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## Drug Hepatotoxicity:

### Environmental Factors

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## INTRODUCTION

It is estimated that more than 1100 drugs or herbal agents are associated with DILI.<sup>1</sup> DILI can present as various forms of both acute and chronic liver disease and, although self-limited in the majority of cases, can have more severe consequences, with approximately a 10% case fatality or transplantation rate within the first 6 months of DILI onset and a 20% rate of progression to chronic liver injury.<sup>2–8</sup> DILI remains the leading cause of acute liver failure (ALF) both in the United States and internationally.<sup>1–3,5,9,10</sup> Geographic variation is common in the most frequently implicated agents<sup>1,9,11</sup> for a variety of reasons, including host and environmental factors, such as excessive alcohol and tobacco consumption, infection, pro-inflammatory states, and variations in circadian rhythm. Although host factors are much more robustly described across the body of literature, the environment promoting hepatotoxicity is an ever-expanding and in some instances unexplored field. Environmental factors are important considerations for both intrinsic, or dose-dependent DILI, and idiosyncratic DILI (iDILI). Intrinsic DILI, although more rare, occurs in individuals at the same toxic dose threshold.<sup>12,13</sup> iDILI remains more problematic, less understood, and much more dependent on both environmental and genetic covariates to produce a milieu of susceptibility at the individual level. Currently available testing to both predict and diagnose iDILI in premarketing and postmarketing trials is largely ineffective<sup>14</sup> and most cases of iDILI are discovered when medications are prescribed in much greater volume after regulatory approval.<sup>15</sup> This review focuses on the available evidence supporting specific environmental factors (Box 1) and their influence on the likelihood and outcomes of DILI.

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## GEOGRAPHIC VARIATION

The World Health Organization (WHO) initially began the Programme for International Drug Monitoring (PDIM) in 1968 involving 10 countries, a majority of which were in the regions of Europe or North America (including the United States), in a collaborative effort to pool national data from spontaneous adverse event reporting systems.<sup>16</sup> Ultimately, this collaboration led to the creation of VigiBase in the mid-1990s, a database system comprised of more than 7 million individual case safety reports that became accessible for medical research in 2012 and publically searchable in a limited fashion in 2015 (<http://www.vigisearch.org>).<sup>16</sup> This collaboration has expanded to more than 80 nations and currently includes the regions of Africa, Asia, and Latin America.<sup>16</sup>

In an analysis of VigiBase that spanned data from 2000 to 2009, Aagaard and colleagues<sup>17</sup> found geographic variation in both frequency of adverse drug reaction (ADR) reporting as well as the type of medication associated with the ADR. Low-income countries, as defined by the World Bank, were less likely to report ADRs.<sup>17</sup> Low-income countries reported a greater frequency of ADRs with antibiotics and antifungal and antiviral medications whereas ADRs were more common for immunomodulatory and antineoplastic drugs in high-income nations.<sup>17</sup> The investigators postulated that ADR reporting was more a feature of income rather than actual geography and highlighted the need to improve ADR reporting rates in low-income nations, in particular African nations that contribute less than 1% of the total individual case safety report volume.<sup>18</sup> Despite this, several important differences between African nations and all other countries in the WHO-PDIM are worth noting. African nations report DILI occurring on average in a younger population (18–44 years of age) compared with 45 to 64 years of age in the rest of the world, and 28% of all ADRs reported were attributable to antiviral medications used to treat HIV.<sup>18</sup> Further highlighting geographic differences in DILI, an analysis of VigiBase by Suzuki and colleagues,<sup>19</sup> limited to the United States, England, and Sweden, found that of the 385 unique medications reported, only 9.7% appeared in all 3 registries. Of the 47 drugs subjected to regulatory action, only 6 were found in all 3 regions.<sup>19</sup> Reports from European centers were also more homogenous compared with reports from the United States.<sup>19</sup> A recent report from a single center in India that does not perform liver transplantation incorporating 303 cases of hepatotoxicity from 1997 to 2008 found that 58% were attributable to tuberculosis agents<sup>10</sup>; strikingly, no cases of APAP toxicity were reported. Despite this, a 17.3% case-fatality rate was reported, owing largely to ALF from anti-TB drugs.<sup>10</sup>

## EXCESSIVE ALCOHOL CONSUMPTION

Although excessive alcohol consumption has historically been incorporated into causality assessment, namely that put forth by the Council for International Organizations of Medical Sciences,<sup>12</sup> only a handful of medications have been demonstrated to have increased hepatotoxic potential in the setting of excessive alcohol use, namely APAP, highly active antiretroviral therapy (HAART), halothane, and anti-TB therapy with isoniazid or methotrexate.<sup>12</sup>

Coined *alcohol-APAP syndrome (AAS)*, the risk of APAP toxicity in the setting of alcohol use has been well described since the 1980s.<sup>20–24</sup> AAS is related to CYP2E1 induction as well as glutathione depletion directly attributable to the toxic effects of alcohol.<sup>22</sup> Concurrent malnutrition can predispose a patient to liver injury in this setting through impaired glucuronidation.<sup>22,25,26</sup>

The chronicity of consumption of alcohol may also a role in hepatotoxicity. In a series of 645 patients with single-dose APAP toxicity, Schmidt and colleagues<sup>20</sup> found that chronic alcohol abuse was an independent predictor for mortality while controlling for other confounding factors (odds ratio [OR] 3.52; 95% CI, 1.78–6.97), including renal failure, which has previously been implicated in the increased mortality in this patient population.<sup>27</sup> When APAP overdose superimposed on chronic alcohol consumption (defined as >21 drinks per week for men and >14 drinks per week for women) presents with acute renal failure with creatinine greater than 3.0 mg/dL, prothrombin time greater than 100 seconds, and grades III–IV portosystemic encephalopathy, the prognosis is uniformly fatal.<sup>27</sup> In a prospective nested case-control study of 150 patients with anti-TB drugs, associated DILI drawn from an overall cohort of 3900 patients exposed to anti-TB drugs, Gaude and colleagues<sup>28</sup> found that 42.2% of DILI cases had significant chronic alcohol consumption and that alcohol abuse was predictive of DILI risk on adjusted multivariable analysis.

On the other hand, acute alcohol ingestion may be protective against hepatotoxicity. In animal models, acute alcohol ingestion inhibits CYP2E1 oxidation of APAP, ultimately resulting in a lower level of *N*-acetyl-*p*-benzoquinone imine, the reactive metabolite responsible for the known hepatotoxic potential.<sup>29</sup> This has been corroborated in human observational study because acute ingestion of alcohol in alcoholic patients was associated with a profound reduction in risk (OR 0.08; 95% CI, 0.01–0.66) of APAP hepatotoxicity.<sup>20</sup>

Alcohol is also thought to play a role in hepatotoxicity attributed to HAART when used for the treatment of HIV (namely protease inhibitors and non-nucleoside reverse transcriptase inhibitors).<sup>30</sup> Excessive alcohol use may also lead to decreased treatment efficacy and acceleration of HIV to AIDS through changes in CYP2E1 and CYP3A4 activity.<sup>31</sup> This is important to recognize given that approximately one-fourth of patients with newly diagnosed HIV are alcohol dependent.<sup>30</sup> With the widespread use of similar classes of medications to treat chronic hepatitis C virus (HCV) as a part of the new all-oral direct-acting antiviral regimens and the overlap with comorbid polysubstance abuse, including alcohol, it will be interesting to see if alcohol consumption with the direct-acting antivirals predisposes to either hepatotoxicity or loss of treatment effect, because reports of the hepatotoxic potential of these medications have already surfaced.<sup>32</sup> There have been several reports of increased hepatotoxicity with HAART in patients with HIV/HCV coinfection who abuse alcohol.<sup>33,34</sup>

Alcohol abuse in heavy quantities is associated with accelerated fibrosis in patients who are prescribed chronic immunosuppressive therapy with the antimetabolite methotrexate.<sup>35,36</sup> In a meta-analysis of 15 studies, including 636 patients, Whiting-O'Keefe and colleagues<sup>36</sup> found the pooled risk of advanced fibrosis was 17.8% versus 4.5% ( $P = .003$ ) in heavy drinkers, which was defined as greater than or equal to 100 g of alcohol per week. This population also had histologic progression more frequently (73% vs 26%,  $P = .002$ ).<sup>36</sup> In

accordance with expert opinion, pretreatment liver biopsy is often considered on an individual basis in patients with a history of heavy alcohol consumption to assess for advanced fibrosis prior to initiation of methotrexate.

Despite the evidence put forth from the aforementioned studies, several large registries have not validated the risk of excessive alcohol consumption and any association with DILI.<sup>5,11,37</sup> A majority of patients in a Spanish registry of 461 subjects with DILI had alcohol consumption less than 40 g/d.

## SMOKING

In contrast to the available body of evidence for excessive alcohol and its role in hepatotoxicity development, the literature describing tobacco smoking is much less prevalent and is based solely on observational studies. A Brazilian series of 131 subjects treated with anti-TB drugs found a decreased risk of developing anti-TB DILI in active smokers compared with lifelong nonsmokers (OR 0.28; 95 CI, 0.11–0.64;  $P < .01$ ).<sup>38</sup> Additionally, the investigators found that CYP2E1, despite known to be induced by smoking, was not associated with hepatotoxicity, confirming previous reports.<sup>39,40</sup> CYP1A2 may also be up-regulated by smoking without known clinically relevant hepatotoxicity.<sup>40</sup> A single-center experience in Denmark of 602 patients with APAP toxicity found that 70% were daily tobacco users and this was predictive of severity of injury (diagnosed by significantly higher peak aminotransferase and international normalized ratio levels) as well as all-cause mortality (OR 3.64; 95% CI, 1.23–10.75).<sup>41</sup> On the other hand, Wada and colleagues<sup>42</sup> found that, of the 33 patients in a series of 123 patients with prostate cancer treated with the antiandrogenic drug flutamide, which is metabolized by both CYP1A2 and CYP3A enzymes, smoking was associated with significantly lower odds of hepatotoxicity.

## INFECTION AND INFLAMMATION

Infection and inflammation, through innate immune responses to the invasion of the body by foreign agents, including bacteria, viruses, and fungus, may predispose a patient to either intrinsic DILI or iDILI. The risk of intrinsic, or dose-dependent, DILI is due largely to a left shift in the dose-response curve, thereby sensitizing hepatocytes to injury,<sup>43–45</sup> through a complex proinflammatory cascade involving pathogen-associated molecular patterns, damage-associated molecular patterns, Toll-like receptors, Kupffer cells, tumor necrosis factor (TNF)- $\alpha$ , natural killer cells, interferon gamma, polymorphonuclear neutrophils, endothelial cells, prostaglandins, dendritic and stellate cells, and both the coagulation<sup>46</sup> and complement systems, the specifics of which are beyond the scope of this review but have been described in detail by other investigators.<sup>13</sup>

Animal models using both lipopolysaccharide (LPS) and TNF- $\alpha$  exposed mice have found that these models of inflammation predispose to intrinsic DILI from both APAP and trovafloxacin.<sup>43,45</sup> The timing of LPS administration varied in hepatotoxicity risk in APAP animal models, where LPS given 2 hours before APAP had significantly greater risk compared with LPS administration 24 hours prior to APAP.<sup>47</sup> Animal models investigating the exogenous stress of cocaine administration have found that LPS augments the injury

from cocaine.<sup>48</sup> Because both TNF- $\alpha$  and LPS are surrogates for circulating endotoxemia, it is surprising that advanced fibrosis and cirrhosis have not been<sup>49</sup> documented to significantly increase the risk of DILI for a large number of medications; however, most medications have not been largely studied in patients with cirrhosis and dose adjustment for cirrhosis is often lacking in the prescribing information, despite changes in both pharmacokinetics and pharmacodynamics in this special population.<sup>49</sup>

Inflammation and infection also seem to play a greater role in iDILI and ultimately hepatic necrosis. Similar to intrinsic DILI, a majority of evidence is afforded from animal models. In the setting of LPS-induced endotoxemia, various medications, such as amiodarone, diclofenac, halothane, ranitidine, sulindac, and trovafloxacin, have been implicated in iDILI.<sup>13,44,50–53</sup> Proinflammatory TNF- $\alpha$  also plays a role in iDILI because blocking TNF- $\alpha$  with pentoxifylline in several of these animal models proved effective in decreasing the severity of liver injury.<sup>44,50</sup> The coagulation system is also activated in periods of acute inflammation and the balance between procoagulation and anticoagulation shifts toward thrombotic risk. LPS administration in animal models has led to increased levels of circulating plasminogen activator inhibitor 1 (PAI-1) and ultimately increased fibrin deposition in experimentally induced iDILI.<sup>54</sup> PAI-1 may also play a role in the mechanism of intrinsic DILI form APAP<sup>46</sup> and has been implicated in other inflammatory processes in the liver (namely nonalcoholic steatohepatitis).<sup>55</sup> Furthermore, anticoagulation with heparin-reduced fibrin deposition and thrombin generation has been shown to lead to an attenuation of the hepatotoxic response,<sup>54</sup> and treatment with tissue plasminogen activator (streptokinase) has been shown to reduce hepatotoxicity through a similar mechanism.<sup>56</sup> Collectively, these animal models suggest that activation of the coagulation cascade leads to fibrin deposition and ultimately tissue hypoxia and worsening cellular death and necrosis, findings that warrant validation in human models where to date, the majority of serum testing has focused on drug-induced ALF and the role of microparticles.<sup>57</sup> These membrane fragments of 0.1  $\mu\text{m}$  to 1.0  $\mu\text{m}$  are derived from systemic inflammation and seem predictive of worse clinical outcomes in ALF, including those cases that are drug-induced.

## CIRCADIAN RHYTHM AND THE HEPATIC CLOCK

Circadian time is an important process affecting both the pharmacokinetic as well as the pharmacodynamic properties of drugs across a 24-hour span.<sup>58</sup> This so-called hepatic clock is driven by the central suprachiasmatic nucleus of the hypothalamus, which organizes the majority of circadian change at the cellular level.<sup>59</sup> Fasting-feeding cycles in association with rest-activity rhythms help synchronize the hepatic clock, including the control of xenobiotic detoxification, in effect allowing for the temporal coordination of metabolism.<sup>59,60</sup>

Although the available data are mostly from animal models investigating anti-TB medications and APAP,<sup>58,61–66</sup> there have been extensions in the human population.<sup>67</sup> Through lipid peroxidation inducing mitochondrial toxicity, Souayed and colleagues<sup>58</sup> found that toxic doses of isoniazid in mice at 1 and 9 zeitgeber time produced severe hepatic necrosis whereas dosing at 17 zeitgeber time did not. Deletion of circadian gene *Per1* has

been shown to change the hepatotoxic risk from alcohol,<sup>62</sup> whereas mPer2 has a role in the diurnal variation of APAP toxicity, both in mice.<sup>64</sup>

Patients taking APAP may also be predisposed due to hepatotoxicity due to 24-hour circadian variation.<sup>59,68</sup> This may be due in part to the normal pattern of intermittent fasting states over a 24-hour period because during times of fasting,<sup>68</sup> glutathione levels are known to drop,<sup>69,70</sup> thus potentially decreasing a protective mechanism that normally prevents toxicity from APAP. Fasting states are also known to disrupt detoxification of anti-TB drugs leading to change in the CYP system, predisposing to liver toxicity.<sup>71,72</sup>

Although recommendations for timing of medication administration or dose reduction based on circadian rhythm and resultant drug metabolism effects is a long way off, these results are nonetheless collectively intriguing. APAP is generally taken during times of illness, namely fever or pain, both of which are associated with fasting states. More prospective study in human based populations is needed.

## GUT MICROBIOME

The role of the gut microbiome is also being explored for its potential as a means to protect against APAP-induced and antimicrobial DILI.<sup>73–75</sup> Possamai and colleagues<sup>73</sup> found that when given an intravenous dose of hepatotoxic APAP, the urinary ratio of APAP-sulphate:glucuronide was significantly different when comparing the conventionally housed mice to the germ-free mice because the germ-free mice were found to have higher concentrations; however, interruption of Toll-like receptor 4 signaling was also protective, leading the investigators to conclude that the microbiome itself may play a role but not offer the complete explanation for the observed differences. Xue and colleagues<sup>74</sup> recently published their experience with 3,4-dihydroxyphenylacetic acid, a microbiota-derived metabolite, and its protective role through nuclear factor-erythroid 2-related factor when exposed to toxic levels of APAP, also in mice. Using urinary bile acids as a surrogate for antimicrobial hepatotoxicity, Bhowmik and colleagues<sup>75</sup> demonstrated that gut microbiota may play a significant role in bile acid homeostasis and metabolism because germ-free mice had elevated levels of cholic acid and  $\alpha$ -muricholic acid/ $\beta$ -muricholic acid, which could predispose to hepatotoxicity in this sterile environment. The authors are unaware of any studies in human models investigated the role of the gut microbiome in predisposing or preventing DILI.

## ENVIRONMENTAL POLLUTION

Exposure through an environment rich with pollution can place an individual at risk for hepatotoxicity and although the majority of liver injury is fairly benign with a modest elevation in liver-associated enzymes,<sup>76</sup> rare instances of fatal hepatitis have been reported.<sup>77</sup> In a retrospective case-control study of 247 subjects, D'Andrea and Reddy<sup>76</sup> found significantly elevated liver-associated enzymes in cases of oil spill clean-up workers exposed to potential toxins from the Gulf oil spill along the coast of Louisiana, perhaps directly attributable to benzenes and paraphenols. Exposure to organic pesticides, such as chlorpyrifos, endosulfan, and pyrethroids,<sup>78,79</sup> often through wastewater exposure,<sup>80</sup> has

also been associated with hepatotoxicity. The importance of this cannot be understated, because a prospective study by Cecchi and colleagues<sup>81</sup> of 97 women living in the rural Rio Negro province of Argentina found a predominant increase in alanine aminotransferase (ALT) values in the second trimester of pregnancy, with ALT greater than aspartate aminotransferase (AST). These laboratory abnormalities were not predictive, however, of worse maternal-fetal outcomes in the immediate postpartum period as measured by incidence rates of premature birth and miscarriage, and no cases of fatal hepatitis or nonfatal ALF were reported.<sup>81</sup>

## SUMMARY

The role of environmental factors in predisposing a patient to both intrinsic DILI and iDILI remains a work in progress. Through the evolution of animal models, the complicated interaction between modifiable risk factors, such as tobacco smoking, excessive alcohol consumption, intestinal microbiome, environmental pollutants, and proinflammatory and/or hypercoagulable states, is only beginning to be understood. Although much research attention remains focused to identifying specific individual risk factors with genome-wide association studies, perhaps more attention should be focused on confirming the environmental observations from these animal models in human-based studies, both on observational and interventional levels. Understanding the environmental risk factors with a goal toward modification and prevention may be fruitful in light of medical treatment of both acute and chronic DILI limited by a lack of specific therapies and antidotes currently available; judicious use of a potentially hepatotoxic drug in a patient with underlying risk factors remains the mainstay of DILI management.

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**Box 1****Environmental risk factors for drug-induced liver injury**

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**Intrinsic**

Circadian rhythm

Hepatic clock

Infection

Inflammation

Intestinal microbiome

**Extrinsic**

Alcohol consumption

Regional geographic variation

Smoking

Socioeconomic status

Environmental pollution

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**KEY POINTS**

- In general, human data on the environment and drug-induced liver injury (DILI) are sparse and the majority of understanding is derived from animal studies of both intrinsic and idiosyncratic injury.
- Smoking can induce cytochrome P450 (CYP) enzymes but this does not necessarily translate into DILI.
- Alcohol consumption is a clear risk factor for hepatotoxicity from acetaminophen (APAP) and may predispose to injury from antituberculosis (anti-TB) medications but large international registries have not found an association between excessive alcohol consumption and DILI in general.
- Understanding of the role of infection, proinflammatory states, the hepatic clock, environmental pollutants, and the microbiome in predisposing an individual to DILI is still evolving.