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Acetaminophen for the Patent Ductus Arteriosus: Has Safety Been Adequately Demonstrated?

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Abstract

Patent ductus arteriosus (PDA) is the most common cardiovascular condition diagnosed in premature infants. Acetaminophen was first proposed as a potential treatment for PDA in 2011. Since that time acetaminophen use among extremely preterm neonates has increased substantially. The limited available data demonstrate that acetaminophen reduces PDA without evident hepatotoxicity. These findings have led some to suggest that acetaminophen is a safe and effective therapy for PDA closure. However, the lack of apparent hepatoxicity is predictable. Acetaminophen induced cellular injury is due to CYP2E1 derived metabolites; and hepatocyte CYP2E1 expression is low in the fetal and neonatal period. Here, we review preclinical and clinical data that support the hypothesis that the lung, which expresses high levels of CYP2E1 during fetal and early postnatal development, may be particularly susceptible to acetaminophen induced toxicity. Despite these emerging data, the true potential pulmonary risks and benefits of acetaminophen for PDA closure are largely unknown. The available clinical studies in are marked by significant weakness including low sample sizes and minimal evaluation of extremely preterm infants who are typically at highest risk of pulmonary morbidity. We propose that studies interrogating mechanisms linking developmentally regulated, cell-specific CYP2E1 expression and acetaminophen-induced toxicity as well as robust assessment of pulmonary outcomes in large trials that evaluate the safety and efficacy of acetaminophen in extremely preterm infants are needed.

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Keywords

CYP2E1; acetaminophen; paracetamol; bronchopulmonary dysplasia

I. Introduction

Patent ductus arteriosus (PDA) is the most common cardiovascular condition diagnosed in premature infants.[1] The incidence of PDA is inversely related to gestational age at birth and can be detected by echocardiography at two months of age in over 50% of infants born less than 26 weeks' gestation.[2] In hopes of avoiding serious morbidities associated with PDA, including bronchopulmonary dysplasia (BPD) and necrotizing enterocolitis, clinicians have sought safe and effective ways to close the PDA via pharmacological or procedural intervention.[3] Since the 1970s, non-steroidal anti-inflammatory drugs (NSAIDs) have been the most common medications used to treat the PDA.[1,4] These drugs inhibit cyclooxygenases, which decrease prostaglandin production and facilitate ductal constriction. Unfortunately, randomized trials have not demonstrated consistent respiratory and long-term neurologic benefit with these medications and evidence indicates they are associated with unwanted adverse drug effects that may negate the potential benefits conferred by earlier ductal closure.[3]

Not surprisingly, there has been interest in identifying safer, alternative treatments for PDA. A case series published in 2011 reported the "incidental observation" that a persistent, hemodynamically significant PDA closed after acetaminophen was administered "for unrelated reason" to 17-day old infant born at 26 weeks' gestational age.[5] In total, the authors described a similar relationship in 5 preterm neonates.[5] Since this initial case series, the use of acetaminophen to treat the PDA has increased substantially and has been identified as a "promising alternative to indomethacin and ibuprofen with a better safety profile."[6] However, pre-clinical and epidemiological data raise concern that the use of acetaminophen to treat PDA may carry risks and that the assumption of drug safety may be premature. In this commentary, we review recent clinical data characterizing the use and outcomes associated with acetaminophen administration in premature infants and highlight the results of pre-clinical studies that point towards potentially important but under evaluated mechanisms of adverse pulmonary drug effects with acetaminophen use in extremely preterm infants.

II. Increasing frequency of acetaminophen use in preterm infants

Since early reports temporally linking acetaminophen administration with closure of the PDA, acetaminophen has become one of the most frequently prescribed medications in neonatal intensive care units (NICU) worldwide. In NICUs managed by the Pediatrix Medical Group, acetaminophen had the eighth highest absolute increase in use relative to other common medications between the years 2010 and 2017.[7] In NICUs in the United Kingdom (UK), acetaminophen demonstrated the fifth highest absolute increase in use during the same time frame.[8] In French Level 3 neonatal wards in 2017–18, only vitamin supplementation exceeded acetaminophen use, with approximately 65% of infants born

less than 27 week's gestation receiving acetaminophen therapy.[9] In the international PDA-TOLERATE trial, acetaminophen was chosen by clinicians as the first line therapy in 26% of extremely preterm infants who were randomized to early drug treatment.[10] Data from an Italian multicenter report indicate acetaminophen was used to treat PDA in 24% of infants born at 25–28 weeks' gestational age and 47% of those born at 23–24 weeks' gestational age.[11] Lastly, survey of clinicians in Australia, New Zealand, and the UK suggest that 70–80% of neonatologists in those countries have prescribed acetaminophen to treat PDA.[12,13]

III. Is acetaminophen effective for PDA closure?

Multiple small, randomized trials have evaluated the efficacy and tolerability of acetaminophen for PDA closure in preterm or low-birth-weight infants. A Cochrane systematic review published in 2022 summarized the data from 27 studies that enrolled a total of 2278 infants.[14] Multiple comparisons were conducted including acetaminophen versus ibuprofen, acetaminophen versus indomethacin, and acetaminophen versus placebo or no intervention. Of these comparisons, acetaminophen versus placebo or no intervention included the fewest number of infants (3 studies, 240 infants). When compared to placebo/no intervention, infants who received acetaminophen were less likely to have a PDA detected by post-treatment echocardiography (16.8% vs. 61.1%, relative risk 0.27, 95% CI 0.18–0.42). Acetaminophen had similar efficacy for preventing subsequent PDA when compared to ibuprofen (18 trials, 1535 infants; rates of treatment failure: 30.3% vs 30.1; RR 1.02, 95% CI 0.88–1.18) and indomethacin (4 trials, 380 infants; rates of treatment failure 29.8% vs. 29.7%; RR 1.02, 95% CI 0.78–1.33). The authors concluded that the available data provided moderate-certainty evidence that acetaminophen and ibuprofen have similar effectiveness for PDA closure, but low-certainty evidence for the other comparisons.

The mechanism of action of acetaminophen to achieve PDA closure is not fully understood. Parts of its activity mimic that of COX-2 selective inhibitors indicating that acetaminophen, similar to NSAIDs, may decrease prostaglandin production.[6,15] With the increasing use of acetaminophen in premature infants and growing evidence that it may achieve similar rates of PDA closure, it is essential to consider whether acetaminophen is truly a safer alternative.

Iv. Is acetaminophen safe to use for PDA closure?

At present, it is unclear whether acetaminophen provides a more favorable safety profile than alternative treatment options. Several limitations in the current data contribute to this uncertainty. Firstly, the available individual trials have been small; the largest reported outcomes for only 200 participants.[14] Secondly, most trials included relatively few infants born less than 28 weeks of gestation, the population that is most likely to be treated for a PDA and potentially most vulnerable to adverse drug effects. Lastly, there is inconsistent reporting of key neonatal outcomes, particularly related to organ systems that might be vulnerable to acetaminophen toxicity. The sections that follow discuss pre-clinical and clinical studies that raise important safety considerations with acetaminophen use in preterm infants.

Is hepatotoxicity the most relevant safety measure in neonates?

The risk of hepatoxicity with excess acetaminophen exposure in children and adults is well-established. In the pediatric population as a whole, acetaminophen overdose is a leading cause of hepatic failure.[16–18] Likely motivated by this known association, trials of acetaminophen therapy for PDA closure in preterm infants have frequently assessed hepatic injury by monitoring serum alanine and aspartate transaminases.[14] However, unlike in older children, acetaminophen-induced hepatotoxicity is rare in the neonatal period.[19,20] As per one recent report, "clinical evidence shows a low or absent hepatic toxicity in neonates, suggesting the existence of a large therapeutic serum concentration range for paracetamol."[21] Understanding the mechanisms underlying acetaminophen-induced hepatoxicity helps explain why this injury is uncommon in newborns.

Acetaminophen toxicity is dependent on cell-type specific expression of the xenobiotic enzyme CYP2E1 (Fig. 1). In adults, hepatic glucuronyl transferases and sulfotransferases convert 80–90% of acetaminophen into non-toxic metabolites.[21–24] Pericentral hepatocytes express CYP2E1 and convert the remaining small percentage of acetaminophen into the toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI). Available glutathione stores readily inactivate this toxic metabolite. However, when these normal metabolizing pathways are saturated and glutathione is consumed, accumulating NAPQI binds to various proteins resulting in mitochondrial dysfunction and cell death. In adults, pericentral hepatocytes express the highest level of CYP2E1, which explains why these cells are the most sensitive to acetaminophen overdose and the zone-specific pattern of resulting hepatotoxicity (Fig. 2).[25,26]

The finding of low hepatic expression of CYP2E1 in the fetus and neonate is consistent across multiple species including humans.[27–31] In preclinical studies, neonatal animals demonstrate resistance to acetaminophen-induced hepatic injury.[32,33] In a similar manner, hepatotoxicity is rarely reported in human neonates following supratherapeutic acetaminophen exposures.[19] While these findings indicate acetaminophen is unlikely to result in hepatotoxicity when used in the neonatal period, they also demonstrate that hepatic expression of the enzyme responsible for acetaminophen-induced cell injury – CYP2E1 - is dynamic during fetal and postnatal development. Thorough examination of whether other cell types express CYP2E1, and whether that expression is dynamic during development may help identify cell populations at risk of acetaminophen-induced injury and inform clinical assessment of acetaminophen safety.

Pulmonary CYP2E1 expression – a potential mechanism of acetaminophen toxicity in the neonate?

In addition to expression within the liver, it is well recognized that CYP2E1 is present within the pulmonary epithelium, club cells, and macrophages of the adult lung.[34,35] These findings suggest a mechanistic framework underlying the observation that *lung injury* is a consistent, co-occurring finding with hepatotoxic acetaminophen exposures in rodents.[19,20,36–41] Moreover, there is evidence that pulmonary injury occurs independent of hepatic injury. Following toxic acetaminophen exposure, glutathione depletion and acetaminophen-adduct accumulation occurs in the adult murine lung.[36,41–44] Direct

administration of acetaminophen or intratracheal NAPQI injures alveolar epithelial cells in culture and in the *in-vivo* lung, respectively.[45–47] Furthermore, pulmonary injury occurs even when hepatic injury is mitigated.[38–40,48,49] These observations had previously been limited to adult rodents *following hepatotoxic exposures*. We recently demonstrated that the adult murine lung is susceptible to acetaminophen-induced injury even in the absence of hepatotoxicity.[48] Potentially more relevant to preterm infants, we have now shown that the murine lung in the early alveolar stage of development (equivalent to late preterm or term gestation in human infants) is similarly susceptible to injury with acetaminophen exposures that do not cause hepatotoxicity.[50]

Until recently, the pulmonary expression profile of CYP2E1 during lung development was not known. However, new data demonstrate dynamic, developmentally-regulated and pulmonary cell type specific expression of CYP2E1. Data from the Molecular Atlas of Lung Development Program (LungMAP) indicate that CYP2E1 expression exhibits two peaks during murine lung development: one at embryonic day 18 during the saccular stage of lung development, and one at postnatal day 14, during the second phase of murine lung alveologenesis.[51] These data have been confirmed in a recent single-cell atlas of mouse lung development and in a single-cell analysis of mouse lung fibroblasts.[52,53] Of note, lung mesenchymal myofibroblasts characterized by *Pdgfra* (platelet derived growth factor receptor alpha) expression[54–56] are potentially susceptible to APAP exposure based on their expression of CYP2E1. These cells are abundant in the developing murine lung (Fig. 3) and multiple studies have demonstrated that disruption of *Pdgfra* signaling or myofibroblast function during lung development results in abnormal alveolar formation characterized by simplification and loss of surface area for gas exchange, a common histological phenotype observed in preterm infants with BPD.[54,57–60] Lastly, data from the lungs of human neonates born at 30 weeks' gestational age also demonstrate lung mesenchymal cell expression of CYP2E1 expression.[61–63] Collectively, these suggest a potential mechanism by which acetaminophen use could contribute to lung injury in preterm infants. However, it is unknown whether acetaminophen exposures that occur during periods marked by high mesenchymal myofibroblast specific CYP2E1 expression result in cellular dysfunction and abnormal lung development in humans.

Is there clinical evidence of adverse effects of acetaminophen exposures during human development?

Although large-scale use of acetaminophen in the preterm population is a relatively new phenomenon, there has been long-standing use of this therapy in other potentially at-risk populations. In recent years, closer examination of the potential adverse effects of acetaminophen exposure have prompted renewed interest in studying the safety of this drug therapy. For instance, acetaminophen use during pregnancy became commonplace in the 1970s and 80s and now occurs in 60–70% of pregnancies in US.[64] Clinical studies in the 1970s of *in utero* exposures confirmed a lack of teratogenicity,[65] and use quickly became regarded as safe[66] and "recommended, without reservation, in standard therapeutic doses during pregnancy."[67] Unfortunately, preclinical studies examining the impact of acetaminophen exposures during pregnancy on fetal development at that time were sparse, and limited to the assessment of the placenta and fetal "growth" (i.e., weight),[68]

and fetal hepatic glutathione consumption.[69] However, emerging clinical data from large epidemiological registries have raised concern that perinatal exposure to acetaminophen may be harmful to the developing offspring. Owing to observations such as this as well as the potential links between acetaminophen and endocrinologic and neurologic morbidity in offspring, one expert panel recommended that women should be cautioned at the beginning of pregnancy to avoid acetaminophen unless it is “medically indicated” and that the lowest effective dose should be used for the shortest possible time.[70] The precautionary conclusions reached by these authors, which are based on observational data and lack mechanistic relationships have been criticized by multiple groups, including the Society of Obstetricians and Gynaecologists of Canada,[71] the American College of Obstetricians and Gynecologists,[72] and the European Network of Teratology Information Services.[73] Greater research in this area will support evidence-based use of acetaminophen in pregnant mothers.

The possibility of adverse respiratory effects with acetaminophen exposure during fetal development and in early childhood has been previously explored. The first clinical evidence that routine acetaminophen use may affect pulmonary outcomes emerged in the early 2000s. During this period, Shaheen and colleagues published a series of manuscripts that demonstrated significant adverse associations between acetaminophen exposure and the development of asthma in children and adults.[74–76] A recent metanalysis comprised of 13 studies and over 1 million subjects found that “prenatal paracetamol exposure could increase the risk of child asthma (OR = 1.19; 95% CI, 1.12–1.27).”[77] Similarly, early childhood acetamionophen exposure has been linked to the development of asthma.[78] Whether this association represents a causal relationship continues to be debated, in part because pre-clinical studies have not yet linked acetaminophen exposure to an allergic or asthmatic phenotype.[79] Notably, these studies were motivated by pre-clinical observations which showed that acetaminophen depletes pulmonary glutathione stores and thus potentially increases susceptibility to oxidant and inflammatory stress.[36,41–44] This demonstration of pre-clinical findings supporting subsequent clinical work provides a useful example that may inform future studies on the safety of acetaminophen in extremely preterm infants.

Is there clinical evidence from randomized trials that acetaminophen for PDA adversely impacts lung development or function in preterm infants?

It is largely unknown whether acetaminophen use contributes to poor pulmonary outcomes in preterm infants. BPD is the most commonly reported pulmonary outcome in trials evaluating acetaminophen to treat PDA. However, the inclusion of this outcome has been inconsistent and might have been motivated more by hopes of observed benefit from ductal closure rather than concerns related to drug toxicity. Among the 27 trials included in the 2022 Cochrane review on acetaminophen for PDA closure in preterm infants, only 15 reported BPD as an outcome and only 8 specified which definition or diagnostic criteria were used for BPD (Table 1). Moreover, only 5 of the 15 trials that reported BPD as an outcome enrolled subjects born less than 28 weeks’ gestational age.[80–84] As a result, the risk of BPD following acetaminophen therapy for PDA has been assessed in randomized trials enrolling fewer than 125 subjects born extremely preterm. None of the few trials that included long-term follow-up assessed pulmonary outcomes.[85] This small amount of data

precludes any clear conclusions regarding the potential risk of adverse pulmonary effects with acetaminophen exposure.

Do data from observational studies raise concern that acetaminophen for PDA may adversely impact lung development or function?

Case series and cohort studies examining acetaminophen use have included larger numbers of high-risk extremely preterm infants. Unfortunately, similar to the trial data, the majority of these studies did not report pulmonary outcomes and many are underpowered to detect potential harm.[19] Among those that evaluated the incidence of BPD, some suggested that acetaminophen may be associated with increased risk of BPD, observing statistically significant differences or large albeit non-significant increases in BPD rates.[86–88] However, these findings conflict with other observational studies which found no association between acetaminophen therapy and BPD.[89–91] Additionally, data from the Experiences in Timing and Choices for Ductal Closure in Patent Ductus Arteriosus (INTERPDA) Study Online Registry (Turkey) demonstrated significant differences in rates of death or BPD in infants treated with ibuprofen (IV/PO) or APAP (IV/PO), with the highest rates recorded in the group exposed to IV APAP ($p<.04$).[92] Higher rates of BPD have also been observed following administration of multiple rounds of continuous intravenous (IV) infusion (54.4%) compared to IV bolus (26.1%, $p<0.001$).[93] As with all observational data, these studies may be subject to bias and unmeasured confounding. Nonetheless, the possible increased risk of BPD observed in some of these reports is hypothesis generating and supports further unbiased investigation of pulmonary outcomes following acetaminophen therapy.

Do data from studies comparing different acetaminophen treatment regimens for PDA suggest potential harm with increased exposure?

A single center randomized non-inferiority trial conducted in infants born less than 30 weeks' gestational age (n=102) compared outcomes among those who received conventional (15 mg/kg q6 × 5 days) versus low dose (10 mg/kg q6 × 3 days) acetaminophen.[94] Rates of treatment failure (continued PDA) were similar between the groups, but BPD at 36 weeks' PMA was more common among those assigned to conventional versus low dose therapy (46% vs. 35%).[94] Although this finding was not statistically significant ($p=0.28$),[94] a true risk difference of 11% would be consistent with clinically significant harm and suggest a worrisome dose-response relationship. Higher rates of BPD have also been observed following administration of multiple rounds of continuous intravenous (IV) infusion compared to IV bolus.[93] Of note, the infants who received continuous IV infusion, despite receiving a significantly higher cumulative dose of acetaminophen, had lower rates of PDA closure.[93] The extent to which more frequent treatment failure or increased acetaminophen exposure may have contributed to the higher rates of BPD is unknown.

Similar hypothesis generating data have been reported with IV comparted to enteral dosing. In contrast to enteral dosing, IV administration avoids hepatic first-pass metabolism and may increase direct exposure of pulmonary CYPE1 expressing cells to APAP. If a consistent signal for harm with IV vs. PO exposure is observed, further work is justified to interrogate this potential relationship. One study that was underpowered to detect potential harm demonstrated that rates of BPD were 85% after IV therapy compared to 73% with enteral

therapy, but the difference was not statistically significant (p=.67).[95] Regardless, these few dose and route comparison studies highlight the need for more robust pharmacokinetic and pharmacodynamic analyses of acetaminophen in extremely preterm infants. Lastly, a recent report indicated acetaminophen exposure may acutely increase pulmonary vascular resistance in premature infants.[96] This finding requires confirmation in future studies, but raises the possibility of additional mechanistic contributors that may affect cardiopulmonary function in extremely preterm infants. .

VI. Remaining questions: issues unique to acetaminophen exposures in the NICU

Neonatologists have brought acetaminophen to the NICU and increased exposures among high-risk infants despite the absence of robust safety data. Several factors unique to the preterm population that potentially increase the toxicity of acetaminophen exposures have thus far not been considered. Many, if not all, neonates receiving acetaminophen to treat PDA are simultaneously treated with supplemental oxygen and are at risk for associated oxidative stress.[97] This exposure may increase mitochondrial dysfunction and deplete the already limited pulmonary glutathione stores present in the preterm lung.[98] Whether these factors act to increase sensitivity to NAPQI mitochondrial toxicity, and limit the ability to detoxify CYP2E1-derived acetaminophen metabolites is unknown.

The clinical implications of acetaminophen metabolism that are unique to the preterm population remain relatively unexplored. Acetaminophen metabolites in neonates born less than 32 weeks' gestational age exposed to 10, 15, or 20 mg/kg IV dosing have been reported.[99] In these neonates, levels of CYP2E1-derived APAP metabolites were significantly higher than in similarly exposed adults.[99] Elevated levels of the same CYP2E1-derived metabolites have been detected in neonates following supratherapeutic exposure to acetaminophen [(200 mg/kg x 4;[100] 600 mg/kg x 1[101]] who did not develop detectable hepatotoxicity. In the absence of clinically obvious hepatotoxicity, these findings may be indicative of extra-hepatic CYP2E1 expression, acetaminophen metabolism and potential cellular toxicity is unknown. Whether these metabolites are derived from developmentally-regulated, cell-type specific expression in the brain, kidney, or lung remains to be determined.

VII. Conclusions

Acetaminophen exposures in the high risk, extremely preterm population are rapidly increasing. This practice change may carry unanticipated adverse effects. The available randomized trials and observational studies examining the safety and efficacy of acetaminophen to treat the PDA are marked by significant weakness including low sample sizes, potential bias, and lack of representation of the smallest and sickest infants at the highest risk of pulmonary morbidity. Although some observational data raise concern for potential increase in risk of BPD with acetaminophen therapy, it is unclear whether this represents a true causal relationship or is attributable to unmeasured confounding. While this review has been focused on acetaminophen for PDA, its use as an analgesic for preterm infants is also increasing and the pulmonary implications of these exposures similarly

deserve further study. Indeed, a recent a large single center report found that that rates of grade 3 BPD increased significantly following implementation of routine IV acetaminophen administration to treat pain and discomfort associated with NICU care.[102]

Preclinical data that support the safety of acetaminophen are lacking. The absence of observed hepatoxicity with acetaminophen use in preterm infants is reassuring, but is predictable given the results from preclinical studies and what is known about developmentally regulated hepatic CYP2E1 expression. Concerningly, however, the preclinical data point to the lungs of preterm infants as a particular site of potential acetaminophen induced injury. Moreover, the outcome of BPD, which is one of the few pulmonary outcomes that has been assessed after acetaminophen therapy in extremely preterm infants, provides incomplete insight into potential adverse drug effects predicted by the preclinical models. Studies interrogating potential mechanisms linking cell-specific CYP2E1 expression and acetaminophen-induced toxicity and robust assessment of pulmonary outcomes measured both before and after when BPD is diagnosed must be performed in large scale trials evaluating the safety and efficacy of acetaminophen in extremely preterm infants. Such efforts will ensure a thoughtful and thorough research approach to understanding the safety and efficacy of acetaminophen in our most vulnerable patients. Fortunately, large clinical trials of acetaminophen for PDA closure in high-risk preterm neonates are ongoing. These studies will hopefully provide meaningful data on the risks and benefits of this increasingly used but incompletely studied therapy.[103,104]

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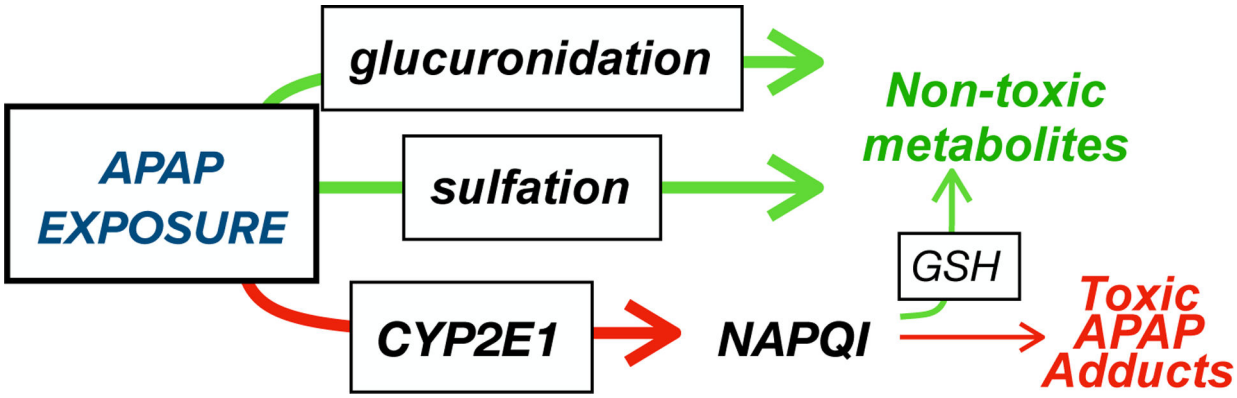

Fig. 1 -
Acetaminophen metabolizing pathways

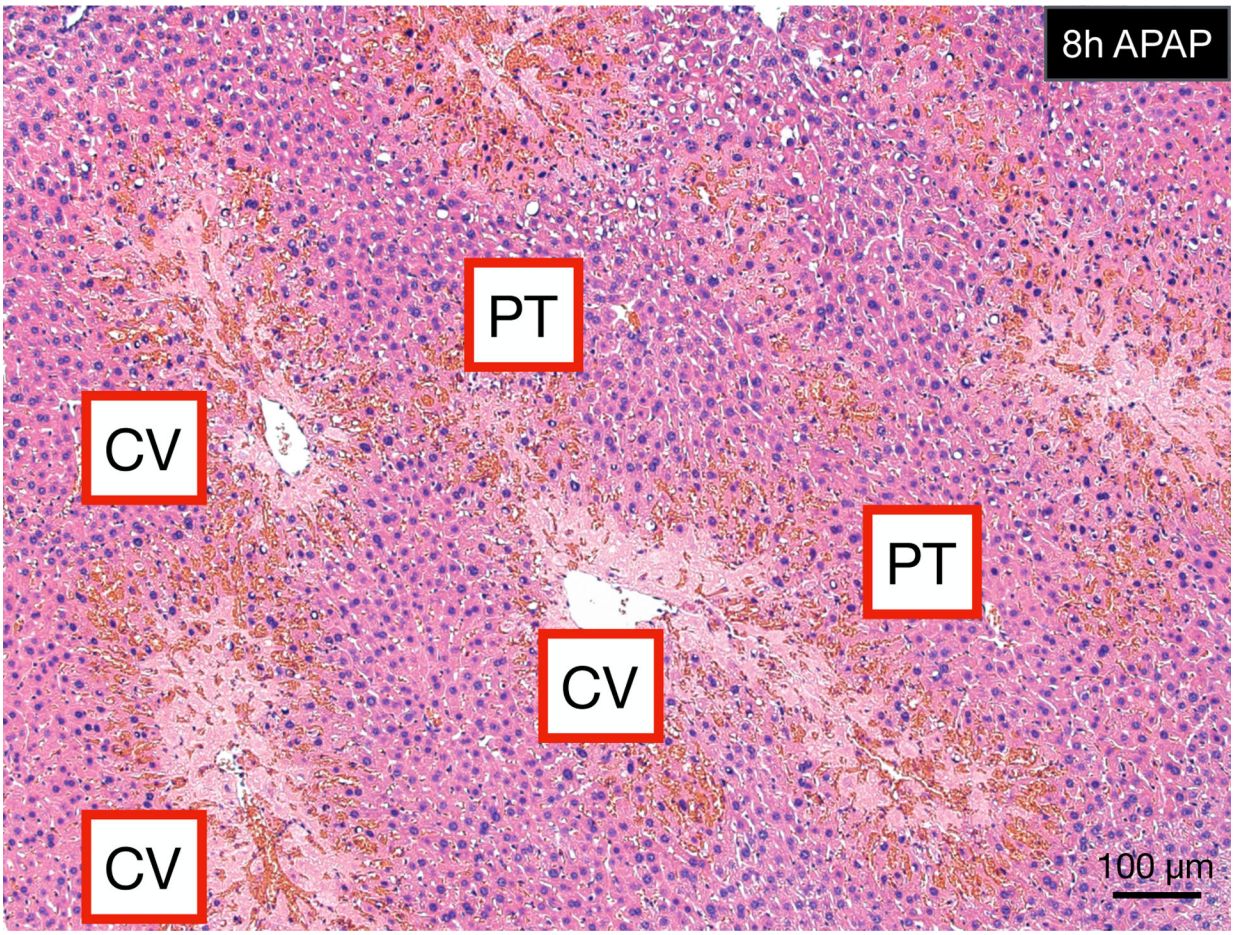

Fig. 2 -

Zonated pattern of hepatocyte injury after toxic acetaminophen exposure. This is a representative H&E stained hepatic section from an acetaminophen exposed (2, 8 and 24 hours; 280 mg/kg, IP) adult male ICR mouse. Areas of necrosis and sinusoidal dilution are located around the central vein (CV) while hepatocytes around the portal triad (PT) are spared. Internal scale bar 100 µm.

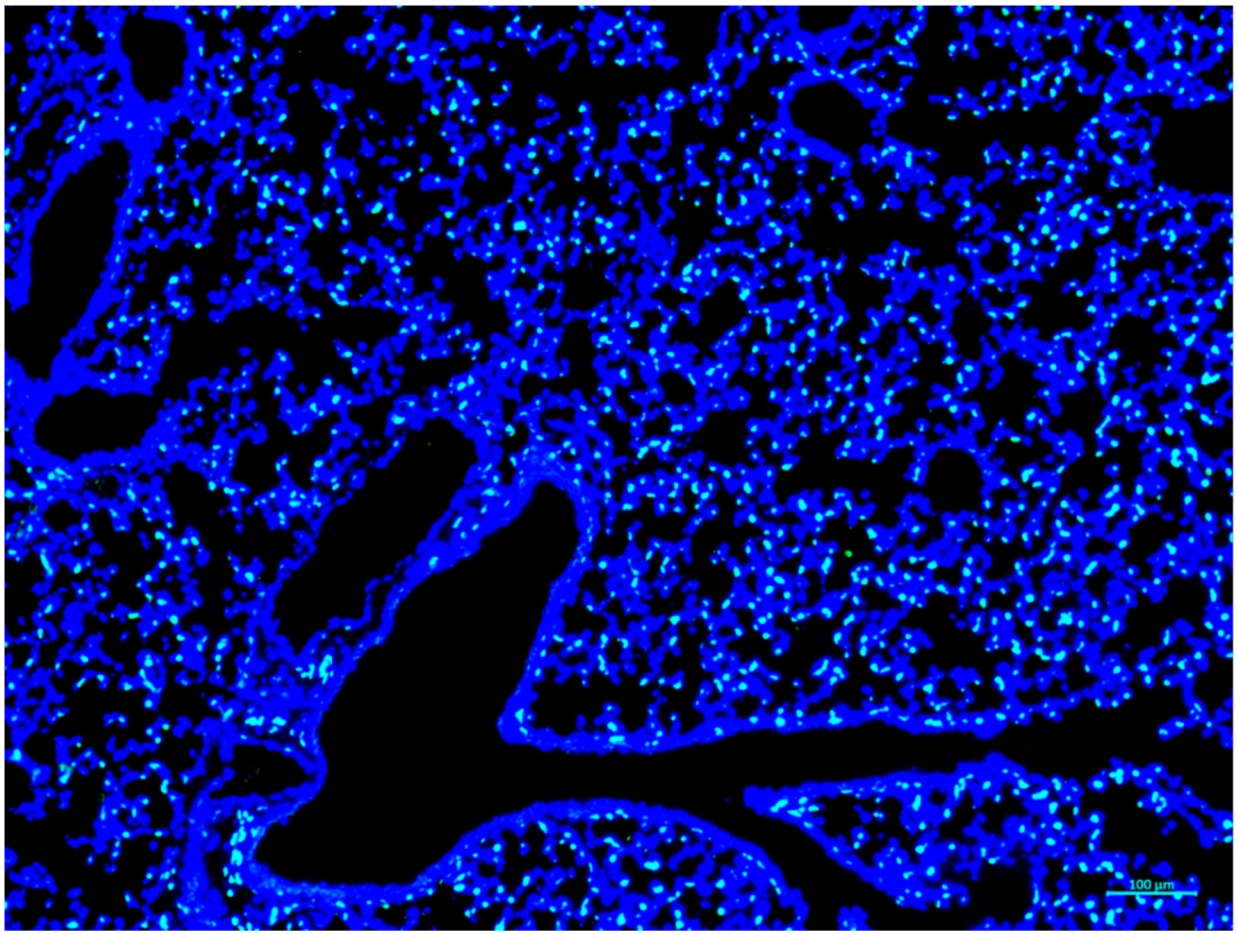

Fig. 3 -

Pdgfr-α positive cells are present throughout the developing murine lung. Representative image of lung tissue isolated from a 14 day old, alveolar stage Pdgfrα-GFP mouse. In these mice, myofibroblast cells that express PDGFRα can be identified by their green fluorescence seen throughout the gas exchange region of the lung.

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Table 1

RCT included in 2022 Cochrane Review Reporting BPD as an Outcome

Treatment Strategy	Author	CONTROL Number Gestational Age	APAP Number Gestational Age	BPD Rate		BPD Definition
				Control number percentage	APAP number percentage	
Prophylaxis	**Schindler**	**Placebo** 29 26.5+1.6	**APAP IV @ <6 hrs** 29 26.6+1.6	11/28 39%	**12/27** **44%**	Unclear
	Harken	**Placebo** 25 28.3 + 2.06	**APAP IV @ <24 hrs** 23 28.4 + 2.36	**12/25** **48%**	7/23 30%	BPD grade 1: O2 at 28 d BPD grades 2–3: supplemental oxygen at 36 wk after conception
Treatment	**Davidson**	**Indomethacin IV** 20 25.3 + 1.8	**APAP IV** 17 25.7 + 1.4	13/20 65%	**14/17** **82%**	Respiratory support at 36 wks
	Hochwald	**Ibuprofen IV** 12 27.2+1.4	**Ibuprofen IV + APAP IV** 12 27.7+1.3	**5/12** **42%**	4/12 33%	Any ventilation or oxygen at 36 wk
	Oncel	**Ibuprofen PO** 40 27.3 + 2.1	**APAP PO** 40 27.3 + 1.7	**17/45** **38%**	12/45 27%	Unclear
	Al-lawama	**Ibuprofen PO** 9 28 (25–35)	**APAP PO** 13 28 (23–32)	**1/9** **11%**	0/13 0%	Unclear
	Dani	**Ibuprofen IV** 49 28.4+2	**APAP IV** 52 28.2+1.4	4/32 13%	**3/21** **14%**	Oxygen at 36 wks
	Kumar	**Ibuprofen PO** 80 28.7 + 1.7	**APAP PO** 81 28.7 + 1.6	6/75 8%	**11/78** **14%**	Unclear
	Dash	**Indomethacin IV** 39 28.9+2.6	**APAP PO** 38 28.5+2.7	**6/30** **20%**	5/27 18.5%	Oxygen at 36 wks
	Dang	**Ibuprofen PO** 80 30.9+2.2	**APAP PO** 80 31.2+1.8	**5/80** **6%**	4/80 5%	2001 definition
	Balachander	**Ibuprofen PO** 55 31.54+2.9	**APAP PO** 55 31.58+2.9	**3/55** **5%**	0/55 0%	Unclear

Treatment Strategy	Author	CONTROL Number Gestational Age	APAP Number Gestational Age	BPD Rate		BPD Definition
				Control number percentage	APAP number percentage	
	elfarash	**Ibuprofen PO** 30 31.73+1.98	**APAP PO** 30 30.53+1.55	2/30 7%	2/30 7%	Oxygen requirement at postmenstrual 36th week or discharge, whichever comes first.
	Yang	**Ibuprofen PO** 43 33.4+2.1	**APAP PO** 44 33.6+2.1	**6/43** **14%**	5/44 11%	Unclear
	Jafari	**Ibuprofen IV** 14 ?	**APAP IV** 16 ?	**1/14** **7%**	1/16 6%	Unclear
Late Treatment	**Kluckow**	**Placebo** 28 27.1	**APAP PO** 27 27	**18/28** **64%**	16/27 59%	oxygen/respiratory support @36 weeks