Preventive Therapy for the Patient With Both Universal Indication and Contraindication for Isoniazid*

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Background: The delphi method of decision making was used to address an unusual clinical case in which various aspects of the case required opposing management strategies.

Methods: A panel of 30 pulmonary experts was surveyed repeatedly until a convergence of treatment approaches was reached for a patient who was considered to have both a universal indication for and a universal contraindication against prevention therapy. Participants were asked to evaluate the appropriateness of proposed treatments on a scale from 1 to 9, with 1 being extremely inappropriate, 5 being equivocal, and 9 being extremely appropriate. The delphi survey data responses were compared using measures of central tendency (ie, the mean and median) and measures of variability (ie, the standard deviation and interquartile range).

Results: Although no treatment was wholeheartedly supported by the experts, analysis of the three-round delphi survey responses resulted in two possible treatments: rifampin, 600 mg daily, for four months, or no treatment with close observation. Interestingly, the experts working in a non-university setting favored the rifampin treatment, and those working in a university setting favored no treatment with close observation.

Conclusions: The delphi method has the potential to be used for clinical decision making. (Chest 1993; 103:825-31)

ATS = American Thoracic Society; CDC = Centers for Disease Control; INH = isoniazid

The delphi approach to decision making "may be characterized as a method for structuring a group communication process so that the process is effective in allowing a group of individuals as a whole to deal with a complex problem."¹ This consensus method requires the selection of a panel of experts and repeated surveying of these experts, presumably until a convergence of opinion has been reached.

The delphi method has been used to address issues in a wide variety of subject areas,¹ including the health field.²⁻¹³ Faced with an "insoluble" treatment problem, we used a delphi analysis of experts. The value of a treatment delphi is that a knowledgeable group of busy clinicians located in various parts of the country can provide recommendations for the treatment of a difficult clinical case. The purpose of this article is to explore the feasibility of such an approach and to suggest modifications for future treatment delphi surveys.

Methods

In our clinical practice, a problem of clinical management was identified. Review of the literature revealed no guidelines regarding management. Various aspects of the case were considered to require opposite strategies of management.

A panel of 30 pulmonary specialists was chosen for this survey; all are members of the American Thoracic Society (ATS) and were considered experts in the area of tuberculosis. Round 1 of the survey of experts was conducted during September 1989. The following clinical case description was sent to each panelist: A 43-year-old black woman presented to the medical service of a university hospital with hepatic coma. She was well until approximately two months prior when she discovered that both women with whom she was sharing living space for two years had active pulmonary tuberculosis. In one case the disease was fatal. The patient's last recollection of a purified protein derivative (PPD) test was many years prior and was "negative." During contact follow-up, a 5 TU PPD was placed that was "positive." The patient was placed on a regimen of isoniazid (INH), 300 mg, which she took daily for approximately four weeks when she developed jaundice followed by fulminant hepatic failure. At an area hospital, her liver profile revealed a bilirubin level of 17, SGOT of 8,444, and alkaline phosphatase of 681. A liver biopsy specimen was "consistent with drug-induced liver disease." She was then transferred to the Sammy Davis, Jr Liver Institute for management of her liver disease. On transfer, the liver profile revealed a bilirubin level of 22, SGOT of 107, SGPT of 535, alkaline phosphatase of 338, and prothrombin time of 51.7 s. At this time, the patient was in hepatic coma. The day following transfer, she received a liver transplant. On pathologic examination, her liver revealed fulminant hepatic necrosis. After transplantation, her encephalopathy rapidly resolved. At the time of hospital discharge, the liver profile revealed a bilirubin level of 1.7, SGOT of 23, SGPT of 37, and alkaline phosphatase of 203. The patient is currently being treated with prednisone, 20 mg daily, cyclosporine, 400 mg twice daily, and azathioprine, 50 mg daily, and will continue to receive this regimen indefinitely.

At this point, the immunosuppressed household contact of two active cases of tuberculosis has presumably not received adequate preventive therapy for her tuberculosis infection. Which of the

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Dr. Reichman is supported by Preventive Pulmonary Academic Career award No. K07-HL-02095-2 and Pulmonary Complications of HIV Infection contract No. 1-HR-76032, both from the Division of Lung Diseases of the National Heart, Lung and Blood Institute, Bethesda, Md.
Manuscript received February 24; revision accepted June 1.
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Panelists were supplied with a list of four possible treatments, asked to comment on the proposed treatments, and to consider any other appropriate treatments. Four additional treatments were thus identified.

Approximately two months later, round 2 of the delphi survey was mailed to all of the experts and included a description of the clinical case along with the treatments identified as clinically useful by the panelists during round 1. Experts were then asked to rank the appropriateness of the proposed treatments on a scale from 1 to 9, with 1 being extremely inappropriate, 5 being equivocal, and 9 being extremely appropriate.12 An "appropriate" treatment is defined as one where the expected health benefits exceed the expected negative consequences by a sufficiently wide margin so that the treatment is worth carrying out. An "inappropriate" treatment is defined as one where the negative consequences outweigh the expected benefits by a sufficiently wide margin so that the treatment is not worth doing. During round 2 of the survey, experts were also asked to propose any additional treatment approaches not already included in the delphi. Ninety percent (ie, 27) of the experts returned the round 2 delphi survey.

Round 3 of the delphi was distributed in February 1990, and included the graphic presentation of the responses from round 2 along with a reminder of one's own previous responses and a restatement of the case. Each expert was then asked to consider his/her opinions in the context of the group's judgment and to reconsider his/her individual responses.

However, during the time period between rounds 2 and 3, a journal article and an editorial directly related to tuberculosis preventive therapy appeared in the American Review of Respiratory Diseases."14 To ensure that all delphi participants were basing their round 3 responses on the same information, copies of the article and editorial were included with the round 3 survey. In addition, two questions were asked: "Have the enclosed articles influenced your choice?" and "Have the opinions of the other participants influenced your choice?" Finally, the participants were once again given the opportunity to propose additional treatment approaches. Twenty-three of the round 2 participants (ie, 85 percent response rate) returned the round 3 survey.

Although in each round respondents were appraised of their colleagues' opinions as a group, to reduce the possibility of communication other than through the delphi procedures, no individuals were identified according to their responses and a list of the delphi panelists was not distributed.

The delphi survey data were analyzed using the SAS statistical computer package.1* The distribution of responses is described using measures of central tendency (ie, the mean or the median) and measures of variability (ie, the standard deviation or interquartile range—the difference between the 25 percent and the 75 percent values). In addition, visual examination of round 2 and 3 responses provides additional information needed to interpret the results of the delphi survey. For this analysis, consensus is assumed to have been reached if the measure of variability is small (ie, if the interquartile range of any round is 2 or less in the nine point appropriateness scale). In addition, median values are used to identify the level of appropriateness for a given treatment.

**RESULTS**

For the specific patient who was considered to have both a universal indication for and a universal contra-indication against preventive therapy, a total of nine treatments were considered by the expert panelists during the three-round delphi survey; eight treatments were evaluated during round 2 and one additional treatment was added by a round 2 participant. The results of round 2 (Table 1) suggest that these experts would opt for either treatment with rifampin, isoniazid, or pyrazinamide with a minimal amount of ethambutol (25 mg/kg daily or less).

Table 1—Proposed Preventive Therapy Regimen: Round 2 Summary Statistics

<table>
<thead>
<tr>
<th>Proposed Treatment</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>IQ Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid, 300 mg daily for 12 mo</td>
<td>27</td>
<td>2.6</td>
<td>2.4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Rifampin, 600 mg daily for 4 mo</td>
<td>27</td>
<td>5.07</td>
<td>2.4</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Rifampin, 600 mg daily for 12 mo</td>
<td>27</td>
<td>5.0</td>
<td>2.3</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Rifampin, 600 mg daily and pyrazinamide, 1.5 g daily for 2 mo</td>
<td>27</td>
<td>3.7</td>
<td>2.2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Rifampin, 600 mg daily and ethambutol, 25 mg/kg daily for 12 mo</td>
<td>27</td>
<td>3.6</td>
<td>2.5</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Ethambutol, 25 mg/kg daily for 12 mo</td>
<td>27</td>
<td>2.9</td>
<td>2.4</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Ethambutol, 25 mg/kg daily and pyrazinamide, 1.5 g daily for 6 mo</td>
<td>27</td>
<td>2.5</td>
<td>1.7</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>No treatment with close observation</td>
<td>27</td>
<td>5.6</td>
<td>2.7</td>
<td>7</td>
<td>8</td>
</tr>
</tbody>
</table>

*IQ range = interquartile range. Interquartile range <=; consensus has been reached.

Table 2—Proposed Preventive Therapy Regimen: Round 3 Summary Statistics

<table>
<thead>
<tr>
<th>Proposed Treatment</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>IQ Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid, 300 mg daily for 12 mo</td>
<td>23</td>
<td>2.4</td>
<td>2.6</td>
<td>1</td>
<td>2</td>
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<tr>
<td>Rifampin, 600 mg daily for 4 mo</td>
<td>22</td>
<td>5.04</td>
<td>2.1</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Rifampin, 600 mg daily for 12 mo</td>
<td>22</td>
<td>4.3</td>
<td>2.0</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Rifampin, 600 mg daily and pyrazinamide, 1.5 g daily for 2 mo</td>
<td>22</td>
<td>4.3</td>
<td>2.0</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Rifampin, 600 mg daily and ethambutol, 25 mg/kg daily for 12 mo</td>
<td>22</td>
<td>3.5</td>
<td>2.5</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Ethambutol, 25 mg/kg daily for 12 mo</td>
<td>22</td>
<td>1.9</td>
<td>1.1</td>
<td>1.5</td>
<td>2</td>
</tr>
<tr>
<td>Ethambutol, 25 mg/kg daily and pyrazinamide, 1.5 g daily for 6 mo</td>
<td>22</td>
<td>1.8</td>
<td>1.0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>No treatment with close observation</td>
<td>22</td>
<td>5.9</td>
<td>2.5</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Ciprofloxacin, 500 mg twice daily for 6 mo</td>
<td>20</td>
<td>3.0</td>
<td>1.4</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

*IQ range = interquartile range. Interquartile range <=; consensus has been reached.
Isoniazid 300 mg daily for 12 months

Ethambutol 25 mg/kg daily for 12 months

Ethambutol 25 mg/kg daily and Pyrazinamide 1.5 gm daily for 6 months

Ciprofloxacin 500 mg twice daily for 6 months

Figure 1. Proposed preventive therapies: group consensus inappropriate. Solid bar = round 2; hatched bar = round 3.

600 mg for 4 or 12 months, or "no treatment with close observation," since the median values for these three distributions were 5 or greater. Although the median value for “no treatment with close observation” was much higher on the appropriateness scale than the rifampin treatments, the diversity of opinion on the appropriateness of this treatment is obvious when one considers the size of the interquartile range (ie, 8 vs 4 for the rifampin treatments).

After round 3 of the delphi (Table 2), consensus was reached on seven of the nine proposed treatments. Among these seven were the following: INH, 300 mg daily for 12 months; ethambutol, 25 mg/kg daily for 12 months; ethambutol, 25 mg/kg daily and pyrazinamide, 1.5 g daily for 6 months; and ciprofloxacin, 500 mg twice daily for 6 months; all had median scale values that suggest that the panelists believed these treatments to be clinically inappropriate. An examination of the round 2 and 3 responses in Figure 1 presents a visual confirmation of the picture suggested by the summary statistics for each distribution.

The administration of rifampin, 600 mg daily for 4 months, rifampin, 600 mg daily for 12 months, and rifampin, 600 mg daily and pyrazinamide, 1.5 g daily for 2 months was considered to be of equivocal value to the proposed case. However, by round 3, rifampin, 600 mg for 4 months, was clearly the most preferred of the treatments considered to be of equivocal value (median value = 5). Visual inspection of the round 2 and 3 distributions for this treatment option suggests that almost equal numbers of experts believed this treatment to be either appropriate or inappropriate (Fig 2).

Finally, there were two treatments for which a consensus was not reached (rifampin, 600 mg daily with ethambutol, 25 mg/kg daily for 12 months and “no treatment with close observation”). Despite this lack of consensus, the magnitude of the median values for these possible treatments and the direction of change in these values suggest that these experts believe the rifampin and ethambutol combination treatment to be inappropriate and that “no treatment
with close observation” is possibly an appropriate treatment (Fig 3).

Thus, after considering the results of the three-round delphi, a split appeared regarding the most reasonable treatment protocol: rifampin, 600 mg daily for four months or no treatment with close observation.

In an attempt to see if any difference in treatment choice might be attributed to some characteristic of the delphi experts, the panelists were identified by the type of institution in which they work (i.e., university or non-university setting). The round 2 and 3 responses for the rifampin treatment and the no treatment options, stratified by work location, appear in Figures 4 and 5. By round 3, the experts working in a non-university setting favored rifampin, 600 mg daily for four months over “no treatment with close observation.” In contrast, the experts working in a university setting favored “no treatment with close observation” over the use of rifampin.

Two additional pieces of information were collected during round 3 of the delphi in the form of two questions: “Have the enclosed articles (on TB preventive therapy) influenced your (treatment) choice?” and “Have the opinions of the other participants influenced your (treatment) choice?” The responses to these questions were recorded on a nine-point scale with 1 being not influential and 9 being very influential. A comparison of the responses to these questions suggests that participants perceived the influence of the articles to be greater than the influence of the other two.
delphi experts; the median "influence" value for the articles was 3.5 (mean = 4.2, SD = 2.2) while the median "influence" value for the opinions of the other participants was only 2.9 (mean = 2.9, SD = 2.1). Statistical analysis of the distributions of responses using a Wilcoxon sign rank test (i.e., the nonparametric analogue to a paired t test) confirms that there was a significant difference in "influence" level at the 0.05 significance level, with a p value of 0.0153. Interestingly, even though the panelists believed that the journal article influenced their decision to a greater extent than did the opinion of the other panelists, the perceived influence of both of these factors was quite small (i.e., on the low end of the influence scale), despite the obvious shift in responses that has been illustrated in Figures 1 through 5.

**DISCUSSION**

Preventive therapy (chemoprophylaxis) is given because of the realization that tuberculous infection, which always precedes active disease, occurs with few organisms that can be reduced or eliminated using one inexpensive drug—INH given for 6 to 12 months. Isoniazid is the only drug proved effective for this indication. However, INH does have hepatotoxicity and the American Thoracic Society and National Centers for Disease Control have issued and updated guidelines as to the specific indications for INH preventive therapy where the risk of the drug is clearly outweighed by benefit in preventing tuberculosis. Obviously, INH is prescribed where the risk of active tuberculosis outweighs the risk of hepatitis from the drug. Treatment with INH is withheld when the opposite set of circumstances occurs.

Within the ATS/CDC guidelines are several extremely high-risk situations that are considered universal indications for INH preventive therapy. Previously demonstrated INH-associated hepatitis is an obvious contraindication.

Our patient was a recent contact to two active cases...
of pulmonary tuberculosis who had demonstrated recent infection by manifesting a newly positive tuberculin test (by history). After her liver transplant, she was placed on a regimen of major pharmacologic immunosuppressives to protect against organ rejection. These are all considered major risk factors for active tuberculosis and each on its own would be considered a universal indication for INH preventive therapy. Immunosuppression from HIV infection, which may be analogous to pharmacologic-induced immunosuppression, is now considered the strongest known risk for active tuberculosis.\(^{20}\) On the other hand, INH-induced hepatitis manifesting itself as acute hepatic necrosis is considered by ATS/CDC a major contraindication for INH preventive therapy.\(^{16}\)

Therefore, we have several universal indications (some would say mandatory) for and at least one universal contraindication against preventive therapy! Since there is neither literature nor guideline for what would be appropriate management in this situation, we turned to the delphi survey technique. We reasoned that a properly chosen, knowledgeable panel of experts (several of whom have been involved in writing ATS/CDC preventive therapy statements) would be able to guide us in the right decision.

Delphi surveys have been used by many health care researchers.\(^2\)\(^{12}\)\(^{21}\) The methods used to conduct these surveys have varied from repeated surveying of experts, as in our study, to “modified” delphi surveys involving a two-step process: an initial round and then a conference where all participants meet to discuss their responses.\(^{24}\) They have also involved panels as small as 9 and as large as 400 experts.\(^2\)\(^{21}\) Unfortunately, few authors report the time interval between rounds. This time interval may be less important for policy surveys, but it could be an issue for delphi surveys relating to the treatment of a particular patient. These methodologic differences must be considered when comparing the responses rates of these studies.

Our three-round survey response rate was 23/30 or 77 percent. This response rate is a little better than the 75 percent response rate found in a previous two-round delphi survey performed by CDC in 1981.\(^{21}\) The CDC delphi looked at preventive therapy for organisms resistant to INH and consensus was reached on treatment with rifampin. While several of the panelists were the same as in the current delphi, some of the survey methods differed.

Our survey results were very surprising in the dearth of opinion regarding a secondary drug for preventive therapy. However, we did find some difference in treatment preferences for those who worked in a university setting vs those in a non-university setting; those in a non-university setting favored treatment with rifampin, 600 mg daily for 4 months, over no treatment with close observation. Since we did not collect demographic information on the respondents, we were unable to see if any of these factors were related to their responses. However, in general, the 9 non-university respondents were a little more likely than the 13 university-affiliated respondents to have been influenced by the opinions of others (median score on a scale from 1 to 9 was 3 compared with 2 for university-affiliated experts) and by the articles provided during the survey (median of 4 compared with 3 for the university-affiliated experts).

Our study revealed several unacceptable interventions but only two possibly acceptable interventions on how to handle a patient at extremely high risk of tuberculosis activation. One possible reason for our inability to reach a strong consensus on a treatment may stem from the static nature of the conventional paper-and-pencil delphi survey. A more fruitful approach to the treatment delphi may be to use a “delphi conference” technique where all responses are entered into a computer conferencing system.\(^{22}\) The computer could be programmed to synthesize the group responses, provide additional information when required, and provide quick feedback to all delphi panelists, thereby increasing the clinical value of such an approach.

ACKNOWLEDGMENTS: The writers thank Murray Turroff, Ph.D., New Jersey Institute of Technology, for his valuable input into the interpretation of the survey results. We would also like to acknowledge the efforts of our delphi experts: William C. Bailey, M.D., University of Alabama Medical School, Birmingham; Paul T. Davidson, M.D., L.A. County Department of Health, Downey, Calif; Asim Kal Dutt, M.D., York VA Medical Center, Murfreesboro, Tenn; Marian G. Goble, M.D., National Jewish Center for Immunology and Respiratory Medicine, Denver; Cole; Philip C. Hopewell, M.D., San Francisco General Hospital, San Francisco; H. William Harris, M.D., Bellevue Hospital Center, New York; Michael D. Isemian, M.D., National Jewish Center for Immunology and Respiratory Medicine, Denver; Thomas S. Moulding, M.D., L.A. County Health Department, Torrance, Calif; William W. Stead, M.D., Arkansas Department of Health, Little Rock; Dixie E. Snider, Jr., M.D., Centers for Disease Control, Atlanta; Jeffrey L. Skolnick, M.D., Northwestern Medical Hospital, Chicago; David L. Cohn, M.D., Bannock Disease Control, Denver; Thomas M. Daniel, M.D., University Hospitals, Cleveland, Ohio; Dean Schraufnagel, M.D., University of Illinois at Chicago; Frits Van Der Kurp, M.D., Metropolitan General Hospital, Cleveland, Ohio; Emanuel Wolinsky, M.D., Metropolitan General Hospital, Cleveland, Ohio; Joseph Bates, M.D., McClellan VA Hospital, Little Rock, Ark; Richard O’Brien, M.D., Centers for Disease Control, Atlanta; Bess Miller, M.D., Centers for Disease Control, Atlanta; George Comstock, M.D., Johns Hopkins School of Hygiene and Public Health, Hagerstown, Md; Laurence Farer, M.D., Atlanta; John Bass, Jr., M.D., University of South Alabama; Mobile, Ala; Charlotte Malasky, M.D., UMDNJ-NJMS-University Hospital, Newark, NJ; Reynard McDonald, M.D., UMDNJ-NJMS-University Hospital, Newark, NJ; Earl Hershfield, M.D., University of Maryland, Baltimore, Md; Robert Loudon, M.D., VA Medical Center, New York; Edward Nardell, M.D., Cambridge Hospital, Boston; Robert Reza, M.D., Bayport, NY; Frederick Ruben, M.D., Montefiore Hospital, Pittsburgh; John Sharbano, M.D., University of Colorado, Denver.

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