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Balancing the benefits and costs of antibiotic drugs: the TREAT model

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Abstract

TREAT is a computerized decision support system aimed at improving empirical antibiotic treatment of inpatients with suspected bacterial infections. It contains a model that balances, for each antibiotic choice (including 'no antibiotics'), expected benefit and expected costs. The main benefit afforded by appropriate, empirical, early antibiotic treatment in moderate to severe infections is a better chance of survival. Each antibiotic drug was consigned three cost components: cost of the drug and administration; cost of side effects; and costs of future resistance. 'No treatment' incurs no costs. The model worked well for decision support. Its analysis showed, yet again, that for moderate to severe infections, a model that does not include costs of resistance to future patients will always return maximum antibiotic treatment. Two major moral decisions are hidden in the model: how to take into account the limited life-expectancy and limited quality of life of old or very sick patients; and how to assign a value for a life-year of a future, unnamed patient vs. the present, individual patient.

Keywords: Antibiotic drugs, cost–benefit, decision support, resistance, review, survival

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TREAT is a computerized decision support system aimed at improving empirical antibiotic treatment of inpatients with suspected bacterial infections [1]. It has been tested successfully in several clinical studies. In a cluster-randomized clinical trial, in three hospitals in three different countries, it significantly increased the percentage of appropriate empirical treatment and shortened the hospital stay, while at the same time reducing the use of broad-spectrum antibiotics and antibiotic costs [2]. TREAT prescribed fewer antibiotic regimens and more prescriptions of 'no antibiotic treatment'. Mortality was reduced, but the study was not powered to show a statistical significance for the reduction in mortality. In a retrospective analysis in a Danish hospital (with very low percentages of resistance), TREAT prescribed appropriate antibiotics significantly more often than the attending physicians; however, it did so by somewhat increasing the consumption of antibiotics, although not of broad-spectrum antibiotics [3].

The TREAT algorithm is composed of two main parts: a causal probabilistic network, which uses patient data and data on the local distribution of pathogens and susceptibilities to provide probabilities for the source of infection, pathogens and their susceptibility to antibiotics; and a model that balances, for each antibiotic choice (including 'no antibiotics'), expected benefits and expected costs. For this balancing act, we have built a cost–benefit model, and the purpose of this article is to describe the model and the assumptions that it entailed.

Cost-effectiveness vs. Cost–benefit

In cost-effectiveness (or cost–utility) models, the cost is divided by the counts for the effectiveness measure: for example, what is the cost of preventing one death, and what is the cost of increasing life-expectancy by one quality-adjusted life-year (QALY)? In cost–benefit models, the costs and benefits are expressed in the same units, and the mathematical function is subtraction. Cost-effectiveness (or cost–utility) models can be compared to relative risk reduction; cost-benefit is comparable to absolute risk reduction. We chose to use a cost–benefit model. We wanted to prevent situations in which very small absolute gains (i.e. in mild infections) in the denominator will drive choices of costly antibiotics. The difficulty inherent in cost–benefit models is that loss of life or function has to be expressed in monetary terms. We still thought that, for decision support, a model that uses absolute gains rather than relative ones is preferable.

Perspective

To start counting costs and benefits, we had to select the perspective: who is counting? The (strict) perspective of the patient would be of no interest in this case. It is easy to show that a model that disregards influence on future resistance, and thus harm to future patients, will return, in most instances, maximum antibiotic treatment [4]. In most European countries (and Israel), the patient does not bear the cost of in-hospital antibiotic treatment directly. To choose the patient point of view would be impractical. The main point made here is that a cost–benefit (or effectiveness) model that regards future resistance and harm to other patients as an externality will return maximum antibiotic treatment, which is unacceptable to most clinicians, and, we hope, to the public as well.

The societal point of view would probably be the most interesting, but is again impractical. What is the societal cost of wasting antibiotic drugs? Is it the cost of developing new antibiotic drugs? What assumptions can we make about the development of new drugs? What do we mean by 'societal'? How wide is the community that we should consider: a country, a continent, or the whole world? The societal perspective is interesting, but not useful for decision support needs. We decided to use the perspective of the institution (hospital); assuming that the main interest of the institution is to prolong the lives of patients, and improve their quality of life.

Benefits

The main benefit afforded by appropriate, empirical, early antibiotic treatment in moderate to severe infections is a better chance of survival. On the basis of our own data, we used an OR of 1.6 for the association of inappropriate treatment with a fatal outcome [5], in a group of patients with a fatality rate of about 30%, to calculate a relative risk for a fatal outcome, and assumed that this relative risk is stable in severe and less severe infections (thatis, the absolute gain in a severe infection is larger). A systematic review and meta-analysis of the 69 prospective studies that examined the same question returned a similar OR [6].

How should we use this result? In order to translate it into a benefit, we have to multiply it by years that were gained, i.e. by the life-expectancy of the patient. For young adults, this will return a very large benefit. Little benefit (i.e. no treatment) will be returned for a 92-year-old patient. This is unacceptable, and differs enormously from the way in which we practise antibiotic treatment worldwide. An opposite approach would be to assign to each death prevented a fixed benefit. However, we are quite convinced that some patients, at the end of their lives, do not benefit from interventions. For example, institutionalized patients with Alzheimer's disease did not benefit from antibiotic treatment [7]. No benefit for appropriate empirical antibiotic treatment could be shown for bacteraemic patients with severe dementia who were bedridden and had pressure sores (M. Chowers and M. Paul, unpublished data). We need to achieve a balance between the following: the recognition that infection is an acute event and, once it is overcome, the patients will return to their life-path, and that age bias should be avoided; and the recognition that antibiotic treatment is sometimes futile, and will incur only costs without benefits.

The solution that we have chosen recognizes the futility of treating patients with a very guarded short-term prognosis because of underlying disorders, but assigns the same benefit to all patients with a favourable short-term prognosis. From a large database on patients with bacteraemia, we derived a logistic model predicting 1-month mortality [5], and then used only terms related to underlying conditions to calculate a probability for 1-month mortality not related to infection. The terms included were malignancy, functional capacity (bedridden vs. others), congestive heart failure, intratracheal intubation (prior to infection), neutropenia, chronic renal failure, dementia, and age. We assigned the same benefit to all 1-month survivors, 5 years of life, this being the mean survival of patients with bacteraemia [8]. Thus, TREAT calculates the probability of being alive at 1 month, independently of the infection, and multiplies it by 5 years. This is the figure used to calculate benefit for the appropriate antibiotic treatment. This is a solution that worked for decision support. The correct solution from the point of view of health economics can be debated. A moral deliberation is required to address the ethics of alternative solutions.

We have assigned a value of €50 000 to a QALY; this is the average cost of 1 year on haemodialysis in the countries that participated in the original TREAT project. The correct value to use can be debated. However, our results did not change when the value of a life-year was increased by a factor of 2 or 4, reflecting the facts that the net cost–benefit is driven by the gain in life-years for the present patient and loss in life-years for future patients, and that the other costs and gains are of lesser magnitude. Appropriate treatment was also assigned a gain of three hospital days [5].