15.23.2 Autoimmune hepatitis 3119

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15.23.2 Autoimmune hepatitis 3119 level and decreased necroinflammation on liver biopsy. Some pa- tients may clear HDV transiently, although HBsAg often persists and most patients experience virological relapse of HDV when therapy is discontinued. Histological response, however, can be maintained for many years. In general, HBsAg clearance is required to cause sus- tained HDV clearance. Chronic hepatitis E HEV infection usually produces an acute, self-limiting illness with clearance of the virus within a few weeks. It is now recognized, how- ever, that HEV infection can induce chronic hepatitis and even cirrhosis in immunosuppressed patients, for example, solid organ transplant patients, those with HIV infection, and those with haem- atological disease. Chronic HEV infection is often asymptomatic and may be de- tected during the investigation of abnormal liver function tests. Alternatively, patients may have symptoms such as fatigue, abdom- inal pain, fever, or jaundice. Chronic infection in the immunosup- pressed is best identified by looking for HEV RNA in plasma since antibody responses may be impaired. In transplant recipients, redu- cing the dose of immune suppression may allow viral clearance in some cases. In the remaining patients, as well as HIV-positive and haematological patients, antiviral therapies such as IFN–ribavirin or ribavirin alone have been found to be efficient in eradicating chronic infection. Liver transplantation for viral hepatitis Liver transplantation is indicated both in fulminant hepatic failure due to acute hepatitis and in advanced chronic hepatitis with cir- rhosis. Recurrence of viral hepatitis after transplantation for chronic viral infection has been a major concern for two decades. The use of HBIg and nucleoside analogues allows control in HBV, but severe recurrence has been a significant problem after transplantation for HCV until recently. IFN-based treatments have been used cautiously in well-selected patients with limited success. The new oral IFN-free regimens offer substantial promise for this high-risk group. FURTHER READING AASLD-IDSA HCV guidance panel (2018). Hepatitis C guidance 2018 update: AASLD-IDSA recommendation for testing, managing, and treating hepatitis C virus infection. Clin Infect Dis, 67, 1477–92. American Association for the Study of Liver Diseases/Infectious Diseases Society of America. HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C. https://www.hcvguidelines.org Balagopal A, Thomas DL, Thio CL (2010). IL28B and the control of hepatitis C virus infection. Gastroenterology, 139, 1865–76. Brown RS Jr, et al. (2015). Antiviral therapy in chronic hepatitis B viral infection during

pregnancy: a systematic review and meta-analysis. Hepatology, 63, 319–33. Coiffer B (2006). Hepatitis B virus reactivation in patients receiving chemotherapy for cancer treatment role of lamivudine prophylaxis. Cancer Invest, 24, 548–52. European Association for the Study of the Liver (2017). EASL 2017 clinical practice guidelines on the management of chronic hepatitis B infection. J Hepatol, 67, 370–98. European Association for the Study of the Liver (2018). EASL recommendations on treatment of hepatitis C 2018. J Hepatol, 69, 461–511. Gutierrez JA, Lawitz EJ, Poordad F (2015). Interferon-free, direct-acting antiviral therapy for chronic hepatitis C. J Viral Hepat, 22, 861–70. Kamar N, et al. (2014). Hepatitis E virus infection. Clin Microbiol Rev, 27, 116–38. Koh C, Heller T, Glenn JS (2019). Pathogenesis of and new therapies for hepatitis D. Gastroenterology, 156, 461–76. Lavanchy D (2012). Viral hepatitis: global goals for vaccination. J Clin Virol, 55, 292–302. Lim TR, Tan BH, Mutimer DJ (2014). Evolution and emergence of a new era of antiviral treatment for chronic hepatitis C infection. Int J Antimicrob Agents, 43, 17–25. Locarnini S, et al. (2015). Strategies to control hepatitis B: Public policy, epidemiology, vaccine and drugs. J Hepatol, 62 Suppl 1, S76–86. Martin A, Lemon SM (2006). Hepatitis A virus: from discovery to vaccines. Hepatology, 43 Suppl 1, S164–72. McQuaid T, Savini C, Seyedkazemi S (2015). Sofosbuvir, a significant paradigm change in HCV treatment. J Clin Transl Hepatol, 3, 27–35. Peters van Ton AM, Gevers TK, Drenth JP (2015). Antiviral therapy in chronic hepatitis E: a systematic review. J Viral Hepat, 22, 965–73. Rehermann B, Nascimbeni M (2005). Immunology of hepatitis B virus and hepatitis C virus infection. Nat Rev Immunol, 5, 215–29. Rizzetto M (2018). Targeting hepatitis D. Seminar Liver Dis, 38, 66–72. Terrault NA, et al. (2018). Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology, 67, 1560–99. Verna EC (2014). Hepatitis viruses and liver transplantation: evolving trends in antiviral management. Clin Liver Dis, 18, 575–601. Webster DP, Klenerman P, Dusheiko GM (2015). Hepatitis C. Lancet, 385, 1124–35. 15.23.2 Autoimmune hepatitis G.J. Webb and Gideon M. Hirschfield ESSENTIALS Autoimmune hepatitis is an idiopathic inflammation of the liver at- tributed to immune responses against self-antigens presumed to be of hepatocyte origin. It is typically a relapsing and remitting cor- ticosteroid responsive condition associated with hepatitic serum liver tests, elevated gammaglobulins, and positive immune serology. Histological features are not specific but often include expanded portal tracts with a lymphoplasmacytic infiltrate. Epidemiology: predominantly affects women (female:male, 8:1), may occur throughout life, has some heritable component, and 40% of patients have other autoimmune diseases (e.g. thyroiditis, type 1 diabetes, or coeliac disease). Clinical features: many patients are asymptomatic and identified through investigation of abnormal serum liver tests. Presentation may be with anorexia, nausea, hepatic discomfort, and jaundice, but others may have nonspecific malaise or extrahepatic manifestations

 such as arthralgia, arthritis, or fever. Clinical signs vary greatly, ranging from none to jaundice and tender hepatomegaly to fulminant hep- atic failure. One-third of patients present as cirrhotic. Diagnosis: characteristic laboratory findings include elevated serum transaminase activities, hypergammaglobulinaemia (as IgG), and circulating autoantibodies (e.g. antismooth muscle antibodies, anti-liver–kidney microsomal antibodies, and antinuclear anti- bodies). Diagnosis depends on the combination of clinical features and biochemical, immunological, and liver biopsy abnormalities, with exclusion of viral and other aetiologies. There may be overlap features with other autoimmune liver diseases (primary sclerosing cholangitis or primary biliary cholangitis). Treatment and prognosis: the condition tends to progress to hepatic fibrosis and cirrhosis. Most cases should be treated with an immunosuppressive regimen, typically prednisolone with azathioprine in the first instance, and

most require long-term im- munosuppression. Crude 10-year survival rate is 65% for those presenting with cirrhosis and greater than 95% for those pre- senting without. End-stage decompensated cirrhosis and acute nonresponsive autoimmune hepatitis with liver failure can be indi- cations for liver transplantation. Introduction Autoimmune hepatitis is an uncommon but treatable immune- mediated liver disease. It is characterized by a destructive immune response to hepatocytes in the absence of an identified causative agent. Disease severity ranges from mild hepatitis to fulminant liver failure. The disease may occur at any age, is female predominant, and is associated with other autoimmune conditions. Active hepa- titis is usually indicated by elevation in serum activity of aspartate aminotransferase and alanine aminotransferase. Characteristically, patients also have elevated immunoglobulin G values. Most patients exhibit autoantibodies which are used to aid diagnosis, subclassify disease, and predict treatment outcome. In the absence of definable aetiological agents, diagnosis re- quires both exclusion of other possible causes of liver injury and identification of sufficient supportive biochemical, serological, and histological features. Many patients have fibrosis or cirrhosis at pres- entation. Fibrosis may progress despite therapy. The mainstay of medical management is immunosuppression in the form of cortico- steroids, followed by later addition of corticosteroid-sparing agents, most commonly azathioprine. Most patients respond to corticoster- oids and require long-term immunosuppression to prevent relapse. A few patients require liver transplantation, and post-transplant re- currence is recognized. Aetiology and pathogenesis The aetiology of autoimmune hepatitis is incompletely understood, but there is evidence for both genetic and environmental influences. Genetic factors In common with many other autoimmune diseases, autoimmune hepatitis has associations with HLA alleles. Certain haplotypes confer increased disease susceptibility and also influence severity. For example, in Caucasian European populations, disease risk is increased by carriage of DRB1*03:01 and DRB1* 04:01. The former predicts more aggressive disease, while the latter predicts later onset. HLA associations, however, vary between populations. Genome- wide association work has associated autoimmune hepatitis risk in Europeans with the gene locus SH2B3, which is shared by several autoimmune diseases. Environmental factors Evidence for a specific environmental trigger is lacking in most cases of autoimmune hepatitis, but a well-established link between cer- tain drugs and development of drug-induced autoimmune hepatitis has led to the proposal of molecular mimicry or alteration of self- antigens as potential mechanisms. Similarly, the industrial agent trichloroethylene may trigger autoimmune hepatitis, although its experimental induction requires the use of autoimmunity- predisposed mice. Several viral infections induce transient expres- sion of the same autoantibodies seen in autoimmune hepatitis, which has led to the hypothesis that antigens introduced or exposed by viral infection may also trigger an autoimmune response. Indeed, classical autoimmune hepatitis following confirmed viral hepatitis is described clinically. Immunological factors Disturbances in regulatory T-cell regulatory function have been proposed as important in autoimmune hepatitis. Animal models with thymic deficiency or with deficiencies in regulatory signalling molecules may develop an analogous hepatitis with autoantibodies. Similarly, humans with the familial disorder auto- immune polyendocrine type 1 syndrome have deficits in thymic self-antigen presentation. This impairs the generation of self- specific regulatory T cells and 20% develop autoimmune hepa- titis alongside other autoimmune phenomena. Immune-mediated hepatitis is also recognized in the context of functional CTLA-4 mutations and GATA-2 deficiency, both of which are genes with immunoregulatory roles. The pathogenesis of autoimmune hepatitis involves the loss of immune tolerance to antigens on hepatocytes. There is the gen- eration of an adaptive immune response and the generation of high-titre autoantibodies. Antibodies typically appear at the same time as inflammation and it is unclear whether they are important to

pathogenesis. Antigen-specific T cells reactive to hepatocyte antigens are described. These develop effector phenotypes and se- crete proinflammatory cytokines, resulting in progressive inflam- mation of the liver of variable severity. When hepatitis is severe and necrosis widespread, there may be acute liver failure. More typically, there is a progressive fibrosis leading to cirrhosis, which may subsequently cause liver failure and/or complications of portal hypertension. Epidemiology Autoimmune hepatitis is relatively uncommon, with an incidence of approximately 1 in 100 000 per year and a prevalence of around 1 in 10 000, but the frequently subclinical nature of autoimmune hepa- titis means that its prevalence may be underestimated. Alongside

15.23.2 Autoimmune hepatitis 3121 nonalcoholic fatty liver disease, ‘burnt-out’ autoimmune hepatitis is a likely cause of those presenting with cryptogenic cirrhosis. Autoimmune hepatitis is the primary indication for approximately 5% of liver transplant activity in the United Kingdom and United States of America. In common with other major autoimmune diseases, auto- immune hepatitis has a marked female predilection. The disease course is similar in men and women. Subclassification into type 1 and type 2 diseases may be made according to autoantibody pro- file (Table 15.23.2.1). Overall, presentation peaks in the fourth to fifth decade, but the disease may occur at any age, with paediatric presentation of type 2 autoimmune hepatitis common. There is geographic variation in the incidence of autoimmune hepatitis with the highest rates in northern Europe, where there is also a higher frequency of the type 2 subtype. In addition, native North American populations have higher incidences than their geographical neighbours of Caucasian background. Patients from non-Caucasian, non-Japanese backgrounds may develop more ag- gressive disease, and African American patients more frequently present with cirrhosis. Pathology Liver biopsy is a cornerstone of diagnosis despite no single feature being pathognomonic. The histology of autoimmune hepatitis is characterized by lymphoplasmacytic infiltrate (Fig. 15.23.2.1). This is most marked around the portal areas but may breach the interface between portal tract and liver parenchyma, so-called interface hepatitis. The infiltrate is rich in both cytotoxic and helper T cells, and also in B cells and mature antibody-producing plasma cells. Of these, the presence of plasma cells is most sug- gestive of the diagnosis and is less typical of viral aetiologies. Emperipolesis, where there is penetration by one cell into and through a larger cell (e.g. lymphocyte through hepatocyte), may be visible. Periportal hepatocytes may exhibit necrosis. In more severe cases, necrosis becomes confluent and may bridge between central hepatic veins. Rosettes of regenerating hepatocytes may be identifiable as well as the full spectrum of mild fibrosis through to established cirrhosis. Fibrosis typically starts in the periportal region. The presence of bridging necrosis or worse is predictive of later development of cirrhosis and associated with poor outcomes when untreated. Steatosis is not a feature of autoimmune hepatitis but may be co- incident. Evidence of cholestasis, iron or copper deposition, or (par- ticularly) marked steatosis, suggests alternative aetiologies. Around 10% of cases demonstrate biliary inflammation without bile duct destruction. There is also recognition that autoimmune hepatitis can ‘cross-over’ with other autoimmune liver conditions, and that in some patients coincident ‘overlap’ of two disease processes can be found. Clinical features The presentation of autoimmune hepatitis spans asymptomatic dis- ease through to fulminant liver failure, with around 25% of patients being asymptomatic at presentation. Where symptoms are present, they are typically nonspecific and include right upper quadrant pain, nausea, arthralgia, pruritus, amenorrhoea, and those of as- sociated autoimmune phenomena such as sicca (Table 15.23.2.2). Symptoms may not remit even when immunosuppression is suc- cessful in controlling inflammation. Patients may describe a per- sonal or family history of autoimmunity. Although having relations with autoimmune hepatitis

increases individual risk, the disease is sufficiently uncommon that most will not have an affected relation. Table 15.23.2.1 Type 1 and type 2 autoimmune hepatitis Type 1 Type 2 Proportion of cases 90% 10% Geography Worldwide More frequent in northern Europe Sex ratio 3:1 9:1 Median age of presentation Fourth to fifth decade First to second decade Presentation Variable Often acute, established cirrhosis common at presentation Autoantibodies ANA, anti-SMA LKM HLA HLA-DRB1*03:01, DRB1*04:01 HLA-DRB1*03:01, DRB1*07:01 Prognosis Good Disease more aggressive with cirrhosis more common Relapse after drug withdrawal 70% Near universal Fig. 15.23.2.1 Representative histology of active autoimmune hepatitis. Liver biopsy specimen with haematoxylin and eosin stain. There is dense lymphoplasmacytic infiltration focused on a portal tract but breaching into the lobule portal, representing interface hepatitis. Several foci of hepatocytes demonstrating ballooning and rosette formation are present.

section 15 Gastroenterological disorders 3122 Attention should be paid to drug exposure, and to symptoms or personal histories suggestive of alternative causes of liver diseases (Table 15.23.2.3). Approximately one-third of cases of autoimmune hepatitis are identified as a result of symptoms, but in current practice most pa- tients are diagnosed following abnormal liver biochemistry without symptoms. Half will have some fibrosis at presentation, and up to a third are cirrhotic. There are no specific features on physical examination. Where there is acute hepatitis, there may be fever, hepatomegaly, upper abdominal tenderness, and jaundice. There may be physical evi- dence of chronic liver disease and/or hepatic decompensation. Severe autoimmune hepatitis may lead to liver failure: either acute fulminant disease or decompensated chronic disease with ascites and encephalopathy. Similarly, there may be evidence of coincident autoimmune phenomena such as hypothyroidism, coeliac disease, inflammatory arthritis, or psoriasis. Differential diagnosis The differential diagnosis of autoimmune hepatitis includes all po- tential causes of hepatic inflammation (Table 15.23.2.3). Both new and long-established drug treatments should be considered as po- tential causes (Box 15.23.2.1). The International Autoimmune Hepatitis Group has produced simplified criteria for the diagnosis of autoimmune hepatitis (Table 15.23.2.4). Investigation Autoimmune hepatitis typically causes elevations in serum alanine aminotransferase and aspartate aminotransferase (together termed transaminases). Serum alkaline phosphatase and γ-glutamyl trans- ferase are typically proportionally less elevated or normal. Other basic laboratory measures may reveal jaundice, evidence of hep- atic synthetic dysfunction, portal hypertension, anaemia, or renal impairment. Elevated serum IgG is characteristic of autoimmune hepatitis and occurs in over 90% of cases. The increase is polyclonal and may be ac- companied by lesser increases in IgA and IgM. An elevated globulin fraction on routine biochemical testing may be a clue to diagnosis. Autoantibodies are present in around 90% of cases (Table 15.23.2.5 and Fig. 15.23.2.2). Specific testing is required to exclude other aeti- ologies, even in the presence of autoantibodies. Tests include viral serology and assessment for metabolic diseases such as Wilson's and α1-antitrypsin deficiency according to the differential diagnosis. Table 15.23.2.2 Disease associations with autoimmune hepatitis Disease Approximate frequency (%) Thyroiditis 10–20 Diabetes 10 Inflammatory bowel disease 5–10 Rheumatoid arthritis 5–10 Psoriasis 3 Sjögren's syndrome 3 Systemic lupus erythematosus 1 Coeliac disease 1 Multiple sclerosis 1 One or more extra-hepatic autoimmune conditions 40 Table 15.23.2.3 Differential diagnosis of autoimmune hepatitis Condition Notes Drug-induced liver injury May be indistinguishable from autoimmune hepatitis, but potential offending agents should be stopped Viral hepatitis: • Hepatitis A • Hepatitis B (± hepatitis D) • Hepatitis C • Hepatitis E • Epstein–Barr virus • Cytomegalovirus Viral hepatitis may induce autoantibodies including low-titre ANA, SMA, and LKM.

These are most frequent with hepatitis C Metabolic conditions: • Nonalcoholic steatohepatitis • Wilson’s disease • α1-antitrypsin deficiency • Haemochromatosis Other autoimmune conditions: • Primary biliary cholangitis • Primary sclerosing cholangitis The presence of antimitochondrial antibodies suggests primary biliary cholangitis particularly when cholestatic liver tests are present; abnormalities on biliary imaging may suggest primary sclerosing cholangitis. Both typically cause marked elevations in alkaline phosphatase Toxic liver injury: • Alcohol • Paracetamol Hepatic complications of pregnancy: • Cholestasis of pregnancy • Acute fatty liver of pregnancy • Haemolysis, elevated liver enzymes, and
low platelets (HELLP syndrome) The development of these conditions is more common than autoimmune hepatitis developing during pregnancy

15.23.2 Autoimmune hepatitis 3123 Imaging, typically ultrasonography, is used to look for evidence of bil- iary pathology and to indirectly assess the degree of fibrosis. In chil- dren, it is recommended to actively seek overlap features of sclerosing cholangitis by magnetic resonance cholangiography; in adults, the po- tential for overlap should also be recognized, especially in treatment- unresponsive disease. Liver biopsy is usually required to reach a confident diagnosis of autoimmune hepatitis and to provide the clinician and the patient with reassurance that long-term immunosuppression is appropriate. Management Pharmacological There are few controlled trials in the treatment of autoimmune hepa- titis and much is based on case series and data from when diagnostic methods were less accurate. However, the American Association for the Study of Liver Disease, the European Association for the Study of the Liver, and the British Society of Gastroenterology have all pro- duced guidelines. See Fig. 15.23.2.3 for a summary treatment algo- rithm for autoimmune hepatitis. Corticosteroids There is consensus that first-line treatment requires corticosteroids. Prednisolone—or its dose-equivalent precursor prednisone—is usually recommended. Initial regimens vary from 20 mg per day to 1 mg/kg per day of prednisolone. Typically, the dosage of prednis- olone is then slowly reduced to the minimum required to maintain normal liver biochemistry and serum immunoglobulin levels. It is then continued at this level for an extended period, with patients typ- ically requiring 12 to 18 months of corticosteroids. Individualized approaches to treatment are important, as is recognition of the need for slow and prolonged therapy. Adherence to therapy is essential for good outcomes, and nonadherence is commonly recognized in patients with treatment-unresponsive disease. In autoimmune hepatitis patients without cirrhosis, an alternative to prednisolone is the synthetic corticosteroid budesonide. This has fewer side effects than prednisolone due to its extensive first-pass hepatic metabolism, and it has been demonstrated to have equal ef- ficacy in noncirrhotic patients. Treatment with budesonide is typic- ally started at 9 mg/day and titrated downwards. Other immunosuppressants The need for long-term immunosuppression in autoimmune hepa- titis requires the use of agents other than corticosteroids to reduce side effects, which are near universal by 2 years. Most commonly, the purine antimetabolite azathioprine is prescribed at, or shortly after, the commencement of prednisolone or budesonide. A delay in commencing azathioprine is advised when liver disease is unstable. Recommended azathioprine dosages vary and are typically 1 to 2 mg/kg per day. Dosing may be titrated to serum thiopurine metab- olite levels. In some, the related antimetabolite mercaptopurine is better tolerated than azathioprine. Follow-up studies have reported improved outcomes of azathioprine combination therapy as compared with corticoster- oids alone. Patients typically require 2 to 5 years of azathioprine treatment and lifelong treatment is increasingly offered, particu- larly in those with significant liver fibrosis. Studies identify the failure to use azathioprine (or equivalent) as one factor associated with poor long-term outcomes.

Transplantation Transplantation should always be considered if patients have de- compensated liver disease or a fulminant presentation. Care of such patients needs to include discussion with a transplant unit so that individualized assessment can be made as to the risk:benefit ratio of immunosuppression versus transplantation. Elective transplantation in the context of autoimmune hepatitis is most commonly indicated in those with decompensated end- stage/portal hypertensive disease. However, first-presentation de- compensated chronic disease with active hepatitis may respond to immunosuppression. Acute severe hepatitis may also respond to im- munosuppression, but a lack of biochemical improvement within a week of corticosteroids is ominous. Fulminant disease with enceph- alopathy necessitates superurgent transplantation. Corticosteroids in this setting are frequently harmful and not beneficial. Box 15.23.2.1 Drugs particularly associated with the induction of autoimmune hepatitis • Minocycline • Nitrofurantoin • Hydralazine • Methyldopa • α- and β-interferons • Infliximab, adalimumab, and etanercept • Ipilimumab • Nonsteroidal anti-inflammatory drugs • Khat and black cohosh Note: many other drugs and herbal remedies may cause variable liver injury distinct from autoimmune hepatitis under the general term ‘drug-induced liver injury’. Table 15.23.2.4 Simplified diagnostic criteria for autoimmune hepatitis Variable Criterion Points ANA or SMA Titre ≥1:40 1 One or more of: 2 ANA or SMA ≥1:80 LKM ≥1:40 SLA Positive Serum immunoglobulin G

> Upper limit of normal 1 ≥1.1 × upper limit of normal 2 Liver histology Compatible 1 Typical 2 Evidence of viral infection Absent 2 Total Probable autoimmune hepatitis ≥6 Definite autoimmune hepatitis ≥7 A maximum of two points is awarded for the presence of autoantibodies. Produced by the International Autoimmune Hepatitis Group.

 Other treatment considerations Prolonged treatment with corticosteroids mandates careful at- tention to their potential side effects. Bone health, glucose tol- erance, the development of cataracts, weight gain, hypertension, opportunistic infection, and adrenal suppression must all be considered. Specific side effects of other immunosuppressants must also be considered, for example, bone marrow suppression with azathioprine and increased long-term cancer risk. Patients should not smoke. For those on azathioprine, sun block is recom- mended, and women should adhere to screening guidelines for cervical malignancy in particular. Superinfection with hepatitis A or B may worsen precarious liver function and immunization Table 15.23.2.5 Major autoantibodies associated with autoimmune hepatitis Antibody Target Notes ANA Variable nuclear antigens including histones, centromeres, DNA, and chromatin Supports diagnosis of type 1 autoimmune hepatitis, especially at higher titres. Primary biliary cholangitis-associated ANA demonstrates a different and distinct staining pattern. SMA Components of smooth muscle including actin Supports diagnosis of type 1 autoimmune hepatitis F-actin Filamentous actin component of smooth muscle and cytoskeleton Supports diagnosis of type 1 autoimmune hepatitis; more specific than SMA. LKM-1 Cytochrome P450 2D6 Supports diagnosis of type 2 autoimmune hepatitis SLA/LP Soluble antigens of liver and pancreas cytoplasm Predicts poorer outcome; specific to autoimmune hepatitis LC-1 Forminino-transferase cyclodeaminase Predicts poorer outcome AMA Pyruvate dehydrogenase complex More consistent with primary biliary cholangitis, present in a small minority of autoimmune hepatitis cases ANA, antinuclear antibodies; AMA, antimitochondrial antibodies; F-actin, filamentous actin antibodies;

LC-1, liver cytosol antibody type 1; LKM-1, liver– kidney microsomal antibody 1; SLA/LP, soluble liver antigen/liver pancreas; SMA, smooth muscle antibodies. These antibodies are detected by indirect immunofluorescence and require expert interpretation; the soluble antigen SLA/LP requires an enzyme-linked immunoabsorbance assay based technique;
F-actin and LKM-1 may also be detected by ELISA. (a) (b) (c) (d) Fig. 15.23.2.2 Autoantibodies associated with autoimmune hepatitis. (a) Antinuclear antibody—there is homogeneous staining of the nuclei of this human epithelial cell line. (b) Antismooth muscle antibody—the muscular walls of arterioles and the muscularis propria are stained in a section of rodent stomach. (c) Anti-liver–kidney microsomal 1 antibody shows homogeneous staining of the cytoplasm of hepatocytes in a section of rodent liver. (d) Anti-liver–kidney microsomal 1 antibody stains the cytoplasm of large proximal tubules but not smaller distal tubules in a section of rodent kidney. These images are of indirect immunofluorescence of patient sera with anti-immunoglobulin G fluorescent secondary antibody.

Working diagnosis of autoimmune hepatitis Commence corticosteroids (prednisolone or, if not cirrhotic, consider budesonide) Addition of azathioprine (usual target dose 1–2 mg/kg). In jaundiced patients, azathioprine is not usually initiated until the bilirubin is < 100 µmol /litre Patients with inactive, ‘burnt-out’ disease on histology may not require immunosuppression Patients with decompensated liver disease or fulminant acute presentations should be managed in conjunction with a liver transplant unit. The risks and benefits of immunosuppression in patients with severe disease need careful consideration Taper corticosteroid dose while attempting to normalize liver biochemistry and immunoglobulin G levels. Corticosteroid taper must be individualized to the patient Mercaptopurine and mycophenolic acid can be considered in patients intolerant of azathioprine. Failure of normalization of transaminases and IgG by 6 months Normalization of liver biochemistry and IgG by 6 months Usually 12–18 months of low- dose corticosteroids and 2–5 years of azathioprine Consider nonadherence and alternative diagnoses. Intensify or alter immunosuppression Monitor for side effects of therapy and survey for complications of cirrhosis. Withdrawal of azathioprine can be considered in noncirrhotic patients with normal liver biochemistry and immunoglobulins. Long-term immunosuppression is often favoured. SLA-positive and LKM-1 positive patients should be considered for lifelong therapy. Response? 3–4 weeks Yes No Fig. 15.23.2.3 Summary treatment algorithm for autoimmune hepatitis. This represents the authors’ approach to treatment, although care of patients with autoimmune hepatitis should always be individualized. Typical starting doses of prednisolone are 20 mg/day to 1 mg/kg/day depending on disease severity. Budesonide is started at 9 mg/ day. Azathioprine is titrated to 1 to 2 mg/kg/day. In presentations with jaundice, azathioprine should be delayed until bilirubin is clearly settling and below 100 µmol/L. Typical long-term maintenance doses of prednisolone are usually less than 10 mg/day. Options for patients unresponsive to treatment after 6 months include increasing corticosteroid and azathioprine doses or the use of tacrolimus, ciclosporin, or rituximab. At all points consideration should be given to referral for transplant assessment or tertiary centre opinion. In responders without cirrhosis or other unstable systemic disease, a single attempt at treatment withdrawal may be attempted after at least a year (usually longer) of normalized laboratory indices.

section 15 Gastroenterological disorders 3126 is recommended. In patients with hepatitis despite apparent ad- equate immunosuppression, consideration of superimposed Epstein–Barr virus, cytomegalovirus, or hepatitis E is sensible. Varicella zoster, influenza, and pneumococcal immunizations are also suggested for immunosuppressed patients. Where cirrhosis is present,

consideration should be given to surveillance for hepatocellular carcinoma, which eventually affects around 1% of cirrhotic autoimmune hepatitis patients. Surveillance for the presence or development of oesophageal varices is standard. Nutritional support may be necessary with advanced cirrhosis. Prognosis Most patients respond to therapy. Overall, 90% achieve remission of laboratory indices with resolution of histological inflammation. Importantly, histological remission typically occurs months after normalization of transaminases and immunoglobulins. Poorer prognosis is associated with onset in those aged less than 18 years, cirrhosis at presentation, and the presence of soluble liver antigen/ liver pancreas (SLA/LP), liver–kidney microsomal antibody 1 (LKM-1), or liver cytosol antibody type 1 (LC-1) antibodies. Some patients, however, do not respond to corticosteroid and azathioprine therapy. Incomplete adherence to the treatment regimen is the most likely explanation, but alternative diagnoses should also be reconsidered. However, liver biochemistry and serum immunoglobu- lins do not respond without explanation in some patients. In these cases, increased doses of corticosteroids and azathioprine have been used with variable success. There are reports of the use of tacrolimus, mycophenolic acid, ciclosporin, rituximab, and infliximab. However, there is considerable heterogeneity in approach between centres and typically subspecialist input is required in these cases. Both patients and physicians may consider ceasing immunosup- pression after a period, usually of at least 2 years, of normal serum biochemistry and immunoglobulins. However, even when repeat biopsy shows no evidence of inflammatory activity, autoimmune hepatitis relapses in over 70% of patients, leading many to manage pa- tients on long-term monotherapy with azathioprine. One approach is a single trial without immunosuppression for those with resolved inflammation on repeat biopsy, in the absence of cirrhosis, and after a prolonged period of normal biochemistry and immunoglobulins. The high risk of relapse means that cessation of immunosuppression is not recommended for those with cirrhosis or those in poor overall health. Relapse usually commits patients to lifelong therapy. Transplantation In autoimmune hepatitis, the prognosis after liver transplantation is good, with 5-year survival rates in excess of 80%. Rates of infection appear higher in the first year after transplantation requiring careful monitoring. Patients awaiting liver transplantation should have their immunosuppression burden reduced. Notably, the require- ment for post-transplantation immunosuppression may be higher than in other conditions, although there is a similar rate of acute episodes of graft rejection. Autoimmune hepatitis may recur in a patient transplanted for the condition. Reported rates of recurrence vary widely and are up to 50%. Disease recurrence is more frequent when active inflammation is found in the recipient explant, and when pretransplantation im- munoglobulins are elevated. The diagnosis requires histological examination in the context of compatible biochemistry and/or im- munoglobulins: autoantibodies typically persist after transplant- ation and are therefore less useful for diagnosis of recurrence. A syndrome resembling autoimmune hepatitis may be seen in liver transplants performed for other indications and is termed de novo autoimmune hepatitis. The process is an alloimmune hepatitis and is considered by many to reflect a variant of rejection. Special circumstances Cross-over syndromes Autoimmune hepatitis may share features with primary biliary cholangitis (previously known as primary biliary cirrhosis) or pri- mary sclerosing cholangitis. Such conditions may be referred to as ‘cross-over’ or ‘overlap syndromes’, but precise definitions are lacking. Typically these presentations are less responsive to im- munosuppression and may evolve over time. In children, autoimmune sclerosing cholangitis is frequent (up to 50%) when sought in those with autoimmune hepatitis. In adult patients, 10% will likely have some cholangiopathy if cholangiog- raphy is performed. Antimitochondrial antibody-negative primary biliary cholangitis may be mistaken for autoimmune hepatitis, and treatment resistant primary biliary cholangitis may also have prom- inent features of hepatitis that lead to consideration of the presence of ‘overlap’. Only a few patients have sufficient

evidence of both hepatitis and biliary disease to represent true ‘overlap’. Some patients present years after a typical diagnosis of primary biliary cholangitis with classical corticosteroid-responsive autoimmune hepatitis and represent clear ‘cross-over’. Inactive disease Some patients may present with ‘burnt out’ disease. Here there is variable fibrosis with no or minimal inflammation but with sero- logical evidence of autoimmune disease. Cohort studies have shown that those with little inflammatory activity on biopsy may not benefit from immunosuppression. Most manage these patients, who are typically elderly, by observation alone. Pregnancy Autoimmune hepatitis may complicate pregnancy, or more com- monly a patient with autoimmune hepatitis may become preg- nant. This situation presents particular management challenges. Typically, therapy with prednisolone and azathioprine is maintained during conception, pregnancy, and breastfeeding with the goal of maintaining stable disease. Particular attention is paid to the pres- ence of portal hypertension including oesophageal varices, altered glucose tolerance in the context of corticosteroid use, the risk of opportunistic infection, and the possibility for fluctuations in dis- ease activity and immunosuppression requirements, particularly postpartum. Classically, disease remits in the second and third tri- mester but over 20% of patients flare within the first few months after delivery. Ideally pregnancy is planned so that the risks and benefits of continuing immunosuppression may be discussed and so that exposure to potentially teratogenic medications, such as mycophenolate, is avoided.

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