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Agreement of Decision Analyses and Subsequent Clinical Studies in Infectious Diseases

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Abstract

Purpose: Decision analysis techniques can compare management strategies when there are insufficient data from clinical studies to guide decision-making. We compared the outcomes of decision analyses and subsequent clinical studies in the infectious disease literature to assess the validity of the conclusions of the decision analyses.

Methods: A search strategy to identify decision analyses in infectious diseases topics published from 1990-2005 was developed and performed using PubMed. Abstracts of all identified articles were reviewed and infectious diseases-related decision analyses were retained. Subsequent clinical trials and observational studies that corresponded to these decision analyses were identified using pre-specified search strategies. Clinical studies were considered a match for the decision analysis if they assessed the same patient population, intervention, and outcome. Agreement or disagreement between the conclusions of the decision analysis and clinical study were determined by author review.

Results: The initial PubMed search yielded 318 references. Forty decision analyses pertaining to 29 infectious diseases topics were identified. Of the 40, 16 (40%) from 13 infectious diseases topics had matching clinical studies. In 12/16 (75%), conclusions of at least one clinical study agreed with those of the decision analysis. Three of the four decision analyses in which conclusions disagreed were from the same topic (management of febrile children).

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These results were presented in part at the 43rd Annual Meeting of the Infectious Diseases Society of America, San Francisco, CA, October 6-9, 2005 (Abstract # 1190).

Clinical Significance:

- Conclusions of decision analyses agreed with conclusions of clinical studies in 75% of the analyses assessed
- These findings support the validity of decision analyses and usefulness for clinical decision-making
- Results of decision analyses may be incorporated into clinical decision-making, but the specific questions addressed and quality of data used in decision analyses must be noted

Conclusions: There was substantial agreement between the conclusions of decision analyses and clinical studies in infectious diseases, supporting the validity of decision analysis and its utility in guiding management decisions.

Keywords

Infectious diseases; Decision support techniques; Clinical trials

INTRODUCTION

Decision analysis can aid in determining the optimal medical management strategy when there are insufficient data from clinical studies to guide decision-making. To perform a decision analysis, a decision model is constructed to account for different clinical outcomes that can result from a specific decision. Data from the medical literature are then used to determine each clinical probability in the decision tree (for an example, see Figure 1). Standard calculations arrive at expected outcome probabilities, or utilities, in the case of quality measures or costs, for the various clinical scenarios. Sensitivity analyses provide an assessment of the stability of the model's findings based on the uncertainty inherent in the probability estimates used. Outcomes can include clinical efficacy, adverse effects, and quality measures. The strategy identified by the model to have the highest utility is the favored strategy.^{1, 2}

Although a quantitative, systematic decision analysis approach is more scientific than “expert opinion,” this technique can be limited by the assumptions that must be made to perform the analysis, insufficient primary data for the clinical probabilities, and limited applicability of the results. Although there are guidelines for assessing the usefulness of decision analyses and their role in clinical care,^{3, 4} we are unaware of studies that have attempted to assess the validity of decision analyses using subsequent clinical study results.

We recently noted that clinical studies had been conducted in areas of infectious diseases research in which decision analyses had previously been performed.^{5, 6} We therefore sought to assess the validity of decision analysis techniques by comparing the results of such analyses with those reported in analogous clinical studies. Such a comparison could provide evidence for or against the usefulness of decision analysis in clinical decision-making.

METHODS

Identification of Infectious Diseases Decision Analyses

Because neither “Infectious Diseases” nor “Decision Analysis” are medical subject heading (MeSH) terms, we developed a search strategy to identify infectious diseases-related decision analyses (Table 1). We performed a PubMed search for articles that included “Bacterial Infections and Mycoses” or “Viruses” and either “Decision Trees” or “Decision Support Techniques” as MeSH terms, or included “decision analysis” in the title or abstract. The search was limited to works published between January 1990 and May 2005. Exclusion criteria included: a) non-English language; b) animal experiments; c) meta-analyses; d) case reports; e) letters, editorials or correspondences; f) “cost”, “cost-benefit analysis” or “cost analysis” as MeSH terms and g) “economics” as a MeSH subheading. Abstracts identified by this search strategy were then reviewed by three of the authors (JNB, TH, and TRS) to confirm that the articles were truly decision analyses of infectious diseases topics.

Identification of Clinical Studies Related to the Infectious Diseases Decision Analysis

To identify clinical trials that matched the infectious disease decision analyses, four different search strategies were employed: 1) a PubMed “related-articles” search limited to “clinical

trials” as a publication type; 2) an ISI Web of Science⁷ citation search to locate works that had cited the published decision analysis; 3) an ISI Web of Science related-articles search to locate articles that shared citations with the published decision analysis; and 4) a topic search of the Cochrane Central Register of Controlled Trials through Ovid.⁸ These searches were limited to years after the publication of the decision analysis.

Criteria for Matching Between Decision Analyses and Clinical Studies

Clinical studies were considered to correspond to a prior decision analysis if they matched on all of the following criteria: 1) patient population; 2) intervention; and 3) outcome assessed. For example, in the decision analysis by Heymann,⁹ the patient population was infants born to human immunodeficiency virus (HIV)-infected mothers in Africa, the intervention was formula vs. breast feeding, and the outcome assessed was infant mortality. In the randomized clinical trial by Nduati, et al.¹⁰ 401 infants of HIV-infected mothers in Kenya were randomized to breast-feeding or formula feeding. The outcomes assessed included infant mortality as well as HIV-1 infection. This decision analysis and clinical trial were considered a match.

After identifying matching clinical studies, each decision analysis and its corresponding clinical study (or studies) were reviewed by three of the authors (JBN, TH, and TRS) and assessed for agreement or disagreement of results and conclusions.

RESULTS

There were 318 references identified by the PubMed search strategy (Figure 2) for decision analyses. Review of these abstracts identified 40 decision analyses pertaining to 29 different infectious disease topics.^{6, 9, 11-48} Of the 278 articles excluded upon abstract review, reasons for exclusion were: an infectious disease topic but not a decision analysis (247 [89%]), a decision analysis not related to infectious diseases (6 [2%]), neither a decision analysis nor an infectious disease topic (24 [8.6%]), and non-human research (1 [0.4%]). Of the 318 references identified, 288 (91%) were infectious disease-related. Only 46 of 318 (15%) were decision analyses and 40/318 (13%) were infectious disease-related decision analyses.

Of the 40 infectious diseases-related decision analyses, 16 (40%) had a total of 23 subsequent matching clinical studies identified^{5, 10, 49-69} (Table 2); these covered 13 infectious diseases topics. The median year of publication among decision analyses with matching clinical studies was 1995, compared with 1998 among decision analyses without subsequent clinical studies. In 12/16 decision analyses (75%; 95% CI: 48-93%), the conclusions agreed with those of at least one subsequent clinical study. Alternatively, of the 23 clinical studies identified, 17 (74%; 95% CI: 52-90%) had conclusions that agreed with a previously published decision analysis. An example of agreement between a decision analysis and a subsequent clinical study is the decision analysis by Holloway and Mushlin²⁹ and the clinical study by Hornef, et al.⁵⁹ on the topic of biopsy in HIV-infected patients with brain lesions who fail two weeks of therapy for toxoplasmosis. The decision analysis concluded that there would be an increase in survival with the biopsy strategy. The clinical trial found that stereotactic brain biopsy in 25 HIV-infected patients revised the pre-biopsy diagnosis in 12 patients, allowing for more appropriate treatment and increased survival.

Three of the four decision analyses in which the conclusion did not agree with the clinical study were on the topic of febrile illness in children.^{12, 33, 36} Management of fever in children,^{12, 33, 36} prevention of vertical transmission of HIV,^{9, 25} and utility of biopsy in acquired immunodeficiency syndrome (AIDS) patients with brain lesions^{28, 29} each had more than one decision analysis with at least one matching clinical study.

Of the 23 identified clinical studies, 9 (39%) were observational cohort studies,^{51, 53, 59, 61-66} and 13 (57%) were randomized, controlled trials (RCT).^{10, 49, 50, 52, 54-58, 60, 67-69} A single study⁵ utilized a randomized, uncontrolled trial design. Of note, one of the topics in which there was disagreement between the decision analyses and clinical studies, management of pediatric fever, was represented by two observational studies only.^{51, 64} In contrast, the remaining topic in which there was disagreement (isoniazid for treatment of latent tuberculosis infection in HIV-infected persons) included results of several RCTs^{50, 55-58} that were discordant with conclusions from the preceding decision analysis.¹⁵ Among the decision analyses in topic areas with at least one subsequent RCT, this was the only one with conclusions that were discordant from later RCTs.

DISCUSSION

To our knowledge, this is first study to quantify the correlation between the results of decision analyses and subsequent clinical trials. We made several notable observations. First, we found 40 published decision analyses addressing infectious diseases topics between 1990 and 2005. Second, of the decision analyses in infectious diseases topics with subsequent clinical studies, the results of the decision analysis were confirmed by the clinical studies in 75%. Although we limited our review to infectious disease topics, and studies of decision analyses and clinical studies in other medical disciplines are needed, this finding provides support for the validity of decision analysis.

Decision analytical techniques have been used as research tools for several years.² Results of decision analyses have been utilized in patient care⁷⁰ and policy decisions⁷¹, especially in settings in which prospective clinical trials or other clinical study data are not available or feasible. Decision analyses may also be used to inform the design of subsequent clinical trials. Nonetheless, the role of decision analyses in influencing patient care has been debated.^{2, 72-74} We utilized careful and reproducible search strategies to optimize the identification of decision analyses and corresponding clinical trials, and then reviewed these for agreement. To our knowledge, this is the first study to characterize published decision analyses within a particular discipline, and the first to attempt to quantify rates of agreement between decision analyses and more definitive data from clinical trials.

Of the articles identified through the initial search, 91% were infectious disease-related, but only 15% were decision analyses. Specifically, the search could not reliably distinguish decision analyses from cohort studies, prospective trials, prediction rules, review articles and clinical trials. This may be due at least in part to the inability to search for “decision analysis” as a specific publication type within PubMed. If “decision analysis” were a MeSH term, such searches could be more efficient and reproducible.

To limit the size and improve the specificity of our search results, we excluded cost analyses-related MeSH terms from our search. Because not all cost analyses are decision analyses, this probably improved our search specificity but likely led to a lower sensitivity, and some studies utilizing decision analysis techniques as part of a cost analysis may have been missed. A preliminary PubMed search that included cost and cost-effectiveness terms yielded more than 100,000 references, making an abstract review not feasible. This highlights the potential value of MeSH terms that would reliably distinguish between cost-effectiveness and decision analyses.

Three of the four decision analyses in which the conclusion did not agree with the clinical study were on the topic of febrile illness in children.^{12, 33, 36} Two clinical studies addressed this issue,^{51, 64} and disagreement between these and the decision analyses likely resulted from at least two separate issues. In one instance the clinical study demonstrated that a complete blood

count proved valuable in stratifying patients;⁵¹ the decision analysis had predicted no additional value would be obtained from a complete blood count. In this instance the new data from the clinical study regarding the use of complete blood count could be applied to create a revised decision analysis. In the second instance differences in study design and inadequate data from the clinical study likely led to disagreement. Bandyopadhyay, et al.⁶⁴ retrospectively evaluated febrile children in an initial blood culture group and a non-blood culture group and concluded that treatment could be reserved for culture-proven bacteremia. This conclusion disagreed with two decision analyses that had favored an observation strategy over obtaining blood cultures.^{33, 36} One possible source of disagreement is that the decision analysis considered a blood culture and empiric treatment as one option whereas the clinical study analyzed the effect of treatment only after a positive culture. The clinical study also failed to report completely on adverse events in the group in which no cultures were taken, which could have affected agreement with the decision analyses. The process of sensitivity analysis (and the more recently described expected value of information calculations⁷⁵) would predict that when there is considerable uncertainty, subsequent clinical studies might very well disagree with the result of the decision analysis. In such a setting, it may be appropriate to conclude from a decision analysis that clinical decisions cannot be guided by the analysis until further data are available.

There are several limitations of our study. First, there were a relatively small number of published decision analyses in this content area, and an even smaller number with clinical studies that matched our search criteria. We did not search for unpublished decision analyses or clinical studies. While this likely improved the quality of the studies assessed and our ability to evaluate them, it may have limited the number of available studies. Second, we selected an arbitrary time frame for our PubMed search. Decision analysis techniques were occasionally applied to clinical scenarios in infectious diseases in the 1980s,⁷⁶ but were reported more frequently after 1990. In this study, decision analyses with matching clinical studies were published earlier in the study period than those without (median publication year 1995 vs. 1998), probably reflecting the time required to design, perform, and report results from clinical studies. If elapsed time after publication of a decision analysis is truly associated with the publication of a subsequent clinical study, it is possible that additional clinical studies that match decision analyses may be published in the future, and the extent of the correlation may change. Third, although identification of matching clinical studies was based on careful review of the articles using objective criteria, determination of agreement of decision analysis and clinical trial results and conclusions was somewhat subjective, and was limited by the complexity and variability of decision analytic techniques, sensitivity analyses, and inconsistencies in reporting methodologies and results for both types of studies. We included only clinical studies in which the study populations, interventions, and outcomes assessed included those examined in a previous decision analysis. In some cases, however, the specific question(s) addressed in the clinical study may not have been the same primary study question (s) in the preceding decision analyses. It is important to note that decision analyses are dependent on the quality of data used and the assumptions made regarding test performance characteristics, intervention efficacy and outcome rates. Some of the disagreement observed between published decision analyses and subsequent clinical studies may have been influenced by variation in underlying data quality.

Despite these limitations, we believe our results are important because they include the description of a novel methodology for identification of decision analyses and subsequent clinical trials, and because of the finding that decision analysis conclusions were frequently confirmed by clinical studies in this content area. Refinement of the search strategies reported here and application to other content areas could add to our understanding of the role of decision analyses in guiding clinical decision-making and policy development.

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Mr. Bress, Dr. Hulan, and Dr. Sterling had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

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Figure 1.
Sample decision tree.

Figure 2.
Flow chart of search results and articles reviewed for the study.

Table 1
PUBMED SEARCH STRATEGY

Search: ("Bacterial Infections and Mycoses"[MeSH] OR "Viruses"[MeSH]) AND ("Decision Trees"[MESH] OR "Decision Support Techniques"[MESH:noexp] OR "decision analysis"[tiab]) AND English[Lang] AND "humans"[MeSH Terms] AND ("1990"[PDAT] : "2005"[PDAT]) NOT (("meta-analysis"[Publication Type] OR "meta-analysis"[MeSH Terms] OR "meta- analysis"[Text Word]) OR ("economics"[Subheading] OR "costs and cost analysis"[MeSH Terms] OR cost[Text Word]) OR "cost-benefit analysis"[All Fields] OR ("case reports"[Publication Type] OR "case reports"[Text Word]) OR ("letter"[Publication Type] OR "correspondence"[MeSH Terms] OR "letters"[Text Word]) OR ("editorial"[Publication Type] OR "editorial"[Text Word]) OR "cost-benefit analysis"[MeSH Terms]) Limits: ignored
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Table 2
DECISION ANALYSES AND SUBSEQUENT MATCHING CLINICAL TRIALS IN INFECTIOUS DISEASES, 1990-2005.

Decision Analysis		Matching Clinical Study			
Topic area	Author (year)	Base-case patient	Management strategies	Outcomes assessed	Primary results
Isoniazid (INH) for tuberculosis (TB) prophylaxis	Jordan (1991) ¹⁵	HIV+ intravenous drug user	INH vs. no INH if tuberculin skin test negative	Death due to TB	INH beneficial regardless of tuberculin test status for all groups except black females
Treatment of febrile children	Downs (1991) ¹²	3-24 month-old with fever	Blood culture and empiric therapy; test-directed therapy; observation	QALE and QOL	Optimal management culture and empiric therapy; complete blood count not useful
	Yamamoto (1998) ³³	36 month-old with fever	Empiric therapy + blood culture + therapy vs. complete blood count vs. observation	Survival; neurologic sequelae; major infections; QALE	Empiric therapy if treatment risk is low; white blood count if risk is high and observation if risk is very high
	Yamamoto (2001) ³⁶	36 month old with fever	Empiric antibiotics vs. complete blood count vs. observation	Survival and permanent sequelae	Revised from Yamamoto 1998 to favor observation; dependent on negative treatment effects
	Heymann (1992) ¹⁷	African with anemia	Transfusion vs. no transfusion	Survival	Blood transfusion is indicated when risk of death due to anemia is 6.6% with a >5% contamination rate of blood supply
Treatment of PCP in HIV+	Jankiewicz (1992) ¹⁸	HIV+ patient with first episode PCP	TMP-SMX vs. parenteral pentamidine	Survival	TMP-SMX preferred; pentamidine response rate of must be <2% below TMP-SMX for difference in adverse effects to affect decision
HIV+ with brain lesions	Holloway (1996) ²⁹	HIV+ with brain lesions; failed 2 weeks of toxoplasma therapy	Brain biopsy vs. no biopsy	Survival	Brain biopsy increased survival by 31 days
	Matthews	HIV+ with	Early brain	1-year	Empiric toxoplasma

Decision Analysis Topic area	Author (year)	Base-case patient	Management strategies	Outcomes assessed	Primary results	Matching Clinical Study	
						Author (year)	Study type (location)
Timing of HIV therapy	Tebas (2001) ³⁷	HIV+ with no prior therapy	Immediate vs. delayed initiation of HAART	Viral load and viral resistance	therapy and biopsy for non-responders equivalent to early brain biopsy for toxoplasma+; Early brain biopsy preferred for toxoplasma negative if there are small survival advantages for early diagnosis if not toxoplasma Delaying initiation of HAART could result in better viral load suppression and less resistance	Lepri (2001) ⁶²	Prospective cohort (Italy)
						Phillips (2001) ⁶³	Prospective cohort (Switzerland, Germany & Denmark)
HIV vertical transmission	Rouse (1995) ²⁵	HIV- exposed neonate	<i>in utero</i> and neonatal ZDV vs. no ZDV	Survival and quality of life	ZDV use associated with increased QALE	Shaffer (1999) ⁶⁰	Decreased transmission with ZDV
						St. John (2003) ⁶⁵	Decreased transmission with ZDV
<i>H. pylori</i> treatment	Heymann (1990) ⁹	Infant born to HIV+ mothers in Africa	Formula vs. breast feeding	Infant mortality	Formula feeding preferred if non-HIV infant mortality rate <10%; transmission rate >12%	Songok (2003) ⁶⁶	HIV-free survival associated with ZDV compliance
						Nduati (2000) ¹⁰	Formula feeding improved mortality (non-HIV mortality ~10%; transmission rate 16%)
Ventilator - associated pneumonia (VAP)	Sonnenberg (2002) ³⁹	General population	Eradication in general population vs. individual	"Upper abdominal" symptoms	Eradication in general population not beneficial	Wildner- Christensen (2003) ⁶⁷	Dyspepsia decreased at 1-year in treatment group, but no improvement in health care utilization or QOL
						Fagon (2000) ⁵	Improvement in health care utilization or QOL
Acute pharyngitis	Sterling (1996) ⁸	Mechanical ventilation with suspected bacterial pneumonia	Invasive diagnostic techniques vs. non-invasive	Survival	Invasive or semi- invasive diagnostic techniques guide therapy and improve survival.	Ruiz (2000) ⁶¹	Invasive management associated with fewer deaths at 14 days VAP was not significantly improved with invasive techniques
						Dagnelie (1996) ⁵⁴	Group A Streptococcus+ patients benefited from penicillin
Circumcision and urinary tract infection	Chessare (1992) ¹⁹	Child with acute pharyngitis	Symptomatic therapy; oral penicillin; intramuscular penicillin; diagnostic testing	Quality- adjusted life-days lost	For symptoms <2 days and 40% pre- test probability, rapid agglutination test and oral penicillin best strategy	Zwart (2003) ⁶⁸	No benefit of penicillin vs. placebo for symptom or school attendance measures
						Wiswell (1993) ⁵³	Increased UTI rate in uncircumcised (multiple)

Decision Analysis		Matching Clinical Study				
Topic area	Author (year)	Base-case patient	Management strategies	Outcomes assessed	Primary results	Study type (location)
(UTI)					circumcision if preferred unless risk of UTI ≥ 0.29 in the 1 st year of life	military sites in USA)
<i>P. acnes</i> therapy	Eady (2003) ⁴⁵	Patient with acne	Topical retinoids vs. oral antibiotics	Acne resolution	Topical retinoids preferred first-line therapy (based on rate of resistance to oral antibiotics)	RCT (UK)
						Ozolins (2004) ⁶⁹
						Topical retinoids and oral antibiotics similar efficacy; topical therapy preferred due to resistance

Shaded cells denote decision analyses and clinical studies with discordant results/conclusions.

CD4= CD4 lymphocyte count; HAART= Highly active antiretroviral therapy; HIV= Human immunodeficiency virus; PCP= *Pneumocystis jirovecii* pneumonia; QALE= Quality-adjusted life expectancy; QOL= Quality of life; RCT= Randomized controlled trial; TMP-SMX= Trimethoprim-sulfamethoxazole; toxoplasma= *Toxoplasma gondii* infection; UK= United Kingdom; USA= United States of America; ZDV= zidovudine