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Abstracts of the A.I.S.F. - Italian Association for the Study of the Liver - Monothematic Conference
"The autoimmune diseases of the liver and the biliary system"
Bologna, October 4th- 5th, 2018

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P-1

From guidelines to uniform pan-healthcare professional practice: development of an international consensus Care Pathway for the diagnosis and management of Primary Biliary Cholangitis (PBC)

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PBC is an infrequent but important, lifelong autoimmune cholestatic liver disease that leads to liver fibrosis, cirrhosis and, ultimately, the need for liver transplantation. Its clinical course is heterogeneous, making it difficult for clinicians to diagnose and risk stratify patients with confidence. Patient management is frequently shared across primary and secondary care, and between physicians, nurse specialists and physician assistants. A key recommendation of recent EASL treatment guidelines was the development of a Care Pathway, to facilitate standardized approaches to management based on current practice. Evidence-based guidelines are critical but do not readily translate into a patient care flow: the objective of this exercise was to leverage clinical expertise to develop this practical translation.

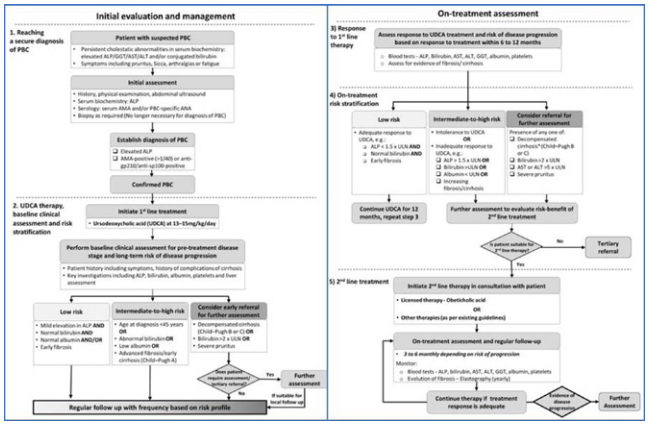

Figure 1. Consensus Care Pathway for the diagnosis and management of PBC.

Twelve PBC specialists convened (with transparent financial support from industry) with the aim of drafting a Care Pathway to support all clinicians in the day-to-day management of PBC patients. It was concluded that the Care Pathway should give practical advice on: confirming PBC diagnosis, performing baseline clinical and risk assessments, initiating first-line treatment, performing on-treatment risk stratification, identifying patients who require second-line treatment and/or further assessments. The experts debated the assessments and criteria that should be included and formed subsequent consensus.

Based on the consensus, a working group of six of the experts further developed and completed the Care Pathway. The working group reached added-consensus on a five-part structure for the Care Pathway based on EASL guidelines alongside their clinical experience (Figure 1).

As an exemplar for all clinicians involved in the care of patients with chronic liver disease, this consensus Care Pathway for the management of PBC, builds on recently-published guidelines to support patient care. It provides an opportunity for more uniform practice, and for safe and timely adoption of varied models of care provision to PBC patients, which go beyond classical physician-lead only management.

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P-2

Hepatobiliary and non-hepatobiliary malignancies in PSC patients from Southern Europe: a comparative study in two European centers

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Primary Sclerosing Cholangitis is a risk factor for the development of hepatobiliary malignancies (HPB) and non-HPB.

Aim: To calculate the risk of malignancies in two Southern European cohorts of PSC and in the general population of the same geographical areas.

Methods: The study was performed in PSC patients from Padova (Italy) and Barcelona (Spain). The cancer incidence was compared with the standardized incidence ratio (SIR) calculated using the Veneto Tumor Registry and the Tarragona Cancer Registry.

Results: We included 165 patients (58% males), 106 from Padova and 59 from Barcelona with a median age at diagnosis of 31and 40 years, a median follow-up of 8.5 [3.8-15.5] and 9.61 [5.9-15.4] years. Association with IBD was observed in 54% and 63% of cases respectively. During follow-up, 22 patients (13%) developed malignancies, (4% HPB 9% non-HPB malignancies). The overall prevalence of malignancies was not significantly different in the two centres (11 vs. 17%, p = ns). The overall cancer incidence in Padova cohort was increased compared to the general population (SIR = 1.91 [95%CI = 1.03-3.24]), this was not the case in the Barcelona cohort (SIR = 1.41 [95CI 0.72-2.51]. An increased incidence of HPB malignancies was observed in both cohorts (SIR = 23.37 in Padova and 14.3 in Barcelona), due to an increased incidence of biliary malignancies (SIR = 67.58 [95%CI 11.33-223.2] in Padova and 34.44 [95%CI 5.77-113.7] in Barcelona). Among the non-HPB malignancies, we noted an increased incidence of CRC in Padova (SIR = 5.78 [95%CI 1.47-15.73]), of small intestine cancer in Barcelona (SIR = 60.43 [95%CI 3.01-297.1] and of cervical cancer in both cohorts (SIR = 19.84 [95%CI 0.99-97.86] and 22.66 [95%CI 1.14-111.8], respectively).

Conclusions: PSC patients from Southern Europe have an increased risk for HPB and intestinal malignancies, although this risk is lower in respect to previous published data. Moreover, these was an increased risk of cervical cancer compared to the general population of the same geographical area.

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P-3

Epidemiology of primary biliary cholangitis in Italy: novel insights on gender and comorbidities

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Primary biliary cholangitis (PBC) is a rare autoimmune liver disease, that mostly affects females. Usually associated with other autoimmune diseases, very little is known about non-autoimmune comorbidities.

The aim of our study was to evaluate the epidemiology of PBC in Italy by administrative data, and to estimate incidence, prevalence, F:M and presence of comorbidities, from 2011 to 2015.

The national hospital discharge database (NHDD) has been used to identify incident and prevalent cases. The study included adult subjects diagnosed with biliary cirrhosis (ICD9-CM: 571.6) as a primary or secondary diagnosis, from 2011 to 2015. Incident rate and prevalence have been estimated by direct standardization method. Main comorbidities have been studied, from 2006 to 2015, and the Standardized Hospitalization Ratio (SHR) has been estimated by indirect standardization method, using the comorbidities of hospitalized (for any cause) italian population as a reference (SHR = 100).

In the study period (2011-15), we identified 5533 PBC cases, 3790 of them were females (68,5%, F:M 2,2:1). Prevalent cases were 9664 (74,6% females, F:M 2,9:1). F:M was stable during the study period. Incident rate was 1,03 × 100.000 in males and 1,92 in females; prevalence was 1,89 for male individuals and 4,75 × 100.000 in female ones. Both measures reduced, with a more significant drop in women. For both genders, an excess in infectious diseases, neoplasms of the liver and biliary tract, endocrine disease, kidney and urinary tract diseases and autoimmune diseases was found in PBC cohort. The most relevant comorbidity was tumors of the liver and biliary tract (SHR = 1250 in males and 791 in females).

To conclude, PBC showed a reduction in incidence and prevalence of hospitalization for PBC from 2011 to 2015; F:M was less than 3. Novel insights on comorbidities have come up from this national study.

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P-4

Epidemiology and clinical impact of non-viral acute hepatitis in a tertiary unit of Hepatology in Italy

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Introduction and Aims: Autoimmune hepatitis have a variable occurrence, clinical phenotype and outcome, and the factors contributing to this variability are uncertain. The goal of this study is to evaluate, through a retrospective analysis, data of severe acute hepatitis (SAH) requiring hospital admission between 1/2017 and 6/2018 in a tertiary inpatient Hepatological Unit. Incidence, clinical impact and outcome of non-viral/autoimmune acute hepatitis (AAH) were analyzed. AAH diagnosis was made using AAH scoring: definite diagnosis when AAH score was >15 pre-treatment and >17 post-treatment, or probable diagnosis when it was <15 and <17 respectively. SAH and Acute-on-Chornic Liver Disease (ACLD) were defined as presence of joundice, hepatomegaly and/or coagulation alteration (showed by an increased INR) and presence of a previous chronic liver disease, respectively.

Results: Among 1302 patients admitted to the Unit in the period, 723 were transferred, from the hospital emergency unit, and the remaining patients were scheduled for diagnostic or oncologic procedures and therapies.

SAH was the admission diagnosis in 29/723 (4%) inpatients; among them 13 (45%) had HBV (3) or HAV (10)-related acute hepatitis and 16/29 were AAH (55%); of them only 9 (56%) were definite and 7 probable with different aspects. Among the 16 patients ACLD was diagnosed in 5 cases.

All the AAH patients were treated with high dose steroid e.v. (predniso(lo)ne 1 mg/kg/die) and in 4 cases azathioprine was added. During the follow-up, lasted at most 18 months, we observed a complete response in 14 patients (87.5%).

Conclusions: An increase of admission for SAH in a non-infective disease/hepatological tertiary inpatient unit was observed in the analyzed period and more than half of them were non-viral/AAH, in a large part (44%) with not definite but probable diagnosis and with comorbilities. This new scenario requires a careful attention in diagnosis and probably a new approach to the long-term immunosuppressive therapy.

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P-5

Two simple magnetic resonance scores are able to predict survival in patients with Primary Sclerosing Cholangitis

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Background: Primary sclerosing cholangitis (PSC) has a variable course. To predict clinical outcome in a single patient is a major need. Magnetic resonance (MR) imaging with 3D-MR cholangiography is the modality of choice for diagnosis. Two MR scores are able to predict radiologic progression of PSC.

Aim: to assess the clinical prognostic value of these two MR scores.

Methods: This retrospective multicentric study included two cohorts of large duct PSC patients with at least one 3D-MRC: a derivation cohort composed by patients from Paris and an external validation cohort composed by patients from Birmingham, Padova and Montreal. All first available MR examinations were revaluated by two radiologists and the two MR scores were calculated: MR score without gadolinium = (1xdilatation of intrahepatic bile ducts) + (2xdysmorphy) + (1xportal hypertension), MR score with gadolinium = (1xdysmorphy) + (1xparenchymal enhancement heterogeneity). Primary endpoint was survival without liver transplantation (LT) and cirrhotic decompensation. Survival was assessed by Cox regression model.

Results: 238 PSC patients were included, equally distributed in derivation and validation cohort. Median age at diagnosis was 37(25-52) years, 66% of patients were males and 72% had IBD. Gadolinium chelates were injected in 64% of patients. During the median follow-up of 4.4(2.6-6.4) and 3.8(1.5-6.2) years, 20 and 25 patients underwent LT, 9 and 5 patients died and 18 and 24 patients

developed cirrhotic decompensation in derivation and validation cohorts, respectively. In univariate analysis total bilirubin, AST, ALT, GGT, albumin, MR score without and with gadolinium were associated with event-free survival. Predictive performances of MR scores without and with gadolinium assessed by c-statistic were 0.89 IC95% (0.84-0.95) and 0.75 IC95%(0.64-0.87), respectively. Independent prognostic factors identified by multivariate analysis were MR scores and total bilirubin. The prognostic value of MR scores was confirmed in the validation cohort.

Conclusion: MR risk scores without and with gadolinium accurately predict clinical outcome in PSC patients.

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P-6

Magnetic resonance cholangiography and biochemical predictive criteria of response to endoscopic treatment of severe strictures in patients with primary sclerosing Cholangitis

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Background: The aim of this study was to assess whether magnetic resonance cholangiography (MRC), clinical and biochemical criteria are able to predict improvement after endoscopic treatment (ET) for dominant stenosis (DS) in patient with primary sclerosing cholangitis (PSC).

Methods: Patients with large ducts PSC with at least one ET for DS were included. MRC were evaluated according to the standard model by Ruiz et al. and a qualitative score of improvement was built. Score 3 (improvement likely) was given in severe common bile duct (CBD) stricture with marked dilatation without severe stenosis of upstream duct, score 1 (improvement unlikely) in case of severe multiple stenosis of secondary ducts without biliary dilatation and score 2 (indeterminate) to an intermediate pattern. Response to ET, assessed at 12 months from inclusion, was defined by the presence of at least one clinical or biochemical criteria.

Results: We included 31 patients who underwent at least one ET for DS. At MRC allpatients had a severe (≤75% of the duct diameter) CBD stricture and half had a severeright (RHD) and/or left hepatic duct (LHD) stricture. According to the qualitative score, 16 patients were scored 3, 7 patients were scored 1 and 9 patients were scored 2. Intraobserver variability of the scorewas 74%, k = 0.6 (substantial agreement) and interobserver variability between the three radiologists was60%, k = 0.40 (fair agreement). Response to ET was obtained in 52% of patients. By univariateanalysis short LHD strictures, higher bilirubin, transaminase, pruritus and qualitative score 3 were associated to response to ET. Total bilirubin and AST were independent predictive factors of response (HR24.0, 95%CI:3.4-170.4,p = 0.001 and 23.8, 95%CI3.4-169.4,p = 0.002).

Conclusion: In PSC patients with severe strictures of extrahepatic bile duct, MRC may contribute to identify patients likely to improve after ET as well as biochemical features. A validation in a larger cohort is warranted to confirm these results.

https://doi.org/10.1016/j.dld.2018.07.025

P-7

Non-invasive B-cell clonality markers may help in the rational approach to HCV SVR cryoglobulinemic patients with persisting manifestations

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Background: Mixed cryoglobulinemia (MC), a both autoimmune and lymphoproliferative disorder (LPD), is characterized by the clonal expansion of B-cell populations, mostly in the liver and, less frequently, in the bone marrow or blood. DAAs can improve or heal MC vasculitis, but persistence or recurrence may be observed after SVR. Rituximab (RTX) is the first-choice therapy in such cases. However, MC persistence may also be due to other causes, including the occurrence of irreversible organ/tissue damage. Consequently, the evaluation of B-cell clonality may consistently help for a correct clinical, prognostic and therapeutic approach.

Methods: The following patients were consecutively enrolled: Group A: DAA-treated SVR MC patients with complete clinical response; Group B: DAA-treated SVR MC patients maintaining symptoms. B-cell clonal expansion was evaluated, after DAA-therapy, by flow-cytometry, Free Light Chains ratio (κ/λ) and t(14;18).

Results: We evaluated 84 patients: 47 group A and 37 group B (mean FU 15.5 months). B-cell clonality markers were not observed in group A. At least one clonality marker was detected in 27/37 (73%) of group B patients, including all (six) patients with lymphoma, in hematological regression after DAAs. Three positive patients had systemic symptoms suggestive of an LPD evolution. Patients negative for B-cell clonality were generally characterized by persisting arthralgia and/or sicca syndrome, and/or neuropathy. κ/λ ratio was altered in 47% of cases, flow cytometry in 16% and t(14;18) in 43%. In >20% of cases more than a marker was detected.

Conclusion: Clonality markers were associated with more severe pre-therapy MC. This suggests the hypothesis of having gone beyond the LPD point of no return and the rationale for RTX treatment. The κ/λ ratio, may be an useful marker in MC patients with persisting symptoms, in the light of a more rational clinical and therapeutic approach to these patients.

https://doi.org/10.1016/j.dld.2018.07.026

P-8

A chromosome X-wide association study in primary biliary cholangitis allowed the identification of 5 novel susceptibility loci

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Genome-wide association studies (GWAS) in primary biliary cholangitis (PBC) failed to find X chromosome genetic variants associated with the disease, but analytical problems arising from X unique mode of inheritance were not taken in account. Aim of our study was to explore the specific contribution of the X chromosome to the genetic architecture of PBC by performing a chromosome X-wide association study (XWAS).

Genotype data on X chromosome derived from 5 GWAS studies (cohorts coming from Italy, UK, Canada, China, Japan), for a total of 5,244 cases and 11,875 controls, were included. Genotype data were quality checked, corrected for population stratification, and imputed by using the IMPUTE2 software. A total of 110,000 single-nucleotide polymorphisms (SNPs), common to all cohorts, were then used for association analyses. These were performed by using the PLINK-XWAS software. A subsequent meta-analysis was performed using METAINTER.

In the single-SNP association analysis we found 11 population-specific loci associated with PBC at a suggestive $p < 5*10^{-5}$, the most significant being a signal mapping within the OTUD5 gene ($p = 4.80*10^{-6}$; OR = 1.39 CI = 1.03-1.58; Japanese cohort). This gene codes for a protein that was demonstrated to suppress the type-I interferon-dependent innate immune response.

A meta-analysis was hence performed separately for Caucasian and East Asian populations. This analysis revealed 7 novel loci, 5 of which (i.e. GRIPAP1, PIM2, OTUD5, LL0XNC01, KCND1) below the threshold for X-wide significance. Finally, we performed a gene-ontology enrichment analysis, evidencing a significant enrichment for genes involved in immune system ($p = 8.4*10^{-11}$).

In this study, by applying a XWAS analysis, we were able to evidence novel association signals with PBC risk, shedding light on the genetic contribution of the "neglected" X chromosome to this immune-mediated disorder.

https://doi.org/10.1016/j.dld.2018.07.027

P-9

Ageing-related expression of Twinfilin-1 regulates cholangiocyte biological response to injury

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Background and Aims: Ageing is a complex biological process that affects the functional capacity of multiple organs and is associated to the development of many diseases. Disorders affecting the biliary tree develop and progress differently according to the patient age. The aim of the study was to identify molecular pathways associated to cholangiocytes ageing and to verify their effects in the biological response to injury of biliary epithelial cells.

Materials and Methods: A panel of microRNAs (miRs) involved in ageing processes was evaluated in cholangiocytes of young and old-mice (2 and 22 months of age respectively), subjected to 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC)-treatment, a model of sclerosing cholangitis. Intracellular pathways common to elevated microRNAs were identified by *in silico* analysis. Cell proliferation was evaluated in Twinfilin-1 (*Twf1*) knocked-down cells, assessed by sulforhodamine B (SRB) assay. Senescence and senescence-associated secretory phenotype (SASP) markers were evaluated *in vitro* by qPCR. *In vivo*, senescence-accelerated prone mice (SAMP8, a model for accelerated ageing), *Twf1*$^{-\backslash-}$ or their respective controls were subjected to DDC. mRNA expression level of Twf1 was evaluated in PBC and PSC patients by qPCR.

Results: Cholangiocytes of DDC-treated mice showed up-regulation of a panel of ageing-related *miRs*. Twf1 was identified by

in silico analysis as a common target of the up-regulated *miRs*. *Twf1* expression was increased both in aged and diseases cholangiocytes, and in human cholangiopathies. Knock-down of *Twf1* in cholangiocytes reduced cell proliferation. Senescence and SASP markers resulted increased in Twf1 knocked-down cholangiocytes upon pro-proliferative stimulation compared to control. *In vivo*, SAMP8 mice with accelerated ageing showed increased biliary proliferation and fibrosis while *Twf1*$^{-\backslash-}$ had a tendency to lower biliary proliferation and fibrosis upon DDC administration compared to control animals.

Conclusions: We identified Twf1 as an important mediator of both cholangiocyte adaptation to ageing processes and response to injury. Our data suggest that disease and ageing might share common intracellular pathways.

https://doi.org/10.1016/j.dld.2018.07.028

P-10

Autoimmune liver disease serology in acute hepatitis E virus infection

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Introduction: Existing data show an increased seroprevalence of HEV among AIH patients, raising the question as to whether HEV as a role as a potential AIH trigger. Our aim was to investigate whether acute HEV infection is associated with the presence of AIH-relevant autoantibodies.

Material & Methods: Sera of adult patients with acute HEV infection were tested for autoimmune liver serology according to the International AIH Group recommendations.

Results: 48 patients were enrolled. 66% were men, median age at HEV infection was 53.5 years. Half of the patients had at least one serological positivity, 16% were positive for two autoantibodies. ANA were positive in one third, SMA in 20.8%, ANCA in 14.6%. AMA, Anti-SLA, anti-LKM1 and anti-LC1 were negative in all patients. At IIF on rat kidney tissue 2/10 SMA positive patients had the VG and VGT patterns, suggestive of AIH. SMA showed a trend toward association with female gender ($p = 0.064$), and were associated with ALT < 500 U/l ($p = 0.037$). There was no statistically significant association of autoantibodies positivity with age, presence of diabetes, cirrhosis, immunosuppression or extrahepatic HEV complications.

Follow-up serum from 7/26 seropositive patients was collected between 10 and 15 months later. Three patients were seronegative at follow-up, two showed the same specificities but at lower titres, and two had unchanged titres and specificities. The SMA-positive patient showing the VGT pattern, was still SMA-positive, but with the non AIH-specific V pattern. Follow-up serum from the SMA-positive patient with the VG pattern was not available. None of the followed-up patients developed AIH.

Conclusion: Our data show that ANA, anti-SMA and/or ANCA positivity is a frequent event in acute HEV infection, being found in about half of the cases. Two patients with coexisting extrahepatic autoimmune diseases had AIH-specific SMA, and deserve long-term follow up.

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