Medical decision analysis in infectious diseases

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Medical decision analysis (MDA) has played an important role in assisting infectious disease physicians make decisions associated with varying levels of complexity. Clinicians are often uncomfortable with some aspects of MDA, particularly when utilities are used as outcome measures. However, as the present paper outlines, MDA may use other outcome variables, including costs and disease complications. In this context, this explicit, reproducible analytic framework is an important tool in the area of infectious diseases, and is frequently applied to many situations, including cost effectiveness analyses, studies involving assessment of risks versus benefits of preventive and treatment strategies, and other situations. The objective of this paper is to assist infectious diseases clinicians to understand better the role of MDA in clinical practice. In this regard, the principles of MDA are reviewed and a common clinical example is used for illustrative purposes.

Key Words: *Decision analysis; Infectious diseases*

Modèle analytique des décisions médicales en infectiologie

RÉSUMÉ : Le modèle analytique de décisions médicales (MDA, pour *Medical Decision Analysis*) aide considérablement les infectiologues à prendre des décisions de complexité variable. Les cliniciens se sentent souvent mal à l'aise d'utiliser certains aspects du MDA, surtout lorsque les services servent de paramètres. Cependant, comme l'explique l'article, le MDA peut utiliser d'autres paramètres, y compris le coût et les complications morbides. Dans ce contexte, ce modèle analytique explicite et reproductible constitue un outil important en infectiologie et sert à de nombreuses applications, y compris les analyses coût-efficacité réelle, les évaluations du rapport risques-bienfaits des stratégies de prévention et de traitement et d'autres situations. L'objectif du présent article est d'aider les cliniciens en infectiologie à mieux comprendre le rôle du MDA dans la pratique clinique. À cet égard, l'auteur passe en revue les principes du MDA et cite un exemple clinique courant pour illustrer son point de vue.

Infectious disease physicians and others are often faced with complex clinical problems. When faced with such problems, physicians often turn to one or more sources of information, including reference textbooks, pocket books, experience and the opinion of experts, as well as review papers and original studies from biomedical databases. It has been suggested that these approaches have various limitations, due in part to the limited nature of our ability to integrate very complex data into a rational and consistent decision (1-3). Our inability to process numerous variables simultaneously is compounded by the fact that none of us can intuitively estimate probabilities accurately. In this regard, simple decision rules may offer advantages over clinical judgment (1).

Medical decision analysis (MDA) enables us to handle the above complex situations using a reproducible framework. It is not intended to replace evidence derived from clinical trials but may be complementary. MDA can be defined as an explicit quantitative analytical framework that systematically considers the trade-off between management options under conditions of uncertainty (4). The analytic framework uses decision trees that are models of the temporal and logical flow of clinical problems (5), the objective being to offer the patient a man-

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TABLE 1
Stages of medical decision analysis

- Defining the problem
- The options or choices
- Tree building and outlining the chance events resulting from the choices made
- Incorporating baseline probabilities that relate to the chance events
- Incorporating outcome measures
- Conducting baseline analyses
- Performing sensitivity analyses

agement option that is likely to result in the greatest expected value. Decision analysis is meant to be prescriptive, not descriptive (4). It is intended to assist clinicians in deciding what should be done under a set of circumstances, so that their decisions will be consistent with the available data, assumptions made and outcomes considered.

INDICATIONS FOR MDA AND ASSOCIATED ADVANTAGES

The most clear-cut indications for MDA are those situations where it is an advantage over other approaches; for example, there are certain clinical problems for which a randomized trial is not feasible. The latter may be due to prohibitive sample size requirements, costs or the likelihood that individuals may not agree to participate in a particular study. In other situations, the outcomes of interest are such that the duration of the study is relatively long, while at the same time the results are needed quickly. In this situation, an explicit, reproducible and relatively inexpensive analytical framework is advantageous.

MDA can incorporate both clinical knowledge and the values attached to various outcomes, including mortality and morbidity (5). It can allow the physician to take into account the patients' individual preference values for different health states (5). MDA also allows physicians to examine whether their decisions in complex situations are compatible with their own knowledge, beliefs and preferences (5).

MDA may identify important questions in need of further research. In many situations, the importance of these questions is not obvious at the outset of a study, but decision analysis may indicate that such questions are critical to the decision-making process.

CRITICISMS OF MDA

Several criticisms have been targeted at MDA. However, many of these criticisms can easily be answered (5-8). Among the most frequently cited complaints are that MDA is difficult to comprehend, time-consuming, tedious, and associated with excessive simplification and unwarranted precision. In addition, some have said that uncertainty exists about how to react to results that are expressed in utilities and that the probability estimates used to derive these results are often in dispute.

The extent to which these concerns apply to particular analyses is variable. The hallmark of an excellent decision analysis is an explicit tree that makes it easy for physicians to understand the options that are being analyzed. In addition, the analytical process should be sufficiently transparent to enable physicians to see exactly how outcomes are derived. The availability of sophisticated, but straightforward, computer programs has reduced the amount of time required to perform analyses as well as reduced the tedious nature of some tasks.

In MDA, the desire for a simple and explicit tree is balanced against oversimplification and plausibility. In subsequent sections of this paper, utilities are discussed and it is shown that they are not the only outcome measures that are used in MDAs.

While the probabilities that may be used in decision analyses will be expected to have varying degrees of uncertainty, they are the same estimates that guide decisions in clinical practice. As is shown in the present paper, the use of sensitivity analyses is one way of determining the impact of alternate probability estimates.

STAGES OF MDA

Four structural elements can be distinguished in MDA. First are the definition of the problem and the clinical starting point. Second are the choices, which are those events that are controlled by the physician. Third are the events that occur by chance and, thus, are not within the control of the physician. The last structural elements are the outcomes that are the endpoints to be considered in the analysis. These structural elements create the stages shown in Table 1. The stages will be illustrated by using an example of a published analysis (9).

The problem: The example that is used to illustrate the stages of MDA relates to percutaneous injuries among health care workers (HCWs) (9). In the early years of antiretroviral postexposure chemoprophylaxis, the United States Public Health Service issued recommendations on the management of occupational exposure to HIV, including considerations for the postexposure use of zidovudine (10). In this example, the working scenario was a HCW who was exposed percutaneously to blood from a patient not previously known to be infected with HIV. The central question was what was the preferred management option for this HCW, including the role of antiretroviral chemoprophylaxis with zidovudine. Current approaches employ combination antiretroviral chemoprophylaxis. For the purposes of simplicity, this paper uses the zidovudine monoprophylaxis example.

The options or choices: The options are meant to reflect the consensus of what is felt to be the likely options used in clinical practice. In this example, the clinician may choose one of three options. He or she may decide to treat no one with zidovudine, treat all with zidovudine, or to stratify and treat only if the 'donor' blood is HIV-positive on testing.

Tree building: The initial decision made by the clinician is to choose a management option as stated above. The more important events that result downstream from the decision form the branches of the decision tree. This can be appreciated by reviewing these events according to the options that were initially chosen in the present example (Figures 1A to C).

'Treat none' option: In the 'treat none' option (Figure 1, top), no one is treated. Patients fall into two groups depending on

whether the blood to which they were exposed is HIV positive. Such persons would not know the status of the blood to which they were exposed, as in the option 'no testing of donor blood'. The HCWs may or may not go on to seroconversion and eventually develop AIDS. There are no iatrogenic complications related to zidovudine because the drug is not used in this option.

'Treat all' option: In the 'treat all' option, all HCWs receive zidovudine (Figure 1, middle). The duration of postexposure treatment was six weeks in the initial analysis at a dose of 200 mg every 4 h (9). Zidovudine therapy has been shown to be associated with short term toxicity (10). Carcinogenicity has been demonstrated in laboratory animals when high doses were used for prolonged periods (10). If other antiretroviral agents are being used, one would need to consider the potential toxicities associated with these agents.

Patients receiving zidovudine therapy may not go on to seroconversion, and some will suffer drug complications. As in the 'treat none' option, the status of the donor is unknown. The proportion of HCWs seroconverting would be less than in the treat none option; the trade-off is the presence of drug-related toxicity in this group.

'Test' option: In the 'test' option, the clinician chooses to give a full course of postexposure treatment with zidovudine only if the 'donor' blood is HIV-positive (Figure 1C). In clinical practice, the results of testing may be available within 48 h. Individuals are usually offered the drug immediately after exposure and it is stopped if the 'donor' blood is found to be HIV negative. Some HCWs in the 'test-positive' branch of this option will have iatrogenic complications and may seroconvert. The proportion of persons who suffer iatrogenic complications will be greater than the 'treat none' option, but less than the 'treat all' option. The proportion of seroconversions follows a similar trend.

Figure 1 shows the decision tree that evolved by virtue of the sequence of events occurring downstream from the clinical starting point of each option. By convention, open circles indicate where events occur by chance; for example, in the 'treat all' option if the donor blood is infected, the HCW may or may not seroconvert despite getting zidovudine, and the clinician has no control over this fate. The blackened squares represent terminal nodes that indicate the end of the sequence of events being considered in the analysis.

Baseline probabilities: In the decision tree, probabilities describe the flow of events that are not within the control of the decision-maker. In MDA, it is important to indicate the source of these estimates. It is also helpful to indicate what alternate estimates were considered. Such estimates are usually derived from the literature wherever data exist. However, baseline probabilities may be derived from sources other than the published literature. Some of these sources include focused analyses of large databases and meta-analyses. By convention, the probabilities are placed below the corresponding chance events. For example, in the 'treat none' option in Figure 1A, the probability of seroconversion is placed below the seroconversion branch of the decision tree. In the present example, the baseline probabilities were obtained from the literature (Table 2).

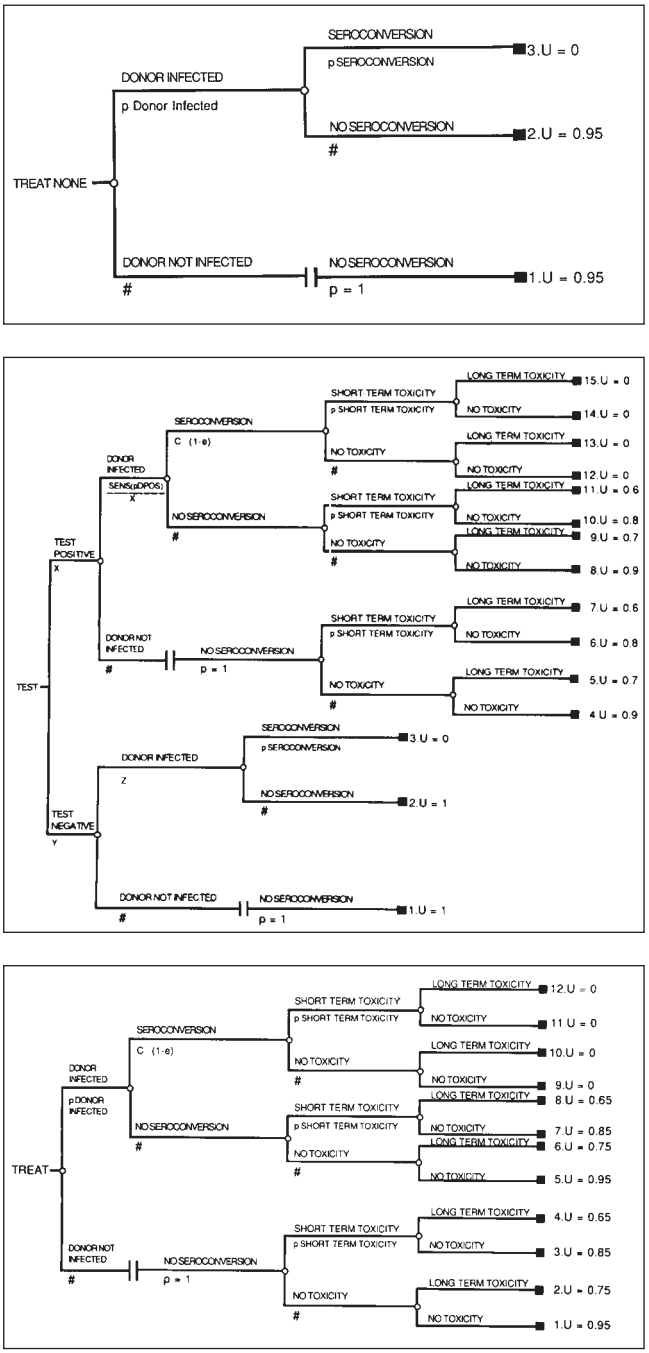

Figure 1) *Three options and outcomes connected with potential exposure to HIV. Health states are numbered at the extreme right.* **Top** *'Treat none' option. No health care worker receives zidovudine following exposure. The serological status of the donor remains unknown.* **Middle** *'Test' option. Health care workers receive zidovudine if the blood to which they have been exposed is HIV-positive on testing.* **Bottom** *'Treat all' option. All health care workers receive zidovudine for six weeks following percutaneous exposure to blood. The serological status of the donor remains unknown for this duration. In the middle and the bottom figures, the probability expressions for long term toxic reaction and no toxic reaction have been omitted for clarity. # The sum of the probabilities at each chance node is equal to 1. C Risk of seroconversion; E Effectiveness of zidovudine; P Probability. X=sens(PDPos)+(1–spec)(1–PDPos), where sens is sensitivity, PDPos is probability of donor being HIV-positive, and spec is specificity. Y=(1–sens)(PDPos)+spec(1–PDpos); Z=(1–sens)(PDPos)/Y*

TABLE 2
Baseline probability estimates used in a decision analysis on percutaneous exposure to blood among health care workers

Variables	Estimates*
Drug toxicity	
Short term	0.20
Malignancy	0.01
Effectiveness of zidovudine	0.80
Test sensitivity†	0.97
Test specificity†	0.994
Seroconversion risk	0.004
HIV prevalence	0.052

**Sensitivity analyses ranged from 0% to 100% for all probability estimates.*
†Conditional sensitivity and specificity of Western blot. Adapted from reference 9

Outcome measures: While outcomes are often expressed as utilities, there are several possible outcomes that could be used depending on the issues being examined. For example, one may be interested in the expected number of clinical complications, disease states, deaths, life years, quality-adjusted life years, costs relative to effectiveness and other outcomes. In the case of costs, several examples in the literature are relevant to infectious diseases (11-16). In the example chosen for the present paper, utilities were used as the outcome measure.

Utilities quantify the values that individuals place on different health states, based on utility theory (17). This theory describes rational decision-making based on a number of axioms that describe how individuals ought to behave when faced with decision-making under conditions of uncertainty (18). Each health state is assigned a utility value that quantifies preferences for these health states. In the present example, two approaches were used to determine utilities (19). First, a consensus rating scale was used. Second, the standard gamble technique was used (19). Baseline analyses were conducted using both of these approaches for comparison.

A detailed discussion of the techniques used to measure utilities is beyond the scope of this paper. However, the basic idea is that at one extreme of the health state scale is death (assuming very few things are worse than death) and at the other extreme is perfect health. The corresponding utilities are 0 and 1, respectively. The closer a health state is to perfect health, the more preferred it will be. Conditions that may reduce the value of the health state after percutaneous exposure to HIV include seroconversion and eventually AIDS, drug toxicity, and not knowing the status of the 'donor' blood and consequently worrying about the possibility of exposure to HIV.

Baseline analyses: The expected outcome is derived by a process commonly referred to as 'folding back' the branches of the decision tree. In this procedure, the expected value of the outcome (utilities in this example) is the weighted average of the utilities at each of the terminal nodes of the given branch, with weights provided by the probability that a person will end up in that health state. Instead of utilities, the outcome could have been dollars. In the latter situation, the expected cost attributable to each option would be derived in a similar fashion to the expected utilities. Computer software is usually used to perform the analyses.

In our example, the baseline results indicated that the 'test' strategy had the highest expected utility, followed by the 'treat none' and 'treat all', 0.99311, 0.94980 and 0.92796, respectively, using the consensus-derived utility estimates. If this was a cost effectiveness analysis, one may choose to express the outcomes as dollars in relation to the cases of AIDS prevented by one option over another.

Sensitivity analyses: In the sensitivity analyses, the effect of varying the baseline variables through a plausible range of estimates is examined. This aspect of the analyses is crucial and typically involves significantly more time and discussion than the baseline analyses. One variable may be examined at a time as is done in many analyses; however, more than one variable may be changed simultaneously as in two-way and three-way analyses. The latter two types of analyses are often referred to as threshold analyses.

In the present example, the test option was preferred throughout the range of probability values from 0 to 1 in one-way sensitivity analyses, for the effectiveness of zidovudine and the risk of seroconversion, respectively. These findings revealed benefits to the test option other than merely identifying individuals for zidovudine therapy. In this regard, even at 0% drug effectiveness and 0% seroconversion rates, the test option was still preferred. In fact, it was found that the main value of the test option was not derived from the identification of persons who should receive zidovudine, but from reduction in the emotional stress (associated with uncertainty over the donor's status) that occurs when the test of the donor's blood is negative for HIV.

The value of testing is also shown when one examines the effect of the prevalence of HIV. The one-way sensitivity analyses showed that the 'treat none' option became the preferred option when the prevalence of HIV positivity exceeded 42% (Figure 2). This seemingly paradoxical finding was because as the prevalence of HIV increased, the number of persons who would be told that they were exposed to HIV-infected blood increased. One-way sensitivity analyses had indicated that drug toxicity was not a major factor. It was the 'worry-factor' associated with knowledge of exposure to seropositive blood that caused the expected utility of testing to fall with increasing HIV seroprevalence. The effect of removing the worrying factor is shown in Figure 3. The overall quality of life (utility) following HIV exposure remains relatively high, due in part to the low seroconversion rate. Consequently, the changes in the slopes of the 'treat none' and 'treat all' options in Figures 2 and 3 are not dramatic even in the presence of increasing HIV seroprevalence.

Sensitivity analyses can also be performed on the utility estimates. In the present example, the direction of the results was not affected by changes in the utilities, with one exception. When the disutility (one utility) associated with knowing that the 'donor' was HIV positive reached a value of 0.035, the test option failed to become the preferred option at a relatively high prevalence of HIV seropositivity.

Comments on results of the percutaneous exposure exam-

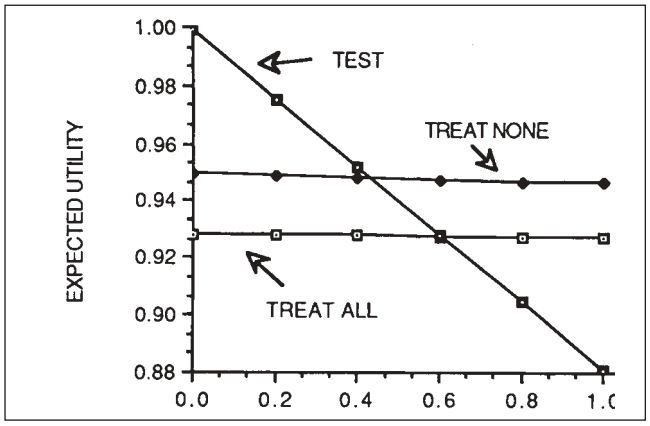

Figure 2) *Varying the prevalence of HIV infection in the patient population (one-way sensitivity analysis). The treat none option becomes preferred when the prevalence of HIV exceeds 42%.*

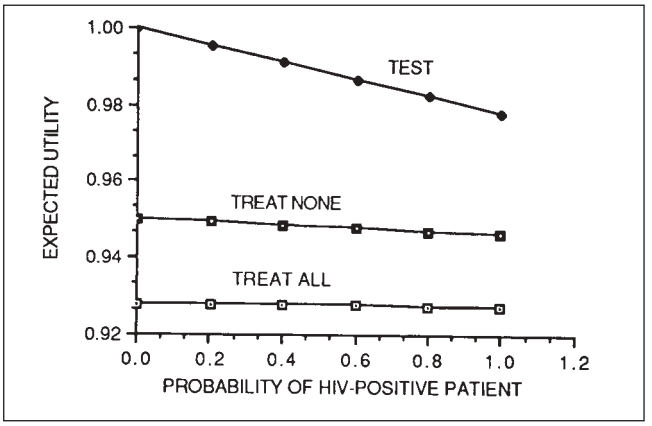

Figure 3) *Varying the prevalence of HIV infection in the patient population and removing the 'worrying factor' due to HIV-seropositive exposure (one-way sensitivity analysis). It was assumed that no units of utility were subtracted as a result of a known HIV-seropositive exposure. The test strategy was the preferred strategy. The dramatic fall in the expected utility of the test option that was seen in Figure 2 is no longer present*

ple: In the example chosen to illustrate the stages of MDA, the test option was the preferred option with the highest expected utility. The benefit of this strategy from the perspective of HCWs was because it would enable HCWs to know the status of the blood to which they were exposed. Zidovudine was not the major factor influencing the individuals' preferences. However, in 1991 when the analyses were performed, zidovudine had a role to play as long as its effectiveness was greater than zero. Today, zidovudine monotherapy has been replaced by combination therapy for HIV postexposure chemoprophylaxis (20,21).

SUMMARY

We can use MDA in several ways in the field of infectious diseases as a tool to improve the quality of care because it can provide a structured and consistent approach to solving complex problems. Many cost effectiveness studies in the infectious diseases literature use a decision analysis approach. Likewise, infectious diseases complications, mortality or other clinical entities have been used as outcome measures. In this regard, decision analysis is more than just a consideration of health state preference values (utilities). It provides us with a systematic, reproducible analytical framework that considers the trade-off among options under conditions of uncertainty in relation to a desired outcome.

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