Appendix. GRADE Evidence-to-Decision Tables for the statement "Management of the patent ductus arteriosus in preterm infants"

QUESTION

Should Prophylactic indomethacin vs. placebo/no treatment be used for preterm infants?	
POPULATION:	Preterm infants
INTERVENTION:	Prophylactic indomethacin
COMPARISON:	placebo/no treatment

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Although majority of extremely preterm infants develop a PDA, decision on pharmacoprophylaxis has always been a contentious issue. The decision has primarily been driven by the perceived benefits versus potential risks as determined by the treating physician. Given the potential risks of NSAID use, it is not surprising that there is wide variation in clinical practice regarding the prophylactic use of NSAIDs in preterm infants. A retrospective cohort study of 4268 extremely preterm infants admitted to Canadian neonatal units between 2010 and 2014 demonstrated marked variation (0-78%) in use of prophylactic NSAIDs across Canadian NICUs.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	19 RCTs have been conducted comparing prophylactic indomethacin with placebo or no treatment[1]	Of the desirable effects, severe IVH (46 fewer per 1000; small effect size), PDA ligation (53 fewer per 1000; moderate effect size) and symptomatic PDA (240 fewer per 1000; large effect size) are appreciably better with prophylactic indomethacin. CLD, severe neurodevelopmental impairment and cerebral palsy are not different between the two groups **Subgroup effects** The largest single trial restricted participation to ELBW infants (Schmidt 2001, TIPP) [2]. Comparison of the effect size estimates of TIPP 2001 trial alone versus the pooled effect sizes of the meta-analyses did not generally reveal major differences with respect to the critical outcomes.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with placebo/no treatment	Risk difference with Prophylactic indomethacin
Mortality at latest follow-up	2769 (18 RCTs)	⨁⨁⨁◯ MODERATE[a]	**RR 0.96** (0.81 to 1.12)	Study population	
				175 per 1,000	**7 fewer per 1,000** (33 fewer to 21 more)

Severe Intraventricular hemorrhage (Grade 3 or 4)	2588 (14 RCTs)	⊕⊕⊕⊕ HIGH	**RR 0.66** (0.53 to 0.82)	Study population		
				136 per 1,000	**46 fewer per 1,000** (64 fewer to 24 fewer)	
Chronic lung disease at 36 weeks' postmenstrual age	999 (1 RCT)	⊕⊕⊕◯ MODERATE[b]	**RR 1.06** (0.92 to 1.22)	Study population		
				427 per 1,000	**26 more per 1,000** (34 fewer to 94 more)	
Necrotizing Enterocolitis	2401 (12 RCTs)	⊕⊕⊕⊕ HIGH	**RR 1.09** (0.82 to 1.46)	Study population		
				63 per 1,000	**6 more per 1,000** (11 fewer to 29 more)	
PDA Ligation	1791 (8 RCTs)	⊕⊕⊕◯ MODERATE[c]	**RR 0.51** (0.37 to 0.71)	Study population		
				108 per 1,000	**53 fewer per 1,000** (68 fewer to 31 fewer)	
Severe neurodevelopmental impairment [one or more of: non-ambulant cerebral palsy, developmental delay (developmental quotient<70), auditory and visual impairment]	1286 (3 RCTs)	⊕⊕⊕◯ MODERATE[d]	**RR 0.96** (0.79 to 1.17)	Study population		
				234 per 1,000	**9 fewer per 1,000** (49 fewer to 40 more)	
Cerebral palsy	1372 (4 RCTs)	⊕⊕⊕◯ MODERATE[e]	**RR 1.04** (0.77 to 1.40)	Study population		
				111 per 1,000	**4 more per 1,000** (26 fewer to 44 more)	
Symptomatic PDA	2193 (14 RCTs)	⊕⊕⊕⊕ HIGH	**RR 0.44** (0.38 to 0.50)	Study population		
				428 per 1,000	**240 fewer per 1,000**	

					(265 fewer to 214 fewer)
Gastrointestinal perforation	1202 (1 RCT)	⨁⨁⨁⨁ HIGH	**RR 1.13** (0.71 to 1.79)	Study population	
				53 per 1,000	**7 more per 1,000** (15 fewer to 42 more)

a. The confidence intervals include moderate benefit (33 fewer deaths per 1000) to small harm (21 more deaths per 1000). Therefore the certainty of evidence was rated down by one level for imprecision
b. The confidence intervals include small benefit (34 fewer per 1000) to moderate harm (94 more per 1000). Therefore the certainty of evidence was rated down by one level for imprecision
c. The confidence intervals include moderate benefit (68 fewer per 1000) to small benefit (31 fewer per 1000). Therefore the certainty of evidence was rated down by one level for imprecision
d. The confidence intervals include small benefit (49 fewer per 1000) to small harm (40 more per 1000). Therefore the certainty of evidence was rated down by one level for imprecision
e. The confidence intervals include small benefit (26 fewer per 1000) to small harm (44 more per 1000). Therefore the certainty of evidence was rated down by one level for imprecision

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	19 RCTs have been conducted comparing prophylactic indomethacin with placebo or no treatment [1].	Of the undesirable outcomes, necrotizing enterocolitis and gastrointestinal perforation is not clinically different between the two groups This holds true for the subgroup of extremely low birth weight infants as the TIPP (2001) trial contributed to 73% of the meta-analytic weight for NEC and 100% for the meta-analytic weight for GI perforation [2]

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with placebo/no treatment	Risk difference with Prophylactic indomethacin
Mortality at latest follow-up				Study population	

	2769 (18 RCTs)	⨁⨁⨁◯ MODERATE[a]	**RR 0.96** (0.81 to 1.12)	175 per 1,000	**7 fewer per 1,000** (33 fewer to 21 more)
Severe Intraventricular hemorrhage (Grade 3 or 4)	2588 (14 RCTs)	⨁⨁⨁⨁ HIGH	**RR 0.66** (0.53 to 0.82)	Study population	
				136 per 1,000	**46 fewer per 1,000** (64 fewer to 24 fewer)
Chronic lung disease at 36 weeks' postmenstrual age	999 (1 RCT)	⨁⨁⨁◯ MODERATE[b]	**RR 1.06** (0.92 to 1.22)	Study population	
				427 per 1,000	**26 more per 1,000** (34 fewer to 94 more)
Necrotizing Enterocolitis	2401 (12 RCTs)	⨁⨁⨁⨁ HIGH	**RR 1.09** (0.82 to 1.46)	Study population	
				63 per 1,000	**6 more per 1,000** (11 fewer to 29 more)
PDA Ligation	1791 (8 RCTs)	⨁⨁⨁◯ MODERATE[c]	**RR 0.51** (0.37 to 0.71)	Study population	
				108 per 1,000	**53 fewer per 1,000** (68 fewer to 31 fewer)
Severe neurodevelopmental impairment [one or more of: non-ambulant cerebral palsy, developmental delay (developmental quotient<70), auditory and visual impairment]	1286 (3 RCTs)	⨁⨁⨁◯ MODERATE[d]	**RR 0.96** (0.79 to 1.17)	Study population	
				234 per 1,000	**9 fewer per 1,000** (49 fewer to 40 more)
Cerebral palsy	1372 (4 RCTs)	⨁⨁⨁◯ MODERATE[e]	**RR 1.04** (0.77 to 1.40)	Study population	
				111 per 1,000	**4 more per 1,000** (26 fewer to 44 more)
Symptomatic PDA				Study population	

	2193 (14 RCTs)	⨁⨁⨁⨁ HIGH	**RR 0.44** (0.38 to 0.50)	428 per 1,000	**240 fewer per 1,000** (265 fewer to 214 fewer)
Gastrointestinal perforation	1202 (1 RCT)	⨁⨁⨁⨁ HIGH	**RR 1.13** (0.71 to 1.79)	Study population	
				53 per 1,000	**7 more per 1,000** (15 fewer to 42 more)

a. The confidence intervals include moderate benefit (33 fewer deaths per 1000) to small harm (21 more deaths per 1000). Therefore the certainty of evidence was rated down by one level for imprecision
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d. The confidence intervals include small benefit (49 fewer per 1000) to small harm (40 more per 1000). Therefore the certainty of evidence was rated down by one level for imprecision
e. The confidence intervals include small benefit (26 fewer per 1000) to small harm (44 more per 1000). Therefore the certainty of evidence was rated down by one level for imprecision

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies		The certainty of evidence for the critical outcomes of severe IVH,NEC and gastrointestinal perforation were high. The certainty of evidence for the critical outcomes of mortality, severe neurodevelopmental impairment and cerebral palsy were moderate. Going by the lowest certainty of evidence among all critical outcomes, the overall certainty of evidence was judged to be ***moderate***

Outcomes	Importance	Certainty of the evidence (GRADE)
Mortality at latest follow-up	CRITICAL	⨁⨁⨁◯ MODERATE[a]
Severe Intraventricular hemorrhage (Grade 3 or 4)	CRITICAL	⨁⨁⨁⨁ HIGH

Chronic lung disease at 36 weeks' postmenstrual age	IMPORTANT	⊕⊕⊕◯ MODERATE[b]
Necrotizing Enterocolitis	CRITICAL	⊕⊕⊕⊕ HIGH
PDA Ligation	IMPORTANT	⊕⊕⊕◯ MODERATE[c]
Severe neurodevelopmental impairment [one or more of: non-ambulant cerebral palsy, developmental delay (developmental quotient<70), auditory and visual impairment]	CRITICAL	⊕⊕⊕◯ MODERATE[d]
Cerebral palsy	CRITICAL	⊕⊕⊕◯ MODERATE[e]
Symptomatic PDA	IMPORTANT	⊕⊕⊕⊕ HIGH
Gastrointestinal perforation	CRITICAL	⊕⊕⊕⊕ HIGH

a. The confidence intervals include moderate benefit (33 fewer deaths per 1000) to small harm (21 more deaths per 1000). Therefore the certainty of evidence was rated down by one level for imprecision
b. The confidence intervals include small benefit (34 fewer per 1000) to moderate harm (94 more per 1000). Therefore the certainty of evidence was rated down by one level for imprecision
c. The confidence intervals include moderate benefit (68 fewer per 1000) to small benefit (31 fewer per 1000). Therefore the certainty of evidence was rated down by one level for imprecision
d. The confidence intervals include small benefit (49 fewer per 1000) to small harm (40 more per 1000). Therefore the certainty of evidence was rated down by one level for imprecision
e. The confidence intervals include small benefit (26 fewer per 1000) to small harm (44 more per 1000). Therefore the certainty of evidence was rated down by one level for imprecision

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability	The relative importance of relevant outcomes as identified by parents of preterm infants in the context of PDA pharmacoprophylaxis has been explored by only one study:	There is paucity of good research exploring parental values and preferences on neonatal outcomes, especially in the context of

● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	Alfaleh et al (2015) conducted a prospective observational study of 299 women (75% were healthy women at 23–28 weeks gestation, 19% were high risk and 6% recently delivered an extremely low birth weight infant) and explored the maternal preference for indomethacin prophylaxis versus symptomatic treatment of a PDA in preterm infants[3]. When asked to assign a value for each potential outcome on a horizontal scale ranging from 0 (worst outcome i.e. death) to 100 (optimum health condition) in increments of 1 unit, IVH was rated as the most undesirable outcome (mean score 28 with a standard deviation of 23), followed by BPD [35 (22)], PDA ligation [38 (24)], presence of symptomatic PDA [41(21)] and oliguria [63(22)].	PDA pharmacoprophylaxis. Therefore, important uncertainty or variability in parental values and preferences cannot be ruled out

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Evidence from RCTs demonstrate the following: Out of the desirable effects, there is high certainty of evidence that severe IVH and symptomatic PDA are appreciably lower with prophylactic indomethacin. There is moderate certainty of evidence that PDA ligation is appreciably better with prophylactic indomethacin. There is, however, moderate certainty of evidence to suggest that prophylactic indomethacin does not reduce the critical outcomes of death, cerebral palsy, severe neurodevelopmental impairment, neither does it reduce the important outcome of CLD. Out of the undesirable effects, prophylactic indomethacin does not appear to increase the risk of NEC or gastrointestinal perforation.	**Evidence from observational studies:** A systematic review and meta-analysis of observational studies (n= 11,289 very preterm infants) exploring the association of prophylactic indomethacin with neonatal outcomes showed that prophylactic indomethacin was not associated with increased or decreased risk-adjusted odds of death or BPD (0.93, 95% CI: 0.76-1.13) and of BPD among survivors (0.94, 95% CI: 0.78-1.12). A statistically significant association between indomethacin prophylaxis and decreased risk-adjusted odds of mortality (0.81, 95% CI: 0.66-0.98) was observed [4] .

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Assuming that the cost of 1 vial of IV indomethacin is $98.97 (canadian dollars), that the contents of the vial in excess of the dose must be discarded (in accordance with United States Pharmacopeia Chapter <797> requirements and the Joint Commission's Medication Management standard 4.4015), and that 1 vial must be used per dose with 3 doses total, then the cost of indomethacin therapy for a singleton preterm infant normally would be $296.91 [5]	Prophylactic use of indomethacin in all preterm infants is likely to incur large costs as around 8% of all infants in Canada are born preterm (<37 weeks) and preterm infants represent 59% of all NICU admissions as per the Canadian Neonatal Network 2018 Annual report[6] . **Subgroup considerations**

		According to the Canadian Neonatal Network 2018 annual report, infants born extremely preterm (<28 weeks) represent around 20% of all preterm NICU admissions[6]. Therefore, selective use of prophylactic indomethacin the subgroup of extremely low gestational age (<28 weeks) or extremely low birth weight (<1000 g) infants is likely to incur moderate costs.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	Evidence related to cost of indomethacin therapy is obtained from a review article exploring pharmacoeconomics of surgical Interventions vs. Cyclooxygenase Inhibitors for the treatment of the PDA in the United States [5] as well as from personal communication with hospital pharmacists in Canada.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the	There exists some evidence on cost-effectiveness of using prophylactic indomethacin in preterm infants. Two studies were identified [7,8] Moya et al conducted a systematic review of RCTs, cohort studies and retrospective case—control studies. The study demonstrated that there was a significant difference between prophylactic indomethacin and control when effectiveness was measured as quality-adjusted life years (QALYs), resulting in 11 and 10 years for the indomethacin and control groups, respectively. The cost-effectiveness analysis per QALY was $8443 for the indomethacin treatment and $9168 for the control group. Therefore, prophylactic use of indomethacin was concluded to be “less costly and more effective within an important range of certainty” [7]. Zupancic et al conducted a retrospective economic evaluation to determine the incremental cost-effectiveness of indomethacin prophylaxis in extremely low birth weight infants enrolled in the Trial of Indomethacin Prophylaxis in Preterms (TIPP). The study showed that indomethacin prophylaxis “cost an additional $67,500 per death or impairment averted. The precision of their	The cost-effectiveness data mostly includes studies on very low birth weight or extremely low birth weight infants. Given the low risk of critical outcomes such as death and severe IVH in older preterm infants, the intervention is unlikely to be cost-effective in infants with low risk of adverse critical outcomes.

intervention ○ Varies ○ No included studies	estimate was low, such that the probability that the estimate was lower than $300,000 per death or impairment averted was 61%". Therefore, this study did not provide an economic rationale for the use of indomethacin prophylaxis in extremely low birth weight infants [8].	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence was identified.	This is an intervention instituted in neonatal intensive care in a very specific population of preterm neonates. Therefore, no difference in effectiveness is anticipated in any disadvantaged subgroup in this particular situation and hence no equity impacts are anticipated

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	A recent retrospective cohort study of 4268 extremely low birth weight infants born at <30 weeks' gestation admitted to Canadian neonatal units between 2010 and 2014 showed that prophylactic indomethacin was associated with increased odds of spontaneous intestinal perforation independently from early feeding in this cohort (aOR 2.43, 95% CI 1.41 to 4.19)[9]. Another recent a recent individual patient data meta-analysis has shown that concomitant use of prophylactic hydrocortisone to improve survival without CLD and use of prophylactic indomethacin to prevent IVH significantly increases the risk of spontaneous intestinal perforation (OR 2.50; 95% CI, 1.33 to 4.69) [10]. This might be a reason why care providers may choose not to use prophylactic indomethacin in centers with low IVH rates in extremely preterm infants, or in centers which routinely use prophylactic hydrocortisone in preterm infants.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Intravenous indomethacin has been used for a long time in Canadian NICUs and most preterm infants, especially those born extremely preterm (<28 weeks) have an intravenous access. So, the intervention is feasible to implement	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention

●	○	○	○	○

CONCLUSIONS

Recommendation

Routine prophylactic treatment of patent ductus arteriosus with prophylactic indomethacin in all preterm infants is not recommended [Strong recommendation, moderate certainty in the evidence of effects]

Selective prophylaxis with intravenous indomethacin may be considered in extremely low gestational age infants at a high risk of severe intraventricular hemorrhage [conditional recommendation, moderate certainty in the evidence of effects]

Justification

The panel determined that overall there was moderate certainty of evidence from RCTs suggesting prophylactic indomethacin may significantly reduce severe IVH, PDA ligation and symptomatic PDA without worsening NEC or gastrointestinal perforation. However, the panel also acknowledged that these benefits did not translate into improvement in rates of death or severe neurodeficits. The results were primarily driven by one large RCT conducted in extremely low birth weight infants.

Given the large costs and uncertain long-term benefits, the panel recommended against use of routine prophylaxis in all preterm infants.

Subgroup considerations

In extremely low birth weight infants with a higher risk of severe IVH, the balance of desirable and undesirable outcomes favors indomethacin prophylaxis with moderate certainty of evidence. However, cost-effectiveness analysis suggest that the using prophylactic indomethacin is unlikely to be cost-effective in this population.

Therefore the panel conditionally recommends use of prophylactic indomethacin in extremely low birth weight infants and encourages shared decision making with the parents/guardians to evaluate their values and preferences with respect to desirable and undesirable outcomes prior to use of indomethacin.

Implementation considerations

Given the higher risk of spontaneous intestinal perforation documented in observational studies, especially in conjunction with use of prophylactic hydrocortisone (as documented in meta-analysis of RCTs), centers with low IVH rates in extremely preterm infants, or centers which routinely use prophylactic hydrocortisone in preterm infants may not choose to use prophylactic indomethacin

Monitoring and evaluation

Given the concern regarding NEC and spontaneous intestinal perforation with use of indomethacin in extremely preterm infants among neonatal care providers, the panel will continually monitor emerging research evidence on the association between use of prophylactic indomethacin and adverse outcomes such as NEC. Upon identification of potentially relevant new evidence, recommendations will be reconsidered and, if necessary, revised.

Research priorities

The panel identified dearth of high quality research on parental values and preferences for PDA pharmacoprophylaxis

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QUESTION

Should prophylactic ibuprofen vs. placebo/no treatment be used for preterm infants?	
POPULATION:	Preterm infants
INTERVENTION:	prophylactic ibuprofen
COMPARISON:	placebo/no treatment

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Although majority of extremely preterm infants develop a PDA, decision on pharmacoprophylaxis has always been a contentious issue. The decision has primarily been driven by the perceived benefits versus potential risks as determined by the treating physician. Given the potential risks of NSAID use, it is not surprising that there is wide variation in clinical practice regarding the prophylactic use of NSAIDs in preterm infants. A retrospective cohort study of 4268 extremely preterm infants admitted to Canadian neonatal units between 2010 and 2014 demonstrated marked variation (0-78%) in use of prophylactic NSAIDs across Canadian NICUs.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	Research evidence presented below is obtained from the latest Cochrane update on prophylactic ibuprofen use in preterm infants [1]	Small benefit noted for the outcomes of severe IVH (38 fewer per 1000; small effect size) and PDA ligation (23 fewer per 1000; small effect size) Large benefit noted for the outcome of symptomatic PDA requiring treatment (272 fewer per 1000) No clinically important benefit noted for mortality

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with placebo/no treatment	Risk difference with prophylactic ibuprofen
All-cause mortality during hospital stay	700 (4 RCTs)	⨁⨁◯◯ LOW[a,b]	**RR 0.90** (0.62 to 1.30)	Study population	
				142 per 1,000	**14 fewer per 1,000** (54 fewer to 42 more)
Severe intraventricular hemorrhage (grades 3 or 4)	925 (7 RCTs)	⨁⨁◯◯ LOW[c,d]	**RR 0.67** (0.45 to 1.00)	Study population	
				114 per 1,000	**38 fewer per 1,000** (63 fewer to 0 fewer)

Necrotizing Enterocolitis (NEC)	1028 (9 RCTs)	⨁⨁⨁◯ MODERATE[e]	**RR 0.96** (0.61 to 1.50)	Study population	
				64 per 1,000	**3 fewer per 1,000** (25 fewer to 32 more)
Gastrointestinal perforation	167 (2 RCTs)	⨁◯◯◯ VERY LOW[f,g]	**RR 4.88** (0.87 to 27.36)	Study population	
				12 per 1,000	**47 more per 1,000** (2 fewer to 318 more)
PDA Ligation	925 (7 RCTs)	⨁⨁⨁◯ MODERATE[h]	**RR 0.46** (0.22 to 0.96)	Study population	
				43 per 1,000	**23 fewer per 1,000** (34 fewer to 2 fewer)
Symptomatic PDA requiring rescue medical treatment	776 (6 RCTs)	⨁⨁⨁◯ MODERATE[i]	**RR 0.17** (0.11 to 0.26)	Study population	
				328 per 1,000	**272 fewer per 1,000** (292 fewer to 243 fewer)
Chronic lung disease at 36 weeks' postmenstrual age	817 (5 RCTs)	⨁⨁⨁◯ MODERATE[j]	**RR 1.06** (0.89 to 1.26)	Study population	
				345 per 1,000	**21 more per 1,000** (38 fewer to 90 more)

a. 3 out of the 4 studies have unclear risk of bias for random sequence generation, one has unclear risk of bias for allocation concealment and 2 have high risk of bias for blinding. Therefore, the certainty of evidence was rated down by one level
b. The confidence intervals include moderate benefit (54 fewer per 1000) to moderate harm (42 more per 1000). Therefore the certainty of evidence was rated down by one level for imprecision
c. Risk of bias for random sequence generation was low in 2 studies and unclear in 5 studies; risk of bias for allocation concealment was low in 5 studies and unclear in 2 studies; risk of bias regarding performance bias and detection bias was low in 3 studies, unclear in 1 study, and high in 3 studies. Therefore the certainty of evidence was downgraded by one level for risk of bias
d. The confidence intervals include moderate benefit (63 fewer per 1000) to trivial benefit or harm (0 fewer per 1000). Therefore the certainty of evidence was rated down by one level for imprecision
e. Risk of bias for random sequence generation was low in 2 studies and unclear in 7 studies; risk of bias for allocation concealment was low in 5 studies and unclear in 4 studies; risk of bias regarding performance bias and detection bias was low in 5 studies, unclear in 1 study, and high in 3 studies. Therefore the certainty of evidence was downgraded by one level for risk of bias
f. Risk of bias for random sequence generation was unclear in 1 study and risk of bias for blinding was high in 1 study. Therefore the certainty of evidence was rated down by one level for risk of bias
g. As there were few events (10 or less) from two small sample RCTs and the CI includes trivial benefit (2 fewer per 1000) and appreciable harm (318 more per 1000), the certainty of evidence was rated down by two levels for imprecision

h. Risk of bias for random sequence generation was low in 2 studies and unclear in 5 studies; risk of bias for allocation concealment was low in 5 studies and unclear in 2 studies; risk of bias regarding performance bias and detection bias was low in 4 studies and high in 3 studies. Therefore the certainty of evidence was downgraded by one level for risk of bias

i. Risk of bias for random sequence generation was unclear in 5 studies; risk of bias allocation concealment was unclear in 3 studies; risk of bias for blinding was high in 2 studies. Therefore the certainty of evidence was rated down by one level due to risk of bias

j. The confidence intervals include small benefit (38 fewer per 1000) to moderate harm (90 more per 1000). Therefore the certainty of evidence was rated down by one level for imprecision

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

○ Large
○ Moderate
● Small
○ Trivial
○ Varies
○ Don't know

RESEARCH EVIDENCE

Research evidence presented below is obtained from the latest Cochrane update on prophylactic ibuprofen use in preterm infants[1]

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with placebo/no treatment	Risk difference with prophylactic ibuprofen
All cause mortality during hospital stay	700 (4 RCTs)	⨁⨁◯◯ LOW[a,b]	**RR 0.90** (0.62 to 1.30)	Study population	
				142 per 1,000	**14 fewer per 1,000** (54 fewer to 42 more)
Severe intraventricular hemorrhage (grades 3 or 4)	925 (7 RCTs)	⨁⨁◯◯ LOW[c,d]	**RR 0.67** (0.45 to 1.00)	Study population	
				114 per 1,000	**38 fewer per 1,000** (63 fewer to 0 fewer)
Necrotizing Enterocolitis (NEC)	1028 (9 RCTs)	⨁⨁⨁◯ MODERATE[e]	**RR 0.96** (0.61 to 1.50)	Study population	
				64 per 1,000	**3 fewer per 1,000** (25 fewer to 32 more)
Gastrointestinal perforation	167 (2 RCTs)	⨁◯◯◯ VERY LOW[f,g]	**RR 4.88** (0.87 to 27.36)	Study population	
				12 per 1,000	**47 more per 1,000** (2 fewer to 318 more)

ADDITIONAL CONSIDERATIONS

Small harm noted for GI perforation (47 more per 1000). In addition, statistically significant increase in GI hemorrhage noted with prophylactic ibuprofen

No clinically important harm noted for NEC

PDA Ligation	925 (7 RCTs)	⨁⨁⨁◯ MODERATE[h]	**RR 0.46** (0.22 to 0.96)	Study population	
				43 per 1,000	**23 fewer per 1,000** (34 fewer to 2 fewer)
Symptomatic PDA requiring rescue medical treatment	776 (6 RCTs)	⨁⨁⨁◯ MODERATE[i]	**RR 0.17** (0.11 to 0.26)	Study population	
				328 per 1,000	**272 fewer per 1,000** (292 fewer to 243 fewer)
Chronic lung disease at 36 weeks' postmenstrual age	817 (5 RCTs)	⨁⨁⨁◯ MODERATE[j]	**RR 1.06** (0.89 to 1.26)	Study population	
				345 per 1,000	**21 more per 1,000** (38 fewer to 90 more)

a. 3 out of the 4 studies have unclear risk of bias for random sequence generation, one has unclear risk of bias for allocation concealment and 2 have high risk of bias for blinding. Therefore, the certainty of evidence was rated down by one level
b. The confidence intervals include moderate benefit (54 fewer per 1000) to moderate harm (42 more per 1000). Therefore the certainty of evidence was rated down by one level for imprecision
c. Risk of bias for random sequence generation was low in 2 studies and unclear in 5 studies; risk of bias for allocation concealment was low in 5 studies and unclear in 2 studies; risk of bias regarding performance bias and detection bias was low in 3 studies, unclear in 1 study, and high in 3 studies. Therefore the certainty of evidence was downgraded by one level for risk of bias
d. The confidence intervals include moderate benefit (63 fewer per 1000) to trivial benefit or harm (0 fewer per 1000). Therefore the certainty of evidence was rated down by one level for imprecision
e. Risk of bias for random sequence generation was low in 2 studies and unclear in 7 studies; risk of bias for allocation concealment was low in 5 studies and unclear in 4 studies; risk of bias regarding performance bias and detection bias was low in 5 studies, unclear in 1 study, and high in 3 studies. Therefore the certainty of evidence was downgraded by one level for risk of bias
f. Risk of bias for random sequence generation was unclear in 1 study and risk of bias for blinding was high in 1 study. Therefore the certainty of evidence was rated down by one level for risk of bias
g. As there were few events (10 or less) from two small sample RCTs and the CI includes trivial benefit (2 fewer per 1000) and appreciable harm (318 more per 1000), the certainty of evidence was rated down by two levels for imprecision
h. Risk of bias for random sequence generation was low in 2 studies and unclear in 5 studies; risk of bias for allocation concealment was low in 5 studies and unclear in 2 studies; risk of bias regarding performance bias and detection bias was low in 4 studies and high in 3 studies. Therefore the certainty of evidence was downgraded by one level for risk of bias
i. Risk of bias for random sequence generation was unclear in 5 studies; risk of bias allocation concealment was unclear in 3 studies; risk of bias for blinding was high in 2 studies. Therefore the certainty of evidence was rated down by one level due to risk of bias
j. The confidence intervals include small benefit (38 fewer per 1000) to moderate harm (90 more per 1000). Therefore the certainty of evidence was rated down by one level for imprecision

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	See table below	The certainty of evidence was low for the critical outcomes of mortality and severe IVH, moderate for NEC and very low for GI perforation Therefore the overall certainty of evidence is very low.

Outcomes	Importance	Certainty of the evidence (GRADE)
All cause mortality during hospital stay	CRITICAL	⨁⨁◯◯ LOW[a,b]
Severe intraventricular hemorrhage (grades 3 or 4)	CRITICAL	⨁⨁◯◯ LOW[c,d]
Necrotizing Enterocolitis (NEC)	CRITICAL	⨁⨁⨁◯ MODERATE[e]
Gastrointestinal perforation	CRITICAL	⨁◯◯◯ VERY LOW[f,g]
PDA Ligation	IMPORTANT	⨁⨁⨁◯ MODERATE[h]
Symptomatic PDA requiring rescue medical treatment	IMPORTANT	⨁⨁⨁◯ MODERATE[i]
Chronic lung disease at 36 weeks' postmenstrual age	IMPORTANT	⨁⨁⨁◯ MODERATE[j]

a. 3 out of the 4 studies have unclear risk of bias for random sequence generation, one has unclear risk of bias for allocation concealment and 2 have high risk of bias for blinding. Therefore, the certainty of evidence was rated down by one level
b. The confidence intervals include moderate benefit (54 fewer per 1000) to moderate harm (42 more per 1000). Therefore the certainty of evidence was rated down by one level for imprecision
c. Risk of bias for random sequence generation was low in 2 studies and unclear in 5 studies; risk of bias for allocation concealment was low in 5 studies and unclear in 2 studies; risk of bias regarding performance bias and detection bias was low in 3 studies, unclear in 1 study, and high in 3 studies. Therefore the certainty of evidence was downgraded by one level for risk of bias
d. The confidence intervals include moderate benefit (63 fewer per 1000) to trivial benefit or harm (0 fewer per 1000). Therefore the certainty of evidence was rated down by one level for imprecision

	e. Risk of bias for random sequence generation was low in 2 studies and unclear in 7 studies; risk of bias for allocation concealment was low in 5 studies and unclear in 4 studies; risk of bias regarding performance bias and detection bias was low in 5 studies, unclear in 1 study, and high in 3 studies. Therefore the certainty of evidence was downgraded by one level for risk of bias f. Risk of bias for random sequence generation was unclear in 1 study and risk of bias for blinding was high in 1 study. Therefore the certainty of evidence was rated down by one level for risk of bias g. As there were few events (10 or less) from two small sample RCTs and the CI includes trivial benefit (2 fewer per 1000) and appreciable harm (318 more per 1000), the certainty of evidence was rated down by two levels for imprecision h. Risk of bias for random sequence generation was low in 2 studies and unclear in 5 studies; risk of bias for allocation concealment was low in 5 studies and unclear in 2 studies; risk of bias regarding performance bias and detection bias was low in 4 studies and high in 3 studies. Therefore the certainty of evidence was downgraded by one level for risk of bias i. Risk of bias for random sequence generation was unclear in 5 studies; risk of bias allocation concealment was unclear in 3 studies; risk of bias for blinding was high in 2 studies. Therefore the certainty of evidence was rated down by one level due to risk of bias j. The confidence intervals include small benefit (38 fewer per 1000) to moderate harm (90 more per 1000). Therefore the certainty of evidence was rated down by one level for imprecision	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	No studies exploring parental values and preferences related to PDA pharmacoprophylaxis with ibuprofen was identified	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	As the intervention may improve (low certainty) a critical outcome (severe IVH) and likely improves (moderate certainty) two important outcomes (PDA ligation and PDA closure) while it may worsen (very low certainty) a critical outcome (GI perforation), the balance of effects “probably favors the intervention".	No long term outcomes were reported in RCTs. There was also no synthesized evidence on the outcomes specifically in the subgroups of extremely preterm and extremely low birth weight infants

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	The intravenous formulation comes in a 2 mL single-use vial (10 mg/mL as a clear sterile preservative-free solution of the L-lysine salt of ibuprofen). The cost of 1 vial of intravenous ibuprofen is $360.81 (CAD). 1 vial of ibuprofen is usually required for each dose in the standard dose ibuprofen regimen (10 mg/kg followed by 2 doses of 5mg/kg at 24 h intervals). Therefore the total cost of a course of standard dose intravenous ibuprofen is $1082.43.	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ● Low ○ Moderate ○ High ○ No included studies	Data on treatment costs (mentioned above) was obtained from personal communication with Canadian hospital Pharmacists. The certainty of evidence was judged as *low*. The certainty was downgraded by two levels as data on treatment costs was obtained from personal communication only. The data was not verified from an alternate source, nor from any peer-reviewed publications.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence on cost-effectiveness of prophylactic ibuprofen use in preterm infants was identified.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	Use of prophylactic ibuprofen may be less acceptable in extremely preterm infants (<28 weeks) following reports of severe pulmonary hypertension in the ibuprofen treated infants which led to premature termination of an RCT on prophylactic ibuprofen in extremely preterm infants[2]. Further reports of pulmonary hypertension following early ibuprofen administration has been reported as case-reports[3]	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Ibuprofen is already in use in both intravenous and oral form in Canadian NICUs	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies

	JUDGEMENT						
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
●	○	○	○	○

CONCLUSIONS

Recommendation

Routine prophylactic treatment of patent ductus arteriosus with ibuprofen in all preterm infants is not recommended [strong recommendation, very low certainty in the evidence of effects]
Selective prophylaxis with ibuprofen in extremely low gestational age infants at a high risk of severe intraventricular hemorrhage is not recommended [conditional recommendation, very low certainty in the evidence of effects]

Justification

The panel determined that overall there was very low certainty of evidence from RCTs suggesting prophylactic ibuprofen may marginally reduce severe IVH, PDA ligation and significantly reduce symptomatic PDA but may marginally increase gastrointestinal perforation and significantly increase gastrointestinal hemorrhage. There were no long term outcomes available from RCT evidence.
Given the moderate costs, potential for small harm and unknown long-term benefits, the panel recommended against use of routine prophylaxis in all preterm infants.

Subgroup considerations

In extremely low birth weight infants with a higher risk of severe IVH, the balance of desirable and undesirable outcomes does not favor prophylactic ibuprofen due to:
1. Uncertain benefits
2. Concerns related to pulmonary hypertension (see acceptability criterion)

Therefore the panel recommends against use of prophylactic ibuprofen in extremely low birth weight infants

References
1. Ohlsson A, Shah SS. Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants. Cochrane Database Syst Rev. 2019 21;6:CD004213.
2. Gournay V, Roze JC, Kuster A, Daoud P, Cambonie G, Hascoet JM, et al. Prophylactic ibuprofen versus placebo in very premature infants: a randomised, double-blind, placebo-controlled trial. Lancet Lond Engl. 2004 Dec 27;364(9449):1939–44.
3. Bellini C, Campone F, Serra G. Pulmonary hypertension following L-lysine ibuprofen therapy in a preterm infant with patent ductus arteriosus. CMAJ Can Med Assoc J. 2006 Jun 20;174(13):1843–4.

QUESTION

Should prophylactic acetaminophen vs. placebo/no treatment be used for preterm infants?	
POPULATION:	Preterm infants
INTERVENTION:	prophylactic acetaminophen
COMPARISON:	placebo/no treatment

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Given the documented adverse effects with prophylactic indomethacin and ibuprofen, there is a growing interest in the use of prophylactic acetaminophen to prevent morbidity and mortality in extremely preterm infants.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	Research evidence presented below is obtained from the latest Cochrane update on acetaminophen use in preterm infants for PDA [1]	No clinically significant benefit was noted for any of the critical outcomes. Persistent PDA was substantially lower with acetaminophen prophylaxis (211 fewer per 1000).

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with placebo/no treatment	Risk difference with prophylactic acetaminophen
Mortality	80 (2 RCTs)	⨁◯◯◯ VERY LOW[a,b]	**RR 0.35** (0.04 to 3.20)	Study population	
				49 per 1,000	**32 fewer per 1,000** (47 fewer to 107 more)
Severe IVH (grades 3 and 4)				Study population	

	48 (1 RCT)	⨁⨁◯◯ LOW[c]	**RR 1.09** (0.07 to 16.39)	40 per 1,000	**4 more per 1,000** (37 fewer to 616 more)
Necrotizing Enterocolitis	48 (1 RCT)	⨁⨁◯◯ LOW[d]	**RR 0.36** (0.02 to 8.45)	Study population	
				40 per 1,000	**26 fewer per 1,000** (39 fewer to 298 more)
Chronic lung disease (supplemental oxygen at 36 weeks' postmenstrual age)	48 (1 RCT)	⨁⨁◯◯ LOW[d]	**RR 0.36** (0.02 to 8.45)	Study population	
				40 per 1,000	**26 fewer per 1,000** (39 fewer to 298 more)
Persistent PDA following prophylaxis	80 (2 RCTs)	⨁⨁⨁◯ MODERATE[e]	**RR 0.49** (0.24 to 1.00)	Study population	
				415 per 1,000	**211 fewer per 1,000** (315 fewer to 0 fewer)

a. >50% of the meta-analytic weight comes from the study with unclear allocation concealment and blinding
b. There were small number of events (<10) obtained from 2 small sample RCTs and the confidence intervals included appreciable benefit and harm. Therefore the certainty of evidence was rated down by 2 levels
c. There were small number of events (<10) from one small RCT and the confidence intervals include small benefit (37 fewer per 1000) to large harm (616 more per 1000). Therefore the certainty of evidence was rated down by two levels for imprecision
d. There were small number of events (<10) from one small RCT and the confidence intervals include small benefit (39 fewer per 1000) to large harm (298 more per 1000). Therefore the certainty of evidence was rated down by two levels for imprecision
e. The confidence intervals include large benefit (315 fewer per 1000) to trivial benefit or harm (0 fewer per 1000). Therefore the certainty of evidence was rated down by one level for imprecision

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large
○ Moderate
○ Small
● Trivial
○ Varies
○ Don't know

Research evidence presented below is obtained from the latest Cochrane update on acetaminophen use in preterm infants for PDA[1]

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with placebo/no treatment	Risk difference with prophylactic acetaminophen
Mortality	80 (2 RCTs)	⨁◯◯◯ VERY LOW[a,b]	**RR 0.35** (0.04 to 3.20)	Study population	
				49 per 1,000	**32 fewer per 1,000** (47 fewer to 107 more)
Severe IVH (grades 3 and 4)	48 (1 RCT)	⨁⨁◯◯ LOW[c]	**RR 1.09** (0.07 to 16.39)	Study population	
				40 per 1,000	**4 more per 1,000** (37 fewer to 616 more)
Necrotizing Enterocolitis	48 (1 RCT)	⨁⨁◯◯ LOW[d]	**RR 0.36** (0.02 to 8.45)	Study population	
				40 per 1,000	**26 fewer per 1,000** (39 fewer to 298 more)
Chronic lung disease (supplemental oxygen at 36 weeks' postmenstrual age)	48 (1 RCT)	⨁⨁◯◯ LOW[d]	**RR 0.36** (0.02 to 8.45)	Study population	
				40 per 1,000	**26 fewer per 1,000** (39 fewer to 298 more)
Persistent PDA following prophylaxis	80 (2 RCTs)	⨁⨁⨁◯ MODERATE[e]	**RR 0.49** (0.24 to 1.00)	Study population	
				415 per 1,000	**211 fewer per 1,000** (315 fewer to 0 fewer)

a. >50% of the meta-analytic weight comes from the study with unclear allocation concealment and blinding
b. There were small number of events (<10) obtained from 2 small sample RCTs and the confidence intervals included appreciable benefit and harm. Therefore the certainty of evidence was rated down by 2 levels
c. There were small number of events (<10) from one small RCT and the confidence intervals include small benefit (37 fewer per 1000) to large harm (616 more per 1000). Therefore the certainty of evidence was rated down by two levels for imprecision
d. There were small number of events (<10) from one small RCT and the confidence intervals include small benefit (39 fewer per 1000) to large harm (298 more per 1000). Therefore the certainty of evidence was rated down by two levels for imprecision

No clinically appreciable harm was noted with acetaminophen prophylaxis

e. The confidence intervals include large benefit (315 fewer per 1000) to trivial benefit or harm (0 fewer per 1000). Therefore the certainty of evidence was rated down by one level for imprecision

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT

- ● Very low
- ○ Low
- ○ Moderate
- ○ High
- ○ No included studies

RESEARCH EVIDENCE

Outcomes	Importance	Certainty of the evidence (GRADE)
Mortality	CRITICAL	⨁◯◯◯ VERY LOW[a,b]
Severe IVH (grades 3 and 4)	CRITICAL	⨁⨁◯◯ LOW[c]
Necrotizing Enterocolitis	CRITICAL	⨁⨁◯◯ LOW[d]
Chronic lung disease (supplemental oxygen at 36 weeks' postmenstrual age)	IMPORTANT	⨁⨁◯◯ LOW[d]
Persistent PDA following prophylaxis	IMPORTANT	⨁⨁⨁◯ MODERATE[e]

a. >50% of the meta-analytic weight comes from the study with unclear allocation concealment and blinding
b. There were small number of events (<10) obtained from 2 small sample RCTs and the confidence intervals included appreciable benefit and harm. Therefore the certainty of evidence was rated down by 2 levels
c. There were small number of events (<10) from one small RCT and the confidence intervals include small benefit (37 fewer per 1000) to large harm (616 more per 1000). Therefore the certainty of evidence was rated down by two levels for imprecision

ADDITIONAL CONSIDERATIONS

	d. There were small number of events (<10) from one small RCT and the confidence intervals include small benefit (39 fewer per 1000) to large harm (298 more per 1000). Therefore the certainty of evidence was rated down by two levels for imprecision e. The confidence intervals include large benefit (315 fewer per 1000) to trivial benefit or harm (0 fewer per 1000). Therefore the certainty of evidence was rated down by one level for imprecision	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	No studies exploring parental values and preferences related to PDA pharmacoprophylaxis with acetaminophen was identified	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies	Current evidence suggests prophylactic acetaminophen neither appreciably improves nor worsens clinically important outcomes	

○ Don't know		

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Acetaminophen: Injectable acetaminophen = **$15.00/100mL bag -** Estimated cost of 3-day treatment course (3 bags) per patient= **$60.00** Enteral acetaminophen = **$2.10/100mL bottle** - Estimated cost of 3-day therapy (12 doses) for a 1 kg patient= **$0.12**	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	Data on treatment costs (mentioned above) was obtained from personal communication with the hospital Pharmacist of the Neonatal Intensive Care Unit, IWK Health Center, Halifax, NS	The certainty of evidence was judged as *low.* The certainty was downgraded by two levels as data on treatment costs was obtained from personal communication only. The data was not verified from an alternate source, nor from any peer-reviewed publications.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No direct research evidence on cost-effectiveness of prophylactic acetaminophen use in preterm infants was identified.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Recent studies have raised concerns regarding the effect of acetaminophen on long-term neurodevelopment. In an ecological study using country level data, prenatal use of acetaminophen was associated with autism or autism spectrum disorder (ASD)[2]. In another Spanish birth cohort study, prenatal acetaminophen exposure was associated with an increased incidence autism-spectrum symptoms in males and showed adverse effects on attention-related outcomes for both genders[3]. However, no studies have definitively established a link between acetaminophen and autism.	

Feasibility

Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Acetaminophen is widely used in enteral formulation for pain management in the NICU. However, the intravenous formulation may not be universally available in all Canadian NICUs. If prophylactic treatment is considered, then the intravenous formulation will mostly be used as most infants will likely be on minimal or no feeds. Therefore, use of prophylactic acetaminophen will be contingent on the availability of the intravenous formulation	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
●	○	○	○	○

CONCLUSIONS

Recommendation

Routine prophylactic treatment of patent ductus arteriosus with prophylactic acetaminophen in all preterm infants is not recommended [strong recommendation, very low certainty in the evidence of effects]
We suggest against using acetaminophen prophylaxis in extremely low gestational age infants [conditional recommendation, very low certainty in the evidence of effects]

Justification

Given that there was no appreciable benefit demonstrated for clinically important outcomes, with moderate costs involved and unknown long term consequences, the panel recommended against use of routine prophylaxis in all preterm infants.

Subgroup considerations

The panel also suggested not using acetaminophen prophylaxis in extremely preterm infants given no appreciable benefit demonstrated for clinically important outcomes.

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Overarching question: Should prophylactic cyclo-oxygenase inhibitors (COX-Is; indomethacin, ibuprofen or acetaminophen) be used to prevent a symptomatic PDA in preterm infants

Question 1: Should Prophylactic indomethacin vs. placebo/no treatment be used in preterm infants?

Question 2: Should prophylactic ibuprofen vs. placebo/no treatment be used in preterm infants?

Question 3: Should prophylactic acetaminophen vs. placebo/no treatment be used in preterm infants?

Summary of judgements

	Prophylactic indomethacin/placebo/no treatment	prophylactic ibuprofen/placebo/no treatment	prophylactic acetaminophen/placebo/no treatment	Importance for decision
Balance of effects	Probably favors the intervention	Probably favors the intervention	Does not favor either the intervention or the comparison	**high**
Certainty of evidence	Moderate	Very low	Very low	
Resources required	Large costs	Large costs	Moderate costs	**low**
Cost effectiveness	Probably favors the comparison	No included studies	No included studies	**moderate**
Equity	Probably no impact	Probably no impact	Probably no impact	**low**
Acceptability	Varies	Probably no	Varies	**high**
Feasibility	Yes	Yes	Varies	**low**

Review

	Prophylactic indomethacin	prophylactic ibuprofen	prophylactic acetaminophen	placebo/no treatment	Importance for decision	Comment
Balance of effects	★★★★	★★	★★	★★	**high**	1
Resources required	★	★★	★★★	★★★★★	**low**	2
Cost effectiveness	★★			★★★	**moderate**	3
Equity	★★★★★	★★★★★	★★★★★	★★★★★	**low**	4
Acceptability	★★	★★	★★★	★★★★★	**high**	5
Feasibility	★★★★★	★★★★★	★★★	★★★★★	**low**	6

Comment 1: There is moderate certainty of evidence that prophylactic indomethacin leads to a small reduction in severe IVH and large reduction in PDA ligation without worsening NEC or GI perforation. There is very low certainty of evidence that prophylactic ibuprofen leads to a small reduction in severe IVH and PDA ligation and a small increase in GI perforation. There is very low certainty of evidence that prophylactic acetaminophen does not appreciably alter clinically important outcomes. There is moderate certainty of evidence to suggest that prophylactic indomethacin does not improve long term neurodevelopmental outcomes (severe neurodevelopmental impairment or cerebral palsy). There is no research evidence on the long term impact of prophylactic ibuprofen and acetaminophen in preterm infants

Comment 2: From a cost perspective, ibuprofen appears to be the costliest followed by indomethacin and finally acetaminophen. No treatment obviously requires the least resources out of the 4 options

Comment 3: No treatment appears to be more cost-effective compared to prophylactic indomethacin in extremely low birth weight infants. There is no data on cost effectiveness for ibuprofen or acetaminophen

Comment 4: No equity issues related to management of preterm infants in the neonatal intensive care unit in the Canadian context

Comment 5: Indomethacin may be associated increased GI perforation, especially when concomitantly used with prophylactic hydrocortisone Ibuprofen may also worsen GI perforation. Furthermore there are reports of severe persistent pulmonary hypertension with prophylactic ibuprofen. For acetaminophen, there is little data on long term neurodevelopmental effects. Multiple observational studies have associated maternal acetaminophen consumption with autistic spectrum disorders in children. However, most studies have a substantial risk of bias due to unaccounted confounding.

Comment 6: Both indomethacin and ibuprofen are readily available being already in use for treatment of PDA in Canadian NICUs. Intravenous formulation of acetaminophen being newer in the Canadian market may not be universally available across all NICUs

Recommendation	Clinicians should not routinely use prophylactic cyclo-oxygenase inhibitor (COX-I) drugs to prevent a symptomatic PDA in preterm infants [Strong recommendation, very low certainty in estimate of effects]
Strength of recommendation Strong	
Recommendation	Clinicians may consider selective prophylaxis with intravenous indomethacin in extremely low birth weight infants (<1000g) at a high risk of severe intraventricular hemorrhage [conditional recommendation, moderate certainty in estimate of effects]. The panel encourages shared decision making with the parents/guardians to evaluate their values and preferences with respect to desirable (severe IVH reduction) vs undesirable (gastrointestinal perforation) outcomes. The panel also recommends against using prophylactic indomethacin and prophylactic hydrocortisone concomitantly in extremely preterm infants.
Strength of recommendation Conditional	
Recommendation	Selective prophylaxis with ibuprofen in extremely low gestational age infants at a high risk of severe intraventricular hemorrhage is not recommended [conditional recommendation, very low certainty in the evidence of effects]
Strength of recommendation Strong	
Recommendation	There is insufficient evidence to consider selective prophylaxis with acetaminophen in extremely preterm infants at high risk of mortality or severe intraventricular hemorrhage [conditional recommendation, very low certainty in estimate of effects].
Strength of recommendation Conditional	

Justification	**Balance of effects** There is moderate certainty of evidence that prophylactic indomethacin leads to a small reduction in severe IVH and large reduction in PDA ligation without worsening NEC or GI perforation. There is very low certainty of evidence that prophylactic ibuprofen leads to a small reduction in severe IVH and PDA ligation and a small increase in GI perforation. There is very low certainty of evidence that prophylactic acetaminophen does not appreciably alter clinically important outcomes. There is moderate certainty of evidence to suggest that prophylactic indomethacin does not improve long term neurodevelopmental outcomes (severe neurodevelopmental impairment or cerebral palsy). There is no research evidence on the long term impact of prophylactic ibuprofen and acetaminophen in preterm infants Therefore, considering effect size and certainty of evidence, prophylactic indomethacin appears to be most effective, especially in extremely low birth weight infants **Resource use** From a cost perspective, ibuprofen appears to be the costliest followed by indomethacin and finally acetaminophen. No treatment obviously requires the least resources out of the 4 options **Cost-effectiveness** Placebo/no treatment appears to be more cost-effective compared to prophylactic indomethacin in extremely low birth weight infants. There is no data on cost effectiveness for ibuprofen or acetaminophen. **Acceptability** Indomethacin may be associated increased GI perforation, especially when concomitantly used with prophylactic hydrocortisone Ibuprofen may also worsen GI perforation. Furthermore there are reports of severe persistent pulmonary hypertension with prophylactic ibuprofen For acetaminophen, there is little data on long term neurodevelopmental effects. Multiple observational studies have associated maternal acetaminophen consumption with autistic spectrum disorders in children. However, most studies have a substantial risk of bias due to unaccounted confounding. Therefore, there appears to be acceptability issues with each medication **Feasibility** Both indomethacin and ibuprofen are readily available being already in use for treatment of PDA in Canadian NICUs. Intravenous formulation of acetaminophen being newer in the Canadian market may not be universally available across all NICUs

Research priorities	Research on parental values and preferences for COX-I prophylaxis in preterm infants is lacking. Research on long term neurodevelopmental outcomes with ibuprofen and acetaminophen is required Research in cost-effectiveness of prophylactic ibuprofen and acetaminophen is required

QUESTION

Should echocardiography vs. clinical signs of PDA be used to diagnose hs-PDA in preterm infants?	
POPULATION:	Preterm infants
INTERVENTION:	Echocardiographic diagnosis of PDA
COMPARISON:	Clinical diagnosis of PDA

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	There is controversy around how to diagnose a PDA and when to label it as hemodynamically significant. Specific clinical signs indicate the possible presence of an hs-PDA in preterm infants, but reliability of these signs have been questioned. On the other hand, use of echocardiography to confirm diagnosis of an hs-PDA implies significant resource use from a hospital perspective.	

Test accuracy

How accurate is the test?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very inaccurate ○ Inaccurate ● Accurate ○ Very accurate ○ Varies ○ Don't know	**Clinical signs** 6 observational studies have explored usefulness of clinical signs such as murmur, high pulse volume, active precordium, CT ratio on chest radiograph, increased vascular markings on chest radiograph, BP less than fifth percentile, palpable dorsalis pedis pulse, worsening respiratory status, systolic and diastolic and mean BP and pulse pressure. **Overall clinical signs alone appear insufficient to rule in or rule out an hs-PDA**[1]**.** Urquhart et al showed that for presence of a murmur alone, assuming a pretest probability of 65%, with a positive LR of 3.23, the post-test probability is increased to 86%. In the absence of a murmur and a negative LR of 0.67, post-test probability falls only to 55%[2]. Therefore, presence of murmur cannot reliably rule in or rule out an hs-PDA. For the clinical sign of increased pulse volume, assuming a pretest probability of 65%, post-test probability is increased to 75% when there are bounding pulses but falls only to 59% when bounding pulses are absent. **Echocardiographic parameters**	Jain et al summarized studies that defined a PDA using clinical and echocardiographic parameters[1]. They confirmed significant variability in test accuracy based on the combination of parameters used. They noted the following: 1. Clinical diagnosis alone is unreliable in ruling in or ruling out an hs-PDA (poor sensitivity and specificity) 2. A PDA diameter of<1.5mm can fairly reliably rule out a large volume PDA shunt

	A number echocardiographic markers have been used to assess hemodynamic significance of a PDA which are broadly divided into (a) markers of PDA size & flow characteristics (direction and velocity of PDA shunt); (b) markers of pulmonary hyperperfusion (such as left ventricular output; left atrium:aortic root ratio; left pulmonary artery diastolic velocity; mitral valve E:A ratio) and (c) markers of systemic hypoperfusion (flow direction in descending aorta, celiac trunk or middle cerebral artery). A combination of different markers have been used to in RCTs and observational studies to define hemodynamic significance of the PDA. PDA size >1.5 mm and left atrium to aortic root (LA:Ao) ratio >1.4 are the two most commonly used measures to define hemodynamic significance in RCTs[3]. A small number of studies of limited size have attempted to define hemodynamically significant PDA by combining multiple echocardiography parameters. Kluckow et al. identified that a ductal diameter >1.6mm on echocardiography assessment at 5 hours of age among VLBW infants predicted the development of pulmonary hemorrhage in the first 3 days of life with 92% sensitivity and 55% specificity[4]. Sehgal et al., retrospectively evaluated the echocardiograms of infants who received pharmacological treatment for PDA (n=52) and evaluated the accuracy of a scoring system in predicting the outcome of BPD. The scoring system consisted exclusively of echocardiography indices, where each parameter was classified, by expert-consensus, into categorical levels of severity. Ordinal levels of severity were assigned an increasing number of 'points' in a linear fashion and the sum of all points from each index formed a cumulative score. The scoring system exhibited excellent discrimination of infants for the development of BPD (area under the receiver operating characteristic curve [AUC] 0.91, 95% CI 0.83 – 1.00)[5]. Krishnappa et al showed that increasing PDA diameter and left ventricular dilatation was associated with earlier time to successful extubation after surgical PDA ligation among ventilator-dependent ELGANs, suggesting that these echocardiography indices may accurately convey the severity of ductal shunting (and impact on pulmonary function) beyond the first two weeks of life (which is when ligation is performed)[6]. El-Khuffash et al. enrolled 141 infants born at GA<29 weeks and prospectively derived a 'PDA severity score', combining GA with echocardiography characteristics estimated at 24 to 48 hours after birth to provide an accurate prediction of the composite outcome of death or bronchopulmonary dysplasia (AUC 0.92, 95% CI 0.86-0.97)[7]. The score had greater discriminatory ability than clinical indices alone and selected echocardiography indices for inclusion based on significant univariable association with the primary outcome.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies	No RCT evidence identified	**Desirable effects of early echocardiographic screening** In a national population based cohort study of 1513 preterm infants screening echocardiography before day 3 of life was associated with lower in-hospital mortality (14.2% vs 18.5% ; OR, 0.73 [95% CI, 0.54 to 0.98]; ARR, 4.3 [95% CI, 0.3 to 8.3]) and a lower rate of pulmonary hemorrhage

○ Don't know		(5.6% vs 8.9%; OR, 0.60 [95% CI, 0.38 to 0.95]; ARR, 3.3 [95% CI, 0.4 to 6.3]). No differences in rates of necrotizing enterocolitis, severe bronchopulmonary dysplasia, or severe cerebral lesions were observed in this study[8]

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	No RCT evidence identified	**Undesirable effects of early echocardiographic screening** None documented. Noori et al showed that targeted neonatal echocardiography in extremely preterm infants (gestational age 25.9±1.2 weeks; range 23 to 27; n=22) was not associated with a clinically appreciable change in arterial oxygen saturation (SPO2), cerebral regional oxygen saturation (CrSO2) and cerebral fractional oxygen extraction (CFOE) in extremely preterm infants during the first 3 postnatal days[9].

Certainty of the evidence of test accuracy

What is the overall certainty of the evidence of test accuracy?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	Given the observational nature of all studies, the certainty of evidence for reliability for all the combination of parameters is low. It appears that a PDA diameter of<1.5mm can reliably rule out a large volume shunt and therefore should not be treated.	

Certainty of the evidence of test's effects

What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the test?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	The evidence for desirable and undesirable effects are obtained from observational studies	

Certainty of the evidence of management's effects

What is the overall certainty of the evidence of effects of the management that is guided by the test results?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ○ Low ○ Moderate ○ High ● No included studies	No RCTs were identified that compared clinical versus echocardiographic diagnosis for the management of PDA in preterm infants	

Certainty of the evidence of test result/management

How certain is the link between test results and management decisions?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	No studies were identified exploring association of clinical versus echocardiographic diagnosis of PDA with management decisions	

Certainty of effects

What is the overall certainty of the evidence of effects of the test?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies		

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	No related evidence on family values and preferences was identified	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know	Given that clinical signs alone are unreliable in ruling in or ruling out a PDA, especially for management decisions, the balance of desirable and undesirable effects favors the use of echocardiography to confirm the presence of PDA prior to treatment	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No formal studies were identified on resource requirement for neonatal echocardiography in the NICU	Billing details from personal communication with neonatologists providing targeted neonatal echocardiography services show that billing amount for each echocardiography varies from approximately $100-150 depending on the province Given that there are no extra costs with clinical examination, it was judged that there will be moderate increase in costs with echocardiographic diagnosis of the PDA

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ○ Low ○ Moderate ○ High ● No included studies		

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies		

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know		Given that most tertiary care NICUs in Canada caring for preterm infants with a PDA have pediatric cardiology services with or without neonatologist performed TNE services, use of echocardiography to confirm the diagnosis of a PDA prior to treatment would be acceptable and feasible for most centers

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know		As above

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
TEST ACCURACY	Very inaccurate	Inaccurate	**Accurate**	Very accurate		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF THE EVIDENCE OF TEST ACCURACY	Very low	**Low**	Moderate	High			No included studies
CERTAINTY OF THE EVIDENCE OF TEST'S EFFECTS	Very low	**Low**	Moderate	High			No included studies
CERTAINTY OF THE EVIDENCE OF MANAGEMENT'S EFFECTS	Very low	Low	Moderate	High			**No included studies**
CERTAINTY OF THE EVIDENCE OF TEST RESULT/MANAGEMENT	Very low	Low	Moderate	High			**No included studies**

	JUDGEMENT						
CERTAINTY OF EFFECTS	Very low	Low	Moderate	High			**No included studies**
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**
○	○	○	○	●

CONCLUSIONS

Recommendation

The panel recommends using echoardiography over clinical signs only to diagnose a hemodynamically significant PDA in preterm infants **[Strong recommendation, low certainty in the evidence of effects]**

Justification

Echocardiography appears to be more accurate in diagnosing as well as ruling out an hs-PDA compared to use of clinical signs only. Given the poor predictive ability of clinical diagnosis in ruling in or ruling out an hs-PDA, the panel felt that using only clinical signs to guide (or withhold) PDA management may be potentially harmful. Therefore, the panel made a strong recommendation for using echocardiography to establish presence of a hemodynamically significant PDA shunt prior to initiating any form of treatment.

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QUESTION

Should very early treatment (initiated within 72 hours of age) vs. conservative management be used for treatment of an hs-PDA?	
POPULATION:	Preterm infants with an hs-PDA
INTERVENTION:	very early treatment (initiated within 72 hours of age)
COMPARISON:	conservative management

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Ideal timing of PDA treatment is controversial. Very early treatment of a symptomatic PDA may expose a large number of infants unnecessarily to COX-I medications, when a substantial proportion of those PDA would have probably closed without consequences. On the other hand, delayed initiation of treatment may not be able to alter early morbidities such as severe IVH, pulmonary hemorrhage, and further treatment may be rendered ineffective due to suboptimal dosage of medications	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	Research evidence presented below is obtained from the most recent Cochrane review on early treatment versus expectant management of the PDA in preterm infants[1]	Moderate reduction in BPD (critical outcome); but results did not reach statistical significance Small reduction in severe IVH (critical outcome); but results did not reach statistical significance

Very early treatment compared to Expectant Management for preterm infants

Patient or population: preterm infants
Setting:
Intervention: Very early treatment
Comparison: Expectant Management

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Expectant Management	Risk difference with Very early treatment
All-cause mortality during hospital stay	384 (7 RCTs)	⨁⨁⨁◯ MODERATE [a]	**RR 0.94** (0.58 to 1.53)	168 per 1,000	**10 fewer per 1,000** (71 fewer to 89 more)
Surgical PDA ligation or transcatheter occlusion	293 (5 RCTs)	⨁⨁⨁◯ MODERATE [a]	**RR 0.88** (0.36 to 2.17)	60 per 1,000	**7 fewer per 1,000** (38 fewer to 70 more)
Receipt of any pharmacotherapy for a hemodynamically significant PDA	156 (4 RCTs)	⨁◯◯◯ VERY LOW [b,c]	**RR 1.64** (1.31 to 2.05)	329 per 1,000	**211 more per 1,000** (102 more to 346 more)
Chronic lung disease	384 (7 RCTs)	⨁⨁◯◯ LOW [d,e]	**RR 0.83** (0.63 to 1.08)	378 per 1,000	**64 fewer per 1,000** (140 fewer to 30 more)
Severe Intraventricular hemorrhage IVH (grades III and IV)	240 (4 RCTs)	⨁⨁⨁◯ MODERATE [a]	**RR 0.64** (0.21 to 1.93)	66 per 1,000	**24 fewer per 1,000** (52 fewer to 61 more)
Necrotizing enterocolitis (NEC; stage 2 or greater)	332 (5 RCTs)	⨁⨁⨁◯ MODERATE [a]	**RR 1.08** (0.53 to 2.21)	83 per 1,000	**7 more per 1,000** (39 fewer to 100 more)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. The CI includes appreciable benefit and harm, therefore the quality of evidence was rated down by one level for imprecision
b. >50% of meta-analytic weight from studies with high risk of bias in blinding personnel and outcome assessors
c. I-squared value 90% suggesting substantial heterogeneity that cannot be explained by subgroup differences. Therefore the quality of evidence was rated down by 2 levels for inconsistency
d. I-squared value of 48% suggests there is moderate heterogeneity which is partly explained by subgroup differences [Test for subgroup differences, p=0.04]. The quality of evidence was therefore rated down by one level
e. The CI includes appreciable benefit favoring very early treatment but crosses the threshold for no difference. Therefore the quality of evidence was rated down by one level

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	Research evidence presented below is obtained from the most recent Cochrane review on early treatment versus expectant management of the PDA in preterm infants[1]	Trivial increase in NEC (critical outcome) Large increase in exposure to any pharmacotherapy (important outcome) One addition recent RCT (TRIOCAPI) that randomized infants born at <28 weeks of gestation with a large PDA on echocardiography at 6-12 hours after birth to ibuprofen or placebo by 12 hours of age showed that there was no statistically significant difference in the primary outcome of survival without cerebral palsy

	Very early treatment compared to Expectant Management for preterm infants **Patient or population**: preterm infants **Setting**: **Intervention**: Very early treatment **Comparison**: Expectant Management	(adjusted relative risk (aRR), 0.98, 95% confidence interval (CI) 0.83 to 1.16, P=.83) (Rozé 2020)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Expectant Management	Risk difference with Very early treatment
All-cause mortality during hospital stay	384 (7 RCTs)	⨁⨁⨁◯ MODERATE [a]	**RR 0.94** (0.58 to 1.53)	168 per 1,000	**10 fewer per 1,000** (71 fewer to 89 more)
Surgical PDA ligation or transcatheter occlusion	293 (5 RCTs)	⨁⨁⨁◯ MODERATE [a]	**RR 0.88** (0.36 to 2.17)	60 per 1,000	**7 fewer per 1,000** (38 fewer to 70 more)
Receipt of any pharmacotherapy for a hemodynamically significant PDA	156 (4 RCTs)	⨁◯◯◯ VERY LOW [b,c]	**RR 1.64** (1.31 to 2.05)	329 per 1,000	**211 more per 1,000** (102 more to 346 more)
Chronic lung disease	384 (7 RCTs)	⨁⨁◯◯ LOW [d,e]	**RR 0.83** (0.63 to 1.08)	378 per 1,000	**64 fewer per 1,000** (140 fewer to 30 more)
Severe Intraventricular hemorrhage IVH (grades III and IV)	240 (4 RCTs)	⨁⨁⨁◯ MODERATE [a]	**RR 0.64** (0.21 to 1.93)	66 per 1,000	**24 fewer per 1,000** (52 fewer to 61 more)
Necrotizing enterocolitis (NEC; stage 2 or greater)	332 (5 RCTs)	⨁⨁⨁◯ MODERATE [a]	**RR 1.08** (0.53 to 2.21)	83 per 1,000	**7 more per 1,000** (39 fewer to 100 more)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. The CI includes appreciable benefit and harm, therefore the quality of evidence was rated down by one level for imprecision
b. >50% of meta-analytic weight from studies with high risk of bias in blinding personnel and outcome assessors
c. I-squared value 90% suggesting substantial heterogeneity that cannot be explained by subgroup differences. Therefore the quality of evidence was rated down by 2 levels for inconsistency
d. I-squared value of 48% suggests there is moderate heterogeneity which is partly explained by subgroup differences [Test for subgroup differences, p=0.04]. The quality of evidence was therefore rated down by one level
e. The CI includes appreciable benefit favoring very early treatment but crosses the threshold for no difference. Therefore the quality of evidence was rated down by one level

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies		Based on the lowest certainty of evidence among the critical outcomes

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	No research evidence on family values and preferences for timing of hs-PDA treatment	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	There is insufficient evidence to suggest benefit of very early treatment (none of the desirable effects reached statistical significance) of hs-PDA. There is however a statistically significant increase in exposure to NSAIDs with very early treatment (very low certainty of evidence)	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Very early treatment would mean 211 more per 1000 preterm infants with PDA will require treatment with cyclo-oxygenase inhibitors. However the costs will vary based on the medication and formulation used: The costs are as follows: 1. Indomethacin: The cost of indomethacin therapy for a singleton preterm infant normally would be $296.91 (see evidence-to-decision tables for prophylactic indomethacin for details) 2. Ibuprofen: The cost of 1 vial of intravenous ibuprofen is $360.81 (CAD). 1 vial of ibuprofen is usually required for each dose in the standard dose ibuprofen regimen (10 mg/kg followed by 2 doses of 5mg/kg at 24 h intervals). Therefore the total cost of a course of standard dose intravenous ibuprofen is $1082.43. The oral formulation comes in a 120 ml bottle (20 mg/ml). The cost of 1 bottle of oral ibuprofen is $2.10 (CAD) which is sufficient to cover a course of oral ibuprofen 3. Acetaminophen: Injectable acetaminophen = **$15.00/100mL bag -** Estimated cost of 3-day treatment course (3 bags) per patient= **$60.00**	

	Enteral acetaminophen = **$2.10/100mL bottle** - Estimated cost of 3-day therapy (12 doses) for a 1 kg patient= **$0.12**	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	Data on treatment costs (mentioned above) was obtained from personal communication with the hospital Pharmacist of the Neonatal Intensive Care Unit, IWK Health Center, Halifax, NS	The certainty was downgraded by two levels as data on treatment costs was obtained from personal communication only. The data was not verified from an alternate source, nor from any peer-reviewed publications.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No direct research evidence on cost-effectiveness of very early treatment of PDA was identified.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	There is a growing trend towards increasing conservative management, especially given the fact that a large proportion of PDAs spontaneously constrict in the first few days of life[2] There is insufficient evidence to extrapolate the evidence to extremely preterm infants with a large symptomatic PDA.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	More resources are required for routine screening echocardiography and initiation of treatment in the very early treatment group versus the conservative management group	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies

	JUDGEMENT						
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
●	○	○	○	○

CONCLUSIONS

Recommendation

The guideline panel recommends using conservative management over very early treatment initiated in the first 72 hours for the treatment of hs-PDA in preterm infants ***[strong recommendation, low certainty in the evidence of effects].***

Justification

There appears to be increased exposure to NSAIDs with very early treatment without appreciable benefit. Furthermore, very early treatment will likely incur more costs as more infants are exposed to NSAIDs. Also, very early treatment might be less acceptable as it would require routine early screening echocardiography which might not be possible in centers without ready access to echocardiography

References

1. Mitra S, Scrivens A, von Kursell AM, Disher T. Early treatment versus expectant management of hemodynamically significant patent ductus arteriosus for preterm infants. Cochrane Database Syst Rev. 2020 Dec 10;12:CD013278

2. Clyman RI, Couto J, Murphy GM. Patent ductus arteriosus: are current neonatal treatment options better or worse than no treatment at all? Semin Perinatol. 2012 Apr;36(2):123–9.

QUESTION

Should early treatment (initiated within 7 days of age) vs. conservative management be used for treatment of an hs-PDA?	
POPULATION:	Preterm infants with an hs-PDA
INTERVENTION:	early treatment (initiated within 7 days of age)
COMPARISON:	conservative management

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Ideal timing of PDA treatment is controversial. Early treatment of a symptomatic PDA (ie, treatment initiated within the first 7 days) may expose a large number of infants unnecessarily to COX-I medications, when a substantial proportion of those PDAs would have probably closed without consequences. On the other hand, delayed initiation of treatment may not be able to alter early morbidities such as severe IVH, pulmonary hemorrhage, and further treatment may be rendered ineffective due to suboptimal dosage of medications	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	Research evidence presented below is obtained from the most recent Cochrane review on early treatment versus expectant management of the PDA in preterm infants [1]	A small reduction demonstrated for clinically important outcomes such as death and BPD (not statistically significant)

Early treatment compared to Expectant Management for preterm infants

Patient or population: preterm infants
Setting:
Intervention: Early treatment
Comparison: Expectant Management

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Expectant Management	Risk difference with Early treatment
All-cause mortality during hospital stay	500 (6 RCTs)	⨁⨁⨁◯ MODERATE [a]	**RR 0.80** (0.46 to 1.39)	109 per 1,000	**22 fewer per 1,000** (59 fewer to 42 more)
Surgical PDA ligation or transcatheter occlusion	432 (4 RCTs)	⨁◯◯◯ VERY LOW [a,b,c]	**RR 1.08** (0.65 to 1.80)	145 per 1,000	**12 more per 1,000** (51 fewer to 116 more)
Receipt of any pharmacotherapy for a hemodynamically significant PDA	232 (2 RCTs)	⨁⨁◯◯ LOW [d,e]	**RR 2.30** (1.86 to 2.83)	430 per 1,000	**559 more per 1,000** (370 more to 787 more)
Chronic lung disease	339 (4 RCTs)	⨁⨁⨁◯ MODERATE [a]	**RR 0.90** (0.62 to 1.29)	263 per 1,000	**26 fewer per 1,000** (100 fewer to 76 more)
Severe Intraventricular hemorrhage IVH (grades III and IV)	171 (2 RCTs)	⨁⨁◯◯ LOW [f]	**RR 0.83** (0.32 to 2.16)	95 per 1,000	**16 fewer per 1,000** (65 fewer to 110 more)
Necrotizing enterocolitis (NEC; stage 2 or greater)	473 (5 RCTs)	⨁⨁◯◯ LOW [b,g]	**RR 2.34** (0.86 to 6.41)	29 per 1,000	**39 more per 1,000** (4 fewer to 156 more)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. The CI includes appreciable benefit and harm, therefore the quality of evidence was rated down by one level for imprecision
b. >50% of meta-analytic weight to studies with high or unclear risk of bias in one of sequence generation, allocation concealment, or blinding. Therefore the quality of evidence was rated by one level for risk of bias
c. I-squared value of 59% suggests there is moderate to substantial heterogeneity that cannot be explained by subgroup differences [test for subgroup differences p=0.59]. Therefore the quality of evidence was rated down by one level for inconsistency
d. There was high risk of bias for blinding in 1 study and low risk of bias across multiple domains for 1 study.
e. Does not meet the optimal information size for detecting a 25% difference in benefit or harm (assuming a two-sided alpha of 0.05 with 80% power). Therefore the quality of evidence was rated down by one level for imprecision
f. As there were few events from two small-sample RCTs and the CI includes appreciable benefit and harm, the quality of evidence was rated down by two levels for imprecision
g. The CI includes appreciable benefit favoring expectant management but crosses the threshold for no difference. Therefore the quality of evidence was rated down by one level for imprecision

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	Research evidence presented below is obtained from the most recent Cochrane review on early treatment versus expectant management of the PDA in preterm infants [1]	Small increase in NEC (Not statistically significant) Large increase in any pharmacotherapy exposure (statistically significant)

Early treatment compared to Expectant Management for preterm infants

Patient or population: preterm infants
Setting:
Intervention: Early treatment
Comparison: Expectant Management

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Expectant Management	Risk difference with Early treatment
All-cause mortality during hospital stay	500 (6 RCTs)	⨁⨁⨁◯ MODERATE [a]	**RR 0.80** (0.46 to 1.39)	109 per 1,000	**22 fewer per 1,000** (59 fewer to 42 more)
Surgical PDA ligation or transcatheter occlusion	432 (4 RCTs)	⨁◯◯◯ VERY LOW [a,b,c]	**RR 1.08** (0.65 to 1.80)	145 per 1,000	**12 more per 1,000** (51 fewer to 116 more)
Receipt of any pharmacotherapy for a hemodynamically significant PDA	232 (2 RCTs)	⨁⨁◯◯ LOW [d,e]	**RR 2.30** (1.86 to 2.83)	430 per 1,000	**559 more per 1,000** (370 more to 787 more)
Chronic lung disease	339 (4 RCTs)	⨁⨁⨁◯ MODERATE [a]	**RR 0.90** (0.62 to 1.29)	263 per 1,000	**26 fewer per 1,000** (100 fewer to 76 more)
Severe Intraventricular hemorrhage IVH (grades III and IV)	171 (2 RCTs)	⨁⨁◯◯ LOW [f]	**RR 0.83** (0.32 to 2.16)	95 per 1,000	**16 fewer per 1,000** (65 fewer to 110 more)
Necrotizing enterocolitis (NEC; stage 2 or greater)	473 (5 RCTs)	⨁⨁◯◯ LOW [b,g]	**RR 2.34** (0.86 to 6.41)	29 per 1,000	**39 more per 1,000** (4 fewer to 156 more)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. The CI includes appreciable benefit and harm, therefore the quality of evidence was rated down by one level for imprecision
b. >50% of meta-analytic weight to studies with high or unclear risk of bias in one of sequence generation, allocation concealment, or blinding. Therefore the quality of evidence was rated by one level for risk of bias
c. I-squared value of 59% suggests there is moderate to substantial heterogeneity that cannot be explained by subgroup differences [test for subgroup differences p=0.59]. Therefore the quality of evidence was rated down by one level for inconsistency
d. There was high risk of bias for blinding in 1 study and low risk of bias across multiple domains for 1 study.
e. Does not meet the optimal information size for detecting a 25% difference in benefit or harm (assuming a two-sided alpha of 0.05 with 80% power). Therefore the quality of evidence was rated down by one level for imprecision
f. As there were few events from two small-sample RCTs and the CI includes appreciable benefit and harm, the quality of evidence was rated down by two levels for imprecision
g. The CI includes appreciable benefit favoring expectant management but crosses the threshold for no difference. Therefore the quality of evidence was rated down by one level for imprecision

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ● Low ○ Moderate ○ High ○ No included studies	Based on the lowest certainty of evidence for the most important outcomes	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	No available research on family values and preferences for early treatment of hs-PDA	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies	There is insufficient evidence to suggest benefit of very early treatment (none of the desirable effects reached statistical significance) of hs-PDA. There is however a statistically significant increase in exposure to NSAIDs with early treatment (low certainty of evidence)	

○ Don't know		

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Early treatment would mean 559 more per 1000 preterm infants with PDA will require treatment with cyclo-oxygenase inhibitors. However the costs will vary based on the medication and formulation used: The costs are as follows: 1. Indomethacin: The cost of indomethacin therapy for a singleton preterm infant normally would be $296.91 (see evidence-to-decision tables for prophylactic indomethacin for details) 2. Ibuprofen: The cost of 1 vial of intravenous ibuprofen is $360.81 (CAD). 1 vial of ibuprofen is usually required for each dose in the standard dose ibuprofen regimen (10 mg/kg followed by 2 doses of 5mg/kg at 24 h intervals). Therefore the total cost of a course of standard dose intravenous ibuprofen is $1082.43. The oral formulation comes in a 120 ml bottle (20 mg/ml). The cost of 1 bottle of oral ibuprofen is $2.10 (CAD) which is sufficient to cover a course of oral ibuprofen 3. Acetaminophen: Injectable acetaminophen = **$15.00/100mL bag -** Estimated cost of 3-day treatment course (3 bags) per patient= **$60.00** Enteral acetaminophen = **$2.10/100mL bottle** - Estimated cost of 3-day therapy (12 doses) for a 1 kg patient= **$0.12**	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ● Low ○ Moderate ○ High ○ No included studies	Data on treatment costs (mentioned above) was obtained from personal communication with the hospital Pharmacist of the Neonatal Intensive Care Unit, IWK Health Center, Halifax, NS	The certainty of evidence was judged as low. The certainty was downgraded by two levels as data on treatment costs was obtained from personal communication only. The data was not verified from an alternate source, nor from any peer-reviewed publications.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No data on cost-effectiveness of early treatment of hs-PDA was identified	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies		

○ Don't know		

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Though there is a growing trend towards increasing conservative management, there is insufficient evidence to extrapolate the evidence to extremely preterm infants with a large symptomatic PDA. Following observational studies suggest prolonged exposure to hs-PDA may be harmful for extremely preterm infants: 1. Schena et al, in their cohort study of 242 preterm infants ≤28 weeks GA showed that each week of presence of a hs-PDA represented an added risk for BPD (OR 1.7), compared to a small, nonsignificant PDA [2] 2. Kaempf et al showed that moving from a pro-active treatment to a conservative strategy in all very low birth weight infants (<1500g) resulted in a significant increase in chronic lung disease (CLD)(34% vs 48%,p<0.01) and a composite of death and CLD (42% vs 57%,p<0.01) [3] 3. A recent Canadian and Japanese study of 6981 VLBW infants showed that infants treated conservatively were more mature [mean GA 27.4(±2.1) vs 25.6(±1.7) weeks], had higher birth weight [mean birth weight 1019(±257) vs 832(±208) grams], and were clinically more stable at birth [Apgar score <7 at 5 min 33% vs 41%] compared to infants who received pharmacotherapy and then went on to receive surgical PDA ligation[4] 4. A multicenter study of 842 preterm infants showed that, infants born at 23–24 weeks' GA had the highest risk of developing a hs-PDA refractory to pharmacological treatment (69 vs. 40%;P<0.001) and eventually requiring surgical closure (19 vs 10%;p=0.011) compared to infants born at 25-28 weeks' GA[5]	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	More resources will be required for echocardiographic assessment and initiation of treatment in the early treatment group rather than conservative management group	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies

	JUDGEMENT						
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

CONCLUSIONS

Recommendation

The guideline panel suggests using conservative management over early treatment initiated in the first 7 days for the treatment of hs-PDA in preterm infants ***[conditional recommendation, low certainty in the evidence of effects].***

Justification

There appears to be increased exposure to NSAIDs with early treatment (initiated within the first 7 days after birth) without appreciable benefit. Furthermore, very early treatment will likely incur more costs as more infants are exposed to NSAIDs. However, acceptability of early conservative management might be variable with observational studies suggesting prolonged exposure to hs-PDA in extremely preterm infants might be harmful

Subgroup considerations

Clinicians should exercise caution in applying the results of existing RCTs to hemodynamically unstable extremely preterm infants with a large PDA shunt

References

1. Mitra S, Scrivens A, von Kursell AM, Disher T. Early treatment versus expectant management of hemodynamically significant patent ductus arteriosus for preterm infants. Cochrane Database Syst Rev. 2020 Dec 10;12:CD013278

2. Schena F, Francescato G, Cappelleri A, Picciolli I, Mayer A, Mosca F, et al. Association between Hemodynamically Significant Patent Ductus Arteriosus and Bronchopulmonary Dysplasia. J Pediatr. 2015 Jun;166(6):1488–92.

3. Kaempf JW, Huston R, Wu Y, Kaempf AJ, Wang L, Grunkemeier G, et al. Permissive tolerance of the patent ductus arteriosus may increase the risk of Chronic Lung Disease [Internet]. Vol. 3, Research and Reports in Neonatology. Dove Press; 2013 [cited 2020 Sep 3]. p. 5–10. Available from: https://www.dovepress.com/permissive-tolerance-of-the-patent-ductus-arteriosus-may-increase-the--peer-reviewed-article-RRN

4. Isayama T, Mirea L, Mori R, Kusuda S, Fujimura M, Lee SK, et al. Patent ductus arteriosus management and outcomes in Japan and Canada: comparison of proactive and selective approaches. Am J Perinatol. 2015 Sep;32(11):1087–94.

5. Dani C, Mosca F, Cresi F, Lago P, Lista G, Laforgia N, et al. Patent ductus arteriosus in preterm infants born at 23-24 weeks' gestation: Should we pay more attention? Early Hum Dev. 2019;135:16–22.

QUESTION

Should treatment initiated between 1-2 weeks of age vs. conservative management be used for treatment of an hs-PDA?	
POPULATION:	Preterm infants with an hs-PDA
INTERVENTION:	treatment initiated between 1-2 weeks of age
COMPARISON:	conservative management

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Ideal timing of PDA treatment is controversial. Both very early treatment (initiated within first 3 days after birth) and early treatment (initiated within first 7 days after birth) of a symptomatic PDA may expose a large number of infants unnecessarily to COX-I medications, when a substantial proportion of those PDA would have probably closed without consequences. On the other hand, delayed initiation of treatment may not be able to alter early morbidities such as severe IVH, pulmonary hemorrhage, and further treatment may be rendered ineffective due to suboptimal dosage of medications. Therefore, researchers have explored whether moderately early initiation of treatment (initiated within 6-14 days after birth) compared to conservative management might improve clinical outcomes.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	Two recent RCTs (PDA TOLERATE by Clyman et al, 2019 and Sung et al 2020) have been done comparing treatment initiated between 6-14 days of age for an hs-PDA in preterm infants **1. PDA TOLERATE trial characteristics and results**[1] • Trial design: RCT • Population: 202 neonates of <28 weeks of gestation age (mean, 25.8 ± 1.1 weeks) with moderate to large PDA shunts • Interventions: Early routine treatment between 6-14 days of age with indomethacin/ibuprofen/acetemaniphen (as per institutional protocol) vs conservative management • Risk of bias: Low • Results on important outcomes: No statistically significant differences observed for the primary outcome of ligation or presence of a PDA at discharge (early routine treatment [ERT], 32%; conservative treatment [CT], 39%), NEC (ERT, 16%; CT, 19%), BPD* (ERT, 49%; CT, 53%), BPD/death (ERT, 58%; CT, 57%), death (ERT,19%; CT, 10%) **2. Sung et al 2020 trial characteristics and results**[2] • Trial design: Noninferiority RCT • Population: 146 preterm infants (gestational age [GA] 23-30 weeks) with hs-PDA (ductal size >1.5mm plus respiratory support diagnosed between postnatal days 6 and 14 enrolled	No statistically significant improvement was observed in clinically important outcomes such as CLD or death

	• Interventions: Treatment initiated between 6-14 days of age with oral ibuprofen vs non-intervention • Risk of bias: Low • Results on important outcomes: The nonintervention approach was noninferior to ibuprofen treatment in terms of BPD incidence or death (nonintervention, 44%; ibuprofen, 50%; 95%CI, −0.11 to 0.22; noninferiority margin −0.2; P = .51). Device closure (ibuprofen, 2 [3%] v nonintervention, 4 [6%], P = 0.40) was not significantly different between the 2 groups, neither was NEC (ibuprofen, 7 [10%] v nonintervention, 3 [4%], P = 0.21) or severe IVH (ibuprofen, 2 [3%] v nonintervention, 4 [6%], P = 0.68) *BPD: Bronchopulmonary dysplasia	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	Two recent RCTs (PDA TOLERATE by Clyman et al, 2019 and Sung et al 2020) have been done comparing treatment initiated between 6-14 days of age for an hs-PDA in preterm infants **1. PDA TOLERATE trial characteristics and results**[1] • Trial design: RCT • Population: 202 neonates of <28 weeks of gestation age (mean, 25.8 ± 1.1 weeks) with moderate to large PDA shunts • Interventions: Early routine treatment between 6-14 days of age with indomethacin/ibuprofen/acetemaniphen (as per institutional protocol) vs conservative management • Risk of bias: Low • Results on important outcomes: No statistically significant differences observed for the primary outcome of ligation or presence of a PDA at discharge (early routine treatment [ERT], 32%; conservative treatment [CT], 39%), NEC (ERT, 16%; CT, 19%), BPD* (ERT, 49%; CT, 53%), BPD/death (ERT, 58%; CT, 57%), death (ERT,19%; CT, 10%) **2. Sung et al 2020 trial characteristics and results** [2] • Trial design: Noninferiority RCT • Population: 146 preterm infants (gestational age [GA] 23-30 weeks) with hs-PDA (ductal size >1.5mm plus respiratory support diagnosed between postnatal days 6 and 14 enrolled • Interventions: Treatment initiated between 6-14 days of age with oral ibuprofen vs non-intervention • Risk of bias: Low • Results on important outcomes: The nonintervention approach was noninferior to ibuprofen treatment in terms of BPD incidence or death (nonintervention, 44%; ibuprofen, 50%; 95%CI, −0.11 to 0.22; noninferiority margin −0.2; P = .51). Device closure (ibuprofen, 2 [3%] v nonintervention, 4 [6%], P = 0.40) was not significantly different between the 2 groups, neither was NEC (ibuprofen, 7 [10%] v nonintervention, 3 [4%], P = 0.21) or severe IVH (ibuprofen, 2 [3%] v nonintervention, 4 [6%], P = 0.68) *BPD: Bronchopulmonary dysplasia	Moderate increase in death noted in the PDA TOLERATE trial in the early treatment group, the results did not reach statistical significance

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies		The risk difference for death, PDA ligation, BPD and severe IVH in the PDA TOLERATE trial included appreciable benefit and harm. Therefore, the overall certainty of evidence was downgraded by one level due to imprecision

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	No research evidence on parental values and preferences on early treatment of PDA was identified	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	There is insufficient evidence to suggest benefit of early treatment initiated within 6-14 days of birth (none of the desirable effects reached statistical significance) of hs-PDA. The PDA TOLERATE trial showed an increase in mortality (19% vs 10%), but the results did not reach statistical significance Overall, the balance of effects appear to favor conservative management	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ● Don't know	No direct evidence on increased resources required with early treatment (6-14 days) was identified in these 2 RCTs	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies		

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No studies on cost-effectiveness of early treatment of PDA (at 6-14 days of age) was identified	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	A follow-up analysis of eligible infants who were not enrolled in the PDA-TOLERATE trial due to lack of physician equipoise showed that infants treated prior to 6 days postnatal age had a significantly lower incidence of BPD and BPD/death in spite of having a significantly lower gestational age or substantially higher initial respiratory morbidity[3]. Therefore, it is unclear if the results can be generalizable to extremely low gestational age infants with higher initial respiratory morbidity.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	More resources will be required for echocardiographic assessment and initiation of treatment in the early treatment group rather than conservative management group	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

CONCLUSIONS

Recommendation

The guideline panel suggests using conservative management over initiation of treatment between 6-14 days of age for the treatment of an hs-PDA in preterm infants ***[conditional recommendation, moderate certainty in the evidence of effects].***

Justification

There is insufficient evidence to suggest benefit of early treatment of hs-PDA initiated within 6-14 days after birth. However, the acceptability of the results might be variable as extremely low gestational age infants requiring significant respiratory support were not included in the larger of the 2 cited trials that provide evidence on this intervention

Subgroup considerations

Clinicians should exercise caution in applying the results of existing RCTs to extremely low gestational age infants requiring significant respiratory support as such infants were excluded from the larger of the two trials that provide evidence on this intervention

References

1. Clyman RI, Liebowitz M, Kaempf J, Erdeve O, Bulbul A, Håkansson S, et al. PDA-TOLERATE Trial: An Exploratory Randomized Controlled Trial of Treatment of Moderate-to-Large Patent Ductus Arteriosus at 1 Week of Age. J Pediatr. 2019;205:41-48.e6.
2. Sung SI, Lee MH, Ahn SY, Chang YS, Park WS. Effect of Nonintervention vs Oral Ibuprofen in Patent Ductus Arteriosus in Preterm Infants. JAMA Pediatr. 2020 Aug;174(8):1–9.
3. Liebowitz M, Katheria A, Sauberan J, Singh J, Nelson K, Hassinger DC, et al. Lack of Equipoise in the PDA-TOLERATE Trial: A Comparison of Eligible Infants Enrolled in the Trial and Those Treated Outside the Trial. J Pediatr. 2019;213:222-226.e2.

Overarching question: Should early pharmacotherapy versus conservative management be used as the initial management approach for an hs-PDA?

Question 1: Should early treatment (initiated within 7 days of age) vs. conservative management be used for treatment of an hs-PDA?

Question 2: Should very early treatment (initiated within 72 hours of age) vs. conservative management be used for treatment of an hs-PDA?

Question 3: Should treatment initiated between 1-2 weeks of age vs. conservative management be used for treatment of an hs-PDA?

Summary of judgements

	early treatment (initiated within 7 days of age)/conservative management	very early treatment (initiated within 72 hours of age)/conservative management	treatment initiated between 1-2 weeks of age/conservative management	Importance for decision
Balance of effects	Probably favors the comparison	Probably favors the comparison	Probably favors the comparison	**high**
Certainty of evidence	Low	Low	Moderate	
Resources required	Moderate costs	Moderate costs	Don't know	**low**
Cost effectiveness	No included studies	No included studies	No included studies	**moderate**
Equity	Probably no impact	Probably no impact	Probably no impact	**low**
Acceptability	Varies	Probably no	Varies	**high**
Feasibility	Probably no	Probably no	Probably no	**high**

Review

	very early treatment (initiated within 72 hours of age)	early treatment (initiated within 7 days of age)	treatment initiated between 1-2 weeks of age	conservative management	Importance for decision	Comment
Balance of effects	★	★★★	★★	★★★★	**high**	1
Resources required	★	★★		★★★★★	**low**	2
Cost effectiveness					**moderate**	
Equity	★★★★★	★★★★★	★★★★★	★★★★★	**low**	3
Acceptability	★	★★	★★	★★★	**high**	4
Feasibility	★★	★★★	★★★	★★★★★	**high**	5

Comment 1:

Very early treatment: There appears to be increased exposure to NSAIDs with very early treatment without appreciable benefit. Furthermore, very early treatment will likely incur more costs as more infants are exposed to NSAIDs. Also, very early treatment might be less acceptable as it would require routine early screening echocardiography which might not be possible in centers without ready access to echocardiography (low certainty)

Early treatment: There appears to be increased exposure to NSAIDs with early treatment (initiated within the first 7 days after birth) without appreciable benefit. Furthermore, very early treatment will likely incur more costs as more infants are exposed to NSAIDs. However, acceptability of early conservative management might be variable with observational studies suggesting prolonged exposure to hs-PDA in extremely preterm infants might be harmful (low certainty)

Treatment between 1-2 weeks: There is insufficient evidence to suggest benefit of early treatment of hs-PDA initiated within 6-14 days after birth. However, the acceptability of the results might be variable as extremely low gestational age infants requiring significant respiratory support were not included in the larger of the 2 cited trials that provide evidence on this intervention (moderate certainty)

Comment 2: With earlier treatment, progressively more resources will be required as more infants will be treated and more infants will receive screening echocardiography

Comment 3: No equity issues related to management of preterm infants in the neonatal intensive care unit in the Canadian context

Comment 4: There is a growing trend towards increasing conservative management, especially given the fact that a large proportion of PDAs spontaneously constrict in the first few days of life. However, whether this evidence can be extrapolated to extremely preterm infants with a large symptomatic PDA is debatable.

Comment 5: More resources are required for routine screening echocardiography and initiation of treatment in the earlier treatment groups versus the conservative management group.

Recommendation	Clinicians may choose to conservatively manage an hs-PDA within the first 1-2 weeks after birth (conditional recommendation, low certainty in evidence of effects).
Strength of recommendation Conditional	
Justification	There is low certainty of evidence to suggest that treatment for hs-PDA initiated with in the first 2 weeks after birth does not appreciably improve clinical outcomes. Earlier initiation of treatment may increase exposure to NSAIDs. Earlier initiation of treatment may result in more resource use as more infants will receive screening echocardiography and more infants will receive pharmacotherapy.
Subgroup considerations	Whether the said evidence can be extrapolated to extremely preterm infants with a large symptomatic PDA is debatable. Therefore, clinicians should exercise caution in applying the results of existing RCTs to clinically unstable extremely preterm infants (especially those born <26 weeks of gestation), where earlier initiation of treatment may be considered.

QUESTION

Should standard dose ibuprofen vs. indomethacin be used for treatment of an hs-PDA?	
POPULATION:	Preterm infants requiring treatment of an-hs-PDA
INTERVENTION:	Standard dose ibuprofen (10 mg/kg followed by 2 doses of 5 mg/kg at 24 h intervals)
COMPARISON:	Indomethacin (0.1 to 0.3mg/kg administered intravenously every 12 to 24 hours for a total of 3 doses)

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Choice of pharmacotherapy is another contentious topic in the management of PDA in preterm infants. A recent systematic review showed that cyclo-oxygenase inhibitors such as indomethacin, ibuprofen and acetaminophen has been used in 15 different combinations of doses and routes in RCTs. In contemporary practice, the most commonly used pharmacotherapeutic options are oral or intravenous formulations of standard dose ibuprofen (10 mg/kg followed by 2 doses of 5 mg/kg at 24 h intervals), higher doses of ibuprofen (15-20 mg/kg followed by 2 doses of 5-7.5 mg/kg at 24 h intervals), oral or intravenous acetaminophen and intravenous indomethacin.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	Research evidence presented below is from the latest Cochrane update on ibuprofen for treatment of PDA in preterm infants [1]	A systematic review and Bayesian network meta-analysis of 68 RCTs (n=4802) showed that standard doses of oral ibuprofen [median rank, 4 (95% Credible intervals, CrI: 2-6)] was similar in efficacy to intravenous indomethacin [median rank, 6 (95% CrI, 4-7)] (Network OR: 1.45 (0.94-2.24)]. However, both standard dose oral ibuprofen [Network OR 2.22 (1.44-3.40)] and IV indomethacin [Network OR 1.53 (1.13-2.09)] was significantly better than standard dose IV ibuprofen[2]. NEC was statistically significantly lower with oral standard dose ibuprofen as compared to IV indomethacin [Network OR 0.41 (0.21-0.75)]. Oliguria was statistically significantly lower with both oral standard dose ibuprofen and IV standard dose ibuprofen compared to indomethacin No statistically significant differences were observed among these medications for any other clinical outcomes. The latest Cochrane systematic review by Ohlsson et al (2020) also showed standard dose IV ibuprofen to be significantly less effective

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with indomethacin	Risk difference with standard dose ibuprofen
Mortality	697 (10 RCTs)	⨁⨁◯◯ LOW[a,b]	**RR 0.79** (0.54 to 1.17)	Study population	
				143 per 1,000	**30 fewer per 1,000** (66 fewer to 24 more)
				Study population	

Need for surgical closure	1275 (16 RCTs)	⨁⨁⨁◯ MODERATE[c]	**RR 1.06** (0.81 to 1.39)	135 per 1,000	**8 more per 1,000** (26 fewer to 53 more)	
NEC	1292 (18 RCTs)	⨁⨁⨁◯ MODERATE[d]	**RR 0.68** (0.49 to 0.94)	Study population		
				111 per 1,000	**35 fewer per 1,000** (56 fewer to 7 fewer)	
Oliguria	576 (6 RCTs)	⨁⨁⨁◯ MODERATE[e]	**RR 0.28** (0.14 to 0.54)	Study population		
				124 per 1,000	**89 fewer per 1,000** (107 fewer to 57 fewer)	
CLD (at 36 weeks' PMA)	357 (3 RCTs)	⨁⨁⨁◯ MODERATE[f]	**RR 1.12** (0.77 to 1.61)	Study population		
				234 per 1,000	**28 more per 1,000** (54 fewer to 143 more)	
Failure to close a PDA	1590 (24 RCTs)	⨁⨁⨁◯ MODERATE[g]	**RR 1.06** (0.81 to 1.39)	Study population		
				280 per 1,000	**17 more per 1,000** (53 fewer to 109 more)	

a. High risk of bias for blinding in 8 out of the 10 studies
b. 95% CI includes appreciable benefit and harm
c. There was low risk of bias for random sequence generation in seven of the studies and there was unclear risk in the remaining 9 studies.There was low risk of bias for allocation concealment in 10 studies, high risk of bias in one study and unclear risk in the remaining 5 studies. The blinding of personnel was adequate in three studies, unclear in two studies and there was high risk of bias in 11 studies. Blinding of outcome assessments was at low risk of bias in 9 studies, unclear in three studies and there was high risk of bias in four studies. Evidence was rated down by one step.
d. There was low risk of bias for random sequence generation in seven of the studies and there was unclear risk in the remaining 11 studies.There was low risk of bias for allocation concealment in eleven studies, high risk in one study and unclear risk in six studies. The blinding of personnel was adequate in two studies, and there was high risk of bias in 13 studies and an unclear risk of bias in three studies. Blinding of outcome assessments was at low risk of bias in ten studies, high risk of bias in five studies and unclear in three studies. The evidence was rated down by one step.
e. There was no heterogeneity (24%) for RR and moderate for RD (69%). The evidence was rated down by one step.
f. 95% CI includes appreciable benefit and harm
g. There was low risk of bias for random sequence generation in 7 of the studies and there was unclear risk in the remaining 17 studies. There was low risk of bias for allocation

in PDA closure than standard dose oral ibuprofen (RR 0.38 [0.26, 0.56]) [1]

concealment in 13 studies, high risk of bias in one study and unclear risk in the remaining 10 studies. The blinding of personnel was adequate in three studies, unclear in six studies and there was high risk of bias in 15 studies. Blinding of outcome assessments was at low risk of bias in 11 studies, unclear in six studies and there was high risk of bias in seven studies. The evidence was rated down by one step.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

- ○ Large
- ○ Moderate
- ○ Small
- ● Trivial
- ○ Varies
- ○ Don't know

RESEARCH EVIDENCE

Research evidence presented below is from the latest Cochrane update on ibuprofen for treatment of PDA in preterm infants[1]

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with indomethacin	Risk difference with standard dose ibuprofen
Mortality	697 (10 RCTs)	⨁⨁◯◯ LOW[a,b]	**RR 0.79** (0.54 to 1.17)	Study population	
				143 per 1,000	**30 fewer per 1,000** (66 fewer to 24 more)
Need for surgical closure	1275 (16 RCTs)	⨁⨁⨁◯ MODERATE[c]	**RR 1.06** (0.81 to 1.39)	Study population	
				135 per 1,000	**8 more per 1,000** (26 fewer to 53 more)
NEC	1292 (18 RCTs)	⨁⨁⨁◯ MODERATE[d]	**RR 0.68** (0.49 to 0.94)	Study population	
				111 per 1,000	**35 fewer per 1,000** (56 fewer to 7 fewer)
Oliguria	576 (6 RCTs)	⨁⨁⨁◯ MODERATE[e]	**RR 0.28** (0.14 to 0.54)	Study population	
				124 per 1,000	**89 fewer per 1,000** (107 fewer to 57 fewer)
				Study population	

ADDITIONAL CONSIDERATIONS

CLD (at 36 weeks' PMA)	357 (3 RCTs)	⨁⨁⨁◯ MODERATE[f]	**RR 1.12** (0.77 to 1.61)	234 per 1,000	**28 more per 1,000** (54 fewer to 143 more)
Failure to close a PDA	1590 (24 RCTs)	⨁⨁⨁◯ MODERATE[g]	**RR 1.06** (0.81 to 1.39)	Study population	
				280 per 1,000	**17 more per 1,000** (53 fewer to 109 more)

a. High risk of bias for blinding in 8 out of the 10 studies
b. 95% CI includes appreciable benefit and harm
c. There was low risk of bias for random sequence generation in seven of the studies and there was unclear risk in the remaining 9 studies.There was low risk of bias for allocation concealment in 10 studies, high risk of bias in one study and unclear risk in the remaining 5 studies. The blinding of personnel was adequate in three studies, unclear in two studies and there was high risk of bias in 11 studies. Blinding of outcome assessments was at low risk of bias in 9 studies, unclear in three studies and there was high risk of bias in four studies. Evidence was rated down by one step.
d. There was low risk of bias for random sequence generation in seven of the studies and there was unclear risk in the remaining 11 studies.There was low risk of bias for allocation concealment in eleven studies, high risk in one study and unclear risk in six studies. The blinding of personnel was adequate in two studies, and there was high risk of bias in 13 studies and an unclear risk of bias in three studies. Blinding of outcome assessments was at low risk of bias in ten studies, high risk of bias in five studies and unclear in three studies. The evidence was rated down by one step.
e. There was no heterogeneity (24%) for RR and moderate for RD (69%). The evidence was rated down by one step.
f. 95% CI includes appreciable benefit and harm
g. There was low risk of bias for random sequence generation in 7 of the studies and there was unclear risk in the remaining 17 studies. There was low risk of bias for allocation concealment in 13 studies, high risk of bias in one study and unclear risk in the remaining 10 studies. The blinding of personnel was adequate in three studies, unclear in six studies and there was high risk of bias in 15 studies. Blinding of outcome assessments was at low risk of bias in 11 studies, unclear in six studies and there was high risk of bias in seven studies. The evidence was rated down by one step.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ● Low ○ Moderate ○ High ○ No included studies		Based on the lowest certainty of the most important outcomes as per GRADE methodology

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	No research evidence on values and preferences around symptomatic PDA treatment in preterm infants	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies	Standard dose ibuprofen appears to be safer than IV indomethacin Standard dose ibuprofen, especially the oral formulation appears to be as effective as indomethacin. The IV formulation appears less effective than indomethacin	

○ Don't know		

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	1. Indomethacin: The cost of indomethacin therapy for a singleton preterm infant normally would be $296.91 (see evidence-to-decision tables for prophylactic indomethacin for details) 2. Ibuprofen: The cost of 1 vial of intravenous ibuprofen is $360.81 (CAD). 1 vial of ibuprofen is usually required for each dose in the standard dose ibuprofen regimen (10 mg/kg followed by 2 doses of 5mg/kg at 24 h intervals). Therefore the total cost of a course of standard dose intravenous ibuprofen is $1082.43.	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	Data on treatment costs (mentioned above) was obtained from personal communication with the hospital Pharmacist of the Neonatal Intensive Care Unit, IWK Health Center, Halifax, NS	The certainty of evidence was judged as low. The certainty was downgraded by two levels as data on treatment costs was obtained from personal communication only. The data was not verified from an alternate source, nor from any peer-reviewed publications.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No data on cost-effectiveness on indomethacin versus standard dose ibuprofen for treatment of PDA was identified	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Better safety profile likely makes standard dose ibuprofen more acceptable	

Feasibility

Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Both interventions are routinely used in Canadian NICUs	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

The panel suggests using standard dose ibuprofen over indomethacin for the treatment of hs-PDA in preterm infants ***[conditional recommendation, low certainty in the evidence of effects].***

Justification

There is low certainty of evidence to suggest that standard dose ibuprofen is similar in efficacy but has a better safety profile compared to indomethacin. From a cost perspective, intravenous formulation of ibuprofen is more expensive than indomethacin

Implementation considerations

Oral formulation of standard dose ibuprofen is preferably as the intravenous formulation of standard dose ibuprofen appears less effective in PDA closure compared to both standard dose oral ibuprofen as well as indomethacin

References

1. Ohlsson A, Walia R, Shah SS. Ibuprofen for the treatment of patent ductus arteriosus in preterm or low birth weight (or both) infants. Cochrane Database Syst Rev. 2020 11;2:CD003481.

2. Mitra S, Florez ID, Tamayo ME, Mbuagbaw L, Vanniyasingam T, Veroniki AA, et al. Association of Placebo, Indomethacin, Ibuprofen, and Acetaminophen With Closure of Hemodynamically Significant Patent Ductus Arteriosus in Preterm Infants. JAMA. 2018 Mar 27;319(12):1221–38.

QUESTION

Should high dose ibuprofen vs. standard dose ibuprofen be used for treatment of an hs-PDA?	
POPULATION:	Preterm infants requiring treatment of an hs-PDA
INTERVENTION:	high dose ibuprofen (15-20 mg/kg followed by 2 doses of 7.5-10 mg/kg at 24h intervals)
COMPARISON:	standard dose ibuprofen (10 mg/kg followed by 2 doses of 5mg/kg at 24h intervals)

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Standard dose ibuprofen (10 mg/kg followed by 2 doses of 5mg/kg at 24h intervals) is the current treatment of choice. However, generalizability of the results from the clinical trials and consequently the effectiveness of standard dose ibuprofen in the real-world has been questioned and centers have increasingly started to use higher doses of ibuprofen. A recent survey conducted through the Canadian Neonatal Network in 2019 identified that 56% of the tertiary care NICUs (14/25 respondents) in Canada use standard dose ibuprofen while 32% (8/25) use higher doses of ibuprofen. Therefore, an evidence-based recommendation on the medication of choice for PDA pharmacotherapy, especially out of standard vs high dose ibuprofen is warranted.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	The following research evidence is obtained from the recent update of the Cochrane review on ibuprofen for the treatment of PDA [1]	A systematic review and Bayesian network meta-analysis of 68 RCTs (n=4802) showed that higher doses of oral ibuprofen had a better likelihood of PDA closure as compared to standard dose ibuprofen[2]. Out of all the available formulations, high dose oral ibuprofen had the best likelihood of PDA closure. The SUCRA (surface under cumulative ranking) scores and median ranks of the different formulations are as follows (in order of likely best to worse): 1. High dose oral ibuprofen: Median rank, 2 (95% CrI, 1-5); [mean SUCRA score 0.89 (SD 0.12)] 2. High dose IV ibuprofen: Median rank, 2 (95% CrI, 1-7); [mean SUCRA score 0.84 (SD 0.20)] 3. Standard dose oral ibuprofen: Median rank, 4 (95% CrI, 2-6) [mean SUCRA score 0.68 (SD 0.10)] 4. Standard dose IV ibuprofen: Median rank, 8 (95% CrI, 7-9) [mean SUCRA score 0.24 (SD 0.07)]

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with standard dose ibuprofen	Risk difference with high dose ibuprofen
Mortality	155 (2 RCTs)	⨁⨁◯◯ LOW[a,b]	**RR 1.02** (0.58 to 1.79)	Study population	
				218 per 1,000	**4 more per 1,000** (92 fewer to 172 more)
NEC				Study population	

	130 (2 RCTs)	⨁⨁◯◯ LOW[a,b]	**RR 1.0** (0.4 to 2.5)	123 per 1,000	**0 fewer per 1,000** (74 fewer to 185 more)
CLD (at 36 weeks' PMA)	70 (1 RCT)	⨁⨁◯◯ LOW[b,c]	**RR 1.60** (0.85 to 3.02)	Study population	
				286 per 1,000	**171 more per 1,000** (43 fewer to 577 more)
PDA ligation	70 (1 RCT)	⨁◯◯◯ VERY LOW[c,d]	**RR 1.00** (0.15 to 6.71)	Study population	
				57 per 1,000	**0 fewer per 1,000** (49 fewer to 326 more)
PDA closure	190 (3 RCTs)	⨁⨁⨁◯ MODERATE[e]	**RR 2.70** (1.64 to 4.50)	Study population	
				589 per 1,000	**1,002 more per 1,000** (377 more to 2,063 more)
Oliguria	120 (2 RCTs)	⨁◯◯◯ VERY LOW[f,g]	**RR 1.57** (0.44 to 5.63)	Study population	
				50 per 1,000	**29 more per 1,000** (28 fewer to 232 more)

a. Both included studies (Dani 2012 & Pourarian 2015) had unclear risk of bias for random sequence generation and blinding of personnel. Therefore the quality of evidence was rated down by one level for risk of bias
b. The confidence interval includes appreciable benefit and harm, therefore the quality of evidence was rated down by one level for imprecision
c. The included study (Dani 2012) had unclear risk of bias for random sequence generation and blinding of personnel. Therefore the quality of evidence was rated down by one level for risk of bias
d. As there were few events (10 or less) from one small sample RCT and the CI includes appreciable benefit and harm, the quality of evidence was rated down by two levels for imprecision
e. Out of the three included studies, two studies (Dani 2012 & Pourarian 2015) had unclear risk of bias for random sequence generation and blinding of personnel and the third (Fesharaki) had unclear risk of bias for random sequence generation, allocation concealment and blinding of personnel as well as outcome assessors. Therefore the quality of evidence was rated down by one level for risk of bias
f. Out of the two included studies, one study (Pourarian 2015) had unclear risk of bias for random sequence generation and blinding of personnel and the other study (Fesharaki 2012) had unclear risk of bias for random sequence generation, allocation concealment and blinding of personnel as well as outcome assessors. Therefore the quality of evidence was rated down by one level for risk of bias

g. As there were few events (10 or less) from two small sample RCTs and the CI includes small benefit (28 fewer per 1000) and appreciable harm (232 more per 1000), the quality of evidence was rated down by two levels for imprecision

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

○ Large
○ Moderate
● Small
○ Trivial
○ Varies
○ Don't know

RESEARCH EVIDENCE

The following research evidence is obtained from the recent update of the Cochrane review on ibuprofen for the treatment of PDA[1]

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with standard dose ibuprofen	Risk difference with high dose ibuprofen
Mortality	155 (2 RCTs)	⨁⨁◯◯ LOW[a,b]	**RR 1.02** (0.58 to 1.79)	Study population	
				218 per 1,000	**4 more per 1,000** (92 fewer to 172 more)
NEC	130 (2 RCTs)	⨁⨁◯◯ LOW[a,b]	**RR 1.0** (0.4 to 2.5)	Study population	
				123 per 1,000	**0 fewer per 1,000** (74 fewer to 185 more)
CLD (at 36 weeks' PMA)	70 (1 RCT)	⨁⨁◯◯ LOW[b,c]	**RR 1.60** (0.85 to 3.02)	Study population	
				286 per 1,000	**171 more per 1,000** (43 fewer to 577 more)
PDA ligation	70 (1 RCT)	⨁◯◯◯ VERY LOW[c,d]	**RR 1.00** (0.15 to 6.71)	Study population	
				57 per 1,000	**0 fewer per 1,000** (49 fewer to 326 more)
PDA closure				Study population	

ADDITIONAL CONSIDERATIONS

Out of other clinical outcomes, incidence of oliguria appeared to be significantly higher with higher doses of ibuprofen compared to standard doses

	190 (3 RCTs)	⨁⨁⨁◯ MODERATE[e]	**RR 2.70** (1.64 to 4.50)	589 per 1,000	**1,002 more per 1,000** (377 more to 2,063 more)
Oliguria	120 (2 RCTs)	⨁◯◯◯ VERY LOW[f,g]	**RR 1.57** (0.44 to 5.63)	Study population	
				50 per 1,000	**29 more per 1,000** (28 fewer to 232 more)

a. Both included studies (Dani 2012 & Pourarian 2015) had unclear risk of bias for random sequence generation and blinding of personnel. Therefore the quality of evidence was rated down by one level for risk of bias
b. The confidence interval includes appreciable benefit and harm, therefore the quality of evidence was rated down by one level for imprecision
c. The included study (Dani 2012) had unclear risk of bias for random sequence generation and blinding of personnel. Therefore the quality of evidence was rated down by one level for risk of bias
d. As there were few events (10 or less) from one small sample RCT and the CI includes appreciable benefit and harm, the quality of evidence was rated down by two levels for imprecision
e. Out of the three included studies, two studies (Dani 2012 & Pourarian 2015) had unclear risk of bias for random sequence generation and blinding of personnel and the third (Fesharaki) had unclear risk of bias for random sequence generation, allocation concealment and blinding of personnel as well as outcome assessors. Therefore the quality of evidence was rated down by one level for risk of bias
f. Out of the two included studies, one study (Pourarian 2015) had unclear risk of bias for random sequence generation and blinding of personnel and the other study (Fesharaki 2012) had unclear risk of bias for random sequence generation, allocation concealment and blinding of personnel as well as outcome assessors. Therefore the quality of evidence was rated down by one level for risk of bias
g. As there were few events (10 or less) from two small sample RCTs and the CI includes small benefit (28 fewer per 1000) and appreciable harm (232 more per 1000), the quality of evidence was rated down by two levels for imprecision

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Very low ○ Low ○ Moderate ○ High ○ No included studies		Based on the lowest certainty of the most important outcomes as per GRADE methodology

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	No research evidence on values and preferences around symptomatic PDA treatment in preterm infants	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies	As the intervention (high dose ibuprofen) likely improves PDA closure (moderate certainty) while it may worsen oliguria (very low certainty), the balance of effects “probably favors the intervention (high dose ibuprofen)".	

○ Don't know		

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**<u>Hospital costs of high dose versus standard dose ibuprofen</u>** ***Intravenous formulation*** The intravenous formulation comes in a 2 mL single-use vial (10 mg/mL as a clear sterile preservative-free solution of the L-lysine salt of ibuprofen). The cost of 1 vial of intravenous ibuprofen is $360.81 (CAD). 1 vial of ibuprofen is usually required for each dose in the standard dose ibuprofen regimen (10 mg/kg followed by 2 doses of 5mg/kg at 24 h intervals). Therefore the total cost of a course of standard dose intravenous ibuprofen is $1082.43. Given the fact that each vial can provide 20 mg of ibuprofen, for infants with weight ≤1000g, 1 vial of ibuprofen will suffice for each dose in the high dose ibuprofen regimen as well (20 mg/kg followed by 2 doses of 10mg/kg at 24 h intervals). Therefore the total cost of a course of high dose intravenous ibuprofen remains $1082.43 for infants ≤1000g. For infants >1000g, 2 vials will be required to provide high dose ibuprofen. Therefore, the total cost of a course of high dose intravenous ibuprofen in infants >1000g will be $2164.86. In summary, when we compare intravenous standard dose ibuprofen versus intravenous high dose ibuprofen, the costs are exactly same for infants with weight ≤1000g. The costs are doubled in the high dose group, only when treating infants >1000 g. ***Oral formulation*** The oral formulation comes in a 120 ml bottle (20 mg/ml). The cost of 1 bottle of oral ibuprofen is $2.10 (CAD). Therefore, in both standard dose as well as the high dose group, the costs remain exactly the same, irrespective of the weight of the infant.	In the Canadian health system, all intensive care costs are borne by the hospital. So, from a patient/family perspective, there is negligible costs and savings with either intervention. From a hospital perspective, there is increase in costs, *only* with use of intravenous high dose ibuprofen *only* in infants >1000 g weight. In all other scenarios the costs are similar to standard dose ibuprofen.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ● Low ○ Moderate ○ High ○ No included studies	Data on treatment costs (mentioned above) was obtained from personal communication with the hospital pharmacists, IWK Health, Halifax, NS	The certainty of evidence was judged as *low*. The certainty was downgraded by two levels as data on treatment costs was obtained from personal communication only. The data was not verified from an alternate source, nor from any peer-reviewed publications.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No data on cost-effectiveness of high dose versus standard dose ibuprofen was identified	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies		

○ Don't know		

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	A recent survey of Canadian NICUs showed that 56% of the tertiary care NICUs (14/25 respondents) in Canada use standard dose ibuprofen while 32% (8/25) use higher doses of ibuprofen. The primary reason for not using high dose ibuprofen by the former group was concerns regarding safety, especially NEC. All such centers acknowledged that though the data on improved efficacy was convincing, they would not switch to high dose ibuprofen until there is more data on safety, especially in the extremely preterm infants at the limits of viability (born between 22-26 weeks of gestation) who are at the highest risk of NEC. Therefore, acceptability of high dose ibuprofen may be an issue for some care providers especially when treating a symptomatic PDA in extremely preterm infants at the limits of viability (born between 22-26 weeks of gestation).	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Both interventions are different doses of the same medication, hence there should be no difference in feasibility	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know

	JUDGEMENT						
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

The panel suggests using high dose ibuprofen over standard dose ibuprofen for treatment of symptomatic PDA in preterm infants ***[conditional recommendation, very low certainty in the evidence of effects]***

Justification

There is very low certainty of evidence to suggest that high dose ibuprofen appreciably improves PDA closure without worsening potential adverse effects.

Subgroup considerations

The current distribution of benefits and harms are likely to be accepted by key stakeholders as PDA closure is clearly better with high dose ibuprofen. Furthermore, current evidence shows no difference between the 2 interventions in the critical adverse effect of NEC. However, a recent survey of Canadian NICUs did suggest that the primary reason for not using high dose ibuprofen in spite of good evidence on effectiveness was concerns regarding safety, especially NEC. Centers continuing to use standard dose ibuprofen acknowledged that though the data on improved efficacy with higher doses was convincing, they would not switch to high dose ibuprofen until there is more data on safety, especially in extremely preterm infants at the limits of viability (born between 22-26 weeks of gestation) who are at the highest risk of NEC. Therefore, acceptability of high dose ibuprofen may be an issue for some care providers especially when treating a symptomatic PDA in extremely preterm infants at the limits of viability (born between 22-26 weeks of gestation).

References

1. Ohlsson A, Walia R, Shah SS. Ibuprofen for the treatment of patent ductus arteriosus in preterm or low birth weight (or both) infants. Cochrane Database Syst Rev. 2020 11;2:CD003481.

2. Mitra S, Florez ID, Tamayo ME, Mbuagbaw L, Vanniyasingam T, Veroniki AA, et al. Association of Placebo, Indomethacin, Ibuprofen, and Acetaminophen With Closure of Hemodynamically Significant Patent Ductus Arteriosus in Preterm Infants. JAMA. 2018 Mar 27;319(12):1221–38.

QUESTION

Should acetaminophen vs. standard dose ibuprofen be used for treatment of an-hs-PDA?	
POPULATION:	Preterm infants requiring treatment of an-hs-PDA
INTERVENTION:	Acetaminophen (15 mg/kg given every 6 hours for 3-7 days)
COMPARISON:	Standard dose ibuprofen (10 mg/kg followed by 2 doses of 5 mg/kg at 24 h intervals)

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Both indomethacin and ibuprofen are known to be associated with GI and renal side effects in preterm infants. In recent years, there has been an interest in exploring the effect of acetaminophen in the treatment of hs-PDA. With its better adverse effect profile, acetaminophen presents itself as a safer alternative to the more well established NSAID medications used for PDA treatment	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	The following GRADE evidence table is based on data from the recent Cochrane systematic review by Ohlsson et al [1]:	A systematic review and Bayesian network meta-analysis of 68 RCTs (n=4802) showed that oral acetaminophen had a better likelihood of PDA closure as compared to standard dose ibuprofen, both oral and IV formulations[2]. The SUCRA (surface under cumulative ranking) scores and median ranks of the different formulations are as follows (in order of likely best to worse): · Oral acetaminophen: Median rank, 3 (95% CrI, 1-5); [mean SUCRA score 0.82 (SD 0.12)] · Standard dose oral ibuprofen: Median rank, 4 (95% CrI, 2-6) [mean SUCRA score 0.68 (SD 0.10)] · Standard dose IV ibuprofen: Median rank, 8 (95% CrI, 7-9) [mean SUCRA score 0.24 (SD 0.07)] No statistically significant differences were observed among these medications for any other clinical outcomes.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with standard dose ibuprofen	Risk difference with acetaminophen
Mortality	272 (5 RCTs)	⨁⨁⨁◯ MODERATE[a]	**RR 0.96** (0.55 to 1.67)	Study population	
				157 per 1,000	**6 fewer per 1,000** (71 fewer to 105 more)
NEC				Study population	

	559 (5 RCTs)	⨁⨁⨁◯ MODERATE[b]	**RR 0.88** (0.46 to 1.70)	61 per 1,000	**7 fewer per 1,000** (33 fewer to 43 more)
BPD at 36 weeks' PMA	90 (1 RCT)	⨁⨁◯◯ LOW[a,c]	**RR 0.71** (0.38 to 1.30)	Study population	
				378 per 1,000	**110 fewer per 1,000** (234 fewer to 113 more)
Failure of PDA closure	559 (5 RCTs)	⨁⨁⨁◯ MODERATE[d]	**RR 0.95** (0.75 to 1.21)	Study population	
				329 per 1,000	**16 fewer per 1,000** (82 fewer to 69 more)
PDA ligation	290 (2 RCTs)	⨁⨁◯◯ LOW[e,f]	**RR 0.68** (0.35 to 1.32)	Study population	
				131 per 1,000	**42 fewer per 1,000** (85 fewer to 42 more)
Gastrointestinal bleeding	537 (4 RCTs)	⨁⨁⨁◯ MODERATE[g]	**RR 0.28** (0.12 to 0.69)	Study population	
				78 per 1,000	**56 fewer per 1,000** (69 fewer to 24 fewer)
Oliguria	337 (3 RCTs)	⨁⨁◯◯ LOW[h,i]	**RR 0.46** (0.20 to 1.10)	Study population	
				89 per 1,000	**48 fewer per 1,000** (71 fewer to 9 more)

a. The 95% CI included appreciable benefit and harm. So, the certainty of evidence was rated down by one level
b. There were concerns about blinding of personnel and of blinding of outcome assessments in all 5 studies. So, the certainty of the evidence was rated down by one level
c. There were concerns about blinding of personnel and of blinding of outcome assessments in the included study. So, the certainty of the evidence was rated down by one level

In the Ohlsson 2020 Cochrane review, gastrointestinal bleeding appears to be statistically significantly better with acetaminophen compared to ibuprofen

d. There were no concerns for random sequence generation in the 5 included trials but the allocation concealment was unclear in 1 of the studies. However, there were concerns about blinding of personnel and of blinding of outcome assessments. The certainty of the evidence was downgraded by one level
e. There were concerns about blinding of personnel and of blinding of outcome assessments in both the included studies. So, the certainty of the evidence was rated down by one level
f. The 95% CI includes moderate benefit to small harm. So, the certainty of evidence was rated down by one level
g. There were no concerns for random sequence generation in the 4 included trials but the allocation concealment was unclear in 1 of the studies. There were concerns about blinding of personnel and of blinding of outcome assessments. So the certainty of the evidence was rated down by one level
h. There were concerns about blinding of personnel and of blinding of outcome assessments in all 3 studies. So, the certainty of the evidence was rated down by one level
i. The 95% CI includes appreciable benefit to trivial harm. So, the certainty of evidence was rated down by one level

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

○ Large
○ Moderate
○ Small
● Trivial
○ Varies
○ Don't know

RESEARCH EVIDENCE

The following GRADE evidence table is based on data from the recent Cochrane systematic review by Ohlsson et al[1]:

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with standard dose ibuprofen	Risk difference with acetaminophen
Mortality	272 (5 RCTs)	⨁⨁⨁◯ MODERATE[a]	**RR 0.96** (0.55 to 1.67)	Study population	
				157 per 1,000	**6 fewer per 1,000** (71 fewer to 105 more)
NEC				Study population	

ADDITIONAL CONSIDERATIONS

No appreciable worsening of any of the outcomes were noted with acetaminophen compared to ibuprofen

	559 (5 RCTs)	⊕⊕⊕◯ MODERATE[b]	**RR 0.88** (0.46 to 1.70)	61 per 1,000	**7 fewer per 1,000** (33 fewer to 43 more)
BPD at 36 weeks' PMA	90 (1 RCT)	⊕⊕◯◯ LOW[a,c]	**RR 0.71** (0.38 to 1.30)	Study population	
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PDA ligation	290 (2 RCTs)	⊕⊕◯◯ LOW[e,f]	**RR 0.68** (0.35 to 1.32)	Study population	
				131 per 1,000	**42 fewer per 1,000** (85 fewer to 42 more)
Gastrointestinal bleeding	537 (4 RCTs)	⊕⊕⊕◯ MODERATE[g]	**RR 0.28** (0.12 to 0.69)	Study population	
				78 per 1,000	**56 fewer per 1,000** (69 fewer to 24 fewer)
Oliguria	337 (3 RCTs)	⊕⊕◯◯ LOW[h,i]	**RR 0.46** (0.20 to 1.10)	Study population	
				89 per 1,000	**48 fewer per 1,000** (71 fewer to 9 more)

a. The 95% CI included appreciable benefit and harm. So, the certainty of evidence was rated down by one level
b. There were concerns about blinding of personnel and of blinding of outcome assessments in all 5 studies. So, the certainty of the evidence was rated down by one level
c. There were concerns about blinding of personnel and of blinding of outcome assessments in the included study. So, the certainty of the evidence was rated down by one level

	d. There were no concerns for random sequence generation in the 5 included trials but the allocation concealment was unclear in 1 of the studies. However, there were concerns about blinding of personnel and of blinding of outcome assessments. The certainty of the evidence was downgraded by one level e. There were concerns about blinding of personnel and of blinding of outcome assessments in both the included studies. So, the certainty of the evidence was rated down by one level f. The 95% CI includes moderate benefit to small harm. So, the certainty of evidence was rated down by one level g. There were no concerns for random sequence generation in the 4 included trials but the allocation concealment was unclear in 1 of the studies. There were concerns about blinding of personnel and of blinding of outcome assessments. So the certainty of the evidence was rated down by one level h. There were concerns about blinding of personnel and of blinding of outcome assessments in all 3 studies. So, the certainty of the evidence was rated down by one level i. The 95% CI includes appreciable benefit to trivial harm. So, the certainty of evidence was rated down by one level	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	Based on the lowest certainty of the most important outcomes as per GRADE methodology	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	No research evidence on values and preferences around use of acetaminophen for PDA treatment in preterm infants	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Acetaminophen appeared to have similar efficacy (moderate certainty of evidence), (likely better based on the network meta-analysis) compared to standard dose ibuprofen; and appears to be significantly better in terms of lower incidence of GI bleeding (moderate certainty of evidence).	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ● Moderate savings ○ Large savings ○ Varies ○ Don't know	1. Ibuprofen: The cost of 1 vial of intravenous ibuprofen is $360.81 (CAD). 1 vial of ibuprofen is usually required for each dose in the standard dose ibuprofen regimen (10 mg/kg followed by 2 doses of 5mg/kg at 24 h intervals). Therefore the total cost of a course of standard dose intravenous ibuprofen is **$1082.43.** The oral formulation comes in a 120 ml bottle (20 mg/ml). The cost of 1 bottle of oral ibuprofen is $2.10 (CAD) which is sufficient to cover a course of oral ibuprofen 2. Acetaminophen: Injectable acetaminophen = **$15.00/100mL bag -** Estimated cost of 3-day treatment course (3 bags) per patient= **$60.00** Enteral acetaminophen = **$2.10/100mL bottle** - Estimated cost of 3-day therapy (12 doses) for a 1 kg patient= **$0.12**	A course of acetaminophen for treatment of PDA appears to be less costly compared to a course of ibuprofen

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ● Low ○ Moderate ○ High ○ No included studies	Data on treatment costs (mentioned above) was obtained from personal communication with the hospital Pharmacist of the Neonatal Intensive Care Unit, IWK Health Center, Halifax, NS	The certainty of evidence was judged as low. The certainty was downgraded by two levels as data on treatment costs was obtained from personal communication only. The data was not verified from an alternate source, nor from any peer-reviewed publications.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No studies on the cost-effectiveness of acetaminophen versus standard dose ibuprofen was identified	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	The acceptability of acetaminophen is likely to be variable based on the availability of the IV formulation which is not universally available across all neonatal intensive care units across Canada. Moreover, the efficacy of intravenous formulation of acetaminophen has not yet been proven to be similar to oral acetaminophen. Recent evidence from RCTs suggest that IV acetaminophen has significantly lower efficacy in closing a PDA as compared to both IV indomethacin[3] as well as IV standard dose ibuprofen [4]. In general, neonatologists will be comfortable with providing oral acetaminophen only if the infant is on enteral feeds. Therefore, for hemodynamically unstable infants, neonatologists are likely to use intravenous standard dose ibuprofen over intravenous acetaminophen based on current evidence.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Acetaminophen (especially enteral formulation) is already used in NICUs for pain management. Therefore, feasibility of use for PDA management is unlikely to be an issue. The intravenous formulation is not universally available across Canadian NICUs. Therefore, feasibility of use of IV acetaminophen might be an issue	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies

	JUDGEMENT						
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

The panel suggests using acetaminophen (oral formulation) over standard dose ibuprofen for treatment of hs-PDA in preterm infants where enteral feeding is deemed appropriate ***[conditional recommendation, low certainty in the evidence of effects]***

Justification

There is overall low certainty of evidence to suggest that oral acetaminophen is as effective as standard dose ibuprofen for PDA closure, does not appreciably alter any clinically important outcomes may lead to lower gastrointestinal bleeding. From a cost perspective, acetaminophen is associated with less resource use compared to IV (but not oral) standard dose ibuprofen

Implementation considerations

The recommendation takes into account the balance of desirable and undesirable effects of **oral acetaminophen *only*.**

Recent evidence from RCTs suggest that IV acetaminophen has significantly lower efficacy in closing a PDA as compared to both IV indomethacin (Davidson 2020) as well as IV standard dose ibuprofen (Dani 2020). Therefore, for hemodynamically unstable infants who are not being fed enterally, neonatologists are likely to use intravenous standard dose ibuprofen over intravenous acetaminophen based on current evidence.

References

1. Ohlsson A, Shah PS. Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low birth weight infants. Cochrane Database Syst Rev. 2020 27;1:CD010061.

2. Mitra S, Florez ID, Tamayo ME, Mbuagbaw L, Vanniyasingam T, Veroniki AA, et al. Association of Placebo, Indomethacin, Ibuprofen, and Acetaminophen With Closure of Hemodynamically Significant Patent Ductus Arteriosus in Preterm Infants. JAMA. 2018 Mar 27;319(12):1221–38.

3. Davidson JM, Ferguson J, Ivey E, Philip R, Weems MF, Talati AJ. A randomized trial of intravenous acetaminophen versus indomethacin for treatment of hemodynamically significant PDAs in VLBW infants. J Perinatol Off J Calif Perinat Assoc. 2020 May 21;

4. Dani C, Lista G, Bianchi S, Mosca F, Schena F, Ramenghi L, et al. Intravenous paracetamol in comparison with ibuprofen for the treatment of patent ductus arteriosus in preterm infants: a randomized controlled trial. Eur J Pediatr. 2020 Sep 4;

Overarching question: Which COX-I drug should be used as the pharmacotherapy of choice for the treatment of an hs-PDA?

Question 1: Should standard dose ibuprofen vs. indomethacin be used for treatment of an hs-PDA?

Question 2: Should acetaminophen vs. standard dose ibuprofen be used for treatment of an-hs-PDA?

Question 3: Should high dose ibuprofen vs. standard dose ibuprofen be used for treatment of an hs-PDA?

Summary of judgements

	standard dose ibuprofen/indomethacin	acetaminophen/standard dose ibuprofen	high dose ibuprofen/standard dose ibuprofen	Importance for decision
Balance of effects	Probably favors the intervention	Probably favors the intervention	Probably favors the intervention	**high**
Certainty of evidence	Low	Low	Very low	
Resources required	Moderate costs	Moderate savings	Negligible costs and savings	**low**
Cost effectiveness	No included studies	No included studies	No included studies	**moderate**
Equity	Probably no impact	Probably no impact	Probably no impact	**low**
Acceptability	Probably yes	Varies	Probably yes	**high**
Feasibility	Yes	Yes	Yes	**high**

Review

	standard dose ibuprofen	indomethacin	acetaminophen	high dose ibuprofen	Importance for decision	Comment
Balance of effects	★★★	★★★	★★★	★★★★	**high**	1
Resources required	★★★	★★★★	★★★★★	★★	**low**	2
Cost effectiveness					**moderate**	
Equity	★★★★★	★★★★★	★★★★★	★★★★★	**low**	
Acceptability	★★★★	★★★	★★★	★★★	**high**	3
Feasibility	★★★★★	★★★★★	★★★★★	★★★★★	**high**	

Comment 1: Efficacy-wise indomethacin, acetaminophen and standard dose ibuprofen appear similar in closing a PDA. High dose ibuprofen appears to be significantly better than standard dose ibuprofen. There are no head to head trials of high dose ibuprofen with indomethacin or acetaminophen. However, indirect comparisons through a network meta-analysis suggests high dose ibuprofen might have the best likelihood for PDA closure

Comment 2: From a cost perspective, acetaminophen appears to be least costly, while high dose IV ibuprofen would incur the maximum costs. However, there appears to be little difference in costs between the oral formulations of ibuprofen and acetaminophen, both being substantially cheaper than any of the IV formulations.

Comment 3: Standard dose ibuprofen is likely to be most acceptable as it is safer than indomethacin while being equally efficacious in closing a PDA. There are some concerns among neonatologists with use of high dose ibuprofen in extremely preterm infants due to lack of robust safety data, though available evidence does not show any increase in clinically important adverse effects. Oral acetaminophen appears to be safer than standard dose ibuprofen in terms of GI bleeding while being similar in efficacy. However, the efficacy of the intravenous formulation is questionable in light of recent studies. Therefore, its acceptability may be less than standard dose ibuprofen based on current evidence.

Recommendation	Ibuprofen should be considered as the pharmacotherapy of choice for treatment of hs-PDA
Strength of recommendation Strong	
Recommendation	High dose ibuprofen may be considered as the preferred dosage, especially in preterm infants beyond the first 3-5 days of age

Strength of recommendation Conditional	
Justification	Out of all the options, ibuprofen appears to have the best balance of safety and effectiveness. Therefore, we strongly recommend ibuprofen as the medication of choice. High dose ibuprofen appears to have the best efficacy. However, given the absence of robust safety data, we conditionally recommend use of high dose ibuprofen as the preferred dosage of administration for ibuprofen.
Subgroup considerations	Caution should be exercised when treating extremely preterm infants (<26 weeks of gestation) with high dose ibuprofen due to limited safety and efficacy data.

QUESTION

Should repeat pharmacotherapy vs. procedural closure be used for treatment of an hs-PDA?	
POPULATION:	Preterm infants with a persistent hs-PDA
INTERVENTION:	repeat pharmacotherapy
COMPARISON:	procedural closure

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	PDA pharmacotherapy is not 100% effective. Often the PDA remains open even after an initial course of treatment leading to persistence of clinical signs. There is debate on whether the infant should be subjected to repeat courses of pharmacotherapy or should undergo a more definitive form of treatment such as procedural closure of the PDA	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Research evidence on repeat pharmacotherapy** **Indomethacin** Evidence from observational study shows that cumulative PDA closure increases with repeat courses of indomethacin[1]. The authors demonstrated that “both the second and the third course of indomethacin are independently associated with a 40% ductal closure rate among those who fail to close with a prior indomethacin course. Our findings also suggest that a cumulative ductal closure rate of 90% is achievable with three courses of indomethacin”. However, the authors noted an increased trend in the incidence of PVL (adjusted OR 4.8; 95% CI: 0.8-30) in infants who received 3 courses of indomethacin compared to those who received 2 courses[1]. No evidence was identified comparing repeat indomethacin courses versus invasive PDA closure. **Ibuprofen** Observational cohort study of 160 infants (mean GA 25.6±1.4 weeks; mean BW 757±127 g) showed that 70 infants closed their PDA after a single course of ibuprofen (45%) and 32/80 (40%) following a second course. Infants of <26 weeks' gestation (n = 83) were less likely to respond after both the first (27.7% vs 63.6%; P < .001) and second (30.9% vs 60.0%; P = .026) courses[2].	**Desirable effects with invasive PDA management** Procedural closure is the most definitive PDA closure procedure with 100% success rate with surgical closure. A recent systematic review of percutaneous closure of PDA showed that infants <6Kg had a technical success of 93%[7]

	Observational study by Olgun et al on effect of repeat courses of oral ibuprofen in preterm infants showed that PDA closure rate was 71% after the first course, 40% after the second course, and 35% after the third course. Although the second course resulted in a significant increase in the closure rate ($p<0.05$), the rate did not increase significantly with the third course ($p>0.05$)[3]. A retrospective cohort study of 164 preterm infants (< 32 weeks' gestational age), showed that the closure rate of PDA after a second (44%) or third (55%) course of ibuprofen was similar to the closure rate after the first course (66%), with no additional side effects following multiple courses[4]. No evidence was identified comparing repeat ibuprofen courses versus invasive PDA closure. **Acetaminophen** A Canadian retrospective cohort study showed that out of 26 infants (mean GA 24.4 weeks at birth) with persistent hs-PDA who failed to respond to indomethacin treatment and were referred for surgical PDA ligation, "echo indices of shunt volume improved in 12 (46%) infants (3 closed and 9 reduced to mild shunt), all of whom avoided ligation. There was no echo improvement in 14 (54%) infants, of which 8/14 underwent ligation, and ligation was deferred in 6/14 infants, mostly owing to improvement in respiratory stability." [5] Another Canadian retrospective cohort study of 92 preterm infants [median (interquartile range) gestational age 25.2 weeks (24.4-26.3)] with persistent large PDA being considered for surgical ligation after unsuccessful medical therapy showed that a trial late oral acetaminophen therapy for infants with persistent PDA was associated with reduced surgical ligation but increased CLD [6]. Of note, in both the above studies the infants received acetaminophen at a dose of 15mg/kg/day every 6 hours for 3-7 days.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	**Research evidence on repeat pharmacotherapy** **As above**	**Undesirable effects with invasive PDA management** PDA ligation is associated with complications such as vocal cord paresis, phrenic nerve palsy, thoracic scoliosis, and inadvertent ligation of the left pulmonary artery and aorta with substantial variation in reported rates between centers A systematic review of studies documenting the incidence of left vocal cord paralysis after PDA ligation in extremely preterm infants showed that the overall pooled estimate was 9% (95% CI, 5-15%) with a wide variability between studies (range 0-67%)[8] For percutaneous transcatheter PDA closure, a systematic review of 38 observational studies reported an overall adverse event rate of 23.3% (95% CI, 16.5–30.8) and clinically significant adverse event rate of 10.1% (95% CI, 7.8–12.5)[7]. Another recent systematic review demonstrated that infants ≤6Kg had an overall adverse event rate of 25% (95% CI 20-31%) and a clinically significant adverse event rate of 10% (95% CI 7-12%) (Bischoff 2020). Clinically significant adverse events include the following (Bischoff 2020): -Death related to the procedure

		- Cardiac tamponade - Guide wire perforation - Event requiring cardiopulmonary resuscitation - Need for repeat catheterization and/or surgery (i.e.: retrieval of malpositioned or embolized device with embolization noted after the patient had already left the procedure room; severe hemolysis requiring device/coil removal) - Significant and/or persistent LPA/aortic obstruction requiring intervention (i.e.: LPA stenosis requiring stent) - Vascular compromise requiring intervention - Post-ligation cardiac syndrome and/or need for initiation or escalation in dose of inotropes/vasopressors in the first 24 hours after the procedure - Significant hemorrhage requiring blood transfusion >20mL/kg - Thrombosis requiring thrombolytics

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	All available evidence obtained from observational studies and therefore rated as low as per the GRADE methodology	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	No research evidence on family values and preferences around repeat pharmacotherapy versus procedural closure for hs-PDA management identified	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Repeat courses with indomethacin appears effective, but safety is questionable with likely increased risk of PVL with 3rd course. No evidence was identified comparing repeat indomethacin courses versus invasive PDA closure. PDA closure rates appear to be substantially improved with repeat courses of ibuprofen compared to single courses. There are no reported safety issues with repeat courses of ibuprofen. No evidence was identified comparing repeat ibuprofen courses versus invasive PDA closure. **Low certainty** evidence suggests, oral acetaminophen at a dose of 15mg/kg/day every 6 hours for 3-7 days (preferably up to 7 days unless contraindicated), may reduce need for surgical PDA ligation. There is insufficient evidence to comment on the effect of this approach on clinical outcomes. The balance of desirable and undesirable effects probably favors use of a 2nd course of pharmacotherapy with (ibuprofen or indomethacin) and possibly a trial of a 3rd course of pharmacotherapy with oral acetaminophen	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ● Large savings ○ Varies ○ Don't know	**Repeat pharmacotherapy** 1. Indomethacin: The cost of indomethacin therapy for a singleton preterm infant normally would be $296.91 (see evidence-to-decision tables for prophylactic indomethacin for details) 2. Ibuprofen: The cost of 1 vial of intravenous ibuprofen is $360.81 (CAD). 1 vial of ibuprofen is usually required for each dose in the standard dose ibuprofen regimen (10 mg/kg followed by 2 doses of 5mg/kg at 24 h intervals). Therefore the total cost of a course of standard dose intravenous ibuprofen is $1082.43. The oral formulation comes in a 120 ml bottle (20 mg/ml). The cost of 1 bottle of oral ibuprofen is $2.10 (CAD) which is sufficient to cover a course of oral ibuprofen 3. Acetaminophen: Injectable acetaminophen = **$15.00/100mL bag -** Estimated cost of 3-day treatment course (3 bags) per patient= **$60.00** Enteral acetaminophen = **$2.10/100mL bottle** - Estimated cost of 3-day therapy (12 doses) for a 1 kg patient= **$0.12** **Invasive treatment** There is limited data on resource use for PDA ligation or transcatheter occlusion in preterm neonates in the Canadian context. Data from the United States on costs of surgical ligation and	

	transcatheter closure in children and young adults showed that the total cost of surgical closure of the PDA was $8509±1615 while that of transcatheter closure was $5273±1940 [9]	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	Data on treatment costs (mentioned above) was obtained from personal communication with the hospital Pharmacist of the Neonatal Intensive Care Unit, IWK Health Center, Halifax, NS Data on treatment costs for invasive treatment was obtained from the observational study by Prieto et al [9].	The overall certainty of evidence was judged as low. The certainty was downgraded by two levels as data on pharmacotherapy costs was obtained from personal communication only. The data was not verified from an alternate source, nor from any peer-reviewed publications. Similarly, data on invasive treatment costs was obtained from observational studies and therefore rated as low as per the GRADE methodology

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies	Pharmacoeconomic study by Turck et al suggests “PDA treatment expenses may be as low as $49,457 for neonates who do not receive surgery and as high as $176,739 for infants who do. The analysis of the database, which contains data from over 2.9 million pediatric discharges from 3,438 community hospitals, specialty hospitals, and academic medical centers in 36 states, demonstrates that the institutional expenses associated with ligation can engender over $77,000 in additional expenses as compared to the nonsurgical resolution of PDA”. [10]	

○ No included studies		

Equity
What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		

Acceptability
Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	A cohort study of 435 children from Sweden showed that "children who had primary PDA surgery faced increased risks of NDI, with an adjusted incidence rate ratio of 1.62 (95% confidence interval [CI] 1.28- 2.06) and a lower adjusted mean difference FSIQ of −7.1 (95% CI −11 to −3.2). Surgery at less than 10 days of life was associated with a significantly increased risk of moderate to severe NDI and lower FSIQ than surgery after 20 days" [11]. The results therefore suggest that "drug treatment followed by deferred surgery appeared to be a safer option for extremely preterm infants severely affected by PDA" Furthermore, given the need for additional resources for interventional management of the PDA (such as cardiothoracic surgery expertise or percutaneous transcatheter device closure expertise) compared to repeat treatment, trial of additional courses of pharmacotherapy is likely to be more acceptable.	There is considerable debate on the usefulness and timing of invasive PDA closure in preterm infants. It has been shown that persistence of an hs-PDA is associated with increased risk of death or CLD. However, outcomes following surgical PDA ligation are controversial as majority of the evidence is obtained from studies that failed to address confounding by indication. A recent Canadian observational study (n=166) showed that a pre-ligation PDA diameter>2.5mm and left ventricular dilatation (z score≥2) predicted earlier extubation following surgical ligation in ventilator-dependent preterm infants suggesting possible benefit of procedural PDA closure in the subgroup of preterm infants with echocardiographic markers of large shunt volume and pulmonary overcirculation[12].

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Repeat pharmacotherapy approach for a persistent PDA appears to be more feasible compared to procedural closure due to the same reasons as mentioned in the acceptability section.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	**Large savings**	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	No included studies
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**

○	○	○	○	●

CONCLUSIONS

Recommendation

Clinicians should provide a second course of pharmacotherapy (with ibuprofen or indomethacin) **(Strong recommendation)** and consider a 3rd course of pharmacotherapy with oral acetaminophen **(conditional recommendation)** over procedural PDA closure for a persistent hs-PDA following failure of primary pharmacotherapy.

Procedural closure of the PDA may be considered in infants with an hs-PDA persistent even after 2 courses of pharmacotherapy in presence of significant clinical symptoms and echocardiographic signs of large shunt volume and pulmonary overcirculation **(conditional recommendation).**

Justification

The balance of desirable and undesirable outcomes favors repeat treatment (2nd course) primarily due to the increased risk of adverse effects with invasive therapy. A 3rd course of pharmacotherapy appears to be harmful with indomethacin, unclear with ibuprofen and possibly beneficial with oral acetaminophen. Earlier surgery appears to adversely impact neurodevelopmental outcomes. From a resource use, cost-effectiveness and acceptability perspective, repeat treatment appears more favorable than invasive management.

References

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QUESTION

Should surgical PDA ligation vs. percutaneous catheter closure of PDA be used for invasive management of a persistent hs-PDA?	
POPULATION:	Preterm infants with a persistent hs-PDA requiring procedural PDA closure
INTERVENTION:	surgical PDA ligation
COMPARISON:	percutaneous catheter closure of PDA

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Surgical PDA closure has been the most definitive therapy to close a PDA. However, surgical PDA closure is associated with numerous complications. Percutaneous transcatheter PDA closure, a minimally invasive procedure, is an emerging alternate option for PDA closure in preterm infants.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	There are currently no head-to-head RCTs comparing the 2 approaches. The desirable and undesirable effects are obtained from systematic review of observational studies.	**Surgical PDA ligation** Surgical ligation of the PDA definitively eliminates a PDA. There appears to be no difference in success rates with either suture ligation or clip application[1] **Percutaneous catheter closure** Technical success reported from 38 observational studies was 92.2% (95% confidence interval [CI] 88.8–95.0)[2] A recent systematic review of 28 observational studies reported a technical success of 96% (95% CI 93-98%) in preterm infants ≤1.5 Kg (Bischoff 2021)

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ○ Moderate ○ Small ○ Trivial ● Varies ○ Don't know	There are currently no head-to-head RCTs comparing the 2 approaches. The desirable and undesirable effects are obtained from systematic review of observational studies.	**Surgical PDA ligation** PDA ligation is associated with complications such as vocal cord paresis, phrenic nerve palsy, thoracic scoliosis, and inadvertent ligation of the left pulmonary artery and aorta with substantial variation in reported rates between centers A systematic review of studies documenting the incidence of left vocal cord paralysis after PDA ligation in extremely preterm infants showed that the overall pooled estimate was 9% (95% CI, 5-15%) with a wide variability between studies (range 0-67%)[3] **Percutaneous catheter closure** A systematic review of 38 observational studies reported an overall adverse event rate of 23.3% (95% CI, 16.5–30.8) and clinically significant adverse event rate of 10.1% (95% CI, 7.8–12.5)[2]. An updated systematic review demonstrated that infants ≤1.5Kg had an overall adverse event rate of 27% (95% CI, 17-38%), clinically significant adverse event rate of 8% (95% CI 5-10%) and a procedure related mortality of 2% (95% CI, 1-4%). (Bischoff 2021).

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	The evidence was exclusively derived from a systematic review of observational studies. Most of the included studies had low risk of bias with regards to study selection criteria on the Newcastle-Ottawa scale [2]. Therefore the certainty of evidence was not rated down further.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Important uncertainty or variability ○ Possibly important uncertainty or variability	There is no research evidence on family values and preferences regarding surgical PDA ligation versus percutaneous catheter closure of PDA in preterm infants	

○ Probably no important uncertainty or variability ○ No important uncertainty or variability		

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	There is insufficient research evidence on benefits versus harms to recommend one approach over the other	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	There is limited data on resource use for PDA ligation or transcatheter occlusion in preterm neonates in the Canadian context. An observational study conducted in the United States between 1993-96 compared cost and clinical outcomes of patients who underwent PDA coil occlusion (n=24) versus those who underwent surgical PDA ligation (n=12) (age range 13 months to 28 years). The study showed that “the average cost to the institution of coil occlusion was $5273 ± $1940 (range, $3356 to $11 273), 38% less than that for surgical closure at $8509 ± $1615 (range, $6463 to $11 827) (P <0.001). The greatest difference was in the cost of inpatient hospital stay, with a cost of $398 ± $217 for coil closure and $2566 ± $626 for surgical closure (P <0.001). Professional cost also was significantly lower for coil closure at $1506 ± $703 than for surgical closure at $2782 ± $516 (P <0.001). The technical cost was similar between the two groups ($2156 ± $797 for coil vs $2151 ± $736 for surgery)”[4] A more recent observational study specifically looking at procedural charges and outcomes of surgical versus percutaneous PDA closure showed that “procedural charges for transcatheter device closure were twice as expensive as those for surgical ligation” driven by device charge and catheterization room utilization[5]	There is unclear evidence at this point on which approach is associated with lesser resource use

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	The evidence on resources required was derived from observational studies. Therefore the certainty of evidence was rated as low.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No formal cost-effectiveness research on surgical PDA closure versus percutaneous transcatheter PDA closure was identified.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		

Acceptability

Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know		If local rates of surgical complications are low then surgical PDA closure is likely to remain a more feasible option. If institutional expertise is available, percutaneous transcatheter PDA closure may be preferred to PDA ligation, especially in centers with high local rates of surgical complications such as vocal cord paralysis

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know		Depends on availability of surgical PDA closure versus percutaneous transcatheter PDA closure options

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		**Varies**	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies

	JUDGEMENT						
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

CONCLUSIONS

Recommendation

There is insufficient research evidence on benefits versus harms to recommend one approach over the other.

If institutional expertise is available, percutaneous transcatheter PDA closure may be considered as an alternative to PDA ligation, especially in centers with high local rates of surgical complications such as vocal cord paralysis **(conditional recommendation)**

Justification

There appears to be marginal difference in the success rates between the two approaches, both having high success rates in closing a PDA. Both approaches are associated with adverse outcomes of differing nature and the rate of adverse outcomes appear to depend on institutional expertise. There is varying data on resource use and insufficient data on cost-effectiveness in the specific population of preterm infants. Therefore, the panel felt both approaches are acceptable and choice should be made depending on institutional expertise and adverse effect profile associated with either procedure.

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QUESTION

Should referral to pediatric cardiology vs. conservative management be used for hemodynamically stable growing preterm infants with a persistent PDA?	
POPULATION:	hemodynamically stable growing preterm infants with a persistent PDA
INTERVENTION:	referral to pediatric cardiology
COMPARISON:	conservative management

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	With increase in conservative PDA management, more infants who are repatriated back to non-tertiary neonatal care units tend to have a persistent PDA. Prolonged persistence of the PDA often poses a management dilemma among general pediatricians caring for these infants as these infants are otherwise well but may have ongoing respiratory symptoms due to BPD. There may be a tendency to refer infants back to tertiary care centers for further evaluation in such instances	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	There is no published data comparing the effectiveness of the two approaches	There are anecdotal reports of growing preterm infants developing severe chronic pulmonary hypertension due to chronic pulmonary overflow which could lead to increased respiratory morbidity and mortality[1]. Therefore, evaluation of a persistent PDA by a pediatric cardiologist will help to rule out chronic pulmonary hypertension and plan follow-up.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	There is no published data comparing the effectiveness of the two approaches	Evidence from multiple observational studies demonstrate that most persistent PDAs in preterm infants close off on their own. The impact of a prolonged persistent PDA on clinical outcomes remains unclear. In a retrospective cohort study conducted in 2 European level-3 neonatal units, Sembrova et al showed that out of 280 very low birth weight infants who received conservative PDA management, the PDA closed before hospital discharge in 237 (85%) infants[2]. Another cohort study showed that in extremely preterm infants born between 23-28 weeks of gestation, 95%(105/111) infants with a hs-PDA had a spontaneous PDA closure by discharge[3]. Furthermore, a retrospective cohort study from Philadelphia, United States, showed that "Among 329 infants with severe BPD (sBPD), 59 had a PDA at ≥36 weeks' PMA. Most PDAs were small (n = 33) and shunted left to right (n = 53). The PDA closed spontaneously prior to discharge in 5 of 21 infants who did not undergo surgical closure and decreased in size in 3. The PDA spontaneously closed by 1 year of age in 6 out of 12 infants with an open duct at discharge" [4] Therefore routine evaluation of a persistent PDA in a clinically stable preterm infant may be unnecessary during hospital stay

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	The primary source of the indirect evidence discussed above is observational and therefore rated low as per GRADE methodology	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or	No research evidence on values and preferences of families regarding routine referral versus conservative management	

variability ○ No important uncertainty or variability		

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		Given that spontaneous PDA closure is highly likely in majority of preterm infants, it is prudent to wait and watch, especially if the infant is otherwise clinically stable.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know		Referral back to a tertiary care center for PDA evaluation of a preterm is likely to incur significant healthcare costs related to repatriation by a medical team and in patient stay at a tertiary care center

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ○ Low ○ Moderate ○ High ● No included studies		

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No cost-effectiveness analysis on immediate pediatric cardiology referral versus conservative management of the PDA in a stable preterm infant in a level II NICU was identified	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know		Given the high rate of spontaneous closure of PDA in preterm infants and the uncertain effect of a persistent PDA on long term outcomes, routine referral back to a tertiary care center for PDA evaluation for a clinically stable preterm infant is unlikely to be acceptable by key stakeholders

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know		Referral back to a tertiary care center for PDA evaluation of a preterm infant is judged to be a low priority transfer and therefore routine referrals are unlikely to be feasible in a center with high referral volume of sicker infants

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	**Favors the comparison**	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**

	JUDGEMENT						
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
●	○	○	○	○

CONCLUSIONS

Recommendation

Routine referral to tertiary care center for echocardiographic evaluation of a persistent PDA in an otherwise clinically stable growing preterm infant prior to discharge is not recommend [Strong Recommendation]

Pediatric cardiology referral should be sought for ongoing evaluation and follow-up if the PDA is deemed to be present at discharge [Strong Recommendation]

Justification

The panel judged that the high rate of spontaneous PDA closure at discharge and unclear benefits of routine PDA evaluation in a clinically stable, growing preterm infant does not justify the excess resource use in terms of repatriation back to a tertiary care center and a pediatric cardiology referral prior to discharge.

However, the panel acknowledged that given the reported risks of chronic pulmonary hypertension and its related complications as a consequence of a persistent PDA in some infants, if the infant is deemed to have a persistent PDA at discharge, pediatric cardiology referral should be sought for ongoing outpatient evaluation and follow-up.

References

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