrointestinal mucosal lesions than dyspeptic controls.
Combined liver injury (overlap syndrome), particular qualities of flow

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**Introduction:** The autoimmune liver diseases primarily include autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC). In 10% of these patients we determined a combination of the above two diagnoses known as overlap syndrome (AIH with PBC, PSC with AIH or PBC with AIH).

**Methods:** We offer the results of patients’ observation with different variants of overlap syndrome during last 5 years in Kyiv City Clinical Hospital No. 8.

Overlap syndrome was diagnosed by clinical, biochemical, serological, instrumental and histological methods of investigation. The AIH international group recommendations (IAHG) for 2010 year were used for the diagnosis of overlap syndrome’s different variant.

**Results:**

<table>
<thead>
<tr>
<th></th>
<th>I group (AIH+PBC)</th>
<th>II group (PSC+AIH)</th>
<th>III group (PBC+AIH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient amount</td>
<td>13</td>
<td>5</td>
<td>18</td>
</tr>
<tr>
<td>Sex F/M</td>
<td>9/4</td>
<td>0/5</td>
<td>15/3</td>
</tr>
<tr>
<td>ALAT/ASAT</td>
<td>5x↑N/3x↑N</td>
<td>5x↑N/4x↑N</td>
<td>3x↑N/4x↑N</td>
</tr>
<tr>
<td>APH</td>
<td>7x↑N</td>
<td>5x↑N</td>
<td>min 2x↑N</td>
</tr>
<tr>
<td>GGTP</td>
<td>5x↑N</td>
<td>7x↑N</td>
<td>min 5x↑N</td>
</tr>
<tr>
<td>γ-globulin</td>
<td>3x↑N</td>
<td>2x↑N</td>
<td>3x↑N</td>
</tr>
<tr>
<td>ANA/SMA</td>
<td>Positive(1:160)/Positive</td>
<td>Positive(1:80)/Positive</td>
<td>Positive(1:320)/Negative</td>
</tr>
<tr>
<td>AMA</td>
<td>Positive</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>FibroTest(Steato)</td>
<td>S3</td>
<td>S2</td>
<td>S4</td>
</tr>
<tr>
<td>Instrumental investigations</td>
<td>MRC–magnetic resonance cholangiography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver biopsy</td>
<td>Hepatitis prevails cholestasis</td>
<td>Cholangitis</td>
<td>More pronounced cholestasis</td>
</tr>
<tr>
<td>Response to treatment, steroids + UDCA</td>
<td>+</td>
<td>± (was offered transplantation)</td>
<td>+</td>
</tr>
</tbody>
</table>

**Discussion/Conclusion:** Among patients with overlap syndrome dominates combination of AIH with PBC, mostly in women. These patients give a good response to therapy with steroids plus UDCA. The combination of PSC with AIH (male-dominated) are less common and these patients give a poor response to therapy with
steroids and UDCA, although the progression rate of the disease was not significantly different from the group of patients with AIH+PBC. Severity of PBC was different according to biochemical parameters and AMA titer and sort. AIH+PBC disease progression was faster than in PBC patients according to FibroTest. The most expressed hepatic steatosis observed in the third group (PBC+AIH) of patients (≈ 80%).
Epidemiological and clinical characteristics of autoimmune hepatitis in Albania

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Introduction: The prevalence of autoimmune hepatitis (AIH) in Albania is unknown. Our aim was to investigate the epidemiological characteristics, biochemical and immunological features of AIH in Albania.

Methods: Our study included 96 consecutive patients (69% female), newly diagnosed with AIH, hospitalized at our clinic, the only academic center in Albania, during 2005–2013. Model for End-stage Liver Disease (MELD) and noninvasive biomarkers of fibrosis: AST to platelet ratio index, platelet count to spleen diameter, AST-to-ALT ratio, the age-spleen-to-platelet ratio index, fibrosis-4 score based on age, ALT, AST and platelet count (FIB-4) were also evaluated for each patient.

Results: The prevalence of AIH was 4.47/100,000 inhabitants. The main characteristics are shown in the table. At diagnosis, 62.5% of patients had cirrhosis and MELD was significantly higher among type 2 than type 1 AIH patients (17.2 ± 8.6 vs. 15.0 ± 6.3, respectively, p < 0.05). 92 patients (96%) presented with symptoms. Mean values of noninvasive biomarkers did not differ significantly between two types of AIH. Other AI diseases were observed in 28 patients (29%).

<table>
<thead>
<tr>
<th>Features</th>
<th>Type 1 AIH (72 patients)</th>
<th>Type 2 AIH (24 patients)</th>
<th>P value1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>53.8 ± 12.62</td>
<td>41.4 ± 17.9</td>
<td>0.001</td>
</tr>
<tr>
<td>ALT, alanine transaminase (UI/l)</td>
<td>131.1 ± 142.9</td>
<td>88.6 ± 57.1</td>
<td>0.16</td>
</tr>
<tr>
<td>Billirubin (mg/dl)</td>
<td>4.0 ± 5.9</td>
<td>5.2 ± 8.3</td>
<td>0.43</td>
</tr>
<tr>
<td>Gamma Globulin (g/l)</td>
<td>27.2 ± 8.8</td>
<td>33.8 ± 12.5</td>
<td>0.006</td>
</tr>
<tr>
<td>INR, international normalized ratio</td>
<td>1.3 ± 0.5</td>
<td>2.0 ± 0.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.3 ± 0.6</td>
<td>3.2 ± 0.8</td>
<td>0.73</td>
</tr>
<tr>
<td>ANA, antinuclear antibodies positive; n (%)</td>
<td>53 (73.6)</td>
<td>13 (54.2)</td>
<td>0.12</td>
</tr>
<tr>
<td>SMA, smooth muscle antibodies positive; n (%)</td>
<td>45 (62.5)</td>
<td>9 (37.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>Anti-LKM1, antibodies to liver-kidney microsome type 1 positive; n (%)</td>
<td>0 (0.0)</td>
<td>22 (91.7)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

1Unpaired test/Fisher’s exact test
2Mean ± SD (all such values)
Discussion/Conclusion: AIH is uncommon diseases in Albania. The presence of cirrhosis in the majority of the patients at diagnosis suggests more awareness for this chronic liver disease.
Epidemiological, clinical and therapeutic characteristics of autoimmune hepatitis. Results of a Tunisian study

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Introduction: Autoimmune hepatitis (AIH) is a chronic inflammatory condition of the liver of unknown etiology. Epidemiological and clinical data are scarce in Tunisia. The aim of this study was to determine epidemiological, clinical and therapeutic characteristics of Tunisian patients with AIH.

Methods: Retrospective study including patients with AIH admitted in our center. The diagnosis of AIH was established according to the criteria of the revised score of the international autoimmune hepatitis group (1999).

Results: Twenty-five patients were recruited. They were 19 women (sex-ratio: 0.3). The mean age was 50 years (17–81). Most patients had type 1 AIH (88%). Sixteen patients (64%) were cirrhotic at presentation. In other cases, AIH was revealed by cytolysis, fatigue and jaundice respectively in 48%, 41% and 40% of patients. Associated autoimmune diseases were observed in 32% of patients, dominated by type 1 diabetes and autoimmune thyroiditis. An overlap syndrome with primary biliary cirrhosis was diagnosed in 12% of cases. Only 12 patients (48%) were treated with glucocorticoids as monotherapy or in combination with azathioprine. Complete remission was achieved in 50% of treated patients.

Discussion/Conclusion: In our series, the frequency of cirrhosis at diagnosis of AIH is high and complete remission is obtained in half of cases. This underlines the importance of an early diagnosis.
Ultrastructural features of hepatic fibrogenesis in children with autoimmune hepatitis

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Introduction: Although autoimmune hepatitis (AIH) in childhood is rare, it is known to develop cirrhosis. This chronic immuno-mediated, autodestructive liver disease is closely related to liver fibrosis. Pathogenic mechanisms underlying liver fibrogenesis in AIH are not fully understood. It is assumed that in chronic liver diseases hepatic stellate cells (HSCs) are involved extracellular matrix (ECM) protein synthesis.

Objective: To assess ultrastructure of perisinusoidally located HSCs in pediatric AIH in pretreatment liver biopsies from 17 children (14 girls) aged 2–17 years with AIH diagnosed clinically and histologically. Interestingly, in all cases histologically pathognomic for the diagnosis of AIH, the organ fibrosis was found to vary in intensity (portal, periportal, bridging, interlobular fibrosis) using the histological scoring system according to Ishak and al. (1995).

Methods: Electron-microscopic examinations were conducted on fresh small fragments of liver biopettes (1 mm³ volume tissue blocks) obtained by needle biopsy, which were fixed with solution of 2% paraformaldehyde and 2.5% glutaraldehyde in 0.1 M cacodylate buffer (pH 7.4), routinely processed for ultrastructural analysis and studied using an Opton EM 900 transmission electron microscope.

Results: In all AIH cases, electron-microscopic analysis revealed increased number of activated perisinusoidal HSCs transforming from star-shaped quiescent HSCs (Q-HSCs) into transitional HSCs (T-HSCs) and myofibroblastic HSCs (Mf-HSCs). T-HSCs were elongated, spindle-shaped, developed long cytoplasmic processes and showed a substantial loss of cytoplasmic lipid material. They contained markedly developed and dilated channels of granular endoplasmic reticulum showing microfibrillar material, well-developed Golgi apparatus and sub-membranous accumulation of cytoskeletal components, which indicated their involvement in intensive synthesis and ECM transport. Cytoplasmic protrusions of T-HSCs extended to hepatocytes undergoing degenerative changes. Immature collagen fibrils and collagen fibers, frequently forming bundles, were found to adhere directly to these cells. Activated Kupffer cells/macrophages were found in very close contact with T-HSCs. These alterations were accompanied by marked morphological changes in the endothelial lining of sinusoidal vessels.

Discussion/Conclusion: The findings indicate high plasticity of hepatic stellate cells and their crucial role, especially of T-HSCs, in liver fibrogenesis in pediatric AIH. The study may lead to new perspectives in early diagnosis of liver fibrosis in AIH children.
Myeloid-derived suppressor cells and the liver microenvironment in autoimmune liver disease

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Myeloid-derived suppressor cells (MDSCs) represent heterogeneous cell populations with remarkable immune suppressor function. To address the role of MDSCs in liver autoimmunity, our goal was to define the phenotypic and functional capacities of MDSCs in patients with autoimmune liver disease. Using peripheral blood derived MDSCs in a cohort of 156 individuals, including 48 PBC, 40 AIH, 39 CHB and 29 healthy controls and also including a tissue targeted determination of MDSCs in liver specimens from 27 PBC, 27 AIH, 25 CHB and 5 healthy controls, we focused on phenotypic and functional data. Our phenotype data revealed that HLA-DR-low CD33+CD11b+CD14+CD15- monocytic MDSCs were significantly enriched using PBMCs in PBC and AIH. Second, there was a significant correlation between levels of circulating MDSCs and disease related biochemical markers in both PBC and AIH. Further, there was a correlation of higher levels of circulating MDSCs in patients with PBC and AIH that responded to UDCA or immunosuppressive drugs respectively. Further, this data correlated with the accumulation of MDSCs in the inflamed portal tracts of both PBC and AIH as well as with the histologic and fibrosis of stages in both diseases. However, there was a significant paucity of peripheral and hepatic MDSCs in PBC patients or AIH patients compared with CHB patients. These data suggest that MDSCs play a functional role in the inflammatory response in autoimmune liver disease and may become a cellular target for immunotherapy.
The most common rheumatic diseases in patients with autoimmune liver disease in a Tunisian center

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Introduction: The aim of this study was to identify the most common autoimmune rheumatic diseases in patients with autoimmune liver disease in a referral Tunisian center.

Methods: This is a transversal and descriptive study, we analyzed medical records of 92 patients who fulfill the diagnostic criteria for autoimmune liver disease, of whom 30 had diagnosis of autoimmune hepatitis(AIH), 49 primary biliary cirrhosis(PBC) and 13 primary sclerosing cholangitis (PSC). In our study group we looked for the clinical and laboratory characteristics most common and the frequency of cases in the HAL.

Results: Of the 30 patients with AIH, 8 (26%) were diagnosed with autoimmune rheumatic disease concurrence. Of these, 2 (6%) patients had Sjögren’s disease (SD), 2 (6%) had systemic lupus erythematosus (SLE) and 3 (1%) had rheumatoid arthritis (RA). We found 49 patients with PBC, 8 (16%) had other associated extrahepatic autoimmune disease, of whom 5 (10%) had SD, 3 (2%) SLE and 1 (1%) RA. The 13 patients with PSC had no concurrence with rheumatic disease.

Discussion/Conclusion: In our study was found that SD is the most common rheumatic disease in patients with AIH and PBC, followed by RA and SLE, with autoimmune liver disease with rheumatic symptoms.
The role of repeat liver biopsies in autoimmune hepatitis: Clinical practice and outcomes

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Introduction: The role of repeat liver biopsies in established autoimmune hepatitis (AIH) is unclear, with limited data on clinical practice and outcomes, and with variation in biopsy practice between physicians.

Methods: We undertook a retrospective review of all patients with AIH who underwent a repeat liver biopsy between 2002–2013 at Frimley Park Hospital (Surrey, England); serving a population 430,000.

The indication for repeat biopsy, liver histology and serological markers were recorded, as well as the clinical outcome/management resulting from each procedure.

Results: 17 patients were identified, all who were on treatment for AIH. Clinical indications included: disease assessment/staging (34%), clinical deterioration (24%), diagnostic uncertainty (24%), medication withdrawal/remission (12%) and insufficient (Bx) sample (6%).

Overall 10/17 patients had normal LFTs and 12/17 had normal IgG levels at repeat biopsy (range 1–108 months). Repeat biopsy led to change in treatment in 11/17 (65%).

9 patients had a repeat biopsy at ≤ 24 months. Within this group 4/9 (44%) had normal LFTs, and 6/9 (67%) had normal IgG levels; repeat biopsy lead to a change in treatment in 2/4 (50%) and 4/6 (67%) respectively. Fibrosis progression was seen in 1/4 (25%) with normal LFTs, and 2/6 (33%) with normal IgG levels.

Baseline cirrhosis was seen in 3 patients (biopsy/imaging), and developed in a further 2 (12%) over 24-48 months; both with raised IgG levels.

Interface hepatitis/periportal inflammation was present in all repeat biopsies.

Discussion/Conclusion: BSG and AASLD guidance suggest the use of repeat biopsies at 12–24 months following normalised transaminases to guide treatment withdrawal/maintenance, with IgG levels also thought predictive of histological response. However, the majority of repeat biopsies in our study were requested due to concerns of disease progression.

Despite normalised LFTs/IgG levels, repeat biopsy led to treatment modification in more than half of this group; as well as demonstrating fibrosis progression. Our results support the need to individualise repeat liver biopsies to the needs of each patient.
Correlations between serologic markers, clinical presentation and response to treatment in patients with autoimmune hepatitis at a tertiary referral center

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Introduction: Autoantibody profiles facilitate the accurate diagnosis of the main autoimmune liver diseases namely autoimmune hepatitis (AIH) while enabling identification of distinct disease subtypes. Our aim was to determine whether the presence of antinuclear antibodies (ANA) and anti-smooth muscle antibodies (ASMA) in patients with AIH correlated with clinical presentation, biological parameters and response to therapy.

Methods: A retrospective study extended over a period of 4 years (March 2011–March 2014) including all patients diagnosed with AIH was conducted at a tertiary center in Iasi Romania. We reviewed all medical charts and extracted epidemiological, clinical, biological, serological and therapeutic data for each patient admitted. The diagnosis of AIH was established on the positivity for ANA and/or ASMA autoantibodies defines AIH type 1 (AIH-1), whereas anti-liver kidney microsomal type 1 (anti-LKM1) and/or anti-liver cytosol type 1 (anti-LC1) define AIH type 2 (AIH-2). All patients received corticosteroid therapy alone (prednisone, prednisolone) or in conjunction with azathioprine.

Results: A total of 32 patients, 26 female 81.3%, mean age 53.94 ±14.24 tested positive for AIH-1, ASMA 53.30 (± 42.01). AIH was asymptomatic in 10 patients (31.2%), 22 patients (68.8%) presented jaundice, chronic fatigue and/or mild abdominal discomfort. In the asymptomatic lot we found higher levels of antibody titers compared to the symptomatic lot. The median level of aspartate aminotransferase at diagnosis was 167.09 ± 43.89, for alanine aminotransferase 231.31 ± 65.73, immunoglobulin G 344.0 ± 262.55, ANA 53.30 ± 42.01 and anti-LKM1 16.83 ± 22.75. There were no correlations established between levels of antibody titers and enzyme levels (r = -0.158, p = 0.450), lipid profile (r = 0.040, p = 0.830) or hematological markers. Furthermore, there was no correlation between antibody status and response to immunosuppressive therapy.

Discussion/Conclusion: Autoimmune hepatitis is found in middle-aged women. The prevalence and titer of specific antibodies did not correlate with the clinical manifestations of AIH at diagnosis.
Aspartate aminotransferase to platelet ratio index for fibrosis and cirrhosis evaluation in autoimmune liver diseases

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Introduction: Aspartate aminotransferase to platelet ratio index (APRI) is an easy and inexpensive marker of liver fibrosis. We assessed the value of APRI for predicting significant fibrosis or cirrhosis in patients with primary biliary cirrhosis (PBC) and autoimmune hepatitis (AIH).

Methods: We performed a retrospective analysis of medical records of patients with PBC and AIH admitted to the Gastroenterology and Hepatology Institute in Iasi, Romania between March 2011 to March 2014. The diagnosis of liver cirrhosis was made based on a combination of clinical, biological, imaging, endoscopic findings and histology analysis. The index was calculated based on formula: APRI = [(AST level/ULN)/platelet counts (10⁹/l)] × 100. APRI values of 0.50 or less and greater than 1.50 were evaluated for predicting significant fibrosis, and APRI values of 1.00 or less and greater than 2.00 for predicting cirrhosis.

Results: A total of 68 patients (61 female, mean age 57.04 ± 12.09) 32 patients AIH (26 female, 53.93 ± 14.24) and 34 PBC (35 female, mean age 59.8 ± 9.14) with urban predominance were enrolled. In CBP group, the APRI levels were ≤ 1.00 (63.9%) or > 2.00 (18.8%) in 29/36 (80.6%) patients. In the HAI group, the APRI levels were ≤ 0.50 (28.1%) or > 1.50 (50%) in 25/32 (78.1%). There was significant difference in the predictive values of ARPI between patients with CBP and HAI. For the diagnosis of significant fibrosis, APRI values delimited an area under de ROC curve (AUC) of 0.371 in CBP and 0.629 in HAI patients. APRI did not offer a significant prediction in patients with CBP, there were low values of sensibility (38.2%) and specificity (40.6%), but in patients with HAI, APRI is a good predictor of fibrosis with sensibility about 72% and specificity 56%.

Discussion/Conclusion: The APRI is useful because of its simplicity and low cost. APRI values tend to increase with the extent of fibrosis. In autoimmune liver diseases, it appears that APRI is a good predictor for fibrosis and cirrhosis among patients with HAI compared to CBP.
Autoimmune hepatitis/primary biliary cirrhosis (AIH/PBC)-overlap syndrome (OS) and hepatic carcinogenesis

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Introduction: The impact of AIH/PBC-OS on the process of hepato/cholangiocellular carcinogenesis is not fully studied. The study aims to investigate on the role of AIH/PBC-OS in the aetiology of hepatocellular carcinoma (HCC) and peripheral intrahepatic cholangiocarcinoma (CCC).

Methods: The first group in the study includes 47 patients with AIH/PBC-OS (all women, aged 38–71, fulfilling histological and serological criteria) followed-up for 2–17 years.
The second group consists of 224 patients with primary hepatic tumors treated in our hospital during the period 2000–2015 with percutaneous ablation (ethanol, radiofrequency, microwave), surgery, targeted therapy. The etiology of the tumor was investigated using virological, immunological, genetic and histological methods.

Results: The patients in group 1 were treated with immunosupression and UDCA, and were followed-up (mean 7.1 years) with ultrasound, biochemistry and upper endoscopy. None of the patients developed hepatic tumor during the follow-up.
The patients in group 2 (179 males, 45 females, aged 26–82, mean 64, Child-Pugh at diagnosis – A – 59%, B – 37%, C – 4%) were diagnosed by histology/immunohistochemistry – 207 patients had HCC, 16 – CCC, and 1 – mixed HCC/CCC tumor. Etiological factors included: HBV – 44.5%, HCV – 32.3%, HBV+HDV – 3.6%, HBV+HCV – 5.5%, occult HBV – 7.1%, glycogenosis – 0.4%, NASH – 0.4%. None of the remainder tested positive for autoantibodies and none has clinical or histological evidence of autoimmune liver disease (AILD).

Discussion/Conclusion:
1. For the period of observation no patient with AIH/PBC-OS developed a liver tumor.
2. Amongst the patients with HCC/CCC no evidence were found for AILD.
3. No role could be established for AIH/PBC-OS in the hepatic carcinogenesis.
Angiotensin converting enzyme for non-invasive assessment of liver fibrosis in autoimmune hepatitis

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²Department of Gastroenterology, Batman State Hospital, Batman Turkey
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Introduction: There are no validated non-invasive markers of liver fibrosis in autoimmune hepatitis (AIH). An activated renin-angiotensin system (RAS) and its key element angiotensin-converting enzyme (ACE) have been implicated in the pathogenesis of hepatic fibrogenesis. We aimed to study the assumed role of activated RAS in the fibrogenic process and whether the serum concentration of ACE can predict different fibrosis stages in AIH.

Methods: Serum samples of 73 consecutive patients who were diagnosed with AIH were analyzed for ACE concentration. All patients underwent a liver biopsy.

Results: Serum ACE levels increased significantly for each fibrosis score. Median ACE was 45 U/l in patients with fibrosis score I, 54 U/l in fibrosis score II, 68 U/l in fibrosis score III and 87 U/l in fibrosis score IV. For significant fibrosis (F2 ≥), a 56 U/l cut-off value of ACE had 95.5% sensitivity, 74.5% specificity and receiver-operating characteristic curves (ROC) revealed an AUC of 0.89. For advanced fibrosis (F3 ≥), a 64 U/l cut-off level of ACE had 85.29% sensitivity, 94.87% specificity and AUC was 0.91. For cirrhosis, a 68 U/l cut-off level of ACE had 100% sensitivity, 84.48% specificity and AUC was 0.95. Table 1, 2, 3 and figure 1, 2, 3 summarize all findings found in our study.

Discussion/Conclusion: Our results suggest that activated RAS may sustain hepatic fibrogenesis in AIH. Measuring serum ACE offers an easy, accurate and inexpensive non-invasive method that differentiates significant from non-significant liver fibrosis in AIH. Blockade of RAS may provide beneficial effects on fibrosis progression in AIH.
### Table 1: General characteristics of patients with autoimmune hepatitis

<table>
<thead>
<tr>
<th>Parameters</th>
<th>AIH (n = 73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (female/male)</td>
<td>54/19</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>41 (18–72)</td>
</tr>
<tr>
<td>ALT (xUNL)</td>
<td>7.6 (1.2–78)</td>
</tr>
<tr>
<td>ALP (xUNL)</td>
<td>1.2 (0–2.1)</td>
</tr>
<tr>
<td>Bilirubin (xUNL)</td>
<td>1.1 (0.1–11.5)</td>
</tr>
<tr>
<td>Serum IgG (xUNL)</td>
<td>1.3 (0.6–4.2)</td>
</tr>
<tr>
<td>ANA n (%)</td>
<td>52 (71)</td>
</tr>
<tr>
<td>SMA n (%)</td>
<td>30 (41)</td>
</tr>
<tr>
<td>ANA and SMA n (%)</td>
<td>18 (25)</td>
</tr>
<tr>
<td>Anti-LKM1 n (%)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Interface hepatitis n (%)</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>10 (14)</td>
</tr>
<tr>
<td>Moderate</td>
<td>27 (37)</td>
</tr>
<tr>
<td>Severe</td>
<td>36 (49)</td>
</tr>
<tr>
<td>Fibrosis scores n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>8 (11)</td>
</tr>
<tr>
<td>1</td>
<td>14 (19)</td>
</tr>
<tr>
<td>2</td>
<td>17 (23)</td>
</tr>
<tr>
<td>3</td>
<td>19 (26)</td>
</tr>
<tr>
<td>4</td>
<td>15 (21)</td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; ALP, alkaline phosphatase; ANA, antinuclear antibody; IgG, immunoglobulin G; LKM, liver kidney microsome type 1; SMA, smooth muscle antibody, ULN, upper limit of normal.

### Table 2: Characteristics of patients with autoimmune hepatitis and healthy controls

<table>
<thead>
<tr>
<th></th>
<th>AIH (n = 73)</th>
<th>Controls (n = 32)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years)</td>
<td>41 (18–72)</td>
<td>44 (22–67)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Female sex, (%)</td>
<td>54 (74%)</td>
<td>25 (78%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>115 (90–135)</td>
<td>118 (90–140)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>70 (65–90)</td>
<td>75 (60–90)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Median ACE (U/l)</td>
<td>58 (38–142)</td>
<td>34.5 (10–59)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ACE &gt; 52 U/l, n (%)</td>
<td>47 (64)</td>
<td>3 (9)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

ACE, angiotensin-converting enzyme; BP, blood Pressure; n.s., not significant
Table 3: Suggested cutoff values for ACE and their performance in the prediction of fibrosis stage

<table>
<thead>
<tr>
<th>Fibrosis stage</th>
<th>Cutoff (U/l)</th>
<th>AUC</th>
<th>SE</th>
<th>95% CI</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>F2 ≥</td>
<td>56</td>
<td>0.89</td>
<td>0.04</td>
<td>0.79–0.95</td>
<td>95.5</td>
<td>74.5</td>
<td>61.8</td>
<td>97.4</td>
<td>78</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>F3 ≥</td>
<td>64</td>
<td>0.91</td>
<td>0.04</td>
<td>0.82–0.96</td>
<td>85.2</td>
<td>94.8</td>
<td>80.6</td>
<td>86.5</td>
<td>83</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>F4</td>
<td>68</td>
<td>0.95</td>
<td>0.02</td>
<td>0.87–0.98</td>
<td>100</td>
<td>84.4</td>
<td>62.5</td>
<td>100</td>
<td>90</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

AUC, areas under the receiver operating characteristic curve; CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value.

Figure 1: ACE levels in patients with AIH according to fibrosis stages and interface hepatitis.
Figure 2: The Spearman’s analysis showing the correlations between the ACE and fibrosis scores.

Figure 3: Receiver-operating characteristic (ROC) curves for ACE in the diagnosis of significant fibrosis (A), severe fibrosis (B) and cirrhosis (C).
Ultrastructural characteristics of sinusoidal Kupffer cells/macrophages in pediatric autoimmune hepatitis – The analysis of 17 cases

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Introduction: Ultrastructural studies on autoimmune liver diseases in children are scarce. The current study is continuation of our previous research into the electron-microscopic picture of Kupffer cells/macrophages (KCs/MPs) and their role in the morphogenesis of autoimmune hepatitis (AIH) in pediatric patients.

Objective: To perform ultrastructural analysis of sinusoidally located KCs/MPs in liver tissue from pretreatment biopsies of 17 children aged 2–17 years (14 girls) with clinically and histologically diagnosed AIH.

Methods: Electron-microscopic studies were conducted on fresh small tissue blocks (1 mm³ in size) obtained from AIH children by percutane needle liver biopsy, which were fixed with a solution of 2% paraformaldehyde and 2.5% glutaraldehyde in 0.1 M cacodylate buffer (pH 7.4) and routinely processed for ultrastructural analysis. Ultrathin sections were double stained in uranyl acetate and lead citrate, and examined using an Opton EM 900 transmission electron microscope.

Results: In all study children the ultrastructural analysis showed substantial abnormalities of cells lining the sinusoidal vessels, especially Kupffer cells/macrophages and endothelial cells. Within hepatic sinusoids, enlarged KCs/MPs with increased phagocytic activity were found. The sinusoid vascular lumen was reduced or blocked by enlarged KCs/MPs, which were accompanied by marked swollen, injured endothelial cells. The activated KCs/MPs, mainly located near damaged hepatocytes, were hypertrophied and showed an increase in the number and size of primary and secondary lysosomes containing hepatocellular remnants. Their cytoplasm showed dilated granular endoplasmic reticulum, altered mitochondria and well-developed Golgi apparatus. Interestingly, such macrophages were frequently seen in close contact with transitional hepatic stellate cells (T-HSCs) and mononuclear inflammatory cells. In the vicinity of activated KCs/MPs and T-HSCs features of marked collagen fibroplasia were seen.

Discussion/Conclusion: The current ultrastructural study indicates that activated KCs/MPs by close cellular interactions, especially with T-HSCs, are involved in the morphogenesis and development of pediatric AIH.
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Introduction: Autoimmune hepatitis (AIH) is a chronic inflammatory process of unknown etiology, usually requiring life-long immunosuppression. Corticosteroids (CST) and azathioprine (AZA) are the standard therapy. Alternative therapeutics are used for patients non-responsive or intolerant to conventional therapy.

Methods: Retrospective review of patients files with the diagnosis of AIH from our institution. Clinical characteristics, response to therapy, side-effects and mortality were analyzed. Mean-follow-up of 9 years. Patients with non-compliance to therapy, follow-up inferior to 1 year or overlap syndrome were excluded.

Results: 27 patients with AIH: 24 females and 3 males. At diagnosis: mean-age of 48.6 years, 45% were symptomatic, 22% presented jaundice. Five patients had more than 1 co-existing extrahepatic autoimmune disease. No family history of AIH was reported. 89% had AIH type 1 and 11% AIH type 2. Initially 9 patients were treated with CST alone (group 1) and 18 patients with CST combined with AZA (group2). In group 1, 4 patients had complete response; 5 had incomplete response with subsequent need of azathioprine association. In group 2, 2 patients were non-responders and 3 were intolerant to AZA therapy. CST were suspended in 9 patients. Three had relapse, which resolved with increase in AZA dose. 6 patients (22%) had CST related adverse effects, being osteoporosis the most frequent. Change in standard therapy was due to: absence of response to CT+AZA (2 patients), side-effects of CST (1), intolerance to AZA (3). Four patients were treated with tacrolimus, one patient was treated with budesonide and another patient with mofetil mycophenolate (MMF). There was no relapse or side-effects with change in therapy. Two patients died due to decompensated cirrhosis. One patient was transplanted but died from graft rejection.

Discussion/Conclusion: New therapeutic strategies with immunomodulator drugs such as MMF and tacrolimus can be useful in AIH. It should be made an individual decision.
Use of tacrolimus in patients with treatment resistant type 1 autoimmune hepatitis

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Introduction: Autoimmune hepatitis (AIH) is an immune mediated liver disease resulting from loss of self-tolerance to hepatocytes. It is characterised by the presence of interface hepatitis and plasma cells infiltrate on liver histology, hypergamaglobulinaemia and positive autoantibodies in the serum along with elevated transaminases. Prednisolone alone or in combination with azathioprine as first line therapy leads to disease improvement within 6–12 months. In patients with resistant AIH or intolerant to other immunosuppressive medications, calcineurin inhibitors such as tacrolimus have been shown as potential alternative therapy.

Aim and methods: The aim is to investigate the clinical efficacy, steroid dose reduction and safety profile of tacrolimus in patients with resistant AIH. Data from 17 patients were collected retrospectively between 1997 and 2014 from two European tertiary liver transplant centres.

Results: The majority of patients were Caucasian (n = 14, 82%) and female (n = 11, 65%) and 94% (16/17) had liver biopsy at the time of diagnosis. 3/17 patients were cirrhotic. 15/17 patients were treated with prednisolone and azathioprine [AZA] as first line treatment prior to tacrolimus therapy. Indication for tacrolimus therapy was due to resistant AIH despite adherence to therapy in 14/17 (82%) patients and, intolerant of first line treatment with AZA in 2/17 (12%) of patients. The median duration of treatment was 24 months and the median dose of tacrolimus was 2 mg (range: 0.5–5 mg).

Decline in bilirubin level was observed throughout treatment. There was a significant improvement in aspartate transaminase (AST) levels (p < 0.05) at 6, 12 months and last follow up. Albumin improved significantly at 12 months and last FU (p = 0.003, 0.047). Immunoglobulin-G (Ig G) improved significant at 3 months of treatment (p = 0.025). Model for End Stage Liver Disease (MELD) scoring improved with treatment (median MELD 11 before treatment to 6.5 post treatment, p = 0.06). Prednisolone dose can be reduced from median 10 mg (range: 0–35) to 5 (range: 0–30) with tacrolimus treatment. Tacrolimus was well-tolerated without no major side effects or renal dysfunction.

Discussion/Conclusion: We report that treatment with tacrolimus can achieve biochemical and immunological response in selected group of patients. It is safe in patients with resistant AIH and the treatment can aid with reduction of prednisolone dosage. Treatment should be introduced in experienced liver centres and renal function and Tacrolimus level should be monitored closely. Magnetic resonance cholangiopancreatography (MRCP) and repeat liver biopsy is recommended to exclude biliary overlap before initiation of Tacrolimus.
Serological differential diagnosis of autoimmune liver diseases by line immunoassay for parallel detection of 9 different autoantibodies

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Introduction: Autoimmune hepatitis (AIH) is associated with different serum autoantibodies against antigens found in mitochondria, membrane and cytosol of the hepatocytes, as well as primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC). We evaluated a robust multiparametric test system for diagnosing autoimmune liver diseases in a Bulgarian cohort of patients.

Methods: We investigated serum samples of 67 consecutive patients with liver diseases: 13 – with AIH, 29 – with liver cirrhosis (15 – with autoimmune and 14 – with viral etiology), 18 – with viral hepatitis (HBV or HCV), 6 – with PBC, 1 – with PSC and 20 healthy persons for the presence of antibodies against AMA-M2 (E2 subunit of pyruvat dehydrogenase complex), M2-3E(BPO – branched-chain oxoacid-, pyruvate- and oxoglutarate dehydrogenases), Sp100 (spot-pattern 100kDa protein), PML (promyelocytic leukemia protein), gp210 (glycoprotein 210), LKM-1 (liver-kidney microsomes), LC-1 (cytosolic liver antigen type1), SLA/LP (soluble liver antigen/liver pancreas antigen) and Ro-52 by lineblot technique and anti-mitochondrial (AMA), anti-smooth muscle (ASMA), anti-nuclear (ANA) and anti-liver kidney (LKM) antibodies by indirect immunofluorescence technique (IIF).

Results: Seven out of thirteen of AIH sera showed antibodies against at least one of these antigens (most frequent AMA-M2, SLA/LP). We detected also 4/6 positive samples in the PBC group, as well as 1/1 positive PSC patient. The tested antibodies of the blot were found with specificity of 100% as referred to the panels of viral hepatitis patients and healthy controls (which all stayed negative). We found good correlation between immunoblot and IIF (r = 0.67; p < 0.05) regarding AMA-M2 and LKM. The represented immunological panel strongly contributes in establishing autoimmune diagnosis for 88% of all investigated patients.

Discussion/Conclusion: Analysis of these antibodies helps to discriminate different autoimmune liver diseases (viral or autoimmune etiology). The line immunoblot represents a diagnostic tool for autoimmune liver diseases and it contributes positively to gold standard detection methods such as IIF.
Infliximab leading to autoimmune hepatitis: An increasingly recognized side effect

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We observed this instance in an ankylosing spondylitis (AS) patient: A 39-year-old woman with a 4-year ankylosing spondylitis (AS) was investigated for elevation in transaminase levels. She had been treated with methotrexate, salazopyrin and hydroxychloroquine until 4 months ago, when infliximab was initiated. After fourth infliximab dosage (5 mg/kg) at fourteenth week of initial infusion, transaminases including alanine and aspartate aminotransferases (ALT and AST) were found to be gradually increasing and finally became 500–600 iu/dl. We investigated and excluded viral, metabolic and toxic causes for hepatitis. Serum anti-nuclear antibody (ANA) was 1/320 positive, and serum IgG was higher than normal (17.5 g/l). The liver biopsy showed an acute autoimmune hepatitis with a predominantly lymphoplasmatic infiltration. Infliximab was ceased and immunosuppressive therapy was started (prednisolone 30 mg and azathioprine 50 mg). Serum AST and ALT became normal range at the second week of immunosuppressive drug therapy. Ozorio et al. reported a similar AS case and suggested that infliximab might be leading to autoimmune hepatitis by: Triggering development of autoantibodies, TNF-α blockade interfering with cytotoxic T lymphocyte suppression of self-reactive B cell production, interference with CD8 T cell death induction which results in accentuated lymphocyte presence [2]. However, another reported case, in which switching to another anti-TNF-α drug, adalimumab, resulted in remission of autoimmune hepatitis, makes identifying the mechanism of this side effect ever more puzzling [3]. Autoimmune hepatitis secondary to infliximab use is an increasingly recognized entity. We believe that extensive surveillance in this class of drugs, and further studies that will lead to the identification of causal mechanisms is warranted.

References:


The use of azathioprine metabolites in monitoring patients with autoimmune hepatitis

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Introduction: Dhaliwal et al demonstrated that thioguine nucleotide (TGN) metabolite levels > 220 pmol/8 x 10\textsuperscript{8} RBCs are associated with remission in autoimmune hepatitis. We aimed to assess the relevance of independent TGN and methylmercaptopurine (MeMPN) metabolite levels and relationship to disease activity.

Methods: Prospective observational study in patients treated with azathioprine and 6-mercaptopurine for autoimmune hepatitis attending an outpatient hepatology clinic at the Royal Liverpool Hospital over 6 months.

Results: We identified 26 patients of who 12 (46%) were in remission. Those in remission had higher TGN levels but lower MeMPN levels than those not in remission (336 pmol vs. 285 pmol and 1434 pmol vs. 3119 pmol respectively). However this was not statistically significant suggesting a type II error given the small numbers (p = 0.45 and p = 0.18). Though there were no statistical differences in MeMPN levels between the two groups, a greater proportion of patients not in remission had levels > 5000 than those in remission (25% vs. 7%). Seventy-one percent (95% CI) of patients in remission had a TGN > 220. Six of these had a TGN of > 220 and an ALT > 33. Causes for the raised ALT were subsequently identified including non-adherence, alcohol excess, hepatitis C, metabolic syndrome and a PBC/AIH overlap. There was no correlation between TGN or MeMP levels and a leukopenia.

Discussion/Conclusion: TGN and MeMP levels are useful in identifying patients with no or partial response to mercaptopurine based therapy or those who may have additional risk factors for transaminitis.
Diagnostic value of autoantibodies to asialoglycoprotein receptor (ASGPR) in children with autoimmune hepatitis

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Introduction: Autoantibodies to liver-specific asialoglycoprotein receptor (ASGPR) has been suggested as a relevant serologic marker of autoimmune hepatitis (AIH) showing a correlation with disease activity. Recently, a novel ELISA anti-ASGPR assay (Generic Assays GmbH, Germany) has been shown to detect readily anti-ASGPR with higher specificity in comparison to assays available so far.

Aim of the study was to evaluate the significance of anti-ASGPR in children with AIH.

Methods: Anti-ASGPR IgG was measured by novel ELISA in sera of 55 children (27 girls, mean age 14.4 ± 3.5 years). Eleven children with AIH (6 girls) and control group included: celiac disease (CD) (n = 18), fatty liver (n = 17), other (n = 9). Anti-ASGPR was correlated with biochemical parameters of disease activity.

Results: Anti-ASGPR were positive in 2/11 AIH patients and in 3/44 controls, all three with CD. Medium ASGPR titer was significantly higher (p = 0.0125) in patients with AIH (0.60 [0.50–0.70 IR]) compared to controls (0.40 [0.30–0.55 IR]), although within normal limits.

One anti-ASGPR positive AIH patient was a boy with newly-discovered AIH I, with highly active disease before therapy introduction and the other had poorly controlled AIH II.

All but one of other AIH patients had a well controlled disease.

In the control group, none had signs of liver disease. Anti-ASGPR positive CD patients had a history of recent EBV infection in one, overlap with other autoimmune diseases in second and recent gluten challenge in the third case.

In newly discovered AIH patient anti-ASGPR correlated with disease activity during 2 years follow-up. (Figure 1).

Discussion/Conclusion: Results of this study confirmed the association of anti-ASGPR with more severe AIH and possible role in monitoring disease activity. Positive anti-ASGPR in a patients with CD, and no signs of liver disease, raises the question whether we can predict which patients will develop AIH. This hypothesis must be tested through further research.

Figure 1: The dynamics of the anti-ASGPR and biochemical parameters of liver function in newly discovered AIH patient.
Perioperative and long-term morbi-mortality associated with surgery for ileocecal Crohn's disease

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Introduction: Surgery in Crohn's disease (CD) is an effective method to induce remission and avoids potential drug-related complications. However, the decision to operate on ileocecal Crohn's disease is usually tempered by concern for early recurrence and the potential for multiple small bowel resections leading to short bowel syndrome.

The aim of this study was to report the long-term clinical outcome of patients undergoing ileocecal resection for Crohn's disease

Methods: From 1995 to 2014, data from patients with ileocecal CD that underwent ileocecal resection were retrospectively analyzed.

We performed a descriptive and analytical study to determine the demographic, clinical, biological features of the patients and looking for independent prognostic factors. Disease recurrence was defined as symptoms in addition to endoscopic or radiological evidence of disease activity.

Results: Two hundred twenty-four patients underwent ileocecal resection for Crohn's disease during the study period, with a median follow-up of 69.3 months. The mean age at the first resection was 32.5 [14–68] years, and the sex-ratio was M/F 132/92.

The indications for the initial resection were mainly stenosis (61.6%; n = 138) and intra-abdominal abscess (25.9%; n = 58). Postoperative complications included prolonged ileus in 8 (3.5%), wound infection in 19 (8.4%), urinary tract infection in 9 (4.0%), intra-abdominal abscess in 6 (2.6%), and wound dehiscence in 3 (1.3%). There was only one operative death.

During follow-up, 18 (8%) patients developed a recurrence requiring further surgery, with a mean time frame between initial ileocecal resection and operation for recurrence being 68.3 months [7–156]. A second recurrence developed in only 6 patients (2.6%) with a mean time interval of 48 months leading to a second resection in five patients. We performed a permanent ileostomy for the last patient.

The most frequent sites of first surgical recurrence were the anastomotic ileum in 15 patients (6.7%). Three (1.3%) patients had experiences recurrences in other ileal sites. Within five years after surgery, the cumulative probability of clinical recurrence was 26.9% and of surgical recurrence 2.12%.

At multivariate analysis, the only independent variable associated with an increased risk of clinical recurrence was active smoking (HR = 3.18; 95% CI; p = 0.002)

Discussion/Conclusion: In our population the results of surgery for ileocecal CD are good with approximately 73% of patients remain symptom-free and only 2% of patients requiring a second surgery after 5 years. Therefore, surgical resection of ileocecal Crohn's disease should not be unduly delayed for fear of risking short bowel syndrome. This approach should minimize overall disease-related patient morbidity by avoiding long periods of chronic illness.
Liver abnormalities in patients with primary Sjögren's syndrome

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Introduction: The autoimmune destruction of exocrine glands characteristic of primary Sjögren's syndrome (pSS) often extends to non-exocrine organs including the liver. We aimed to determine the abnormal liver biochemistries and clinical liver disease in patients with pSS.

Methods: We reviewed 114 patients with pSS that fulfilled the European Epidemiology Center Criteria, seeking evidence for abnormal liver biochemistries and clinical liver disease.

Results: Of 114 (100 women and 14 men, mean age 51.48 ± 11.1 years) patients screened. Thirty-one (27.1%) had abnormal hepatic biochemistries, and of these 24 patients (21%) had clinical liver disease. Patients with abnormal hepatic biochemistries had higher frequency of antinuclear and antimitochondrial antibodies than patients with normal liver biochemistries (p < 0.05). The causes of clinical liver disease were primary biliary cirrhosis in 7 (6.1%), hepatitis C virus infection 1 (0.8%), hepatitis B virus infection 6 (5.2%), fatty liver 10 (8.7%). In 7 (6.1%) patients, the cause could not be identified.

Discussion/Conclusion: Abnormal liver biochemistries and clinical liver disease could be detected in 27.1% patients of pSS. Liver involvement is a common complication of pSS and its presence is associated with markers of autoimmunity and inflammation. We consider that this complication should be routinely sought in patients with pSS.
Assessment of coagulation status in cirrhotic patients

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Introduction: It has long been thought that cirrhosis is associated with a hypocoagulable state. However, in recent observational studies, thromboembolic events have been reported to be more common in cirrhotic patients than in the general population. The aim of our study was to investigate hemostatic parameters in cirrhotic patients in comparison with controls, so as to determine the possible hemostatic anomalies in cirrhotic patients.

Methods: A comparative case-control study was conducted in cirrhotic patients matched by age and sex with controls. Laboratory tests including conventional coagulation tests (platelet count, prothrombin time (PT), activated partial thromboplastin time (aPTT), INR and fibrinogen level), procoagulant and anticoagulant factors assays and immunological tests (anti-phospholipid antibodies) were performed. To assess hemostatic balance, ratios procoagulant to anticoagulant factors were calculated and thrombin generation test was performed. Biological findings were compared between cirrhotic patients and controls.

Results: We included 51 cirrhotic patients and 50 controls. Mean age of cirrhotics was 57.7 years. There were 24 males and 27 females. PT and aPTT were significantly lower in cirrhotic patients than controls. All procoagulant factors were significantly lower in cirrhotics than controls (p < 0.0001) with exception of FVIII which was significantly higher in cirrhotic patients (115.8% vs. 87.7%; p = 0.007). PC and AT were significantly lower in cirrhotics than controls (p < 0.0001). PS was as high in cirrhotics as in controls (49.62 vs. 81.6; p = 0.8). Most ratios procoagulant to anticoagulant factors were significantly higher in cirrhotics (p < 0.001) than controls and increased as much as the liver disease was severe. Without PC activator, ETP was significantly lower in cirrhotics than controls (p = 0.004). However, ETP ratio (ETP with PC activator/ETP without PC activator) was as high in cirrhotics as in controls (p = 0.55). Among ratios, V/PC and XII/PC were positively correlated to ETP ratio (respectively p = 0.01 [rho = 0.4] and p = 0.024 [rho = 0.39]). VII/AT was negatively correlated to ETP ratio: p=0.04, rho=-0.22. Immunological tests revealed that anti-B2 glycoprotein antibodies were significantly more frequent in cirrhotics than in controls.

Conclusion: Our study revealed that, despite abnormal conventional coagulation tests, thrombin generation was, at least, as high in cirrhotic patients as in controls. These findings disprove the concept of hypocoagulability in cirrhotic patients, and thus elucidating the high frequency of thromboembolic events in such population. Preventive or curative anticoagulant treatment should, probably, be indicated given this thromboembolic risk.
Anomalies of bone tissue metabolism during cirrhosis

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Introduction: It is established that osteopenia and osteoporosis complicate chronic cholestatic liver disease. In the same way, it was recently noted that these anomalies are also found during cirrhosis independently of its aetiology with a frequency varying between 20 and 50%.

Aims: Evaluate the frequency of anomalies of bone tissue in cirrhotic patients and identify the risk factors of low bone mineral density.

Patients and methods: We included hospitalised cirrhotic patients. Patients with primary biliary cirrhosis, autoimmune or metabolic causes of cirrhosis and menopausal women were excluded from the study. All patients had hepatic analysis and a blood and urinary and phosphocalcic assessment. The bone mineral density (BMD) was assessed by dual-energy X-ray absorptiometry (DEXA) at the lumbar spine and femoral neck. The variables taken into consideration were: gender, nutritional status (body mass index – BMI), aetiology of liver disease, presence of cholestasis, severity and duration of disease.

Results: Twenty-five patients were included (14 men and 11 women) with a mean age of 52 years. The average duration of the disease was 4 years (1–9 years). The bone mineral density was normal in 5 patients (20%). An osteopenia and an osteoporosis were observed at respectively 11 (44%) and 9 patients (36%). We find a statistically significant correlation between the presence of bone changes and hypocalcaemia, hepatic cytolysis and elevated urinary urea.

Conclusion: The disorders of the bone tissue metabolism are frequent during the cirrhosis and can be responsible for an added morbidity. A systematic study of bone mineral density should be necessary to detect osteoporosis and to treat it.
Hepatobiliary manifestations in Tunisian inflammatory bowel disease patients

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Introduction: Inflammatory bowel disease (IBD) patients often exhibit common manifestations, which are not characterized as “classic” extraintestinal manifestations, posing clinical dilemmas. The aim of our study was to investigate the prevalence and characteristics of certain common manifestations from the liver and biliary tree, in IBD patients followed-up in our department.

Methods: Data from 112 IBD patients (females: 43.1%, Crohn’s disease: 46%, median age at IBD diagnosis: 43.5 [16–77], have been retrospectively enrolled. The impact of certain demographic and IBD characteristics on results was studied.

Results: Cholelithiasis was present in 8 (7%) patients mainly in females (p = 0.007) with Crohn’s disease ileitis or extensive ulcerative colitis (p = 0.04), in those with perianal Crohn’s disease (p = 0.019), and those having undergone a surgery (p = 0.021). Liver steatosis was detected in 5 (4.4%) patients mainly in females (p = 0.01) with ulcerative colitis (p = 0.05). Primitive sclerosing cholangitis was diagnosed in 4 (3.5%) patients, complicated by cholangiocarcinoma in one case; no predictive factors was associated with PSC. Drug-induced perturbations of liver tests were found in 6 (5.3%).

Discussion/Conclusion: One tenth or less of our IBD patients exhibited at least one hepatobiliary, manifestation. A different pattern of appearance was observed between Crohn’s disease and ulcerative colitis patients.
Does the implementation of a new research-focussed clinical care model improve research activity in autoimmune liver disease?

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Introduction: Autoimmune liver disease (ALD), encompassing primary biliary cirrhosis, autoimmune hepatitis and primary sclerosing cholangitis are rare diseases with significant unmet need. A proportion of patients will progress to end stage liver disease with conditions associated with symptoms impacting on quality of life. Investment to develop NHS and university partnerships through the National Institute for Health Research (NIHR) UK resulted in the Biomedical Research Centre (BRC) in Newcastle. CRESTA (Clinics for Research and Service Themed Assessments) a novel research-focussed model for clinical care forms part of this service. Our service moved to CRESTA in January 2014. With an increasing number of clinical trials and research studies in ALD it is vital that the clinical service adapts to accommodate this. Aim of this study – to assess whether a dedicated, research-focussed clinic can improve research activity, deliver excellent clinical care and meet the needs/expectations of patients.

Methods: Patient survey sent to random sample of patients attending ALD Clinic in Newcastle-upon-Tyne assessed patient’s awareness of ongoing research and overall satisfaction with new service. Research activity monitored by number of patients recruited into studies over two time periods. CRESTA model implemented in January 2014. The year prior to and year after were evaluated.

Results: Recruitment into research increased from 81 to 226 patients in the first year (280% increase). Service evaluation completed by 68 of 133 patients – 77% made aware of potential research studies at their appointment. 90% agreed or strongly agreed their needs had been properly addressed.

Discussion/Conclusion: Implementing a new research-focussed clinical service resulted in increased number of patients recruited to clinical trials and research studies. Majority of patients are aware of ongoing research, giving them the opportunity to participate. This new approach will be key in improving our understanding of ALD, developing new treatments and improving clinical care.
Epidemiological and clinic-pathological survey of patients with autoimmune diseases of the liver in the Austrian Federal State Salzburg: Experience of a single center

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Introduction: Autoimmune liver diseases (ALD) are clinically important differential diagnoses of chronically increased liver enzymes. The major challenges of this disease entity are to establish the diagnosis as well as to prevent the development of hepatic fibrosis and cirrhosis. Therefore, we started epidemiological and clinic-pathological investigations of cases with ALD in a single center to obtain information about the (i) incidence, (ii) histological staging/grading and (iii) outcome.

Methods: A retrospective digital data query covering the years 1997 up to 2015 was carried out at the Institute of Pathology Salzburg to gather data of ALD such as autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC). To access diagnosis of autoimmune diseases, liver specimen and laboratory investigations were taken into account. Additionally, a review of the clinical data records was done.

Results: Overall, we observed an irregular increasing incidence of ALD over the last eighteen years reaching up to 15 new cases per year (altogether 128 cases with ALD; in decreasing incidence frequency: AIH >> PBC >> PSC > overlap syndrome), whereby the basic clinical characteristics are widely comparable to known data. At our center, more inpatients (58.6%) than outpatients (41.4%) were diagnosed with ALD. The initial liver specimen displayed a lower grade of activity (70.3%) and a lower stage of fibrosis (78.5%) (according to Batts&Ludwig and METAVIR scoring systems). The laboratory findings of auto-antibodies could essentially support the interpretation of histomorphological liver findings. Finally, cases with PBC showed the highest lethality rate (up to 15.8%).

Discussion/Conclusion: Our single center experience with ALD largely confirms already published epidemiological series. Nevertheless, the detected increasing incidence of ALD as well as the high lethality rate of PBC demands an integrated and multidisciplinary approach for diagnostics and therapeutics in future.
Impact of viral etiology on hemostatic state in cirrhotic patients

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Introduction: Coagulation anomalies in cirrhotic patients are mainly due to decrease in serum levels of pro-coagulant and anti-coagulant factors.

The aim of our study was to investigate the impact of viral etiology of cirrhosis on the serum levels of pro and anticoagulant factors and on hemostatic balance, assessed by ratios of pro to anticoagulant factors and thrombin generation.

Methods: We conducted a prospective study. Hemostatic state was assessed for each patient by: conventional coagulation tests (prothrombin time, INR and activated partial prothrombin time), levels of pro (II, V, VII, XII) and anti-coagulation factors (PC, PC, AT), ratios of pro to anticoagulation factors and thrombin generation test. All these parameters were then compared between patients having viral etiology of cirrhosis (group A) and those having non-viral etiology of cirrhosis (group B).

Results: We included 51 patients (24 males and 27 females) of mean age of 57 years old. Major etiology of cirrhosis was chronic viral hepatitis (62.3%): viral hepatitis C (41.5%), viral hepatitis B (20.8) et une co-infection B and C (1.9%). Twenty-three patients had Child-Pugh B cirrhosis at inclusion (45.5%). Levels of pro and anticoagulation factors were similar in group A and group B except for factor VII which was significantly lower in group A than in group B (0.82 vs. 1.29 respectively, p = 0.007). Thrombin generation test showed no difference between both groups: endogenous thrombin potential (ETP) without PC activator (625 nM. min versus 588.4 nM. min respectively, p = 0.7), endogenous thrombin potential (ETP) with PC activator (561.4 nM. min versus 441.6 nM. min respectively, p = 0.8) and ETP ratio (ETP with PC activator/ETP without PC activator) (0.9 vs. 0.7 respectively, p = 0.6).

Conclusion: Low FVII serum level seems to be associated with non-viral etiology of cirrhosis. However, this correlation had no impact on hemostatic balance in such patients with comparison with patients having viral cirrhosis. Larger studies are necessary to confirm our findings.
Autoimmune disorders in celiac disease

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Introduction: The risk of developing a concordant autoimmune disorder (AID) in coeliacs has been described and has been estimated to be 10–30 times higher than in a healthy population.

Methods: To assess the prevalence and type of AID in celiacs and to find out the relationship between the duration and course of coeliac disease and the onset of AID. A total of 45 celiacs, that were regularly followed (median of 7 years) as outpatients at our department, were enrolled. The data were reviewed retrospectively.

Results: Out of 45 patients, 9 (20%) were treated with another AID. The median age of these patients, at which coeliac disease (CD) was diagnosed, was 39 years. In 3 cases the diagnosis was based on atypical symptoms only, in 6 patients the manifestation of CD was both intestinal and atypical. AID was diagnosed at a median age of 36.5 years (range 2–70). In most (7) patients the diagnoses of CD and AID were made simultaneously, in the other patients AID preceded CD (by the average of 2.3 years). Autoimmune thyroiditis is the leading AID (5 patients) in CD patients, followed by autoimmune liver disease (4), connective tissue disorders (3), and diabetes (2). There is no significant difference between the age at which CD was diagnosed in both groups (p = 0.7). In CD subjects without AID, intestinal symptoms were more frequent than atypical (p < 0.05).

Discussion/Conclusion: The prevalence of AID in our series was 20% and autoimmune thyroiditis and liver diseases were the most frequent disorders. The age of CD diagnosis was not significant for the onset of AID. Female sex and atypical symptoms of CD may be important in the development of AID.
The role of ultraviolet phototherapy in treatment of cholestasis-induced pruritus

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Pruritus is a frequent and disabling complication of cholestatic liver disorders. Pruritus occurs in 25% of patients with cholestasis and nearly 100% of patients with primary biliary cirrhosis (PBC) and its management is still a challenge. Aim of our study was to evaluate the results of treatment with UVB phototherapy in patients with cholestasis-induced pruritus.

**Methods**: Seventeen patients (5 males, 12 females, mean age 43 years) with cholestatic pruritus have been included. 10 patients have been diagnosed with PBC, 4 patients had PSC and 3 with autoimmune hepatitis had an unusual severe pruritus. Virus B and C were negative in all patients. Conventional treatment with ursodeoxycholic acid, cholestyramine and antihistamines had failed to control pruritus for all of them. All patients were treated with UVB phototherapy and we kept the previous medications with the same dose from the beginning to the end of the study. The perception of pruritus was recorded with a visual analogue scale (VAS) where 0 represented no pruritus and 10 very severe pruritus.

**Results**: We begun with 3 sessions of phototherapy weekly and after 2 weeks of treatment in all patients we had a reduction of intensity of pruritus. Mean VAS score decreased from 8.1 to 3.4 in this time. We continued with 2 sessions /week for 2 months and mean VAS decreased from 3.4 to 1.8. Than we continued with 1 session/week for another 2 months. In one month after stopping the treatment 5 patients relapsed and they started a second phototherapy session. Main side effect seen was erythema but none patient discontinued the treatment for this reason.

**Conclusion**: UVB therapy is an option for the treatment of cholestasis induced pruritus, especially in those patients with severe symptoms and poor response to conventional therapy.
Presepsin as a new biomarker for old expectations in the diagnosis and prognosis of bacterial infection in cirrhosis

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Introduction: Bacterial infections are frequent complications in cirrhosis with significant mortality. Early diagnosis is essential but still a diagnostic challenge from both the clinical and the laboratory part. The aim of this study is to evaluate and compare the diagnostic and prognostic value of presepsin plasma levels with CRP and PCT in bacterial infections of patients with cirrhosis.

Methods: A total of 216 patients with cirrhosis (54.4% males, age: 57.6 ± 10.3 years and median MELD score: 13 [95% CI: 10–17]) were consecutively enrolled. At admission enrollment presence of bacterial infection was assessed on the basis of conventional criteria; liver-oriented scores were calculated and plasma presepsin, CRP and PCT levels were measured. A short-term follow-up study was conducted to assess the development of organ failure(s) and 28-day mortality associated to bacterial infections.

Results: Bacterial infection was found in 75 (34.7%) patients. Plasma presepsin levels were significantly higher in patients with infection as compared to those without (1002 pg/ml [575–2149] vs. 477 [332–680] pg/ml, p < 0.001), increasing correspondingly with the severity of the infection. Presepsin levels were obviously higher in infectious episodes complicated by organ dysfunction(s), namely acute-on chronic liver failure (ACLF) (32%), than those without (2358 pg/ml [1398–3666] vs. 710 pg/ml [533–1277], p < 0.001). The diagnostic accuracy of presepsin for identifying patients with severe infection was similar to PCT and clearly superior to CRP established by ROC analysis (AUC: 0.846, 0.845 and 0.659, respectively, p = n.s. for presepsin vs. PCT, and p < 0.01 for both presepsin vs. CRP and PCT vs. CRP). At the optimal cut-off value of presepsin (> 1206 pg/ml) sensitivity, specificity, PPV and NPV were as follows: 87.5%, 74.5%, 61.8% and 92.7%, respectively. Rate of 28-day mortality was higher among patients with presepsin > 1277 pg/ml compared to those with ≤ 1277 pg/ml (46.9% vs. 11.6%, p < 0.001). In a binary logistic regression model, comprising gender, age, MELD score and acute phase proteins (APPs) one-by-one, MELD score > 21 point (OR = 5.24, p = 0.025), PCT > 0.5 pg/ml (OR = 9.10, p = 0.006) or CRP > 40 mg/l (OR = 4.03, p = 0.039) but not presepsin level were independent risk factor for 28-day mortality.

Discussion/Conclusion: Presepsin is a valuable new biomarker for defining severity of infections in cirrhosis proving same efficacy as PCT. However, for the prediction of short-term mortality, liver-oriented scores and admission level of conventional APP proteins, particularly PCT are appropriate.
Hypereosinophilic autoimmune liver disease: A report of three unusual cases

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Introduction: Gastrointestinal hypereosinophilia is usually reported in the context of idiopathic hypereosinophilic syndrome (HES) and manifests as gastroenteritis or oesophagitis. Rarely, it is associated with sclerosing cholangitis (ESC), chronic active hepatitis and cirrhosis. Here we present three cases of autoimmune liver disease associated with hypereosinophilia.

Methods: We searched our databases for patients with hypereosinophilia and deranged liver function tests (LFTs) in whom haematological disorders and parasitic infections were excluded.

Results:
Case 1: A 62-year-old lady presenting with dysphagia and hepatic discomfort. Blood results revealed hypereosinophilia 3.62 x 10^9/l, Bilirubin 120 μmol/l, ALP 256 U/l, AST 67 U/l, ALT 74 U/l, CRP 48 mg/l normal clotting and negative autoimmune serology. Liver biopsy showed portal expansion with lymphoid follicles and eosinophilia. ERCP favoured sclerosing cholangitis. She was successfully treated with prednisolone and ursodeoxycholic acid (UDCA).

Case 2: A 24-year-old gentleman with previous colectomy for ulcerative colitis, presenting with pruritic jaundice. Blood results revealed hypereosinophilia 2.75 x 10^9/l, bilirubin 272 μmol/l, ALP 200 U/l, ALT 700 U/l, raised CRP 89 mg/l, INR 1.4 and negative autoimmune serology. The MRCP was consistent with primary sclerosing cholangitis (PSC). Liver biopsy revealed chronic hepatitis, eosinophilia and normal bile ducts. He was referred for liver transplantation (OLTx) but made remarkable recovery on Prednisolone, Azathioprine and UDCA.

Case 3: An 18-year-old presenting with lassitude and splinter haemorrhages. Blood results showed hypereosinophilia 17 x 10^9/l, bilirubin 20 μmol/l, ALP 187 U/l, ALT 289 U/l, mildly raised CRP 14 mg/l, ESR 45 mm/h, normal synthetic function, and strongly positive pANCA (negative MPO/PR3). MRCP showed hepatosplenomegaly, with mild diffuse intrahepatic dilatation. Liver biopsy showed incomplete (early) cirrhosis with minimal (lymphocytic) portal tract inflammation. He was treated successfully with Rituximab (intolerant to thiopurines/mycophenolate), prednisolone and UDCA.

Discussion/Conclusion: Hypereosinophilic autoimmune liver disorders present nonspecifically and often with normal autoimmune screen and raised inflammatory markers. Distinguishing PSC from ESC and diagnosing hypereosinophilic autoimmune liver disease remains challenging. All patients in our series made a remarkable recovery with immunosuppression/UDCA escaping the need for OLTx.
Soluble CD163 (sCD163) is a marker of infection in patients with cirrhosis and acute decompensation and an independent predictor of the short-term mortality

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Introduction: sCD163 is shed from macrophages in response to inflammatory stimuli and suggested to modulate the inflammatory response. We aimed to determine the predictive potential of sCD163 levels in the determination of disease phenotype and disease course in a prospective referral cirrhotic cohort.

Methods: 378 consecutive patients with cirrhosis (LC) of different etiology (54.0% males, 70.6% alcoholic) and severity (ChildA/B/C: 39.2/38.1/22.7%, acute decompensation [AD]: 48.9%) were enrolled and followed until death or last attendance. Serum levels obtained at enrollment were assayed for sCD163 by ELISA. Detailed clinical phenotypes regarding first decompensation event (ascites formation, variceal bleeding [VB], hepatic encephalopathy or systemic bacterial infection [INF]), development of hepatocellular carcinoma [HCC] and mortality were determined prospectively during the follow-up (median [IQR], 778 [182–1720] days). Control group comprised 150 healthy subjects (HC).

Results: Serum levels of sCD163 were significantly higher in patients with LC compared to HC (median, 3724 vs. 1104 ng/ml, p < 0.001). In LC, sCD163 levels were associated to disease severity, as rated by the Child-Pugh stage (p < 0.001) but not to the presence of varices or prior VB. In non-AD patients, sCD163 levels were not able to predict the advent of the first decompensation events, development of HCC and also not the long-term mortality. In patients with AD episodes, sCD163 levels were significantly higher compared to non-AD patients but only in the presence of INF (AD-INF: 4969, AD-NON-INF: 3497 and NON-AD: 3471 ng/ml, p < 0.001 for both). Furthermore, during INF episodes (n = 119), sCD163 levels were significantly higher in those complicated with organ failure (31%) and increased gradually according to ACLF grade (No-ACLF: 4121, ACLF gr1: 7335, gr2: 7490, gr3: 12610 ng/ml, p = 0.001). Rate of 28-day mortality was higher among patients with sCD163 level > 7110 ng/ml compared to those with ≤ 7110 ng/ml (46.5% vs. 15.8%, p < 0.001). This cut-off level of sCD163 was associated with a shorter time to death (pLogRank < 0.001) in Kaplan-Meier analysis and was identified as an independent predictor in multivariate Cox- regression model (HR = 2.91, 95% CI: 1.34–6.32, p = 0.007) comprising age, gender, etiology, co-morbidity and MELD score as covariates.

Discussion/Conclusion: Admission sCD163 levels may be an additional help in rapid identification of patients with high-risk for death during AD episodes complicated with INF in LC.
Attitude to and practice of diagnostic paracentesis on the general medical take: Room for improvement?

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Introduction: EASL clinical guidelines recommend diagnostic paracentesis in all patients with cirrhosis and ascites at hospital admission to exclude SBP: delay can lead to increased mortality and health care costs due to complications associated with untreated SBP. We aimed to assess our institution’s compliance with these guidelines and to explore reasons for non-compliance.

Methods: Barnet Hospital is a busy district general hospital serving a population of 500,000. A retrospective case note review was undertaken of all medical admissions with ascites over a 12-month period from March 2013–2014. We conducted a survey of doctors of all grades working in our hospital regarding their knowledge and competence in performing diagnostic paracentesis.

Results: 23 patients were admitted with ascites secondary to cirrhosis. Diagnostic paracentesis was considered by the admitting physician in 61% (n = 14; 95% CI: 41–81%) and performed in 70% (n = 16; 95% CI: 51–88%). 30% of patients did not have paracentesis. The mean time from initial medical clerking to paracentesis was 17.6 hours (95% CI: 11.1–24.0 hours).

The survey was completed by 37 doctors: 54% were aware that cirrhotic patients with ascites should undergo diagnostic paracentesis on admission; 62% were aware that this should be performed by the admitting doctor. Doctors who had completed a gastroenterology rotation were significantly more likely to be able to perform diagnostic paracentesis independently and aware that this should be performed on admission (p ≤ 0.05).

Discussion/Conclusion: Compliance with recommendations to expedite diagnostic paracentesis on admission in patients with ascites and liver cirrhosis is poor. However there is no doubt that a period of gastroenterology training for junior doctors enhances their knowledge and confidence in the management of these patients. We have instituted local changes to address this, highlighting the need for more aggressive investigation and treatment where there is a risk of SBP.
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<tr>
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<td>24, 25, 60</td>
<td>Bezna, M.C.</td>
<td>35</td>
<td></td>
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<td>Bian, Z.</td>
<td>51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agar, K.</td>
<td>44, 67</td>
<td>Bibani, N.</td>
<td>21</td>
<td></td>
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</tr>
<tr>
<td>Agostinho, C.</td>
<td>8, 9</td>
<td>Bicek, A.</td>
<td>17</td>
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<td>Akbulut, S.</td>
<td>28</td>
<td>Boubaker, J.</td>
<td>1, 14, 15, 19,</td>
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<td>Akshija, I.</td>
<td>48</td>
<td></td>
<td>29, 34, 44, 52,</td>
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<td>Ala, A.</td>
<td>18, 53, 76</td>
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<td>65, 67, 68, 72,</td>
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<td>Aleksiev, A.</td>
<td>61</td>
<td>Bougassas, W.</td>
<td>38, 39, 40</td>
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<td>Boyer, J.L.</td>
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<td>75, 77</td>
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<td>2, 12</td>
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<td>Cardoso, C.</td>
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<td>22</td>
<td>Cazzagon, N.</td>
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<td>11, 24, 25</td>
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Autoimmune Diseases of the Liver

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Lisbon, Portugal

Abstracts
Poster Abstracts