A stochastic model of susceptibility to antibiotic therapy—The effects of cross-resistance and treatment history

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1. Introduction

Several reports have suggested that the use of a medical decision support system (MDSS) based on computerised algorithms can assist the physician in

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Summary

Objective: Selection of antibiotic therapy is a complicated process, depending on, among others, the effect of cross-resistance between antibiotics. We propose a model, which incorporates information about treatment history in the form of information on the success or failure of the current treatment and which combines this with data on cross-resistance to predict the susceptibility to future antibiotic treatments, thus providing a systematic basis for revision of antibiotic treatment.

Methods and material: The stochastic model was built as a causal probabilistic network (CPN). Data used in the model were based on a bacteriology database including data on patient and episode unique pathogens cultured from a microbiological sample.

Results: In this paper, we develop a CPN that can exploit knowledge about cross-resistance between two consecutive treatments, explore the properties of this CPN and consider how the CPN can be integrated into a complete decision support system for selection of antibiotic therapy.

Conclusion: The model presented may be useful both as a theoretical tool describing cross-resistance between antibiotics and as a part of complete decision support system for selection of antibiotic therapy.

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selecting antibiotic treatment [1–6]. We have recently developed TREAT [1,9,10], a computerised MDSS for diagnosis and treatment of infections, using a CPN, sometimes also called a Bayesian Network [1,4,6]. The system was tested in a randomised controlled clinical multicenter trial. The percentage of inappropriate antibiotic treatment, defined as non-covering subsequently isolated pathogens, was reduced from 36% without TREAT to 27% in departments using TREAT [7]. In this trial, we addressed only empirical treatment, initiated at the onset of the infection, although the system can be used at any decision point during the course of antibiotic therapy.

The current paper addresses the problem of revising antibiotic treatment during the infectious episode. During this time, the patient may improve, remain stable or deteriorate. In about two-thirds of patients, the identity of the infecting pathogen remains unknown [7] and this also implies that the antibiogram (i.e. the in vitro susceptibility to a range of antibiotics) remains unknown. The percentage of patients where the infecting pathogen is known ranges from less than 20% among patients with community-acquired pneumonia, to 60% for urinary tract infections [7]. In about 40% of patients non-significant, colonizing bacteria are isolated from microbiological samples [7]. Revision of antibiotic treatment involves an assessment of the patient’s status, the presumed diagnosis, response to current empirical treatment, and available microbiology. The choice of a new treatment is complicated by the mechanisms of cross-resistance and/or co-resistance, in the following collectively referred to as cross-resistance. Empirically, the knowledge that a pathogen is resistant to a given antibiotic will typically increase the probability that the pathogen is also resistant to certain other antibiotics, thereby reducing their suitability as part of a revised treatment. Likewise, the knowledge that a pathogen is susceptible to a given antibiotic will typically increase the probability that the pathogen is susceptible to certain other antibiotics. Without addressing previous antibiotic treatment and antibiotic modifications, antibiotic MDSSs for diagnosis and treatment of infections will always remain non-sufficient.

The purpose of this study is to devise a method for incorporation of the information about success or failure about the current treatment into the revision of the treatment and accounting for cross-resistance. We briefly illustrate the properties of this method using a small CPN with a single pathogen for demonstrative purposes. The input includes information about the probability of the pathogen at the onset of the illness, current empirical treatment and the patient’s response to this treatment. The CPN will determine the probability of susceptibility to a revised treatment. The paper will specify how a bacteriology database can be used to provide statistical material for derivation of cross-resistance between antibiotics.

2. Methods and material

The stochastic model of the effect of success or failure of the current treatment was built as a CPN, in the following referred to as the cross-resistance CPN. A CPN is a graph, where the nodes in the graph represent stochastic variables and the directed edges represent conditional probabilities. The conditional probabilities are entered into the CPN during its construction and this subsequently allows the calculation of the marginal probability distributions for each of the stochastic variables. The model is implemented using the HUGIN tool [8]. The cross-resistance CPN has been constructed such that it can be incorporated into the larger CPN, which is part of the TREAT system.

2.1. The TREAT system

TREAT was developed to advice on the diagnosis and treatment of severe infections [1,9,10]. Input data include the patient’s demographic characteristics, background conditions, previous antibiotic treatment, devices, laboratory test results, signs and symptoms of sepsis and local infection, microbiological and radiological results.

2.1.1. Structure

In the TREAT CPN 11 sites of infection are modelled, representing for example infections of the urinary tract or of the lungs. For each site, the model contains stochastic variables representing the presence of each of the most common pathogens. For example, the model of urinary tract infections is represented by 13 pathogens or groups of pathogens. Since each pathogen is represented by its own stochastic variable in the CPN, the model can handle infections with multiple pathogens and even simultaneous infections at several sites. A simplified structure of the CPN, reflecting the principle of how several sites of infection are handled in the CPN and how several pathogens are organized in a single site has been published previously [10]. The TREAT CPN has 155 stochastic variables representing different pathogens at different sites of infection.

The presence of sepsis and infection at a given site are assessed from 214 other clinical variables included in the TREAT CPN. Overall, the current
version of the TREAT CPN contains more than 8000 nodes.

2.1.2. Output
Based on the data available at the onset of the episode of infection (e.g. sepsis symptoms and symptoms of infection at a given site), the TREAT CPN predicts the probabilities of the presence of individual pathogens.

The TREAT system uses the pathogen predictions in the CPN to recommend antibiotic treatment. For each potential treatment, the TREAT CPN provides the probability that the treatment is appropriate, which is derived from the in vitro susceptibilities, adjusted by TREAT for pharmacodynamic and pharmacokinetic factors affecting antibiotic’s efficacy, including availability at the site of infection, the difference between bacteriocidal and bacteriostatic effects, synergism and antagonism of antibiotic combinations, and the inoculum effect. Ranking of treatments and selection of the most appropriate treatment is performed using a decision theoretic approach [1,11]. This implies that the benefits of the therapy, mainly improved survival of the patient, are balanced against the cost of drugs, side-effects and future resistance.

The TREAT system was tested in two clinical trials (a non-interventional and a randomised controlled multicenter) in hospitals in Germany, Italy and Israel. Results show that TREAT can improve the percentage of patients receiving appropriate treatment and reduce the cost of treatment [7].

2.2. Database structure and analysis
Prior probabilities used in the model were based on a bacteriology database collected at Rabin Medical Center, Beilinson Campus (six departments of internal medicine), in Israel during the prospective cohort study (July 2002–January 2003) and the interventional cluster randomised trial (May–November 2004) of the TREAT system [7,12]. Inclusion criteria for the study were: adult in-patients with suspected infections. Demographic features of the patients and full inclusion criteria have been described elsewhere [7,12]. The data collected during the trial were entered into the TREAT database.

The bacteriology database included 643 patients and episode unique isolates with susceptibility results for at least one antibiotic. The database contains only the clinically significant pathogens [7]. When a susceptibility test result fell in the intermediate category, the organism tested was considered resistant. When several isolates of the same pathogen were recovered from cultures of a single patient with different susceptibility outcomes, the most resistant pathogen was considered for analysis. A fragment of the bacteriology database is shown in Table 1. This table specifies in vitro susceptibility to four following antibiotics: ofloxacin (OFL), cefotaxime (CTX), amikacin (AMK) and imipenem (IMI).

For every pathogen, a table with the probabilities of susceptibility was constructed. A fragment from the table for Escherichia coli infection is shown in Table 2. The top corner contains the number of E. coli

<table>
<thead>
<tr>
<th>Episode</th>
<th>Pathogen</th>
<th>OFL</th>
<th>CTX</th>
<th>AMK</th>
<th>IMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acinetobacter spp.</td>
<td>R</td>
<td>R</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>2</td>
<td>E. coli</td>
<td>R</td>
<td>R</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>3</td>
<td>Moraxella spp.</td>
<td>S</td>
<td>NA</td>
<td>NA</td>
<td>S</td>
</tr>
<tr>
<td>4</td>
<td>Proteus spp.</td>
<td>R</td>
<td>NA</td>
<td>S</td>
<td>S</td>
</tr>
</tbody>
</table>

Amongst other information, the database contains attributes (columns) specifying the infectious episode (only first episode included for analysis), the name of the pathogen and the in vitro susceptibility (S, sensitive; R, resistant; NA, not assessed) to a total of 36 antibiotics, out of which only 4 are shown here.

### Table 2: Probabilities in percent for susceptibility of *E. coli*

<table>
<thead>
<tr>
<th>Treat1 (N = 220)</th>
<th>No</th>
<th>OFL</th>
<th>CTX</th>
<th>AMK</th>
<th>IMI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P&lt;sub&gt;S1&lt;/sub&gt;</td>
<td>P&lt;sub&gt;R1&lt;/sub&gt;</td>
<td>P&lt;sub&gt;S1&lt;/sub&gt;</td>
<td>P&lt;sub&gt;R1&lt;/sub&gt;</td>
<td>P&lt;sub&gt;S1&lt;/sub&gt;</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>100</td>
<td>75</td>
<td>25</td>
<td>90</td>
</tr>
<tr>
<td>Treat2</td>
<td>No</td>
<td>OFL</td>
<td>CTX</td>
<td>AMK</td>
<td>IMI</td>
</tr>
<tr>
<td></td>
<td>P&lt;sub&gt;S2&lt;/sub&gt;</td>
<td>P&lt;sub&gt;S2&lt;/sub&gt;</td>
<td>P&lt;sub&gt;S2&lt;/sub&gt;</td>
<td>P&lt;sub&gt;S2&lt;/sub&gt;</td>
<td>P&lt;sub&gt;S2&lt;/sub&gt;</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>OFL</td>
<td>75</td>
<td>75</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>CTX</td>
<td>90</td>
<td>90</td>
<td>99</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>AMK</td>
<td>95</td>
<td>95</td>
<td>99</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>IMI</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Probabilities of susceptibility to treatment 1 are marked in bold; probabilities of susceptibility to treatment 2 conditional on susceptibility to treatment 1 are marked in italics; NA, not assessable.
isolates \((N = 220)\) in the database. The first row contains the abbreviations for four of the treatments in use at Rabin Medical Center. We note that one of the treatments represents no treatment (No). The next two rows contain the probabilities of susceptibility \(P_{S1}\) or probabilities of resistance \(P_{R1} = 1 - P_{S1}\) to the first treatment. It can be seen that \(E. coli\) is susceptible to OFL with probability \(P_{OFL=S} = 75\%\) and to CTX with probability \(P_{CTX=S} = 90\%\). The following rows provide cross-resistances between the antibiotics, \(i.e.\) probabilities of susceptibility to the second treatment, given either that the pathogen was susceptible to the first treatment or not \(P_{S2|S1}, P_{S2|R1}\). These conditional probabilities for the susceptibility to the second treatment are derived from the same bacteriology database as the probabilities for susceptibility to the first treatment. For example, given that \(E. coli\) was not susceptible to CTX, the probability for susceptibility to OFL is reduced to \(P_{OFL=S|CTX=R} = 6\%\) and given that \(E. coli\) was susceptible to CTX the probability for susceptibility to OFL is increased to \(P_{OFL=S|CTX=S} = 89\%\).

3. Results

3.1. The stochastic model without cross-resistance

We will consider a situation where the CPN predicts a certain pathogen with a probability of 100\% (leftmost node in Fig. 1, Ecoli = Yes 100\%). This is usually not the case, but for simplicity we will consider this example first. The clinician decides that the patient should be treated with CTX and we can therefore assign the value CTX to the node Treat1, which represents the first treatment.

During the construction of the CPN, values from the line with the bold-face probabilities in Table 2 are entered as the probability table for the node Sus1, representing the susceptibility of the pathogen to the first treatment. In accordance with this, Hugin shows the current probability of Sus1 = Yes to 90\%.

We can now determine the probability that the infection will continue during the period where Treat1 is administered to the patient. This is represented by the node Ecoli1, where the state Ecoli1 = Yes means that the infection continues during Treat1. We assume a simple conditional probability table for Ecoli1, where Ecoli1 = Yes, if and only if Ecoli = yes and Sus1 = No. With this information, Hugin can now calculate that the probability of Ecoli1 = Yes is 10\%.

3.2. The stochastic model with cross-resistance

We are now in a position to add the components that allow us to model the effect of cross-resistance on the revision of the antibiotic treatment.

3.2.1. The case of non-covering first treatment

Let us assume that the patient did not improve and the attending physician decides that the current treatment with CTX has not successfully eliminated the ongoing infection. This allows us to assign the value “Yes” to the node Ecoli1 (Fig. 2A—D), indicating that infection with \(E. coli\) continues following the first treatment, Treat1 = CTX. As can be seen from Fig. 2A—D, this observation forces us to believe that the first treatment was not covering, as indicated by the probability of the state Sus1 = No being calculated by Hugin to 100\%.

A revised treatment and the corresponding susceptibilities to this treatment are represented by the nodes Treat2 and Sus2, respectively. The links from Treat1 and Sus1 to Sus2 represent the effect of cross-resistance, \(i.e.\) that knowledge about the susceptibility to Treat1 affects the probability of susceptibility Treat2. During the construction of the CPN, the probabilities given in Table 2 in italics are entered as the conditional probability table for the node Sus2.

Let us assume that the physician has decided to treat the patient with OFL, \(i.e.\) Treat2 = OFL (Fig. 2B). In this case, the susceptibility to OFL is 6\%, drastically lower than the prior probability of 75\% due to the knowledge about the failure of therapy. This can be seen from Table 2 in the column labeled with CTX as Treat1 and the row labeled with
OFL as Treat2, and is also indicated in Fig. 2B. The resulting reduction in susceptibility to amikacin is not so drastic, but still considerable: from the prior probability of 95—76% (Fig. 2C). However, the susceptibility to imipenem remains 100% (Fig. 2D). Thus, the failure of CTX has not only eliminated itself as a candidate for the revised treatment (Fig. 2A), but it has also substantially reduced the usefulness of OFL and AMK, while IMI remains a valid choice.

3.2.2. The case of covering first treatment

We can also consider what would have happened, if the patient had a good response to CTX. In that case, the susceptibility to OFL as a second treatment would have increased from the prior value of 75—89% (Fig. 3), thus making a step-down to OFL a relatively safe choice for the revised treatment.

3.2.3. The case of uncertainty about susceptibility to the first treatment

Let us consider the situation where the patient was given CTX as the first treatment and where, for some

![Figure 2](image-url)  It is assumed that CTX was given as the first treatment (Treat1 = CTX) and that *E. coli* infection persisted (Ecoli1 = Yes) following this treatment. A—D provide predicted susceptibilities to CTX, OFL, AMK and IMI as second treatment, respectively (light grey bars in Sus2 nodes). The probabilities shown above the Sus2 nodes are the *a priori* probabilities of susceptibility to the second treatment.

![Figure 3](image-url)  Susceptibility to OFL as second treatment. It is assumed that CTX was given as first treatment (Treat1 = CTX) and that *E. coli* infection was eliminated (Ecoli1 = No) with this treatment. The probability shown above the Sus2 node is the *a priori* probability of susceptibility to the second treatment.
reason, it is not possible to determine with certainty whether the patient responded to the antibiotic treatment. Let us also assume, that the clinical findings support the opinion that infection with *E. coli* has been eliminated, with a strength corresponding to a likelihood factor of 2. This can occur in the CPN in a patient with urinary tract infection and persistent isolation of *E. coli* from urine obtained from a chronic catheter despite clinical improvement. In Fig. 4, this has been entered into the CPN by multiplying a likelihood factor of 2 onto the node Ecoli1, thereby increasing the probability of the infection being eradicated from 90% (Fig. 1) to 94.7% (Fig. 4). In this case, the susceptibility to OFL as the second treatment is increased from the prior value of 75% (Table 2) to 84.6% (Fig. 4). This result is less marked than the increase seen when it was certain that CTX eliminated the infection, where the susceptibility to OFL as second treatment increased to 89% (Fig. 3).

### 3.2.4. The case of uncertainty about the identity of the pathogen

The last example will illustrate the typical situation when the identity of the pathogen at the onset of infection is not known for certain. In Fig. 5, it was assumed that the weight of the combined evidence for and against an *E. coli* infection within a specific site of infection resulted in a probability of 25%. Subsequently, it was entered into the CPN that in the period following initial treatment with CTX, the infection seemed to be eliminated. This information was entered by setting Ecoli1 = No. Propagation of this new evidence in the CPN resulted in a reduced belief in the presence of an *E. coli* infection \( P(E. coli) = 23\% \) and an increased belief in the infection being susceptible to the initial CTX treatment \( P(Sus1) \) changed from 90 to 92.3\%). These modified probabilities in turn increased the probability of the infection being susceptible to OFL from 75% (Table 2) to 82.6% (Fig. 5). This increase is of course smaller than the increase to 89%, obtained in the case of certain knowledge about identity of the pathogen at the onset of infection (Fig. 3).

### 4. Discussion

The examples above illustrate how information about success or failure of the current treatment may be used to revise antibiotic therapy, taking into account the effect of cross-resistance. Failure of the current treatment may reduce the number of antibiotics eligible for the revised treatment, while success may increase the number of eligible antibiotics allowing step-down treatment to narrow spectrum antibiotics and/or oral antibiotic treatment. If only weaker evidence for success or failure of treatment was available, the effect on the susceptibility of the revised treatment was reduced, but still showed the same trend. Clinically this uncertainty about the effect of the treatment is quite relevant, since it may take several days for sepsis symptoms to subside, even when antibiotic treatment is appropriate [13].

The system described uses three novel mechanisms to assist the selection of treatment at the time of antibiotic modification. Firstly, we used a bacteriology database to obtain actual local data on cross-resistance by observing the pathogens’ susceptibility rates given the susceptibility to other antibiotics. Secondly, we combined cross-resistance data with information on resolution of infection following
antibiotic treatment. Finally, we modelled these variables into a CPN computing susceptibility, given a priori pathogen probability, a priori susceptibility, cross-resistance, and clinical success of the previous treatment.

The proposed cross-resistance CPN may have practical use in two different situations. If the cross-resistance CPN is used in connection with the modern rapid diagnostic tools, such as the polymerise chain reaction, then the identity of the pathogen will be known, and the cross-resistance CPN can be used essentially as presented here. A clinical trial could determine the extent to which its estimates of susceptibility to the revised treatment could help reducing the use of broad spectrum antibiotics, while keeping the probability of appropriate antibiotic treatment high. If used in situations without a reliable identification of the pathogen, then the cross-resistance CPN may be useful in connection with TREAT, where the TREAT CPN is used to estimate probabilities for potential infecting pathogens. A unique feature of the TREAT system is the in-built possibility for calibration to different locations, or to temporal or other epidemiological changes [7]. The cross-resistance module can be similarly calibrated using a simple bacteriology database as the one presented in this study. The database should contain susceptibility data for bacterial isolates. Preferably, patient and episode-unique isolates that are clinically significant should be used. A patient-unique bacteraemia database is thus suitable and is easily available in most microbiology laboratories.

Although only a very limited selection of antibiotics have been considered in the examples given, it is apparent that the treatment history of the patient can have profound influence on the susceptibility of the patient’s infection. The cross-resistance CPN presented here therefore has the potential for substantially improving antibiotic treatment, a hypothesis that should be tested in a clinical trial.

References