Drug-Induced Hepatic Injury in Newborns and Children in Intensive Care Unit: A Retrospective Study of China

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Research Article

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Abstract

Purpose

Drug-induced liver injury (DILI) is a common adverse reaction in the clinic; however, there are relatively few reports of DILI in critically ill newborns and children. Making use of the Pediatric Intensive Care database (PIC), this study identifies which drugs are related to DILI in neonates and children in China.

Methods

Using the PIC, we screened for patients whose liver was suspected of being injured by drugs during hospitalization. The medicine they used was then assessed by the Roussel Uclaf Causality Assessment Method (RUCAM). We also collated drug combinations that may affect CYP enzyme metabolism, which may be one of the mechanisms that lead to DILI.

Results

A total of 13,449 patients were assessed, of whom 77 newborns and 261 children were finally included. The main type of liver injury in neonates was mixed (83.1%), while children's hepatic injury types were mostly distributed between hepatocellular (59.4%) and cholestatic (28.4%). In terms of the assessment by the RUCAM, in newborns, the drugs that were most considered to cause or associated with hepatic injury comprised medium and long chain fat emulsion (17%), sodium glycerophosphate (12%) and meropenem (9%); while omeprazole (11%), methylprednisolone sodium succinate (10%) and meropenem (8%) are the primary culprit of DILI in children. Drug combinations that may affect CYP enzyme metabolism frequently seen in neonates are omeprazole + budesonide (16.9%), dexamethasone + midazolam (10.4%) and midazolam + sildenafil (10.4%). In children, the commonly used drug combinations are fentanyl + midazolam (20.7%), ibuprofen + furosemide (18.4%) and diazepam + omeprazole (15.3%).

Conclusions

The drugs that have been found to have hepatotoxicity (meropenem, medium and long chain fat emulsion, ibuprofen.etc.) are also related to DILI in newborns and children. When giving these drugs to newborns and children, physicians need to be more cautious. Also, pay attention to the effect on CYP 450 enzymes when using multiple drugs at the same time.

Introduction

DILI is defined as a liver injury caused by various medications, herbs, or other xenobiotics, leading to abnormalities in liver tests or liver dysfunction with the reasonable exclusion of other etiologies [1]. DILI is one of the most common adverse drug reactions, showing elevated serum transaminase and bilirubin

when mild, but causing acute liver failure and even death if it is severe. DILI represents 3.5% of all inpatients due to jaundice [2] and accounts for 11% of the acute liver failure cases in America [3]. According to a recent retrospective study [4], in mainland China, the annual incidence rate of DILI in the general public was estimated to be 23.80 per 100,000 persons, which is higher than that reported in western countries. Regrettably, there is little clinical research data about DILI in newborns or children, and most comes from small-scale clinical observations in China. DILI is an under recognized cause of pediatric liver diseases. Pediatric DILI is relatively rare compared to DILI in adults and is infrequently reported (only 1% of total) as a suspected ADR in children and adolescents [5].

Changes in the activity of hepatic drug enzymes at different stages in neonates and children can affect the metabolism of the drug, thus increasing or decreasing its toxicity. Without a doubt, CYPs are the most significant enzymes of phase I metabolism. These enzymes metabolize 70–80% of drugs in the body, and these enzyme-mediated metabolisms are often the basis for drug interactions [6]. The most important forms of CYPs include CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19,CYP2D6, CYP2E1, CYP3A4, and, in newborns and children, CYP3A7 etc. [7]. Within these, the activities of CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 enzymes differ significantly in neonates, children, and adults, and play a pivotal role in drug metabolism. Thus, we collected information relating to the drugs associated with these six enzymes in patients. When two or more drugs are used together and act on the same enzyme, the metabolism of the drugs can be affected, resulting in accelerated metabolism or accumulation of the medicine, which may cause liver damage.

The increase in the number of newborns and children is an unchangeable outcome of the gradual opening of the Family Planning Policy in China, and especially the comprehensive opening of the Three-child Policy. The incidence of DILI in children has an upward trend as awareness grows. However, the lack of comprehensive information is about DILI in children and newborns in China. Therefore, this study aimed to access information about which drugs may be associated with hepatic injury in the newborn and pediatric population using the PIC.

Methods

Data source

This is a retrospective study. We selected cases from all patients in the PIC database. The PIC database is a large pediatric-specific, single-center, bilingual database containing information relating to children admitted to intensive care unit from 2010 to 2019 at a large children's hospital in Zhejiang, China. The data that is available in the PIC database includes demographic information, laboratory test results, observation program results during the patient's hospitalization, vital signs, drug use records, and structured symptoms recorded while the patient was under supervision. All patients' information, including demographics, laboratory test results, symptoms, and medications, were collected from the PIC database.

Data extraction

We defined newborns as babies aged one to thirty-one days year old. The age range of children was from 32 days to 14 years old. The criteria for liver injury: (1) alanine aminotransferase(ALT) ≥5 times; (2) alkaline phosphatase(ALP)≥2 times of upper limit of normal value (ULN); (3) ALT≥3 ULN and Total bilirubin (Tbil)≥2 ULN [8]. Then, we excluded the patients with known primary liver diseases, such as autoimmune hepatitis, or other diseases that could confound the diagnosis. Hepatic injury was categorized as hepatocellular, cholestatic, and mixed, based on the value of R. The R value is equal to the ratio of serum ALT and its maximum value to ALP and its maximum value. If the R value was ≥ 5, we considered it to be hepatocellular type; if the R value was ≤ 2, we defined the type as cholestatic; if the R value was between 2 and 5, then the type was classified as mixed. After collecting information on all the medicines used by the included patients, we used the RUCAM [9] to evaluate the relationship between the drugs that patients used during the period of hospitalization and their liver injury. RUCAM is the most widely used scale around the world [9, 10], and the RUCAM values were categorized as “highly probable” (≥9), “probable” (6-8), “possible” (3-5), “unlikely” (1-2), or “excluded” (≤0). All evaluations are performed independently by the three authors. The website Hepatoxic (http://www.hepatox.org/) and drug instructions were used as the drug information source to verify the relationship between the drugs and hepatotoxicity.

Combination of CYP metabolizing enzyme-related drugs

After searching the literature for CYP-related drugs, we compared and summarized the following CYP enzymes, which differ in their activities in neonates, children and adults: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. These differences may lead to undesirable consequences on the liver function in neonates and children when some drugs are used in combination. We extracted all relevant drug combinations from all patients’ medication information.

Effect of DILI on length of stay and prognosis

We selected several diseases that occur most frequently in neonates and children with DILI. The length of stay and mortality of patients with DILI under these diseases were then collected and counted, and these were compared with patients who had the same diseases but without DILI in PIC.

Statistical analysis

Values are presented as percentages, medians, or means ±standard deviations. Data with normal distribution were subjected to an independent sample t-test, while data with non-normal distribution were subjected to the Wilcoxon rank sum test for comparison of two independent samples and a chi-square test or Fisher’s exact test for categorical variables. All of the calculations were performed by SPSS 17.0. $p < 0.05$ was considered statistically significant.

Results

The baseline characteristics of DILI

A total of 13,449 patients were assessed during the study, of which 3,075 were newborns and the remaining were children. The flow chart of the case ascertainment of DILI patients is showed in Fig.1.

Table1 shows the characteristics of the study population. In newborns (n=77), the majority of patients were male, with an average age of 8.5 days. The main initial diagnoses were respiratory diseases (22.1%) and digestive diseases (20.8%). The average length of hospitalization days was 56 days. There were 2 (2.6%) patients whose clinical outcome was death. In children (n=261), the proportion of male patients was about half, with an average age of 2.83 years. The main admission diagnoses for children were cardiovascular diseases (15.7%) and respiratory diseases (22.6%), 31(0.12%) of whose clinical outcome was death. The average number of days of hospitalization in children was 30 days. There were 31(11.9%) patients whose clinical outcome was death.

Biochemical abnormalities

Based on the R value, we divided the patients into 3 types. Among newborns, 9.1% were considered hepatocellular, 7.8% were cholestatic, and 83.1% were mixed. Most children were considered hepatocellular (59.4%), with 28.4% cholestatic and only 12.2%mixed. The distribution of liver injury types in newborns and children is distinct (P<0.01). We compared the classification results with other similar studies (Supplementary Table 1), and found that there was some difference. Unlike the critically ill neonates in this study, the distribution of liver injury types in other studies was predominantly hepatocellular. That is to say, the major types of hepatic injury in severely ill newborns in China differ from those in Asian children and adults, as well as from those in American children and adults. Except for the distribution of adult liver injury types in the United States, which had similar proportions of cholestatic and mixed types, the number of patients with mixed types was greater than cholestatic types in all other studies. This is also dissimilar to the distribution of liver injury types in children with severe disease in our study in which the number of cholestatic types was greater than the number of mixed types.

Implicated drugs and causality assessment

The likelihood outcomes of updated RUCAM are presented in Table 2. The mean RUCAM scores are 2.70 in newborns and 2.54 (P<0.01) in children. Among all neonatal cases, 41 cases (53.2%) of DILI causative agents were classified as “highly probable”, and 34 cases (44.2%) were “possible”. Among all children’s cases, 167cases (64%) of DILI causative agents were classified as “highly probable” and 86 cases (33%) were “possible”. The difference in distribution between the two was not significant (P=0.202). The PIC comprises information relating to patients admitted to critical care units, in which the patients usually used more than one single drug. Every newborn used an average of 23 drugs during hospitalization, and almost every child used 26 drugs on average (P=0.124).

Fig. 2 shows the distribution of drugs that caused neonatal DILI. In neonates, a total of 398 drugs were suspected of being responsible for DILI. In newborns, the major categories were nutritional preparation (n=70), followed by antimicrobial (n=67) and gastrointestinal (n=43). Among the nutritional preparations,

the most common agent was medium and long chain fat emulsion (17%), while meropenem (9%) was the main antimicrobial, and sodium glycerophosphate also played an important role (12%).

Fig. 3 shows the drug categories for DILI in children. The numbers of drugs regarded as causative agents was 1,461. Among them, major classes were antimicrobial (n=226), followed by gastrointestinal medication (n=189) and glucocorticoid (n=160). The bulk antimicrobial drug was meropenem (8%), as for the newborns. The main causative gastrointestinal medication was omeprazole (11%), with methylprednisolone sodium succinatealso being a large component (10%). Meanwhile, we couldn't ignore ibuprofen (7%).

In other related studies (Supplementary Table 2), antibacterial drugs, NSAIDs, Chinese herbal medicine, and nutritional preparations are the main implicated classes of agents that cause hepatic injury.

Drug combinations related to CYP450

We collected information on all the drugs related to the six enzymes, CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4 (Table3). During the collection process, we found that there was no combination of drugs related to CYP2D6 and CYP2E1, so these are not reflected in Table3.

In Table5, the drug combinations frequently seen in neonates are omeprazole+ budesonide (16.9%), dexamethasone + midazolam (10.4%) and midazolam + sildenafil (10.4%). In children, the commonly used drug combinations are fentanyl + midazolam (20.7%), ibuprofen + furosemide (18.4%),diazepam + omeprazole (15.3%),omeprazole + budesonide (12.3%),omeprazole + methylprednisolone (9.6%),budesonide + methylprednisolone (8.8%), and fentanyl + methylprednisolone + midazolam (8.8%). It is clear that the combination of drugs in children with severe illness is more numerous and complex.

The impact of DILI on length of stay and prognosis

From the data in table 3, we can see that in the three conditions of neonatal respiratory of neonatal asphyxia, and gastrointestinal dysplasia, DILI significantly prolongs the length of stay and the difference with the non-DILI group is statistically significant. There was no statistical difference in length of stay between the DILI and non-DILI groups for the three diseases of pneumonia, enterocolitis, and congenital heart disease, but it was seen that the median length of stay was greater in the DILI group than in the non-DILI group for all the three diseases. In six diseases including neonatal respiratory distress syndrome, there was no apparent difference between the DILI and non-DILI groups.

In table 4, there is a significant and statistically meaningful difference in the length of stay between the DILI and non-DILI groups in children with pneumonia and congenital heart disease. In terms of mortality, the differences between DILI and non-DILI groups were not statistically significant for any of the four diseases.

Discussion

In this study, we screened the children with DILI in the PIC database in the past ten years, collecting their medication information and evaluating the drugs by RUCAM. In this retrospective, single center study, antibiotics and nutritional preparation agents were considered to be causative drugs of newborns' DILI. Antibiotics and gastrointestinal medicine were found to give rise to children's DILI during hospitalization. Meropenem was the most common individual antibiotics drug. Between the DILI patients of newborns and children, there was not much difference in the peak level of laboratory findings and number of drugs used during hospitalization. Neonates and children varied in the type of DILI. After dividing the patients by R ratio, we found that newborns' DILI were dominant in mixed type, while children were dominant in the hepatocellular type. The distribution of types of liver injury in critically ill children in our study differed slightly from the types summarized in other studies. After collecting information on the drugs associated with important CYP enzymes, we compiled a summary of the combinations that are commonly seen in clinical practice. The combination of these drugs may lead to competition for the same enzyme's site of effect or a conflict of action, which may in turn result in accumulation of the drug and cause liver injury. Finally, we compared the impact of length of stay and prognosis of patients with DILI in some common diseases.

For the first time, we focused on the issue of drug-related hepatic injury in neonates as opposed to children and adults, who are often studied, and also compared the results to children. The neonate is a very special patient population and a unique recipient [11], as a result of immaturity at birth and the daily evolution of many metabolic functions, including drug carriers in blood or the enteric canal, drug metabolizing enzymes in liver cells and renal function. These factors all influence the efficacy and toxicity of medicines [12]. As a consequence of the incomplete maturity of such vital functions at birth, neonates show significant differences in absorption, distribution, metabolism, and excretion, compared to adults [13]. The main types of liver injury in neonates are mixed and cholestatic, which may also be related to the way we currently determine the type of liver injury, using the R value, which is calculated as the ratio of serum ALT and its maximum value to ALP and its maximum value. The laboratory biochemical assessments for DILI including ALP are not quite appropriate in newborns. ALP is expressed in liver tissue and is increased in hepatic dysfunction, but increased serum ALP can also be a result of bone growth and excessive enzyme secretion by osteoblasts [14], which may cause some inaccuracy in our results. The predominant type of liver injury in children was roughly the same as in other studies, with the vast majority being hepatocellular.

In other studies in China [4, 15], the drugs that mainly cause liver damage are Chinese herbs, drugs for tuberculosis, antibiotics, and NSAIDs, and in antibiotics are responsible for most liver damage in studies of other countries [16–18]. In our newborns, the main causes of liver damage are nutritional agents and antibiotics; in our pediatric patients, the main cause is antimicrobials and digestives system drugs. This may be related to the common diseases in critically ill patients. In our study, gastrointestinal and respiratory diseases were common in patients, who required dietary supplements and more advanced antibiotics, also the demand for traditional Chinese herbal medicine would be reduced. Moreover, newborns and children are at an essential period of growth and development, and the diseases of critically ill children often lead to malabsorption of nutrients that affect their development, thus creating a

greater need for nutritional preparations. This result suggests that pediatricians and pharmacists should also pay more attention to the liver function indicators of critically ill newborns and children when using nutritional preparations.

As seen in Tables 4 and 5, the length of hospital stay was remarkably or slightly longer in DILI groups than in non-DILI groups. The treatment of patients with liver protection while not interfering with the treatment of other diseases, or DILI aggravated the pre-existing conditions, which made the treatment of critically ill patients more complicated and prolonged the treatment time. However, we can find that DILI did not dramatically increase the mortality rate of neonates and children with the same disease, which may be due to the following reasons: First, statistical bias caused by the small number of patients in the DILI groups. Then, detection and measures taken by health care professionals to effectively stop the deterioration of the diseases. Finally, the mild degree of DILI is in patients, which didn't cause irreversible and sever damage to liver function.

Although we cannot precisely evaluate the relationship between the drugs and hepatic injury, it is generally perceived that DILI is rare in newborns and children. They use fewer medicines that are well known to induce hepatotoxicity, often for a much shorter duration [19].

It is noteworthy that chronic liver injury did not develop in any of our patients, and the mortality was lower than 1% in both neonates and children. The death cases all died of other etiologies, such as organ dysfunction or tumor, which means that hepatitis and liver injury did not have much to do with the death in these cases. Most patients with DILI were expected to recover or improve their condition after withdrawing the suspected drug and beginning supportive treatment.

According to our statistics, newborns and children both used at least five and more medications during their hospitalization. The concomitant use of drugs acting on the same enzyme can have some impact on drug metabolism and excretion, and may also be implicated in liver damage. Hines et al. suggested that there are three patterns of the developmental expression of CYP450: 1. Expression in the fetal liver, decreasing gradually with gestational age (e.g., the subtype CYP3A7); 2. Expression begins in the early neonatal period (e.g., CYP2D6 and CYP2E1); 3. Expression starts in late neonate development (e.g., CYP1A2 and CYP3A4) [20]. The most abundant is enzyme in the human liver is CYP3A4, which is widely considered to be involved in the metabolism of more than half of medicines [21]. CYP3A4 activities in the liver of neonates are much lower than in adults, resulting in lower metabolism and clearance of antibiotics, antiviral, hormones, and other drugs in the liver, and the easy accumulation of drugs [22]. After birth, CYP1A2 activity towards its substrates, caffeine and theophylline, is low but reaches adult levels at 4–5 months [23]. One of the substrates of CYP2E1is acetaminophen and, if glutathione is depleted, the enzyme irreversibly damages the liver tissue [24]. The amount of this enzyme increases rapidly after roughly three months [25]. Co-administration of the same substrates of CYP2E1 was not found in this study. Neonatal CYP2D6 activity is only about 3–5% of that of adults, resulting in less hepatotoxicity metabolites being converted when substrates are ingested and a lower incidence of DILI than in adults [26]. Typical substrates for CYP2C9 and CYP2C19 include NSAIDs, sartans, proton pump inhibition,

warfarin and propranolol. At around five months of age, about half of children reach adult levels [25]. That is to say, most enzyme activities in newborns and some children are lower than in adults. From the results of Table 3 we could also find many drugs related to DILI that were summarized in this study, such as omeprazole and budesonide, which are frequently seen in neonatal species, like midazolam and ibuprofen which are commonly seen in children, especially when multiple drugs with the same metabolic enzymes are combined at the same time, which can significantly affect drug metabolism and may cause drug accumulation thus liver damage.

Our study has several limitations. First, it is a retrospective and single center study, which means a smaller sample size. Second, due to the lack of thresholds of hepatic injury in newborns and children, we refer to the DILI standard for adults, which may lead to the deviation in the screening results. Third, subjective bias existed when the drugs were assessed by RUCAM. Throughout the study, most of the research focused on DILI in patients during hospitalization [18, 27];thus, our research on outpatients is deficient.

Due to the particularity of neonates and children, they are seldom of concern in DILI. However, DILI is a potential but preventable cause of hepatic injury, drug interactions in combination with multiple drugs are also a problem that cannot be ignored, and more accurate standards of diagnosis and higher attention are urgently needed in DILI in neonatal or children.

Conclusion

With the ultimate aim of decreasing DILI cases of newborns and children, we screened patients and assessed the relationship between patients and suspected drugs, using the PIC database. We have summarized the drugs that cause liver damage in newborns and children. We hope these results can give physicians and pharmacists some reference when administering medication to newborns and children to try to avoid adverse reactions.

Declarations

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Conflicts of interest

The authors declared that there is no conflict of interest.

Ethics approval and consent to participate

The data used in this study were de-identified according to the Health Insurance Portability and Accountability Act (HIPAA) criteria and Accountability Act (HIPAA) criteria. Therefore, the statement of ethical approval and informed consent from the Institutional Review Board was waived for this study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are available in the Pediatric Intensive Care (PIC) database repository, http://pic.nbscn.org/

Authors' contributions

LY, Chengxian Guo, GY and QH contributed to the study design, data analysis and manuscript writing. ZF, LH, XW and Chengjun Guo contributed to data analysis and data extraction. XW, WF, YW and XW contributed to data extraction and manuscript revision. BH, TL, and LH contributed to manuscript revision. All authors read and approved the final manuscript.

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Tables

Due to technical limitations, table 1,2,3,4 is only available as a download in the Supplemental Files section.

Figures

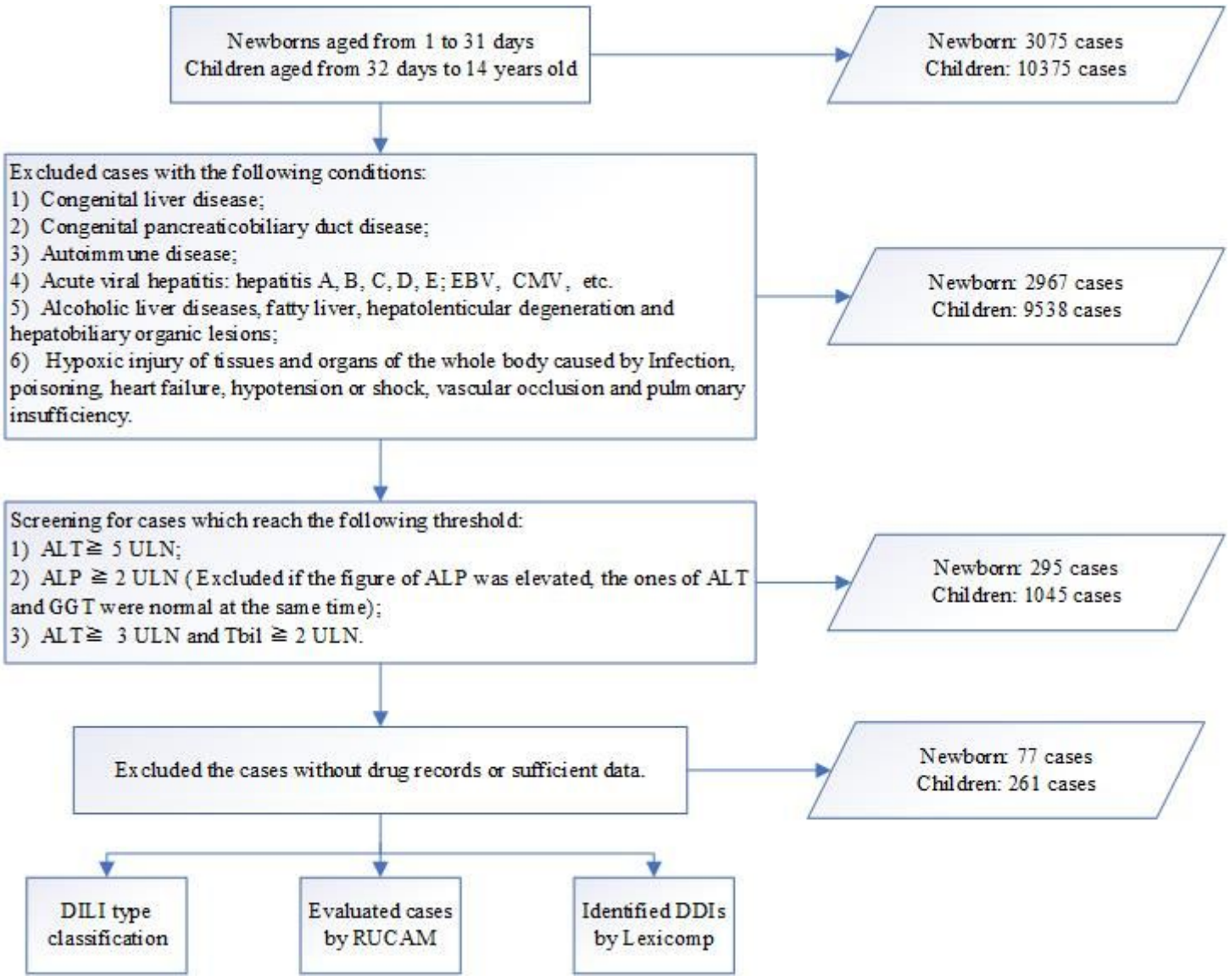

Figure 1

Workflow for diagnosis, classification and evaluation of drug-induced liver injury (DILI). ALT, alanine transaminase; ALP, alkaline phosphatase; Tbil, total bilirubin; ULN, upper limit of normal; RUCAM, Roussel Uclaf Causality Assessment Method; DDIs, drug-drug induced interactions.

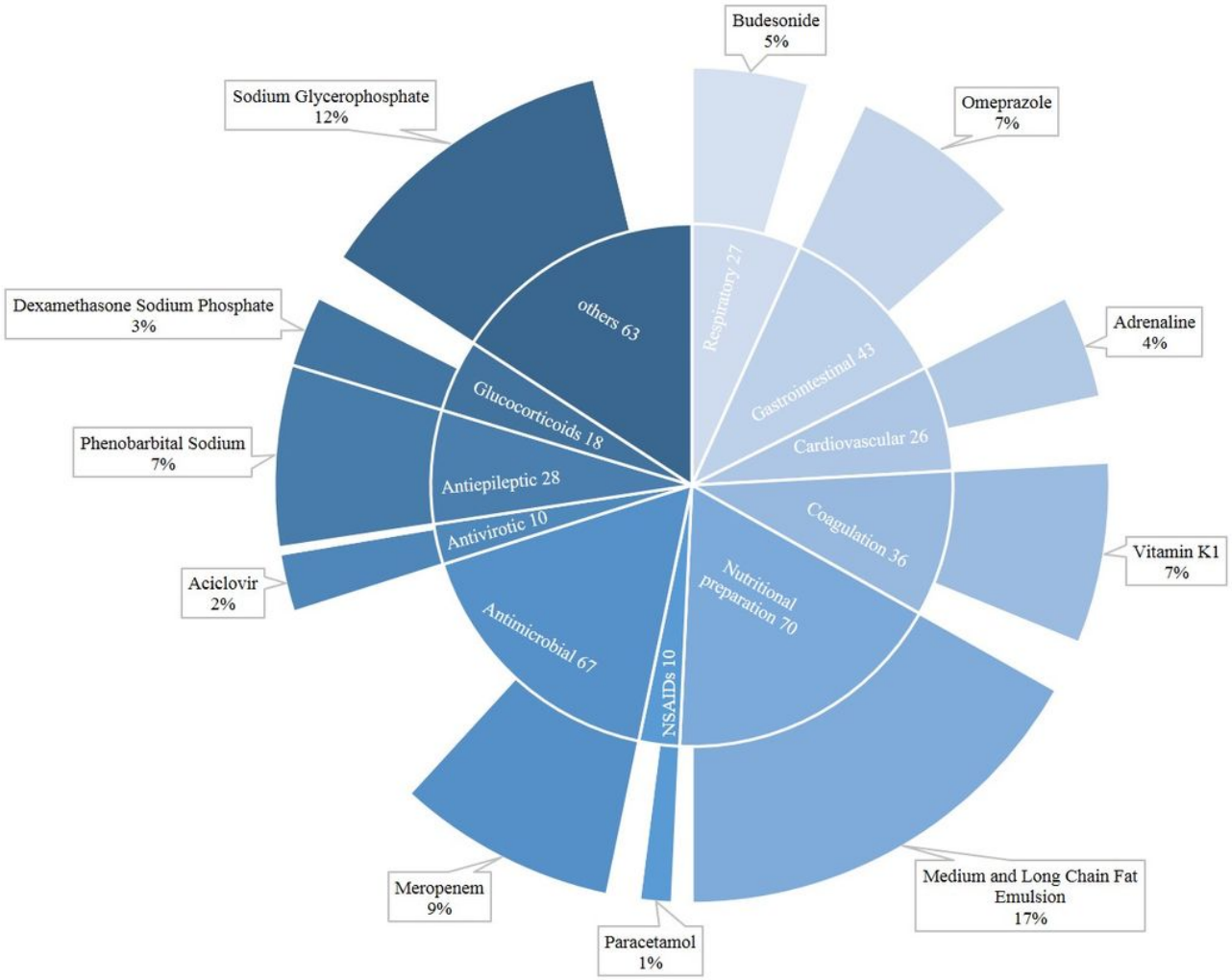

Figure 2

Drug categories for neonatal drug-induced liver injury.

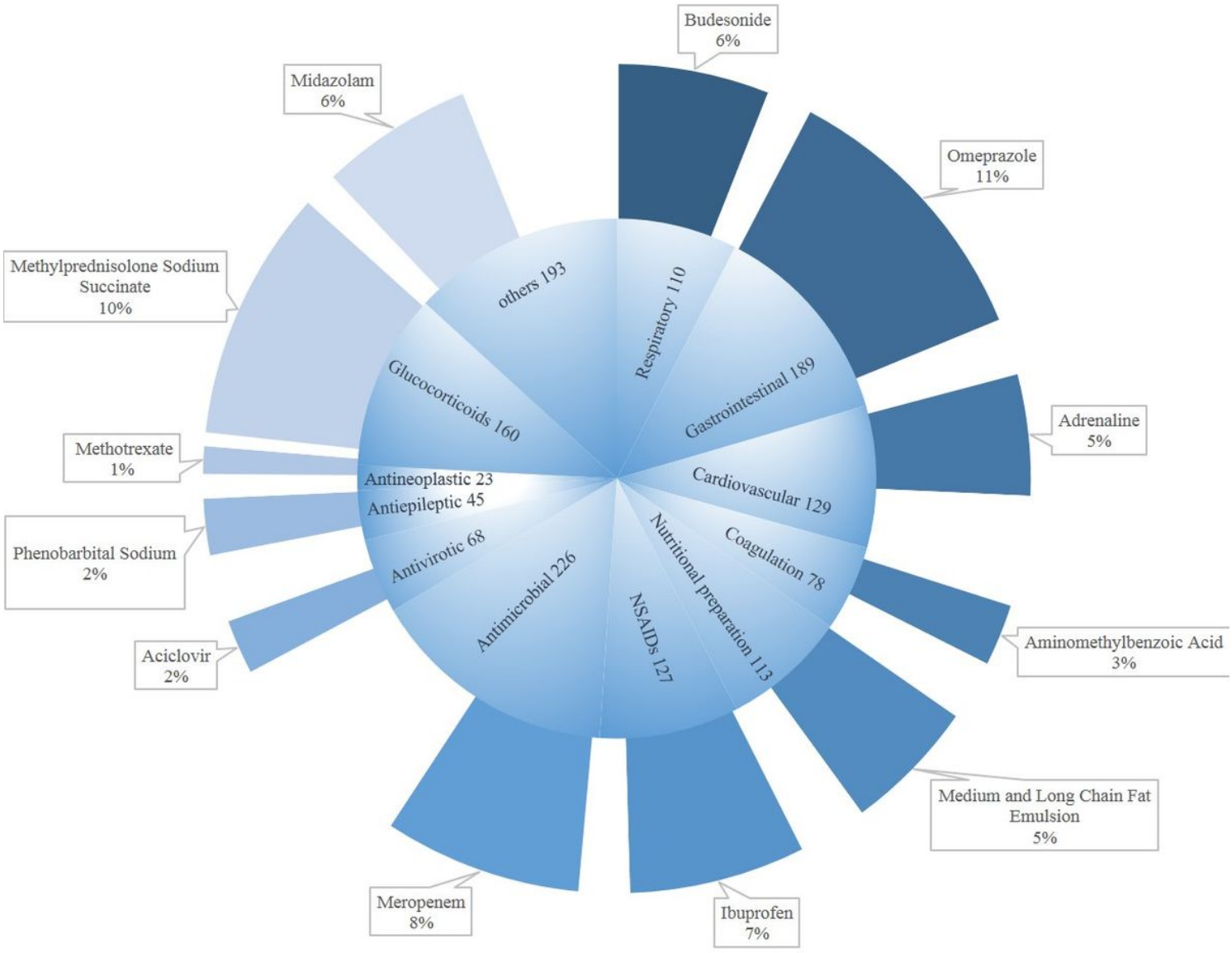

Figure 3

Drug categories for DILI in children.

Supplementary Files

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