# 15.24.3 Drug- induced liver disease 3155

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15.24.3 Drug-induced liver disease 3155 Therapy Gawrieh S, Chalasani N (2015). Pharmacotherapy for non-alcoholic fatty liver disease. Semin Liver Dis, 35, 338–48. Lombardi R, et al. (2017). Pharmacological interventions for non- alcohol related fatty liver disease (NAFLD): an attempted network meta-analysis. Cochrane Database Syst Rev, 3, CD011640. Nguyen V, George J (2015). Non-alcoholic fatty liver disease manage- ment: dietary & lifestyle modifications. Semin Liver Dis, 35, 318–37. 15.24.3 Drug-induced liver disease Guruprasad P. Aithal ESSENTIALS Drug-induced liver disease encompasses a wide range of pathology including idiosyncratic drug-induced liver injury (DILI), acute fatty liver, autoimmune hepatitis, sclerosing cholangitis, granulomatous hepatitis, and nodular regenerative hyperplasia, as well as drug- associated fatty liver disease, cirrhosis, and liver tumours. The vast majority of commonly used drugs are reported to be as- sociated with DILI, including over-the-counter preparations, herbal remedies, and dietary supplements. It is important to consider drug therapy as an aetiology when assessing patients presenting with hepatocellular or cholestatic patterns of liver injury. Systematic evaluation and prompt diagnosis followed by discontinuation of the particular medication is crucial to prevent the development of acute liver failure and to avoid inappropriate investigations. Both candidate gene and genome-wide association studies have identified the critical role of the adaptive immune system in the pathogenesis of idiosyncratic DILI. Human leucocyte antigen alleles that are strongly associated with DILI have the potential to assist in the clinical investigation of patients suspected to have DILI in par- ticular circumstances. Introduction The term hepatotoxicity has been used nonspecifically in the litera- ture to describe the pathological process leading to hepatocyte death and liver injury from medications, alcohol, illicit drugs, and envir- onmental toxins as well as overdoses. Drug-induced liver disease encompasses a wide range of pathologies where drug therapy has been implicated as an underlying aetiology. Over 350 medications have been associated with adverse effects on the liver, which is prob- ably due to the central role of the liver in the metabolism and clear- ance of most drugs. Idiosyncratic drug-induced liver injury (DILI) is defined as an adverse hepatic reaction that is unexpected on the basis of the pharmacological action of the drug administered; this includes acute liver injury, the most common form, and should be distinguished from the consequences of drug overdose. Case definitions and phenotypes Liver

biochemical tests are most commonly used in clinical prac- tice to detect liver injury. These generally include serum alanine aminotransferase (ALT), alkaline phosphatase (ALP), bilirubin, and albumin. Case definitions for DILI include one of the following thresh- olds: (1) fivefold or higher elevation above the upper limit of normal (ULN) for ALT, (2) twofold or higher elevation above the ULN for ALP (particularly with accompanying elevations in concentrations of γ-glutamyl transferase in the absence of known bone pathology driving the rise in ALP level), or (3) threefold or higher elevation in ALT concentration and simultaneous elevation of bilirubin con- centration exceeding twice the ULN. Liver injury is designated 'hepatocellular' when there is a fivefold or higher rise in ALT alone, or when the ratio of serum activity (activity is expressed as a mul- tiple of ULN) of ALT to ALP is 5 or more. Liver injury is designated 'cholestatic' when there is a twofold or higher rise in ALP alone, or when the ratio of serum activity of ALT to ALP is 2 or less. When the ratio of the serum activity of ALT to ALP is between 2 and 5, liver injury is termed 'mixed'. Several other distinct phenotypes of drug-induced liver diseases are discussed in this chapter. Each of these forms is identified using the same characteristic features as used to define the primary condi- tion such as autoimmune hepatitis, primary sclerosing cholangitis, and others. Epidemiology Standard toxicological studies during the preclinical phase of drug development do not reliably detect potential hepatotoxicity of a novel agent; the concordance between liver toxicity in animals and humans is poor. Hepatic adverse reactions are therefore one of the top three organ toxicities identified in phase I to III trials, and are responsible for 22% of 79 drug candidates being dropped from clin- ical development. As hepatic adverse reactions are too low in inci- dence to be detected in clinical trials, the hepatotoxic potential of new medications may only be recognized when a large number of people have been exposed to the drug; therefore, hepatotoxicity has been the second most common reason for withdrawal of approved drugs from the market worldwide, accounting for 32% of 47 such drug withdrawals between 1975 and 2007. Incidence and prevalence of DILI Idiosyncratic DILI due to commonly used medications continues to be encountered in clinical practice. A prospective population-based study from Iceland estimated the crude incidence of DILI to be 19 per 100 000 inhabitants per year. The incidence of DILI was similar in women and men, but increased from 9 per 100 000 among 15- to 29-year-olds to 41 per 100 000 among those over 70 years of age. The increase in DILI incidence with age has been attributed to increasing use of medications with age. The incidence of acute serious liver in- jury requiring hospitalization has been estimated to be 0.7 to 1 per 100 000 population per year. In a recent audit from the United Kingdom, involving 881 con- secutive patients presenting with jaundice in whom biliary ob- struction had been ruled out by imaging, DILI was the underlying

section 15 Gastroenterological disorders 3156 aetiology in 15% of cases and the second most common cause of hepatocellular jaundice after alcoholic liver disease, which ac- counted for 25% of cases. Idiosyncratic DILI contributes to 7 to 22% of cases of acute liver failure worldwide, highlighting the potentially serious consequences of this adverse reaction. Drugs implicated Spontaneous reporting, case reports or series, and more recently hepatotoxicity registries have been the main source of information regarding hepatic adverse reaction due to specific drugs or a class of drugs. In addition to variability of reporting, lack of an accurate denominator (number of people taking the particular medica- tion) means that neither the incidence of DILI due to a particular medication nor its relative contribution to the burden of DILI can be reliably estimated. This issue has been exemplified by the find- ings of a recent prospective study which estimated that 1 in 2350 taking co-amoxiclav and 1 in 133 on azathioprine developed DILI when compared to previous estimates of 1 in 10000 and 3.4 in 100, respectively. A systematic evaluation of reports of

hepatotoxicity due to drugs compiled at the website LiverTox (established by the National Institutes of Health, Bethesda, Maryland, United States of America) has resulted in the categorization of drugs based on the number of convincing reports in the published literature. This process concluded that 353 drugs (excluding herbal remedies, dietary supplements, and illicit substances) were linked to DILI, of which 48 were implicated in more than 50 cases each and included in the highest category of causes of DILI (the vast majority are listed in Table 15.24.3.1). Over 80% of the drugs included in this category were associated with more than 100 reports of DILI, positive rechallenge (recurrence of DILI on re-exposure) were described with over 90% of these agents, and all of these drugs were linked to death. Table 15.24.3.1 includes a list of common agents associated with particular forms of drug-induced liver disease. Prognosis In the population-based cohort, 1% of patients presenting with DILI die, while large registries of idiosyncratic DILI (consisting mainly of cases from secondary care) report that 5 to 10% of patients die or receive liver transplantation in a period of 6 months after DILI onset. Those who present with jaundice are more likely to reach these outcomes compared to those who present with less severe manifestations (13 vs 4%), and a hepatocellular pattern of DILI has a worse prognosis than a cholestatic or mixed pattern. The prognosis of those who develop acute liver failure as a consequence of idiosyn- cratic DILI is worse than that due to other aetiologies. Once acute liver failure develops in patients with DILI, 50 to 80% either die or require transplantation in contrast to 15 to 40% of those secondary to paracetamol overdose. Acute liver injury due to drugs resolves in those who survive the initial episode, but evidence of persistent liver injury (‘chronicity’) 12 months after the onset of DILI has been observed in a small, yet significant proportion of patients on long-term follow-up. Several longitudinal cohorts have reported that 6 to 14% of patients have persistent elevation of liver enzymes. In those who were investigated with liver biopsy, chronic hepatitis, fibrosis, ductopenia (vanishing bile duct syndrome), and cirrhosis have been detected histologically. Among 685 survivors of DILI with jaundice at presentation from one cohort, 3.4% were hospitalized over 10 years of follow-up for reasons related to their liver disease. Diagnoses of autoimmune Table 15.24.3.1 Common drugs associated with specific forms of drug-induced liver diseases Phenotype of liver disease Drug group Medications Idiosyncratic DILI Antimicrobials Co-amoxiclav, erythromycin, flucloxacillin, interferon alpha/peginterferon, isoniazid, ketoconazole, minocycline, nevirapine, nitrofurantoin, pyrazinamide, rifampicin, co-trimoxazole, and sulphonamides Central nervous system Carbamazepine, chlorpromazine, dantrolene, halothane, phenytoin, and valproate Cardiovascular Amiodarone, hydralazine, methyldopa, quinidine, statins (atorvastatin and simvastatin) Immunomodulatory Azathioprine/6-mercaptopurine, infliximab, interferon beta, methotrexate, and thioguanine Antineoplastic Busulfan, floxuridine, and flutamide Rheumatological Allopurinol, auranofin/gold products, diclofenac, ibuprofen, nimesulide, and sulindac Endocrine Anabolic androgenic steroids, oestrogens/progestins, and propylthiouracil Others Disulfiram and ticlopidine Autoimmune hepatitis Diclofenac, halothane, indomethacin, infliximab, methyldopa, minocycline, nitrofurantoin, and statins Secondary sclerosing cholangitis Amiodarone, atorvastatin, co-amoxiclav, gabapentin, infliximab, 6-mercaptopurine, sevoflurane, and venlafaxine Granulomatous hepatitis Allopurinol, carbamazepine, methyldopa, phenytoin, quinidine, and sulphonamides Acute fatty liver Amiodarone, didanosine, stavudine, valproate, and zalcitabine Drug-associated fatty liver disease Methotrexate, 5-fluorouracil, irinotecan, and tamoxifen Nodular regenerative hyperplasia Azathioprine, busulphan, bleomycin, cyclophosphamide, chlorambucil, cysteine arabinoside, carmustine, doxorubicin, 6- thioguanine, and oxaliplatin Ductopenic (vanishing bile duct) syndrome Azathioprine, androgens, co-amoxiclav, carbamazepine, chlorpromazine, erythromycin, oestradiol, flucloxacillin, phenytoin, terbinafine, co-

trimoxazole Liver tumours Anabolic androgenic steroids and oral contraceptives

15.24.3 Drug-induced liver disease 3157 hepatitis as well as cirrhosis leading to decompensation and death were observed as long-term outcomes. Risk factors Pathogenesis of DILI involves interaction of a number of drug and host-related factors which determine the occurrence of these rare events during entirely appropriate therapeutic use of medications (Fig. 15.24.3.1). There are indications that certain risk factors may also influence the phenotype of the adverse reaction, its severity, or duration. Nongenetic factors Idiosyncratic DILI is clearly distinct from overdose, but the thera- peutic dose of a drug could influence the amount of reactive metab- olite formed and hence make further downstream events leading to clinical DILI more likely. Drugs with a daily dose of up to 10 mg are less likely to be associated with DILI than those with a dose of at least 50 mg/day dose. The latter group of drugs is also associated with severe consequences of DILI, such as acute liver failure, transplant- ation, and death. Similarly, medications with greater than 50% hep- atic metabolism and biliary excretion are more frequently associated with severe DILI. Although there is no clear association between age and sex and susceptibility to DILI, these host factors may influence the phenotype of DILI; while hepatocellular pattern of DILI is more common in women less than 50 years of age, men over 60 years of age develop a predominantly cholestatic pattern of DILI. Genetic susceptibility Absorption, distribution, metabolism, and excretion genes Since drug absorption, distribution, metabolism, and excretion are the key determinants of variability in drug responses in humans, genes that encode proteins involved in regulating these aspects of drug disposition have been investigated as risk factors for DILI. Cytochrome P450 Genes from the cytochrome P450 family have potentially a key role in determining susceptibility to DILI due to the involvement of these enzymes in oxidative metabolism of drugs, including the formation of reactive intermediates. One such example is that of bosentan (the endothelin receptor antagonist)-related DILI with the CYP2C9*2 variant which is associated with decreased enzyme activity. Isoform CYP2B6 has been linked to DILI secondary to ticlopidine and efavirenz; oxidative metabolism of both of these drugs is mediated by CYP2B6 enzyme activity. The alleles CYP2B6*1H and *1J associ- ated with increased CYP2B6 activity have been found to increase the risk of ticlopidine DILI, while the CYP2B6*6 allele, associated with decreased CYP2B6 activity and higher levels of plasma efavirenz, is a risk factor for DILI from this drug. UDP glucuronosyltransferases Conjugation with glucuronic acid is a major pathway of drug me- tabolism. Drugs which include carboxylic acid groups form acyl glucuronides, and these conjugates may form covalent adducts with cellular proteins leading ultimately to DILI. Other glucuronides such as phenol glucuronides have also been implicated in DILI. Slow metabolism of tolcapone may be associated with hepatotox- icity as polymorphisms in the gene encoding the main tolcapone metabolizing enzyme UGT1A6 are significantly associated with ele- vated transaminase levels. Another UDP-glucuronosyltransferase gene UGT2B7 has been linked to liver injury from diclofenac. Possession of UGT2B7*2 *is associated with higher glucuronidation and increased hepatic levels of diclofenac acyl glucuronide, hence an increased risk of hepatic adverse reaction. In addition, a recent genome wide association study (GWAS) demonstrated that two intronic single nucleotide polymorphisms (SNPs) in UGT2B7 and another in the adjacent UGT2B4 gene were associated with DILI due to diclofenac. N-acetyltransferases The N-acetyltransferases conjugate xenobiotics with acetyl groups; NAT1 and NAT2 are two isoforms. Isoniazid, an essential compo- nent of most antituberculosis regimens, is metabolized by genetic- ally polymorphic N-acetyltransferase 2 (NAT2). NAT2 metabolic activity depends on the number of active alleles (NAT2*4 and *12). A meta-analysis of 38 studies involving 2225 patients and 4906 controls concluded that slow acetylators (without any active alleles) develop hepatotoxicity more

often than rapid acetylators (with two active alleles); the risk ratio of the association between NAT2 genotype and adverse hepatic reaction varied among dif- ferent ethnic groups. ATP-binding cassette transporters ATP-binding cassette (ABC) transporter family gene products transport both bile acids and drugs. ABCC2 has a major role in the biliary excretion of many glucuronide conjugates. Carriage of an up- stream SNP in ABCC2 (C-24T) has been associated with the risk of DILI among diclofenac users; this SNP lowers the expression of the ABCC2 protein and leads to cellular accumulation of the reactive diclofenac acyl glucuronide. In a study based in Korea, one SNP in linkage disequilibrium with C-24T and another in the promoter region of ABCC2 were risk Daily dose, hepatic metabolism, biliary excretion HLA genotypes Cytochrome P450, UDP-glucuronosyl transferase, N- acetyltransferases, pregnane X receptor, ABC transporters
Fig. 15.24.3.1 Genetic and nongenetic risk factors that contribute to the development of DILI.

section 15 Gastroenterological disorders 3158 factors for DILI caused by a range of drugs. Genotypes of ABCB1 which codes for another transporter have been associated with DILI due to nevirapine. Pregnane xenosensing receptor The nuclear receptor pregnane xenosensing receptor (PXR) is a transcriptional regulator for several genes responsible for metab- olism and disposition of both drugs and endogenous factors such as bile acids. Numerous drugs act as PXR agonists. SNPs in the PXR gene (NR1I2) have been associated with an increased risk of DILI due to flucloxacillin and diclofenac. Antioxidant genes It is plausible that an individual's ability to deal with oxidative stress generated by reactive metabolites is one of the determinants of sus- ceptibility to DILI. Accordingly, genotypes of isoforms of gluta- thione S-transferases (GSTM1 and -T1), glutathione peroxidase I (GPX1), and mitochondrial manganese-dependent superoxide dismutase (SOD2) have been investigated as risk factors for DILI. Perspective Overall, it is difficult to draw firm conclusions from the studies dis- cussed previously due to heterogeneity between the cohorts and lack of replication. It is also important to note that most of the evidence related to the role of absorption, distribution, metabolism, and ex- cretion genes in DILI has come from candidate gene case–control studies with small sample sizes, variable case definitions, and the modest relative risks associated with particular alleles or genotypes. Human leucocyte antigen genetic risk factors Several candidate gene studies and GWAS have found consistent as- sociations between both human leucocyte antigen (HLA) class I as well as class II alleles and DILI. Strongest of such associations is that between HLA-B*5701 and flucloxacillin-induced liver injury, where 84% of patients carried the risk allele (compared to 5% of the population-based controls) with an 81-fold increased risk of DILI. HLA class II haplotype DRB1*1501-DQB1*0602 has been found to be a risk factor for co-amoxiclav DILI consistently across different ethnic groups; the haplotype is found in 53 to 70% of patients com- pared to 12 to 33% of controls. Association between DILI due to lapatinib (a kinase inhibitor) and DRB1*07:01-DQA1*02:01 has also been confirmed in two different cohorts. However, as there is extensive linkage disequilibrium in the major histocompatibility complex (MHC) region, it is difficult to conclude that HLA alleles which have the strongest associations are causally related to par- ticular forms of DILI. In addition to influencing the susceptibility to DILI, specific HLA genotypes have also shown protective associations; an 80% reduc- tion in co-amoxiclav DILI was seen in those carrying the DRB1*07 allele. In contrast, DRB1*07 is associated with an increased risk of flucloxacillin DILI, while DRB1*15 is associated with a reduced risk. Recently, a GWAS demonstrated an association between the HLA class I allele A*33:01 and DILI in general, and the cholestatic or mixed form of DILI in particular. DILI secondary to a number of struc- turally dissimilar compounds including terbinafine, fenofibrate, ticlopidine, sertraline, enalapril, and erythromycin contributed to this association, highlighting a crucial role for adaptive immune re- sponse in the pathogenesis

of DILI. Pathogenesis It is increasingly clear that the grouping of DILI as metabolic or immunological idiosyncrasy is too simplistic. The rarity of idio- syncratic DILI among those exposed to a drug indicates that com- binations of a number of drug-specific and host-related factors are involved in its pathogenesis. Formation of protein reactive molecules (haptens) Drugs (prohaptens) in general are low molecular weight organic chemicals and therefore too small to be antigenic. The liver is central to the biotransformation of most drugs, a process which generally leads to the formation of stable metabolites and their safe excretion. Genetic and environmental factors that influence the expression and activities of the drug metabolizing enzymes (phases I and II), transporters involved in the excretion (phase III) of drug metabolites, and PXRs that regulate a number of these pro- cesses, together determine the rate of formation and accumulation of reactive metabolites. Overwhelming oxidative stress induced by reactive metabolites can lead to hepatocellular injury, particularly when cellular defence is impaired or these reactive metabolites covalently bind to cellular proteins interfering with vital cellular function. However, unlike in the case of hepatotoxicity as a result of paracetamol overdose, for- mation of reactive metabolites alone is insufficient to cause clinically significant idiosyncratic DILI. Instead, development of subclinical hepatocyte injury may underlie asymptomatic elevations of liver enzymes seen more frequently in association with exposure to medications. These initial steps are probably necessary precursors of downstream events in pathogenesis (Fig. 15.24.3.2), hence drug- specific factors such as daily dose, lipophilicity, hepatic metabolism, and biliary excretion influence the hepatotoxic potential of a par- ticular compound. Role of drug-specific antigens and antibodies The importance of further downstream events in the development of DILI is highlighted by the fact that an increasing number and range of medications such as diclofenac, antibiotics, and antitubercular agents taken in their standard therapeutic doses have been asso- ciated with drug metabolite–protein adducts. Antibodies to drug- related adducts have also been found in those taking diclofenac in the absence of DILI, although these adducts have been detected more frequently in patients with DILI. A wide range of anti-isoniazid, anticytochrome P450, and autoantibodies have been demonstrated in most of a group of patients with antituberculosis therapy-induced acute liver failure, although the role of these antibodies in the devel- opment of organ damage remains unclear. Adaptive immune response The observations that there is a period of latency between the ex- posure to the drug and manifestation of DILI, as well as its re- currence with the re-exposure to the drug (consistent with the formation of memory T cells) following its initial resolution on drug withdrawal, suggest that the adaptive immune response contributes to underlying mechanisms. Emerging evidence from recent GWASs further establishes a central role of components of the adaptive im- mune system, especially drug-specific T cells, in mediating the im- mune responses in the pathogenesis of DILI.

15.24.3 Drug-induced liver disease 3159 HLA molecules are central to the activation of T cells responsible for initiating the inappropriate immune response that underlies DILI. Both branches of the highly specific adaptive immune re- sponse rely on the selective presentation of antigens to T cells by HLAs, highly polymorphic proteins also known as MHC proteins. MHC class I molecules are expressed by almost all nucleated cells, including hepatocytes as well as biliary epithelial cells, and these are encoded by the HLA-A, HLA-B, and HLA-C loci. MHC class I pro- teins usually associate with peptide antigens consisting of 9 to 11 amino acids generated by the partial degradation of self-proteins which could include drug metabolite–cellular protein adducts. The MHC I–antigen complex is then expressed on the cell surface and elicits an immune response if a non-self antigen is recognized, causing the activation of CD8+ T cells, which leads to the cell- mediated killing of the original cell. The first GWAS involving DILI demonstrated that possession of the HLA-B*5701 allele*

*was associated with an 81-fold increased risk of DILI on exposure to flucloxacillin when compared with ancestry-matched controls. Another GWAS involving co-amoxiclav DILI described a novel association involving HLA-A*02:01. Both flucloxacillin and co-amoxiclav DILI cohorts include a predom- inantly cholestatic/mixed pattern of DILI cases. Most recently, a GWAS demonstrated an association between DILI, treated as a single phenotype, and HLA-A*33:01; this association was stronger with cholestatic/mixed pattern of cases and strongest with terbinafine DILI. HEPATOCYTE BILE CANALICULUS DRUG DRUG DRUG DRUG endogenous protein no presentation so no response metabolite Covalent adduct damage 'danger' signals proliferation Antibodies processing + HLA processing + HLA Hapten pathway self protein gives no response MHC I presentation activated T cell destroys hepatocyte MHC II presentation TCR activates cytotoxic immune response activates immune responses if costimulation by cytokines/danger signals Hapten pathway pathways altered peptide repertoire pi pathways pi pathway non-covalent direct binding no APC required APC Covalent adduct Covalent adduct Covalent adduct other endogenous proteins MEMORY B CELL B CELL Y Y Y Y Y CD4+ T CELL CD8+ T CELL metabolite metabolite endocytosis endogenous protein Covalent adduct Fig. 15.24.3.2 Putative mechanisms underlying the pathogenesis of idiosyncratic DILI. pi, pharmacological interaction.

section 15 Gastroenterological disorders 3160 MHC class II proteins are only expressed by specialized antigen- presenting cells and are encoded by the HLA-DP, HLA-DQ, and HLA-DR loci within the MHC genetic region. MHC class II proteins have a larger binding cleft that can accommodate 12 to 25 residues of an antigenic peptide often derived from an extracellular, non-self protein (processed in the endosome following endocytosis). These MHC class II–antigen complexes are recognized by CD4+ T cells, which subsequently elicit an immune response. The asso- ciation of a single HLA allele with DILI due to several chemically unrelated compounds has been observed in relation to the associ- ation of DRB1*15:01 with co-amoxiclav and lumiracoxib, as well as DRB1*07:01 with DILI from lapatinib and ximelagatran. The associations of A*33:01 with DILI in general and DILI sec- ondary to a number of structurally dissimilar compounds including terbinafine, fenofibrate, ticlopidine, sertraline, enalapril, and erythromycin, together with recent findings from in vitro studies on T-cell responses to flucloxacillin and amoxicillin–clavulanate, support the hypothesis that either the parent drug or metabolites bind covalently to cellular or circulating protein to form adducts. The drug metabolite–protein complex then binds to the peptide binding groove of HLA molecules leading to activation and differentiation of T cells with a consequent adaptive immune response-mediated liver injury (Fig. 15.24.3.2). Evidence that most drugs showing the A*33:01 association undergo hepatic metabolism and biliary excre- tion may explain the association of A*33:01 with a cholestatic pat- tern of DILI and could indicate that metabolites contribute to the mechanism leading to hepatotoxicity. In the case of co-amoxiclav, neither the amoxicillin nor the clavulanic acid components are subject to P450-mediated metabolism, and in the case of flucloxacillin, the extent of metabolism is very limited. However, activation of T cells by flucloxacillin requires covalent binding to protein and presentation of the drug by antigen- presenting cells expressing HLA-B*57:01; broadly similar findings have been reported for co-amoxiclav-induced T-cell proliferation. Pharmacological interaction concept The pharmacological interaction concept hypothesizes that drugs act directly via noncovalent interactions with MHC proteins or T- cell receptors without the presence of an antigenic peptide. Drugs could also interact with peptides that are already associated with an MHC molecule to activate T cells. In the case of ximelagatran, neither the drug nor its metabolites bind covalently to proteins specifically, hence neoantigen formation required for the hapten pathway does not occur. However, in vitro studies

have demon- strated that ximelagatran as well as its intermediate metabolite melagatran-ethyl can directly bind to an HLA-DRB1*0701 mol- ecule, indicating that pharmacological interaction may be the underlying mechanism leading to the activation of immune re- sponse (Fig. 15.24.3.2). Altered peptide repertoire model According to this model, drugs can noncovalently occupy sites within the peptide binding groove of MHC proteins, hence altering the specificities of the MHC peptide binding. This leads to the pres- entation of self-peptide antigens that are different to those normally bound. This has been proposed as the central mechanism mediating the cutaneous hypersensitivity reaction secondary to abacavir. In the experiments that described this mechanism, flucloxacillin did not modify the affinity of HLA-B*5701-binding peptides for HLA, indicating that the particular mechanism may not be involved in DILI. Danger signal This 'costimulation or danger hypothesis' proposes that immune ac- tivation requires two signals, first an engagement of the T-cell re- ceptor with an MHC–peptide complex presenting the antigen, then a second costimulatory 'alarm or damage signal' from injured or dis- tressed cells. Danger signals are released by cells following damage caused by infection, toxins, and sterile inflammation. Immune rec- ognition of danger signals occurs through pattern recognition re- ceptors including Toll-like receptors expressed by most cells found in the liver. In this context, it is interesting to note that antibiotics—even with their short duration of exposure (as prescribed in courses of days to weeks)—are a group of drugs commonly associated with DILI; it plausible that ongoing sepsis could act as a costimulatory signal. In addition to pathogen-associated molecular patterns (rep- resenting exogenous danger), damage-associated molecular pat- terns (representing endogenous damage) can also be recognized by Toll-like receptors. Drugs or their reactive metabolites may cause subtle hepatocyte injury or bind to cellular components disrupting their function. Damage-associated molecular patterns released as a result of subclinical injury may act as the neces- sary costimulatory signal leading to the activation of antigen- presenting cells to trigger an immune-mediated hepatocyte and/ or cholangiocyte damage. Diagnosis Hepatotoxicity shares its manifestations with liver diseases from other aetiologies and therefore has to be considered in the differ- ential diagnosis of all acute presentations of liver disease, including those presenting with what appears to be hepatic manifestations of systemic diseases. Specific drugs could also be risk factors for certain forms of chronic liver diseases. Both misinterpretation of liver biochemistry results and failure to recognize the possibility of specific drug therapy as an underlying reason behind a particular pattern of liver biochemical abnormalities continue to occur. One hospital-based study found that a proactive system identified a 12-fold higher incidence of acute drug-induced liver enzyme elevations compared to that identified in routine clinical practice, hence raising suspicion is the first step in the process of diagnosis of DILI (Fig. 15.24.3.3). Diagnosis of DILI is incorrectly made in half of cases; failure to identify a drug as the cause of clinical manifestation, as well as missing a correct alternative diagnosis, both occur in routine practice. Accuracy of clinical diagnosis of DILI (about 45%) is a problem both in primary care and in hospital settings. Delay in diagnosis can mean continued exposure to the offending medi- cation, with consequent worsening of DILI leading to acute liver failure in some cases. Prolonged exposure to drugs has also been associated with delayed resolution of DILI, even after withdrawal of the drug, and with chronicity in a few cases. Missed diagnoses such as biliary obstruction from gallstones and autoimmune hepa-titis due to incorrect attribution of the clinical problem to DILI can

 have serious consequences, hence systematic assessment is the key to an accurate diagnosis. Causality assessment methods These involve structured evaluation of several factors in relation to the clinical presentation that support or refute

the link between the drug and the manifestations. The temporal relationship be- tween intake and discontinuation of the suspected drug and onset and disappearance of the manifestation is one of the important factors to consider in the diagnosis. This requires precise informa- tion regarding all the drugs, their doses, and durations, including nonprescription (over-the-counter), herbal, and complementary medications which patients may not consider as relevant. Most DILI occurs between day 4 and 3 months of initial therapy, although some occur later during the first year of treatment. By contrast, DILI due to some drugs (e.g. nitrofurantoin) typically appears more than a year after initial exposure. Ischaemic hepatitis with its characteristic rapid ALT elevation peaking within the first 72 h following circula- tory shock, cardiorespiratory arrest, or exacerbation of heart failure is an important differential diagnosis to consider, especially in sec- ondary care. Similarly, perioperative hypotension manifests with liver injury earlier during the postoperative period than DILI from anaesthetic agents. Different components that form causality assessment have been incorporated into tools that assist in a structured evaluation of cases suspected to have DILI. Two such tools are the Roussel Uclaf Causality Assessment Method, developed by Council for International Organizations of Medical Sciences, and the Clinical Diagnostic Scale. These tools attribute scores (numerical weighting) with regards to specific domains that include the temporal relationship between drug exposure and clinical features, the course of these manifestation once the drug is discontinued, the recur- rence of liver injury on re-exposure to the drug, rigour of exclu- sion of alternative diagnoses, the presence or absence of risk factors and extrahepatic features of an adverse liver reaction, as well as the strength of previous reports of a particular type of DILI. These val- idated tools were developed to facilitate pharmacovigilance of hep- atic adverse reactions and have been effectively used to harmonize phenotyping of DILI between international groups of researchers. Although it is unrealistic to apply causality assessment tools rou- tinely in clinical practice, these provide a template on which a reli- able process of diagnosis and decision-making can be based. Acute biliary obstruction (e.g. from gallstones within the common bile duct) accounts for more than half the cases of jaundice, and one- quarter of cases presenting with an acute hepatocellular pattern of liver enzyme increase (AST >400 IU/litre) and 5% of those with ALT greater than 1000 IU/litre. It is therefore imperative to perform hepatobiliary imaging first to exclude this aetiology. Autoimmune hepatitis has an acute presentation in about 40% of people, and it can have a remitting and relapsing course. Early diagnosis and intervention is crucial to improve outcomes in both DILI and autoimmune hepatitis, hence in-depth investigations are of paramount importance. Ischaemic hepatitis is associated with greater than 50% in-hospital mortality and should be distinguished from DILI as comorbidity associated with ischaemic hepatitis precludes the consideration of liver transplantation, even when fulminant liver failure ensues. In about 80% of patients with ischaemic injury, lactate dehydrogenase reaches very high concentrations with an ALT/lactate dehydro- genase ratio less than 1, a pointer that can be used in the diagnostic Acute rise in liver biochemistry New-onset manifestations Consider DILI Drug history Causality assessment Consider specific tests for DILI • HLA genotyping • Lymphocyte transformation test New systemic manifestations • Skin rash • Eosinophilia • Generalized itching • Jaundice • Acute liver failure • New medication introduced (with in the past 3 months in particular) • Course of antibiotics in the past 6 weeks • Over-the-counter medications • Herbal remedies or complementary medications • Temporal relationship with the drug and the manifestation • Exclusion of biliary obstruction • Evidence to support or refute alternative explanation for the manifestation • Tests that support or refute alternative diagnosis

- ALT ≥ 5 × ULN

- ALT ≥ 3 × ULN and Bilirubin ≥ 2 × ULN
- ALP ≥ 2 × ULN Fig. 15.24.3.3 Clinical approach to the diagnosis of DILI.

section 15 Gastroenterological disorders 3162 process. Recently, hepatitis E infection has become a more common cause of acute viral hepatitis than hepatitis A, B, and C infections; cytomegalovirus, Epstein–Barr virus, and herpes zoster virus also contribute a few cases, all of which resemble DILI in their clinical features. The list of other exclusions to secure a confident diagnosis of DILI is exhaustive: investigations should be tailored to suit the particular clinical context. Role of liver biopsy DILI can cause any known pattern of liver pathology, but certain histological features are particularly suggestive of drug-induced aetiology although there are no specific diagnostic histological fea- tures. The benefits of performing a liver biopsy should be weighed against the disadvantages and its limitations. Liver biopsy is worth- while when (1) autoimmune hepatitis is one of the differential diag- noses under consideration (Fig. 15.24.3.4), (2) the event does not resolve as expected on drug discontinuation, and (3) in circum- stances where the clinical/laboratory features are atypical, or (4) the patient appears to suffer an as yet unrecognized form of DILI. Genetic tests A strong and consistent association between HLA genotypes and DILI has raised the prospect of the potential use of genetic testing in the risk stratification of patients prior to therapy, but the incidence of DILI is too low to use such testing routinely. However, most HLA alleles associated with DILI have a very high negative predictive value of greater than 0.95; hence, they can be used to rule out ad- verse hepatic reactions due to particular drugs when the certainty of diagnosis is of paramount importance. Key examples of associ- ations of specific HLA alleles with DILI from particular medications include HLA-B*5701 with flucloxacillin, HLA-DRB1*1501 with co-amoxiclav, and HLA-A*33:01 with terbinafine and other drugs (fenofibrate, ticlopidine sertraline, enalapril, and erythromycin). A high negative predictive value of a genetic test can also be used to identify the correct agent underlying DILI when the patient has been exposed to two concomitant medications, both with the pro- pensity to cause DILI. HLA genotyping is being carried out regularly in centres with transplantation programmes and these services are readily access- ible to other secondary care hospitals. In particular, HLA B*5701 genotyping is routinely performed prior to prescription of abacavir (effectively reducing cutaneous hypersensitivity due to the drug), hence protocols and processes are well established with an ability to perform genotyping within 1 day of receipt of a sample. Lymphocyte transformation test This investigation, also called the lymphocyte proliferation or stimu- lation test, measures the proliferation of T cells from the blood sam- ples of a patient suspected to have suffered DILI in response to that particular drug. Principles underlying this test have been supported by the generation of drug-specific T-cell clones from individuals who have had a positive response, and also by the pharmacological interaction concept which states that drugs can directly interact with the T-cell receptor, without previous metabolism or need to bind to proteins. When applied to a cohort of well-characterized patients with DILI, results of lymphocyte transformation tests have been variable, ranging from occasional positive cases based on reports from Europe to about a 45% positive rate in cohorts from Japan. In addition, when evaluated in the context of cutaneous hypersensi- tivity, the test has an estimated 15% false-positive rate. The lympho- cyte transformation test is cumbersome, technically demanding, and hence not widely available. Other forms of drug-induced liver disease Drug-induced autoimmune hepatitis Many drugs have been reported to have induced the syndrome that shares many features of idiopathic autoimmune hepatitis. In a cohort of cases with the diagnosis of autoimmune hepatitis, 9% were con- sidered to be induced by drugs, and conversely drug-induced auto- immune hepatitis accounts for 9% of all

DILI. Most of these drugs have appeared in case reports or small case series and include nitro- furantoin, minocycline, diclofenac, statins, and antitumour necrosis factor-α agents (Table 15.24.3.1). Drug-induced autoimmune hepa- titis is difficult to distinguish from the idiopathic form as both have very similar biochemical, clinical, and liver histological features, hence the causal relationship between the drug and autoimmune hepatitis can be best established only when the manifestations re- solve completely on drug withdrawal and do not recur on prolonged follow-up (over 2 years). Secondary sclerosing cholangitis Previously, sclerosing cholangitis had been described following transarterial infusion of chemotherapeutic agents, but these are re- sults of ischaemic injury to the biliary tract rather than toxicity from chemotherapeutic agents themselves. However, secondary scler- osing cholangitis with diffuse inflammatory stricturing of the biliary tree on magnetic resonance cholangiopancreatography has more re- cently been described in a small proportion of patients presenting with acute cholestatic DILI (Fig. 15.24.3.5), over 90% of whom were women, with two-thirds presenting with jaundice. Drugs impli- cated were co-amoxiclav, sevoflurane, amiodarone, infliximab, 6- mercaptopurine, gabapentin, venlafaxine, and atorvastatin. Fig. 15.24.3.4 Liver biopsy showing portal inflammation and interphase hepatitis secondary to diclofenac-induced autoimmune hepatitis.

15.24.3 Drug-induced liver disease 3163 Granulomatous hepatitis Granulomata are circumscribed accumulations of macrophages, some of which may fuse to form multinucleated giant cells, with a surrounding rim consisting of lymphocytes that have developed with stimulation of mononuclear cells from a variety of cytokines. Considering the long list of infectious and immunological conditions associated with hepatic granulomata, the diagnosis of drug-related granulomatous hepatitis depends upon a temporal relationship be- tween exposure to the drug and the clinical manifestation, ruling out an alternative explanation for histological changes, and previous reports in the literature. Allopurinol, carbamazepine, phenytoin, quinidine, methyldopa, and sulphonamides are some of the medi- cations which have been associated with this form of hepatotoxicity. Acute fatty liver This is a distinct form of acute hepatotoxicity associated with drugs that affect mitochondrial function. Microvesicular steatosis and the absence of glycogen in the hepatocytes are characteristic histological features as the liver uses glycolysis to compensate for the lack of ATP produced by mitochondria. Impaired mitochon- drial function leads to apoptosis and liver failure manifesting with hypoglycaemia, lactic acidosis, hyperammonaemia, and cerebral oedema. Dramatically rapid development of organ failure precedes the clinical syndrome, with an acute rise in liver enzymes and jaun- dice that follow, hence having a high index of suspicion is crucial in identifying the drug aetiology when approaching a patient with ‘anicteric hepatic encephalopathy’. Described initially as ‘Reye’s syndrome’ in children treated with salicylate, the incidence of this condition has been reduced markedly by restricting the use of aspirin in those under the age of 16 years and the use of parenteral preparations of tetracycline. Sodium valproate is one of the drugs currently used that has been linked to the de- velopment of acute fatty liver; idiosyncratic hepatotoxicity occurs 1 in 37 000 people taking the drug, and the risk increases to 1 in 500 in children on combination of multiple drugs. A case–control study demonstrated an association between variation in the polymerase γ gene, POLG, which codes for the mitochondrial DNA polymerase γ, and valproate-induced hepatotoxicity. Nucleoside analogue reverse transcriptase inhibitors are one class of drugs which are liable to cause hepatotoxicity by interfering with mitochondrial function. Symptomatic adverse hepatic reac- tions occur with an incidence of 1.2 times per 1000 person/year. Stavudine, zalcitabine, and didanosine have higher affinities for mitochondrial DNA polymerase γ, leading to the depletion of mito- chondrial DNA, and hence have

a higher rate of hepatotoxicity than abacavir, zidovudine, lamivudine, and tenofovir. Early recognition and withdrawal of the drug is the critical step in the management of these potentially life-threatening adverse events. Fatty liver disease Nonalcoholic fatty liver disease (NAFLD) is an entity associated with accumulation of fat in more than 5% of hepatocytes, with or without inflammation and fibrosis, in those who do not consume alcohol over the amount considered moderate (14 units in men and women per week). When the condition is associated with metabolic syndrome or idiopathic it is considered primary NAFLD; drugs are the aetiology behind some secondary NAFLD cases. This entity is different from acute fatty liver described previously. Methotrexate After more than five decades of clinical use, methotrexate is the most frequently used nonsteroidal immunosuppres- sant therapy worldwide, with rheumatoid arthritis and psoriasis being common indications for its use. Reports that long-term methotrexate therapy is associated with fatty infiltration and fi- brosis with a potential to progress to cirrhosis have resulted in a plethora of guidelines recommending intense monitoring regi- mens, including liver biopsies at regular intervals. The proportion of patients estimated to have any degree of liver fibrosis varies from 6 to 72%; with advanced fibrosis ranges from 0 to 33%, and cirrhosis from 0 to 26%. Such wide ranges of reported pathology are due largely to heterogeneity of cohorts, study designs, methods of evaluating histological changes, and case mix. A recent study highlighted the rarity of decompensated cirrhosis associated with methotrexate therapy; of over 150 000 adults who had been listed for or received liver transplantation during a 24-year period, only 117 (0.07%) had methotrexate-associated cirrhosis. Methotrexate polyglutamate within the cell interferes with pyrimidine and purine synthesis, through which it exerts its therapeutic effect. In addition, methotrexate indirectly affects methylenetetrahydrofolate reductase and hence the generation of methionine from homocysteine. Excess homocysteine induces endoplasmic reticulum stress, which, when unresolved, leads to fatty infiltration of the liver. Homocysteine, in addition, can also ac- tivate proinflammatory cytokines and activate hepatic stellate cells, leading to liver fibrosis. The development and progression of chronic drug-associated liver disease is determined by interaction between a number of fac- tors related to the drug (such as cumulative dose), the host (such as SNPs in the methylenetetrahydrofolate reductase gene), and/or the environment (such as alcohol consumption, obesity, and type 2 diabetes). Caucasian ethnicity and female sex are associated with Fig. 15.24.3.5 Magnetic resonance cholangiopancreatography showing diffuse structuring of intra- and extrahepatic bile ducts due to drug-induced sclerosing cholangitis.

 decompensated cirrhosis although it is unclear whether this merely reflects the predominance of women and Caucasians among pa- tients with rheumatoid arthritis and psoriasis respectively. Assessment of the risk:benefit ratio of long-term methotrexate therapy depends upon the efficacy of the drug in an individual weighed against the rate of progression of hepatic fibrosis. The pri- mary objective of monitoring is to detect hepatic fibrosis that is of clinical significance, yet reversible on withdrawal of the drug. Several clinical algorithms that incorporate noninvasive markers of liver fibrosis such as ‘enhanced liver fibrosis’ panel and transient elastography are currently being evaluated as tools to monitor pa- tients on methotrexate therapy. Tamoxifen Treatment with tamoxifen, an oestrogen-receptor antagonist, has been associated with accumulation of fat within the liver. In a multicentre trial involving more than 5000 women, tamoxifen therapy was associated with a twofold risk of developing fatty liver over a 5-year period, with an incidence of 0.4% per year in the treated group compared with 0.2% in the placebo group. This as- sociation was restricted to overweight and obese women, and the increased risk manifested within the first 2 years of treatment. Other factors associated with the

development of nonalcoholic fatty liver disease included hypercholesterolaemia and arterial hypertension. Among those who had a liver biopsy, most had mild to moderate nonalcoholic steatohepatitis histologically (Fig. 15.24.3.6), but none progressed to cirrhosis after a median follow-up of 8.7 years. In a large registry of 810 patients with breast cancer treated with tamoxifen, 16 (2%) developed fatty liver on treatment. Tamoxifen was associated with an eightfold risk of developing fatty liver; age and body mass index were other risk factors. The median time from the start of tamoxifen to the diagnosis of drug-associated fatty liver disease was 22 months; when tamoxifen was discontinued, liver en- zymes improved. Only two patients had biopsy-documented cir- rhosis in this registry, although a few more have been described in case reports. Chemotherapy-associated steatohepatitis Reactive oxygen species generated by chemotherapy and intended to induce tumour cell apoptosis can also lead to the development of steatohepatitis, especially in those with pre-existent hepatic steatosis; obesity is associated with an increased risk. Drugs com- monly associated with steatohepatitis include 5-fluorouracil and irinotecan. Chemotherapy-associated steatohepatitis increases the risk of infections, liver failure, and overall mortality following major liver resections (for hepatic metastasis). Nodular regenerative hyperplasia Some drugs can injure endothelial cells of sinusoids and portal venules with consequent occlusion or dropout of smaller radicles. Widespread vascular changes lead to diffuse nodularity within the hepatic parenchyma. The hepatocytes within the nodule are arranged in plates that are more than one cell in thickness, while hepatocytes are compressed and atrophic into thin, parallel plates between nodules (Fig. 15.24.3.7). Characteristically, the nodules are not separated by fibrosis, although there can be perisinusoidal fibrosis and incomplete fibrous septa. In patients on azathioprine therapy, the cumulative rate of development of nodular regenerative hyperplasia has been estimated to be 0.5% over 5 years and 1.5% in 10 years. Other drugs associated with this form of liver disease are 6-thioguanine, busulphan, bleomycin, cyclophosphamide, chlor- ambucil, cysteine arabinoside, carmustine, and doxorubicin. In re- cent literature, oxaliplatin is the most common drug associated with this pathology. In a large group of patients treated with oxaliplatin, nodular regenerative hyperplasia was found on histology in 25% and features consistent with sinusoidal obstruction syndrome in over 50% of patients. Liver tumours Liver cell adenoma is a benign neoplasm of the liver with an esti- mated incidence of 3 per million per year. Among regular users of oral contraceptives, its annual incidence is at 3 to 4 per 100 000 al- though it may be lower with newer pills. The hormonal dose and duration of medication have been associated with the risk of ad- enoma development, which is highest in women over 30 years of age after using oral contraceptives for more than 24 months. The morphology of hepatic adenomas, with their extensive prolif- eration of blood-filled sinusoids supplied by high-pressure arterial Fig. 15.24.3.6 Liver biopsy showing evidence of fat-laden hepatocytes and fibrosis due to tamoxifen-associated fatty liver disease. Fig. 15.24.3.7 Liver biopsy with reticulin stain demonstrating hypertrophic cell plates surrounded by atrophic cell plates typical of nodular regenerative hyperplasia attributed to azathioprine therapy.

 flow, makes 20 to 40% of them bleed spontaneously causing right upper quadrant pain; intraperitoneal bleeds and ruptures leading to deaths have been reported. Progression to hepatocellular carcinoma occurs in about 10% of adenomas. Ultrasonographic features of hepatic adenomas are nonspecific, but triple-phase CT scanning or MRI are able to distinguish them from haemangiomas, fibronodular hyperplasia, and hepatocellular carcinomas in the vast majority of patients. A causal association between oral contraceptives and hepatic tumours has been accepted as there have been several reports of regression or resolution of adenomas after cessation of the drugs, although such regression may be less likely when the

exposure to oral contraceptives is prolonged. Hormone receptors have also been found in many hepatic adenomas. However, there have also been reports of progression to hepatocellular carcinoma 3 to 5 years after stopping oral contraceptives; hence, surgical resection should be considered based on the site, size, and number of hepatic tumours, as well as certainty regarding their nature on imaging. An association of liver tumours with androgens was first de- scribed in patients with Fanconi's anaemia on anabolic androgenic steroids. Hepatic adenomas, hepatocellular carcinomas, and others (cholangiocarcinoma and angiosarcoma) occur in those who take androgens for Fanconi's anaemia and other forms of aplastic an- aemia as well as for other reasons (such as body builders, hereditary angio-oedema, and immune thrombocytopenia). In a large series including 133 cases, hepatocellular carcinomas were associated with oxymetholone and methyltestosterone, while adenomas were as- sociated with danazol. Both oral and parenteral therapies were as- sociated with the development of tumours, which appeared after a median period of 4 to 6 years of exposure to the medications. Male predominance among cases may be related to exposure of males to this medication. The causal association between anabolic andro- genic steroids and hepatic tumours has been inferred from obser- vations of regression of hepatic lesions upon discontinuation of the medications, but the occurrence of tumours many years after dis- continuation of therapy has been reported. Management The importance of drug-induced liver disease and DILI in particular lies not in the overall number of cases alone, but in the severity of some reactions and their potential reversibility on prompt discon- tinuation of the offending medication. The role of corticosteroids in the treatment of DILI has not been systematically evaluated, but corticosteroid therapy does not improve clinical outcomes in drug-induced acute liver failure. However, it is difficult to distinguish drug-induced autoimmune hepatitis from the idiopathic form; hence, in practice, some pa- tients are treated with corticosteroids at the time of acute presen- tation. Under such circumstances, one should consider withdrawal of all immunosuppressant drugs when clinically appropriate, and then monitor closely. Patients who do not relapse within a period of 24 months of complete withdrawal of immunosuppressive therapy can be considered to have suffered drug-induced autoimmune hepa- titis. There is no clear evidence that ursodeoxycholic acid therapy changes outcome in the cholestatic form of DILI, although the drug has been widely used for all forms of cholestasis. In 11 to 30% of patients with DILI, re-exposure to the particular agent will result in the recurrence of the adverse reaction. Recurrent DILI develops more rapidly (generally after days or weeks) than following initial exposure, manifests with jaundice in two-thirds, requires hospitalization in half of cases, and in 13% leads to death. Inadvertent re-exposure to the particular drug must there- fore be avoided. The only exception to this could be the first line antituberculosis regimen that is highly effective, relatively inexpen- sive, and yet associated with the well-recognized risk of DILI. If second-line antituberculosis medications are entirely unaffordable, then the benefits of reintroduction of the same drugs following resolution of the initial event with careful monitoring should be weighed against the risks of recurrent DILI. Prevention Recent advances in the understanding of the molecular basis of DILI have highlighted the role of adaptive immunity and the contribution of host susceptibility in the pathogenesis of these adverse reactions. Incorporating these factors into the in vitro models used during pre- clinical evaluation of new compounds would improve the detection of the hepatotoxic potential of these molecules early during drug devel- opment. However, it is unrealistic to expect each and every effective drug to be entirely free from adverse effects. Although preprescription pharmacogenetics testing is currently not cost-effective, it is foresee- able that both genetic and nongenetic factors are incorporated into refined algorithms which will allow minimizing the risk of a particular medication in an individual under specific circumstance. FURTHER READING Aithal GP (2011). Hepatotoxicity related to antirheumatic drugs. Nat Rev

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