JACC Vol. 8, No. 5
November 1986:1125–30

Application of Information Theory to Decision Analysis in Potentially Prostaglandin-Responsive Neonates

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To define settings in which use of prostaglandin E_1 before transfer from a community hospital to a tertiary care center benefits neonates with possible heart disease, information theory was used to predict the probability of a favorable response to prostaglandin therapy from the limited information of clinical variables. Records of 250 patients, newborn to 7 days old, with suspected heart disease were reviewed to assess six clinical variables (cyanosis, respiratory distress, heart murmur, pulse contour, hepatomegaly and prematurity). According to the anatomic and hemodynamic cardiovascular condition, each case was categorized as to whether a favorable response to prostaglandin E_1 could be anticipated. Information content of each clinical variable with respect to prostaglandin responsiveness was determined, and patients were classified according to the most informative clinical variable. Stepwise extraction of information proceeded until remaining clinical variables added no significant information. Bayes' rule gave estimates of probability of prostaglandin-responsive defect in final subgroups for use in decision analysis.

Cyanosis, murmur, small volume pulses and prematurity gave information about prostaglandin-responsive defects. Decision analysis indicated that frequency of poor outcome is minimized by early prostaglandin treatment of cyanotic term infants with a murmur or poor pulses, regardless of how ill they appear, and by treating any critically ill term newborn who has either cyanosis or poor pulses. Acyanotic patients with normal pulses are best untreated with prostaglandin until after definitive diagnosis is made. Advantage to either course was not seen in some small subgroups. Information theory with decision analysis is a rigorous approach to identify relevant clinical variables and define their roles in critical decisions in pediatric cardiology.

(J Am Coll Cardiol 1986;8:1125–30)

Prostaglandin E_1 is a very effective method for maintaining patency of the ductus arteriosus in newborns with ductal-dependent congenital heart disease (1). However, serious complications related to prostaglandin E_1 administration (2) preclude its indiscriminate use. The referral of a neonate with suspected congenital heart disease from a distant hospital to a cardiology center poses an immediate clinical dilemma that must be approached with limited information. Should prostaglandin therapy be started before definitive diagnosis, or should it be withheld for a time to allow for transfer of the infant and echocardiographic or angiocardiographic diagnosis? A telephone description of the history and physical examination is usually available to the consultant. On the basis of this limited information, rather than on an anatomic diagnosis, the consultant must decide about administering prostaglandin therapy before transfer or en route.

To assist in making such decisions, the clinical diagnostic process can be modeled as the stepwise reduction of diagnostic uncertainty on the basis of sequential observation and testing (3,4). Sequential applicaton of Bayes' theorem has allowed the determination of probability estimates for some rheumatologic, gastroenterologic and cardiovascular diseases on the basis of laboratory testing (5–7). Information theory is a relatively new mathematical technique that can be applied to select those observations and tests with significant information content from those that are less informative, and thus focus clinical attention and resources on worthwhile testing (8–11).

This investigation applied information theory to the immediate prostaglandin decision by identifying the observations that supply relevant information. On the basis of

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Manuscript received April 7, 1986; revised manuscript received May 28, 1986, accepted June 11, 1986.

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0735-1097/86/$3.50

simple empiric observations about an infant, an estimate of probability of a prostaglandin-responsive lesion is derived, suitable for application in classical decision analysis.

Methods

Patients. We reviewed the records of 250 patients, 7 days of age or younger, who were referred to our hospital for known or suspected cardiovascular disease. Six clinical findings were assessed at the time of referral, and described as either positive or negative (cyanosis, respiratory distress, heart murmur, poor pulses, hepatomegaly and prematurity). The patients were classified on the basis of their cardiovascular lesion as either potentially prostaglandin E_1-responsive or not potentially responsive. Lesions designated potentially responsive were: interrupted aortic arch, coarctation of the aorta, hypoplastic left heart, critical aortic stenosis, critical pulmonary stenosis, pulmonary valve atresia-intact ventricular septum, transposition of the great arteries and tetralogy of Fallot or tricuspid atresia in those patients who required a systemic to pulmonary artery shunt procedure later in the first week of life. The first four anomalies listed would theoretically be benefited by an open ductus arteriosus, which would allow systemic perfusion. The other five anomalies are palliated by a left to right shunt through the ductus arteriosus.

Decision analysis. Using methods previously established (12–14), a contingency tree was generated for the decision whether or not to give prostaglandin E_1 before precise diagnosis (Fig. 1). An adverse outcome of this decision is defined as a serious complication resulting from a wrong decision; if prostaglandin E_1 is given, this is the rate of life-threatening complications or serious permanent sequelae from prostaglandin E_1 administration (Fig. 1, route I). If prostaglandin E_1 is withheld, this is the frequency of prostaglandin-responsive lesions times the frequency of life-threatening events or events with serious permanent sequelae while awaiting transfer and diagnosis (Fig. 1, route II).

To justify the early administration of prostaglandin E_1, the probability of an adverse outcome if prostaglandin is given must be less than the probability of an adverse outcome if it is withheld. Using the contingency tree in Figure 1, prostaglandin E_1 should be given early if:

$$p(\text{compl PGE}) < p(\text{PGER}) \cdot p(\text{compl no PGE}), \quad (1)$$

where p(compl PGE) = probability of serious complication from prostaglandin E_1, p(PGER) = probability of prostaglandin E_1-responsive lesion and p(compl no PGE) = probability of serious complication from withholding prostaglandin E_1.

The probability of serious complication from prostaglandin E_1 was estimated from a large cooperative study (2) which reported that the incidence of all prostaglandin E_1-related intercurrent medical events is 21%. Not all events were potentially life-threatening, and not all events could be expected to occur in the first 6 hours, so we estimate the probability of a prostaglandin-related event causing an adverse outcome at 10%.

It is more difficult to estimate the probability of serious complication from withholding prostaglandin E_1. In patients in extremis (with shock, acidemia or severe respiratory distress), we estimate that the probability of an adverse outcome from withholding prostaglandin E_1 from a potentially responsive patient for 6 hours to allow for transfer and diagnosis could be as high as 70 to 100%. For other potentially responsive patients who are not critically ill at the time of referral, the probability of a serious complication

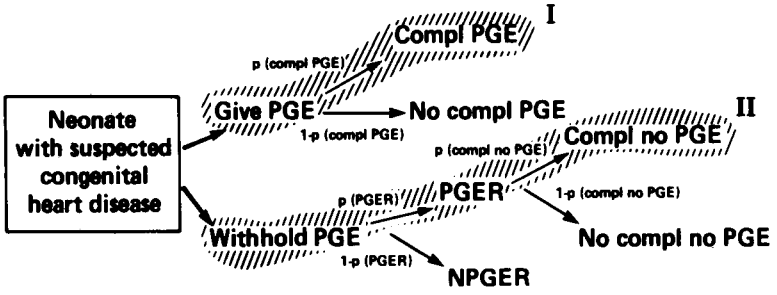

Figure 1. Contingency tree for the decision to administer prostaglandin E_1 (PGE) before anatomic diagnosis. The probability of arriving at an individual end result is the product of the probabilities encountered between the prostaglandin decision and the end result. Adverse outcomes are reached by following either route I or route II. The probability of adverse result I is, therefore, p (compl PGE) and the probability of adverse result II is p(PGER)·p(compl no PGE). To show an advantage for prostaglandin E_1 treatment, the probability of adverse results from giving prostaglandin E_1 (route I) must be less than the probability of adverse results from withholding it (route II). The criterion for early prostaglandin E_1 treatment is, therefore, when p(compl PGE) < p(PGER)·p (compl no PGE). Compl no PGE = complication from withholding of prostaglandin E_1; Compl PGE = complication from administration of prostaglandin E_1; NPGER = no potentially prostaglandin-responsive cardiac lesion; p = probability; PGER = potentially prostaglandin-responsive cardiac lesion.

from withholding prostaglandin E_1 is probably much lower, perhaps 25 to 33%.

Using these figures, the inequality (1) can be solved for the probability of a prostaglandin-responsive cardiac lesion. Figure 2 shows the relation between the threshold probability of a prostaglandin-responsive cardiac lesion, which one would wish to treat before transfer is completed, and the probability of a serious complication from withholding prostaglandin E_1. In very ill patients with a high probability of a serious complication from withholding prostaglandin E_1, relatively large changes in probability of a serious complication from withholding prostaglandin E_1 result in small changes in the threshold for treatment. For patients in extremis with a 70 to 100% probability of a serious complication from withholding prostaglandin E_1, the threshold probability of a prostaglandin-responsive cardiac lesion for treatment is 10 to 14%. For patients who are not so acutely ill in whom the estimated probability of a serious complication from withholding prostaglandin E_1 is 25 to 33%, the threshold probability of a prostaglandin-responsive cardiac lesion for treatment is 30 to 40%.

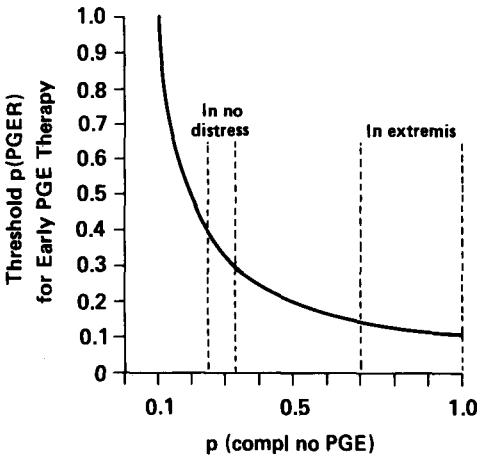

Figure 2. The threshold p(PGER) for early prostaglandin E_1 (PGE) treatment shown on the vertical axis is that probability of a responsive lesion above which a clinician theoretically would minimize adverse outcome by treating with prostaglandin E_1 before definitive diagnosis. The threshold is a function of the probability of a complication from withholding of prostaglandin E_1 [p(compl no PGE)], which in turn depends on how ill the patient is. This curve is a sensitivity analysis of the influence of varying p(compl no PGE) on the threshold for early prostaglandin E_1 treatment. At high values of p(compl no PGE), relatively large changes in p(compl no PGE) result in relatively small changes in threshold for treatment. Abbreviations as in Figure 1.

Information theory. As reviewed recently by Diamond and Forrester (3), information theory defines a quantity of uncertainty or entropy, which can be derived from the probability of a disease state. Entropy (S) can be defined mathematically as:

$$S = -p(D+)\log_2 p(D+) - p(D-)\log_2 p(D-), \quad (2)$$

where $p(D+)$ is the probability of disease, and $p(D-)$ is the probability of no disease. After a test or observation (T) with n possible outcomes:

$$S = -\sum_{i=1}^{n} p(D+/T_i)\log_2 p(D+/T_i), \quad (3)$$

where $p(D+/T_i)$ is the probability of disease given test result i. When there are only two possible test results (positive or negative), equation 3 simplifies:

$$S = -p(D+/T+)\log_2 p(D+/T+) - p(D+/T-)\log_2 p(D+/T-). \quad (4)$$

Information content (IC) of a test then is simply the reduction of uncertainty achieved by the test:

$$IC = S_{pretest} - S_{post\text{-}test}. \quad (5)$$

Entropy and information content are expressed in terms of bits. When total uncertainty exists, entropy is at its maximal value of one bit. When perfect certainty exists, entropy is zero. Information content of a perfect test in the setting of total pretest uncertainty is maximal (one bit). Test imperfections (false positives and false negatives) decrease the information content. The information content of a test is also limited by pretest entropy. For example, when perfect certainty exists before the application of a test, the information content of even a perfect test is zero because the pretest entropy of zero cannot be further reduced by the test. The significance of information content can be tested using a chi-square distribution after the method of Ulm et al. (8).

Algorithm. The six clinical observations were subjected to analysis of information content for the question of prostaglandin E_1 response potential using equations 4 and 5. The observation or test with the highest information content was selected to divide the group into higher and lower likelihood subgroups. The remaining five observations were subjected to analysis of information content within the subgroups, and the factor with the greatest value was selected to divide the subgroups. This procedure was continued sequentially until no remaining factor provided significant information within any of the subgroups ($p < 0.05$ by chi-square analysis for large samples or Fisher exact test for small samples) (8).

Probability estimates. Estimates of probability of a potentially prostaglandin E_1-responsive lesion by direct calculation of the incidence of responsive lesions in each subgroup may be misleading because of the small numbers in some of the subgroups. The probability of a responsive lesion was therefore estimated by sequential application of Bayes' theorem where applicable (15);

$$p(D+/T+) = \frac{p(D+)p(T+/D+)}{p(D+)p(T+/D+) + p(D-)p(T+/D-)}. \quad (6)$$

Table 1. Information Content of Each Variable in the Entire Group of 250 Patients

Finding	Information Content (bits)	
Cyanosis	0.138	$p < 0.05$*
Weak pulses	0.065	
Prematurity	0.023	
Heart murmur	0.021	
Hepatomegaly	0.020	
Respiratory distress	0.002	

*Relative to the potential response to prostaglandin E_1 (by modified chi-square analysis).

The values for probability of disease [p(T+/D+) and p(T+/D−)] were taken from the entire group of 250 patients only if the observed incidence of p(D+/T+) satisfactorily matched the estimate from Bayes' theorem ($p < 0.05$ on goodness of fit testing by chi-square or Fisher exact test) (16). Because Bayes' theorem is appropriate only when tests are independent of one another (17), the goodness of fit test in effect measures the independence of the sequential tests. If independence could not be established among all the sequential tests, then p(T+/D+) and p(T+/D−) were taken from the largest subgroup, after which the final test was independent of the preceding tests; p(D+) was thus calculated for all the terminal subgroups. The beta-probability distribution (18) was used to determine the median and 95% confidence limits of the probability of a responsive lesion, after the method of Diamond and Forrester (3).

Results

The information content of all six clinical variables for the group as a whole is shown in Table 1. Cyanosis was by far the most informative variable and was, therefore, used to divide the group into subgroups with a high probability of a prostaglandin E_1-responsive lesion (cyanotic) and a low probability of a responsive lesion (acyanotic). In the cyanotic subgroup (Table 2), a heart murmur was the most informative variable, whereas weak pulses were most informative in the acyanotic subgroup. These variables were used to subdivide the subgroups. This process was continued until no observation or laboratory test provided further significant ($p < 0.05$) information. In this way, the information tree in Figure 3 was generated.

Some findings carried significant information within the group as a whole, but became insignificant after subdivisions were made. This illustrates that information carried by different variables may overlap or that one finding may be dependent on another. Observations that carried significant information content were cyanosis, heart murmur, weak pulses and premature gestational age. Eight final subgroups were generated, each with its own estimated probability of a potentially responsive lesion (Fig. 4).

Patients in extremis. Among very ill newborns, if prostaglandin E_1 is withheld from those with potentially responsive heart disease, the probability of an adverse course approaches 1.0. The threshold probability of a prostaglandin-responsive lesion necessary to sway the clinician to administer prostaglandin E_1 to infants in such dire straits is relatively low (approximately 0.10) (Fig. 2). The estimated probability of a responsive lesion is much higher than the threshold for treatment before diagnosis in all term cyanotic patients and in all term patients with weak pulses if they are in extremis. It is also clear that probability values in acyanotic patients with good pulses fall below the threshold for treatment before diagnosis. Acyanotic premature infants with weak pulses and cyanotic premature infants with weak pulses but no murmur are ambiguous groups lacking standard statistical certainty (95% confidence) that probability values are above or below threshold. However, the bulk of the probability distribution is above threshold for early treatment in both of these groups.

Patients not in extremis. Among patients not in extremis at the time of referral, who might be expected to have 0.25 to 0.33 probability of a complication if prostaglandin is withheld, values in cyanotic infants with murmurs or cyanotic term infants with weak pulses are above the threshold for treatment. Values in acyanotic infants with good pulses are far below the threshold for treatment. The

Table 2. Information Content Regarding Prostaglandin E_1 Responsiveness for Each Remaining Variable After the First Division of the Group (cyanotic versus acyanotic)

Cyanotic			Acyanotic		
Finding	Information Content (bits)		Finding	Information Content (bits)	
Heart murmur	0.063	$p < 0.05$*	Weak pulses	0.157	$p < 0.05$*
Weak pulses	0.062		Hepatomegaly	0.079	
			Gestational age	0.044	
Prematurity	0.016				
Respiratory distress	0.003		Respiratory distress	0.031	
Hepatomegaly	0.000		Heart murmur	0.004	

*Relative to the potential response to prostaglandin E_1.

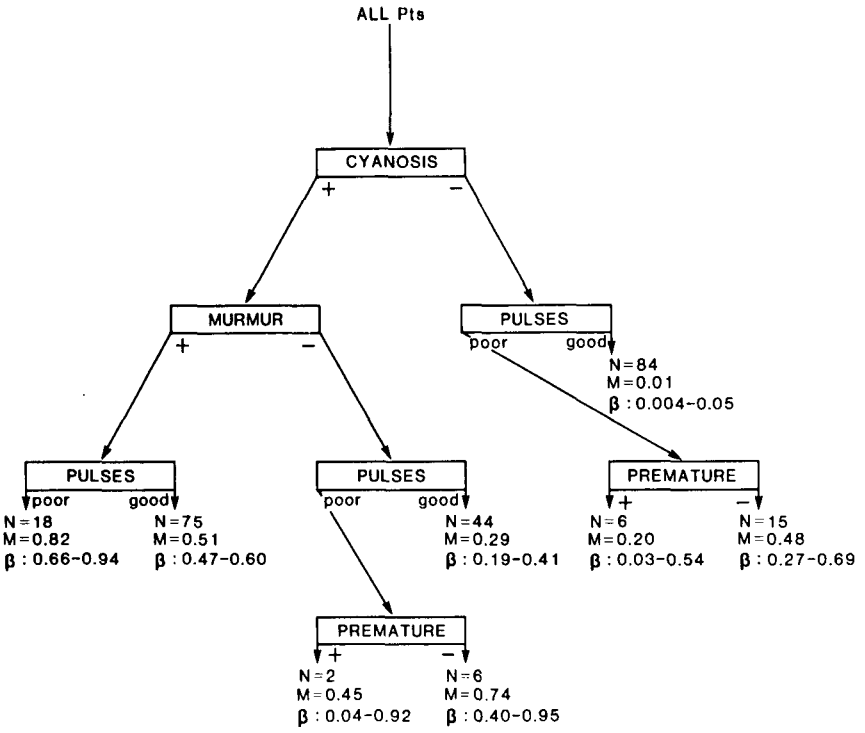

Figure 3. The information tree produced by the algorithm. β = lower and upper 95% confidence limits for the beta-probability distribution for the probability of a potentially prostaglandin-responsive lesion; M = median of beta-probability distribution (because of the asymmetry of the beta-probability distribution, the median does not equal the mean; the median has been advocated as the appropriate statistic for decision making [3]); N = number of patients in each subgroup; pts = patient; + = finding present; − = finding absent.

probability distributions for the remaining groups straddle the threshold for treatment to a greater or lesser extent. The bulk of the probability distribution is above the threshold for treatment of term acyanotic infants with weak pulses and in cyanotic premature infants with weak pulses. Most of the distribution for infants with cyanosis only and for acyanotic premature infants with weak pulses is below threshold for early prostaglandin E_1 therapy.

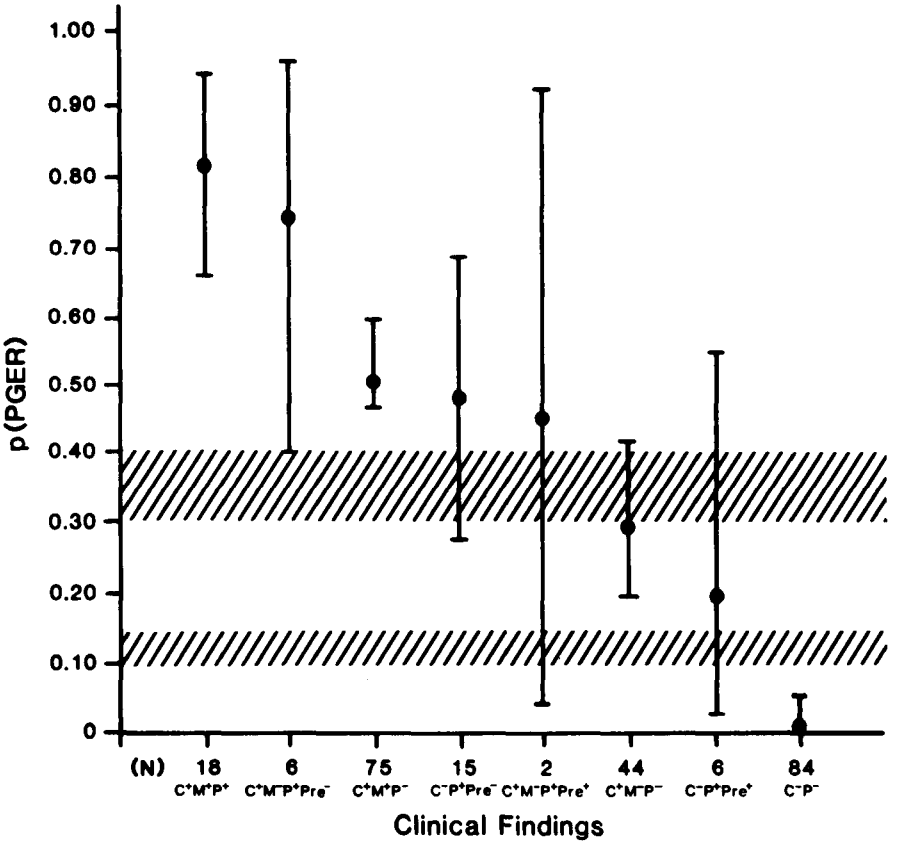

Figure 4. Medians and 95% upper and lower confidence limits are shown for the likelihood of a potentially prostaglandin-responsive lesion [p(PGER)] for each terminal subgroup. The **upper shaded area** represents the threshold probability of a responsive cardiac lesion for early prostaglandin E_1 treatment of patients not in extremis. The **lower shaded area** is the threshold for early prostaglandin E_1 treatment of patients in extremis. C = cyanosis; M = murmur; P = poor pulses; Pre = premature; + = finding present; − = finding absent.

JACC Vol. 8, No. 5
November 1986:1125–30

Discussion

With the increasing availability of prostaglandin E_1 at referring hospitals, an empiric method to determine which infants would profit from its administration before definitive diagnosis is important. This type of problem in which crucial clinical decisions must be made with limited information, is well suited to analysis based on information theory. Important clinical variables relevant to the probability of a prostaglandin E_1-responsive lesion are the presence or absence of cyanosis, the presence or absence or a heart murmur, the quality of pulses and the gestational age. Whether or not the patient is in extremis at the time of referral alters the decision-making process by changing the threshold for treatment. This analysis substantially reduces the observations that might be considered or tests that might be ordered before making a decision that cannot safely be delayed. In most cases, the probability of prostaglandin E_1 responsiveness clearly is above or below threshold, allowing a decision that is well justified.

Advantages and disadvantages of the method. Decision analysis has rarely been applied in pediatric cardiology (13,14,19,20) and, to our knowledge, formal information theory has not been applied and published before. This approach has the advantage of being mathematically rigorous. If underlying assumptions are sound, the method should provide reliable results. The guidelines for early prostaglandin therapy derived here are clinically reasonable, a fact that tends to validate the method. Information theory with decision analysis does not require access to a computer for the analysis of each case. Instead, easily applicable guidelines for decision making may be formulated in advance. The disadvantages of the approach are, first, that it requires a large data base for meaningful information analysis. Second, the decision in cases where the probability distribution straddles the threshold for action is ambiguous. As long as information is incomplete, categories of patients will exist in which it will be difficult to prove an advantage for one course of action over another. Although a clinician could not be proved wrong for choosing otherwise, it is probably best to compare the median of the probability distribution with the threshold for decision making in ambiguous circumstances. Finally, the generalization of the results of our study to other practices of pediatric cardiology is contingent on similarities of patient populations seen, transfer times and the like. Similarly, as diagnostic and treatment options improve over the years, studies such as this will require review to determine if the assumptions on which they are based are still true.

Applications. Many potential applications of this method exist in pediatric cardiology, a field in which the information available is often incomplete and dispersed throughout many observations and laboratory results. Improvements in clinical practice through the elimination of noncontributory testing and the minimization of adverse outcome are the potential rewards of a more general application of this type of analysis.

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