Variation in the diagnosis and management of patent ductus arteriosus in premature infants

Lillian SW Lai MD MHA, Brian W McCrindle MD MPH FRCPC
Department of Pediatrics, Division of Cardiology, The Hospital for Sick Children, Toronto, Ontario

LSW Lai, BW McCrindle. Variation in the diagnosis and management of patent ductus arteriosus in premature infants. Paediatr Child Health 1998;3(6):405-409.

OBJECTIVES: To determine variations in neonatology practice regarding the diagnosis and management of patent ductus arteriosus (PDA) in premature infants.
DESIGN: Standardized telephone interview of preferences and practices.
SUBJECTS: Canadian neonatologists in active clinical practice.
RESULTS: Of 136 eligible Canadian neonatologists, 100 respondents (74%) estimated the proportion of infants with suspected PDA who have echocardiography to be a median of 80% (range 0% to 100%), with considerable variation both within and between centres. Only two centres had written guidelines. More recent medical school graduates were significantly more likely to use echocardiography. Increased use of echocardiography was also significantly related to increased availability. Fluid restriction and indomethacin was used as initial therapy by 89% of respondents, with the indomethacin dose standardized for 83%; surgical ligation was used when indomethacin therapy was contraindicated or had failed. Personal guidelines directed decisions regarding therapy for the majority of neonatologists.
CONCLUSIONS: Among Canadian neonatologists, there is considerable variation regarding practices related to the diagnosis and management of PDA in premature infants. This variation may potentially affect the cost effectiveness of care for these patients.

Key Words: *Echocardiography, Indomethacin, Neonatologists, Patent ductus arteriosus, Practice variations*

La variation dans le diagnostic et la prise en charge de la persistance du canal artériel chez les prématurés

OBJECTIFS : Déterminer les variations en pratique néonatalogique dans le diagnostic et la prise en charge de la persistance du canal artériel (PCA) chez les prématurés.
MÉTHODOLOGIE : Entrevue téléphonique normalisée des préférences et des pratiques.
SUJETS : Néonotalogues canadiens en pratique clinique active.
RÉSULTATS : Sur 136 néonatalogues canadiens admissibles, 100 répondants (74 %) ont estimé que la proportion de nourrissons atteints d'une PCA présomptive ayant subi une échocardiographie se situait près du 80^{e} percentile (sur une échelle de 0 % à 100 %) et que la variation était considérable à la fois au sein et en périphérie de ce percentile. Seulement deux centres disposent de directives écrites à ce sujet. Les jeunes diplômés des facultés de médecine sont beaucoup plus susceptibles de recourir à l'échocardiographie. L'accroissement de l'utilisation de l'échocardiographie dépend aussi énormément de l'augmentation de sa disponibilité. La restriction liquidienne et l'indométacine constituent le traitement initial selon 89 % des répondants, la dose d'indométacine étant standardisée chez 83 % d'entre eux, et ceux-ci optent pour une ligature chirurgicale en cas de contre-indication ou d'échec de l'indométacine. Des directives personnelles orientent les décisions de traitement de la majorité des néonotalogues.
CONCLUSIONS : Parmi les néonotalogues canadiens, la pratique varie de manière significative pour ce qui est du diagnostic et de la prise en charge de la PCA chez les prématurés. Cette variation risque de nuire à l'optimisation des coûts dans les soins de ces patients.

Persistent patency of the ductus arteriosus (PDA) is a cause of significant morbidity in premature infants (1-5). An incidence of 20% in infants with birth weights less than 1750 g and 42% in infants less than 1000 g has been reported (6). Often, a combination of clinical, radiological and echocardiographic criteria are used to diagnose PDA in practice. However, clinical and radiological clues are unreliable (6-14). Echocardiography is the most accurate noninvasive method to detect a hemodynamically significant PDA (15,16), but there are no guidelines as to its use in this setting. Given the high morbidity associated with PDA in premature infants (1-5), the predictive value of echocardiographic features has been increasingly explored (1,9,12,17).

While indomethacin is the drug of choice for medical treatment of symptomatic PDA in premature infants, there is insufficient evidence to favour a single therapeutic regimen (2,5,18). Due to the potentially life threatening

Correspondence: Dr Brian W McCrindle, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario M5G 1X8. Telephone 416-813-7609, fax 416-813-7547, e-mail brian.mccrindle@mailhub.sickkids.on.ca

TABLE 1: Reported practices regarding use of echocardiography in a survey of 100 Canadian neonatologists practising in Canada

Question	Cue Never	% of respondents 1	2	3	4	5	Cue Always
How often do you use echocardiography							
for routine surveillance of PDA regardless of clinical suspicion?		39	19	17	14	11	
to confirm clinical suspicion of PDA in symptomatic patients?		3	13	11	21	52	
to confirm clinical suspicion of PDA in asymptomatic patients?		11	20	17	23	29	
to guide therapeutic decisions regarding PDA?		9	17	21	37	16	

PDA Patent ductus arteriosus

adverse effects and contraindications of indomethacin (18-23), alternative drugs are being studied (24,25). Variations in physician practice patterns have been documented in other areas of medicine (26-29). Given the lack of evidence in the literature regarding the optimal strategy for the diagnosis and treatment of PDA, the development of new diagnostic and treatment approaches, and the need to assess not only effectiveness but also efficiency in practice during these times of fiscal constraint, we sought to assess how Canadian neonatologists diagnose and treat PDA in the premature infant, and to determine variations in self-reported practice. We also sought to determine factors associated with variations in use.

SUBJECTS AND METHODS

Study population

An initial list of Canadian neonatologists was obtained from the Fetus and Newborn Committee of the Canadian Paediatric Society. As separate subspecialty certification in neonatal-perinatal medicine was not available, a neonatologist, for the purposes of our study, was defined as a practising staff physician in a level 3 or specialized level 2 neonatal intensive care unit (NICU) who had either completed a Royal College of Physicians and Surgeons of Canada accredited residency in neonatal-perinatal medicine, or was recognized by other trained neonatologists as being a neonatologist. Eligible neonatologists had to be practising in NICUs where they were primary decision-makers regarding the diagnosis and management of PDA.

Data collection

Eligible neonatologists were contacted by telephone and eligibility criteria verified. Physicians who were noted to not be in practice, who were not neonatologists or who were not involved in decision-making regarding PDA were excluded. Respondents were asked to identify other neonatologists in their practices or in the community, and these physicians were contacted and assessed for eligibility. A standardized telephone interview was performed to collect information on physician and practice characteristics, opinions and practices regarding the role of echocardiography to guide diagnosis and treatment of PDA, and opinions and practices regarding the management of PDA in premature infants.

Data analysis

Responses were tabulated as frequencies and medians with ranges. Differences between centres regarding frequency of use of echocardiography were sought using Kruskal-Wallis analysis of variance. Nonparametric measures of association (Kendall's tau-b coefficient, gamma coefficient) were used to relate estimates of use of echocardiography to physician and practice characteristics.

RESULTS

Study participation

From an initial list of 153 physicians from 53 centres, 51 physicians were excluded because they had moved from Canada, were retired or in part-time practice, were not affiliated with an eligible centre, were not neonatologists or could not be located. During the study, 34 additional physicians were included based on responses from those physicians contacted. From a final list including 136 neonatologists from 45 centres, completed interviews were obtained from 100 (74%) neonatologists from 42 centres. Up to three attempts were made to contact all nonrespondents. There appeared to be no response bias regarding geography or centres.

Respondent characteristics

Twenty-six neonatologists were heads of NICUs, and 74 were staff neonatologists. The median year of medical school graduation was 1974 (range 1943 to 1988). Of the 42 centres, the median number of neonatologists per centre was three (range one to 10), and the median number of full-time nurses was 80 (range five to 150). Six centres had more than six staff neonatologists. The median number of patient beds was 26 (range four to 60), with a median number of ventilated patients per day of six (range 0 to 22).

Availability of echocardiography

Echocardiography was available at 95% of centres, and the service was provided primarily by paediatric cardiologists in 54%, adult cardiologists in 17%, radiologists in 17%, paediatricians with a cardiology interest in 7% and by a technician with telephone transmission to a paediatric cardiologist in 5%. Echocardiography was available directly in 59% and only with a cardiology consulta-

TABLE 2 : Personal indications for use of echocardiography

Indication	% of respondents
Before closure to exclude the presence of ductal-dependent congenital heart lesions	55
To confirm clinical findings regardless of condition of infant	18
To confirm clinically suspected PDA in symptomatic infants	18
Dysmorphic infants or infants with other congenital anomalies	10
Recurrence of clinical signs after treatment for PDA	10
Infants with a persistent murmur and no symptoms	5
All premature infants with a heart murmur	4
Routinely in infants weighing less than 1500 g	4
Routinely in infants weighing less than 1000 g	2
Failure of infant to wean from ventilator as expected	1
Routine surveillance before discharge from nursery	1

PDA Patent ductus arteriosus

tion in 41%, and was available within 2 h of request in 12% of centres, 12 h in 42%, 24 h in 34% and within 48 h in 12%. Availability was related somewhat to who provided echocardiography, with echocardiography available within at least 12 h of request for 73% when provided by radiologists, 44% when by paediatric cardiologists and 33% when provided by adult cardiologists. Only two centres had clearly specified guidelines for the use of echocardiography for infants regarding PDA.

Physician use of echocardiography

Physicians were asked to rank their frequency of use of echocardiography under various circumstances from 1 (never) to 5 (always) on a 5-point Likert scale (Table 1). There was marked variation among individual neonatologists for each circumstance, but the responses were all significantly correlated, with gamma correlation coefficients ranging from 0.26 to 0.64 for each pairwise comparison (ie, high users of echocardiography tended be high users in every situation). When asked to estimate the percentage of infants under their care with a clinically suspected PDA who would ever have an echocardiogram, the median response was 80%, with a range from 0% to 100%. The majority (95%) of physicians offered some personal guidelines regarding their use of echocardiography (Table 2).

Variations in the use of echocardiography

Variations within and between centres for reported use of echocardiography were explored for 12 centres for which four or more neonatologists completed interviews.

TABLE 3: Personal guidelines for treatment of PDA*

Treatment protocol			
First-line	Second-line	Third-line	% of respondents
Fluid restriction and observation	Up to two courses of indomethacin	**Surgery**	52
Fluid restriction and indomethacin course	Surgery		37
Fluid restriction and indomethacin course	Dexamethasone	**Surgery**	8
Fluid restriction	Indomethacin course and maintenance indomethacin	**Dexamethasone and surgery**	1

**9% of physicians indicated that under certain conditions they would use surgery as first-line treatment. PDA Patent ductus arteriosus*

Significant variation within these institutions, arbitrarily defined as a range of responses for each question in Table 1 of more than two categories among individual neonatologists within each institution, was noted for 67% of centres for routine surveillance, 33% for confirmation in symptomatic patients, 33% for confirmation in asymptomatic patients and 25% to guide decisions about therapy. Significant differences among centres regarding the median category at each centre was noted for use of echocardiography for confirmation in symptomatic (Kruskal Wallis ANOVA P=0.005) and asymptomatic infants (P=0.01) suspected of having PDA, and to guide decisions about therapy (P=0.03), but not for routine surveillance (P=0.18). The estimated percentage of infants receiving echocardiograms varied by more than 50% among individual physicians within six (50%) of the 12 centres, and the median value ranged from 5% to 90% among centres.

Some factors associated with use of echocardiography were explored. More recent graduation from medical school was significantly correlated with increasing use of echocardiography for confirmation of PDA in symptomatic patients (Kendall r=0.22, P=0.03), but was not related to use in other circumstances. Increasing waiting time to obtain an echocardiogram was significantly related to decreasing use for routine surveillance (gamma 0.33, P=0.002), and confirmation in both symptomatic (gamma 0.27, P=0.03) and asymptomatic patients (gamma 0.20, P=0.04). Use of echocardiography was not significantly related to the type of provider performing the echocardiogram.

Pharmacological management of PDA

Only two centres had written policies regarding the treatment of PDA, although neonatologists at these centres did not comply with the written guidelines. Personal guidelines were used by 98% of neonatologists (Table 3). All neonatologists used indomethacin as treatment for

PDA. Indomethacin regimen was standardized for 83% of physicians, with a dose of 0.2 mg/kg/day divided in up to three doses and given for three consecutive days. The remainder used a variety of dosages and regimens, ranging from 0.1 to 0.3 mg/kg/day divided up to three times a day and given for up to five consecutive days. The majority (72%) did not individualize indomethacin regimens according to patient characteristics. Indomethacin regimen was modified for infants less than 1000 g in 25% (decreased dose amount and increased number of doses) and for infants older than seven days of age for 2% (tapered dosage regimen). Dexamethasone was also used as medical mangement in five (12%) centres.

The prophylactic use of indomethacin was advocated by 14% of neonatologists and in eight (20%) centres. Among these neonatologists, the indications for prophylactic use included infants receiving surfactant in 43%, and infant birth weight, with 43% recommending it for infants less than 900 g, 36% for 1250 g and 14% for less than 1500 g. Dosage amounts and regimens used by neonatologists varied from 0.1 to 0.2 mg/kg/day divided in up to two doses and given for two to seven consecutive days.

Surgical management of PDA

All neonatologists used surgical ligation and/or division as treatment for PDA, although this was available at only 88% of centres. Surgery was performed by a paediatric cardiovascular surgeon at 67% of centres, general paediatric surgeon in 14%, adult cardiovascular surgeon in 11%, either a paediatric cardiovascular or general surgeon in 5% and either a paediatric or adult cardiovascular surgeon in 3%. Stated indications for surgery included persistent PDA after up to three courses of indomethacin for 100% of respondents and the presence of contraindications to indomethacin treatment for 99%. Some neonatologists (9%) choose surgery as first-line treatment for infants, 4% choosing it for infants 23 to 26 weeks' gestation, 2% for infants older than 21 days of age, and 2% for infants weighing less than 1000 g and 1% for infants weighing less than 800 g. No neonatologist used surgery for prophylactic treatment.

DISCUSSION

Study limitations

We have shown that there is considerable variation in the use of echocardiography and treatment regimens for PDA in premature infants. The results must, however, be viewed in light of the limitations of this study. The study population may be incompletely enumerated because no certification for neonatologists exists. The response rate was good but suboptimal, and the degree to which nonrespondents may be systematically different from respondents is unknown. For the purposes of this analysis, we assumed that reported practices reflect the respondents' actual practices and that these results represent neonatologists' practices across Canada.

Role of echocardiography

Studies comparing clinical, radiological and echocardiographic methods of diagnosis show that echocardiography is required for a confident diagnosis of PDA in the premature infant (30,31). Trivial PDAs can now be successfully detected by colour Doppler flow mapping (32-34), and shunt size can be quantitated by M-mode echocardiography (35-37). However, given the medical complexity of these patients, it is unlikely that echocardiography alone will accurately identify patients with PDA for whom the benefits of therapy outweigh the risks. Evidence defining the role of echocardiography is lacking, although a recent study concluded that its use was appropriate in one nursery (38).

Variations in use

Variation in the use of echocardiography is not surprising given that 95% of respondents stated that they follow their own set of guidelines and 25% stated that they 'never/rarely' use echocardiography to guide their therapeutic decisions. The presence of guidelines has not been shown to be useful in guiding physician practice patterns (39), and our results are consistent with this finding; physicians who were aware of written protocols opted to use their own personal guidelines instead of the written guidelines.

Previous studies (27) have shown that the availability of certain procedures affects their use, as confirmed in our study. Waiting time was shown to be somewhat related to who provided the service. Variations in access can be based on the time of day or week at which an echocardiogram is requested, or on the inconvenience of having to acquire a consultation by a specialist. In the majority of Canadian centres echocardiography is available on site and is interpreted within 12 to 24 h of request. In more isolated centres, the decision to request an echocardiogram may mandate transfer of the patient. Telephone transmission has been used by some Canadian centres to provide echocardiography to remote neonatology units. Variations in use by neonatologists may also reflect the effects of continuing education and clinical experience. We show that recent medical school graduates were more likely to use echocardiography for confirmation of PDA in symptomatic patients.

Controversies in the management of PDA

It is well documented that indomethacin should be used to close a PDA in premature infants because it is effective, improves the cardiorespiratory status, decreases mortality and may have some protective effect against the development of intraventricular hemorrhage (5,18,40,41). Individual randomized, controlled clinical trials have failed to provide convincing evidence to favour any one management strategy in the diagnosis and treatment of PDA in premature infants. Two main factors are responsible for this failure. The first is the lack of clear, consistent definitions regarding the presence and significance of

a PDA in this clinical setting (1,6,9,42,43). The second is the lack of adequate sample size in many studies to ensure sufficient statistical power to detect relevant differences in the incidence of morbidity between treatment groups. Only one large multicentre randomized trial has taken place, but this study used clinical criteria primarily for the diagnosis of PDA (18).

Variations in medical management.

Personal treatment protocols of neonatologists showed considerable variation, as reflected in the published literature. The recommendations of the National Collaborative Trial (18) support the use of fluid restriction and diuretics as first-line therapy, while other studies have shown a higher morbidity with medical management alone versus using indomethacin (2,5). The National Collaborative Trial (18) recommends a standard three-dose indomethacin regimen (0.1 to 0.2 mg/kg every 12 h for three doses). However, many neonatologists adjust this regimen based on patient characteristics and condition. Prophylactic treatment with indomethacin has been advocated for premature infants with birth weight less than 1750 g (5) to prevent the development of symptomatic PDA and intraventricular hemorrhage (5), and to decrease the need for ventilatory support (44,45). Our results show that only a small percentage of neonatologists (14%) use indomethacin prophylactically with a variety of dose amounts and regimens, not all consistent with the published literature (5,18). Some studies advocate the use of routine echocardiography to target high risk infants for prophylactic treatment (12,17). This practice is not in use by Canadian neonatologists.

Variations in surgical management

With a failure rate of 20% to 40% in PDA closure by indomethacin (18,46-48), surgical ligation has been used as alternative therapy (5,18). However, a randomized, controlled clinical trial in 1987 (49) found that infants who had surgical ligation instead of indomethacin spent less time on ventilation, required fewer medications, had central venous lines removed earlier and were able to maintain appropriate feeds earlier. No significant difference in mortality was found. As a result, the study concluded that premature infants with a PDA would improve faster if surgery was the first-line therapy. However, surgery continues to be promoted as second-line therapy after failed indomethacin therapy (5,18) or if indomethacin is contraindicated, and this is the practice followed by the majority of Canadian neonatologists. A few respondents use surgical ligation as first-line therapy in very low birthweight babies (less than 1000 g or less than 800 g) or in very premature babies (23 to 26 weeks' gestation). This practice is consistent with a recent study that found higher mortality and morbidity rates associated with indomethacin use in these infants (46). Although one study used prophylactic surgical ligation of PDAs within 24 h of birth in premature neonates who weighed less than 1000 g and required oxygen, and noted a reduction in the incidence of necrotizing enterocolitis (5), no respondent in our study used this approach.

CONCLUSIONS

We document considerable variation among Canadian neonatolgists regarding the use of echocardiography, and medical and surgical treatment regimens for the diagnosis and managment of PDA in premature infants. This reflects the wide variety of strategies and quality of evidence in the published literature. If the maximal amount of morbidity due to PDA is to be prevented, studies comparing different treatment regimens need to be conducted using echocardiographic indexes of ductal patency and hemodynamic significance to complement clinical assessment. An evidence-based approach is needed if use of echocardiography and management is to be cost effective. This might be accomplished with an in-depth meta-analysis of the published literature, the development of evidence-based practice guidelines or recommendations, and large scale clinical trials incorporating standardized definitions related to diagnosis of PDA and the effect of interventions.

REFERENCES

1. Mellander M, Larsson LE, Ekstrom-Jodal B, Sabel KG. Prediction of symptomatic patent ductus arteriosus in preterm infants using Doppler and M-mode echocardiography. Acta Paediatr Scand 1987;76:553-9.
2. Merritt TA, Harris JP, Roghmann K, et al. Early closure of the patent ductus arteriosus in very low-birth-weight infants: a controlled trial. J Pediatr 1981;99:281-6.
3. Kitterman JA, Edmunds LH, Gregory GA, Heymann MA, Tooley WH, Rudolph AM. Patent ductus arteriosus in premature infants: incidence, relation to pulmonary disease and management. N Engl J Med 1972;287:473-7.
4. Brown ER. Increased risk of bronchopulmonary dysplasia in infants with patent ductus arteriosus. J Pediatr 1979;95:865-6.
5. Nehgme RA, O'Connor TZ, Lister G, Bracken M. Patent ductus arteriosus. In: Sinclair JC, Bracken MB, eds. Effective Care of the Newborn Infant. New York: Oxford University Press, 1992:281-18.
6. Ellison RC, Peckham GJ, Lang P, et al. Evaluation of the preterm infant for patent ductus arteriosus. Pediatrics 1983;71:364-72.
7. Roberson DA, Silverman NH. Color Doppler flow mapping of the patent ductus arteriosus in very low birth weight neonates: echocardiographic and clinical findings. Pediatr Cardiol 1994;15:219-24.
8. Skelton R, Evans N, Smythe J. A blinded comparison of clinical and echocardiographic evaluation of the preterm infant for patent ductus arteriosus. J Paediatr Child Health 1994;30:406-11.
9. Kupferschmid CH, Lang D, Pohlandt F. Sensitivity, specificity and predictive value of clinical findings, M-mode echocardiography and continuous wave Doppler sonography in the diagnosis of symptomatic patent ductus arteriosus in preterm infants. Eur J Pediatr 1988;147:279-82.
10. Hammerman C, Strates E, Valaitis S. The silent ductus: its precursors and aftermath. Pediatr Cardiol 1986;7:121-7.
11. Reller M, Lorenz JM, Kotagal UR, Meyer RA, Kaplan S. Hemodynamically significant PDA: an echocardiographic and clinical assessment of incidence, natural history and outcome in very low birthweight infants maintained in negative fluid balance. Pediatr Cardiol 1985;6:17-24.
12. Evans N. Diagnosis of patent ductus arteriosus in preterm newborns. Arch Dis Child 1993;68:58-61.
13. McGrath RL, McGuinness GA, Way GL, Wolf RR, Nora JJ, Simons MA. The silent ductus arteriosus. J Pediatr 1978;93:110-3.
14. Higgins CB, Rausch J, Friedman WF, et al. Patent ductus arteriosus

in preterm infants with idiopathic respiratory distress syndrome. Radiology 1977;124:189-95.
15. Gutgesell HP, Huhta JC, Latson LA, Huffines D, McNamara DG. Accuracy of two-dimensional echocardiography in the diagnosis of congenital heart disease. Am J Cardiol 1985;55:514-8.
16. Sharma S, Anand R, Kanter KR, et al. The usefulness of echocardiography in the surgical management of infants with congenital heart disease. Clin Cardiol 1992;15:891-7.
17. Kluckow M, Evans N. Early echocardiographic prediction of symptomatic patent ductus arteriosus in preterm infants undergoing mechanical ventilation. J Pediatr 1995;127:774-9.
18. Gersony W, Peckham GL, Ellison RC, Miettinen OS, Nadas AS. Effects of indomethacin in premature infants with patent ductus arteriosus: results of a collaborative study. J Pediatr 1983;102:895-906.
19. Canarelli JP, Poulin H, Clamadieu C, Ricard J, Maingourd Y, Quintard JM. Ligation of the patent ductus arteriosus in premature infants – indications and procedures. Eur J Pediatr Surg 1993;3:3-5.
20. Edwards AD, Wyatt JS, Richardson C. Effects of indomethacin on cerebral haemodynamics in very preterm infants. Lancet 1990;335:1491-5.
21. Van Bel F, Guit GL, van de Bor M, Baan J. Indomethcain-induced changes in renal blood flow velocity waveform in premature infants investigated with color Doppler imaging. J Pediatr 1991;118:621-6.
22. Coombs RC, Morgan ME, Durbin GM, Booth IW, McNeish AS. Gut blood flow velocities in the newborn: effects of patent ductus arteriosus and parenteral indomethacin. Arch Dis Child 1990;65:1067-71.
23. Van Bel F, Van Zoeren D, Schipper J, Guit GL, Baan J. Effect of indomethacin on superior mesenteric artery blood flow velocity in preterm infants. J Pediatr 1990;116:965-70.
24. Ito K, Niida Y, Sato J, Owada E, Umetsu M. Pharmacokinetics of mefenamic acid in preterm infants with patent ductus arteriosus. Acta Paediatr Jpn 1994;36:387-91.
25. Heymann E, Ohlsson A, Shennan AT, Heilbut M, Caceani F. Closure of patent ductus arteriosus after treatment with dexamethasone. Acta Paediatr Scand 1990;79:698-700.
26. Brown RL, Edwards JA, Nutz JF. Variation in a medical faculty's decisions to transfuse: Implications for modifying blood product utilization. Med Care 1992;30:1083-96.
27. Pilote L, Califf RM, Sapp S, et al. Regional variation across the United States in management of acute myocardial infarction. GUSTO-1 Investigators. Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries. N Engl J Med 1995;333:565-72.
28. Roark R, Petrofski J, Berson E, Berman S. Practice variations among pediatricians and family physicians in the management of otitis media. Arch Pediatr Adolesc Med 1995;149:839-44.
29. Raby B, Pater J, Mackillop WJ. Does knowledge guide practice? Another look at the management of non-small cell lung cancer. J Clin Oncol 1995;13:1904-11.
30. Davis P, Turner-Gomes S, Cunningham K, Way C, Roberts R, Schmidt B. Precision and accuracy of clinical and radiological signs in premature infants at risk of patent ductus arteriosus. Arch Pediatr Adolesc Med 1995;149:1136-41.
31. Stevenson JG, Kawabori I, Guntheroth WG. Pulsed Doppler echocardiographic diagnosis of patent ductus arteriosus: sensitivity, specificity, limitations and technical features. Cathet Cardiovasc Diagn 1980;6:255-63.
32. Reller MD, Colasurdo MA, Rice MJ, McDonald RW. The timing of spontaneous closure of the ductus arteriosus in infants with respiratory distress syndrome. Am J Cardiol 1990;66:75-8.
33. Swensson RE, Valdes-Cruz LM, Sahn DJ, et al. Real-time Doppler color flow mapping for detection of patent of ductus arteriosus. J Am Coll Cardiol 1986;8:1105-12.
34. Liao PK, Su WJ, Hung JS. Doppler echocardiographic flow characteristics of isolated patent ductus arteriosus: better delineation by Doppler color flow mapping. J Am Coll Cardiol 1988;12:1285-91.
35. Hiraishi S, Horiguchi Y, Misawa H, et al. Noninvasive Doppler echocardiographic evaluation of shunt flow dynamics of the ductus arteriosus. Circulation 1987;75:1146-53.
36. Mellander M, Larsson LE. Effects of left-to-right ductus shunting on left ventricular output and cerebral blood flow velocity in 3-day-old preterm infants with and without severe lung disease. J Pediatr 1988;113:101-9.
37. Linder W, Seidel M, Versmold HT, Dohlemann C, Reigel KP. Stroke volume and left ventricular output in preterm infants with patent ductus arteriosus. Pediatr Res 1990;27:278-81.
38. Sanatani S, Smythe JF. Use of echocardiography in the neonatal intensive care unit. Paediatr Child Health 1997;2:187-92.
39. Lomas J, Anderson GM, Domnick-Pierre K, Vayda E, Enkin MW, Hannah WJ. Do practice guidelines guide practice? The effect of a consensus statement on the practice of physicians. N Engl J Med 1989;321:1306-11.
40. Friedman WF, Hirschklau MJ, Printz MP, Pitlick PT, Kirkpatrick SE. Pharmacologic closure of patent ductus arteriosus in the premature infant. N Engl J Med 1976;295:526-9.
41. Heymann MA, Rudolph AM, Silverman NH. Closure of the ductus arteriosus in premature infants by inhibition of prostaglandin synthesis. N Engl J Med 1976;295:530-3.
42. Hirsimaki H, Kero P, Wanne O. Doppler ultrasound and clinical evaluation in detection and grading of patent ductus arteriosus in neonates. Crit Care Med 1990;18:490-3.
43. Furzan JA, Reisch J, Tyson JE, Laird P, Rosenfeld CR. Incidence and risk factors for symptomatic patent ductus arteriosus among inborn very-low-birth-weight infants. Early Hum Dev 1985;12:39-48.
44. Mahony L, Carnero V, Brett C, Heymann MA, Clyman RI. Prophylactic indomethacin therapy for patent ductus arteriosus in very-low-birthweight infants. N Engl J Med 1982;306:506-10.
45. Kaapa P, Lanning P, Koivisto M. Early closure of patent ductus arteriosus with indomethacin in preterm infants with idiopathic respiratory distress syndrome. Acta Paediatr Scand 1983;72:179-84.
46. Trus T, Winthrop AL, Pipe S, Shah J, Langer JC, Lau GY. Optimal management of patent ductus arteriosus in the neonate weighing less than 800 g. J Pediatr Surg 1993;28:1137-9.
47. Ivey HH, Kattwinkel J, Park TS, Krovetz LJ. Failure of indomethacin to close persistent patent ductus arteriosus in infants weighing under 1000 grams. Br Heart J 1979;41:304-7.
48. Mellander M, Leheup B, Lindstrom DP, et al. Recurrence of symptomatic patent ductus arteriosus in extremely premature infants treated with indomethacin. J Pediatr 1984;105:138-43.
49. Cotton RB, Stahlman MT, Bender HW, Graham TP, Catterton WZ, Kovar I. Randomized trial of early closure of symptomatic patent ductus arteriosus in small preterm infants. J Pediatr 1978;93:647-51.