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Towards evidence-based CDSSs implementing the medical reasoning contained in CPGs: application to antibiotic prescription

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Abstract. Clinical practice guidelines (CPGs) are documents giving recommendations based on expert reasoning, weighing up the pros and cons of treatments on the basis of the available evidence. We propose a new approach to the construction of clinical decision support systems (CDSS), making use of the evidence-based medical reasoning used by experts in CPGs. In this study, we determined whether this approach could retrieve the recommendations for antibiotic prescription for empirical treatment in primary care. Methods: We manually extracted, from CPGs, all the properties of antibiotics underlying recommendations for their prescription or non-prescription. We then used these properties to establish an algorithm in the form of a sequence of conditions, leading to a list of recommended antibiotics. The optimal sequence was determined by studying, for each sequence, the degree of similarity between the list of antibiotics recommended in CPGs and the list obtained with the algorithm. Results: 12 antibiotic properties were used in the form of conditions in an algorithm. For 95% of clinical situations, 10 sequences retrieved the recommended treatment. Discussion: This algorithm could be used in a CDSS for antibiotic treatment and would be useful for experts drawing up CPGs.

Keywords: Clinical practice guidelines, knowledge-based reasoning, evidence-based medicine, antibiotic prescription, primary care.

Introduction

Many of the first clinical decision support systems (CDSSs) required cooperation between computer engineers and experts in the medical domain concerned [1]. These expert systems aimed to capture the knowledge of the expert, to reproduce his or her decision-making behavior (e.g. in the domain of infectious disease, the Mycin system [1] implemented expert knowledge in the form of production rules). In the 1990s, the concept of evidence-based medicine (EBM) emerged, leading to the diffusion of clinical practice guidelines (CPGs) textual documents generated by a group of experts. These CPGs were then implemented in CDSSs, mostly according to a set of rules or decision trees dealing with patient conditions and medical action [2,3].

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However, the use of CPGs in CDSSs raised two problems: (i) many clinical situations are not described [4]; (ii) CPGs are often updated at a pace slower than that of advances in medical knowledge [5]. We propose a new approach designed to overcome these limitations by implementing the evidence-based medical reasoning used by experts to recommend therapeutic strategies in CPGs. The use of such reasoning should make it possible to retrieve the therapeutic strategies recommended by experts, and to facilitate the updating of recommendations. We focus here on a case study: the empirical prescription of antibiotics in primary care. The updating problem is particularly serious in this domain, because rapid changes in resistance lead to equally rapid changes in available evidence [6].

In this study, we aimed to extract, from CPGs, the evidence-based medical reasoning used by experts in empirical antibiotic treatment, and to determine whether this approach could retrieve the antibiotics recommended by the experts.

1. Methods

We first identified the properties of antibiotics used by the experts to weigh up the pros and cons of their use. We studied seven CPGs (five French, and two from the US) relating to 21 clinical situations in the domain of urinary infections (cystitis, pyelonephritis, prostatitis), higher and lower respiratory tract infections (pharyngitis, otitis, sinusitis, pneumonia). For each clinical situation, we manually extracted all expressions relating to the properties of the antibiotics on which recommendations were based. We then grouped similar expressions into categories (e.g.: "prevalence of resistance", "frequency of acquired resistance" were grouped into the property "likely activity of the antibiotic").

We then determined how best to order these antibiotic properties to reproduce, as closely as possible, the reasoning used by experts in the construction of lists of recommended antibiotics. For each clinical situation, we analyzed the way in which these properties were used in medical reasoning. We established an algorithm, including a sequence of conditions that an antibiotic must satisfy to be recommended, leading to a list of recommended antibiotics.

We then obtained a generic algorithm, by identifying the optimal sequence of conditions satisfactory for the largest number of clinical situations. We implemented the algorithm and created a database containing all the antibiotic properties identified. We then tested all possible sequences of conditions for all clinical situations. A sequence was considered "satisfactory" if it retrieved the antibiotics recommended in the CPGs.

2. Results

2.1. Properties of antibiotics determining the choice of molecule

Twelve antibiotic properties were extracted from CPGs (Table 1). Six properties (A to F) were identified as "necessary" conditions for the prescription of an antibiotic in a given clinical situation. An antibiotic should only be prescribed if it is (i) usable, i.e. available in the country concerned and not contraindicated in the patient and (ii) potentially effective, i.e. active against wild-type strains of bacteria, probably active against modified strains of bacteria, capable of achieving a sufficiently high concentration in the infected organ, and with proven clinical efficacy in the clinical situation concerned. Antibiotics that are usable and potentially effective are considered to be "appropriate antibiotics".

Six properties (G to L) were identified as conditions that should be met by the antibiotic for it to be chosen ahead of other molecules in a list of appropriate antibiotics. Such preferred antibiotics are referred to as "recommended antibiotics".

Table 1. Antibiotic properties determining the choice of antibiotic for empirical use in primary care

Antibiotic Properties		**Conditions used in the algorithm Examples given in italics**
Availability	A	Is the antibiotic available in the country? *No, pivmecillinam is not available in North America*
Natural activity	B	Is the antibiotic sufficiently active against wild-type strains of the bacteria? *Yes, cephalosporins are active against wild-type strains of E. coli*
Concentration	C	Does the antibiotic reach a sufficiently high concentration in the infected organ? *Yes, fluoroquinoles reach high concentrations in the prostate*
Evidence of efficacy	D	Has the clinical efficacy of the antibiotic been proven? *No, there is no evidence that fosfomycin is effective in complicated cystitis*
Likely activity	E	Is the antibiotic probably active against the etiologic bacteria? *No, S. pneumoniae has a rate of acquired resistance to erythromycin of 52%*
Contra indication	F	Can the antibiotic be used in the patient? *No, pristinamycin is contraindicated in children under the age of six years*
Protocol characteristics	G	Does the protocol promote higher levels of compliance than for the other antibiotics? *Yes, amoxicillin is prescribed for shorter periods for the treatment of pharyngitis*
Class characteristics	H	Does the antibiotic belong to a less precious class than the other antibiotics? *No, fluroquinolone use is restricted to severe conditions*
Side effects	I	Is the risk of side effects lower or are the side effects less serious than with the other antibiotics? *No, pefloxacin is associated with a higher risk of tendinopathy*
Level of efficacy	J	Is the antibiotic more effective than the other antibiotics? *No, Beta-Lactams are less effective than other antibiotics for the treatment of cystitis*
Activity spectrum	K	Does the antibiotic have a narrower spectrum of activity than the other antibiotics? *No, levofloxacin and moxifloxacin are newer, broad-spectrum antibiotics*
Ecological adverse effects	L	Is the antibiotic associated with a lower risk of collateral damage than the other antibiotics? *No, fluoroquinolone use promotes the acquisition of resistance in bacteria*

2.2. Algorithm for the choice of antibiotic for empirical use in primary care

We established a model reproducing expert reasoning, to weigh up the pro and cons of antibiotics for empirical antibiotic treatment. The resulting algorithm includes 12 conditions relating to 12 properties of antibiotics (Table 1) and generates a list of recommended antibiotics. The algorithm (Figure 1) begins with a list of antibiotics that are "potential candidates" for recommendation in a particular instance. Each question relating to antibiotic properties is asked in order, and with each successive question, none, one or several antibiotics may be removed from the list of potential candidates. Thus, the list gradually decreases in length, with each question. Once all 12 questions have been asked, the antibiotics remaining in the list should correspond to the list of recommended antibiotics from the CPGs.

2.3. The optimal sequences for retrieval of the recommended antibiotics

We investigated whether one or more sequences of conditions made it possible to retrieve the recommended antibiotics for all clinical situations. The six first conditions

(A to F, see Table 1) relate to essential properties of appropriate antibiotics. The order of these conditions in the sequence is unimportant, because all these individual conditions must be met for the antibiotic to be prescribed, regardless of the properties of the other antibiotics in the list.

The six next conditions (G to L, see Table 1) concern properties that are used to differentiate between molecules in the list of appropriate antibiotics. These conditions should generate the list of recommended antibiotics. However, the results obtained depend on the order in which the conditions are presented, because, at each step, antibiotics are excluded on the basis of comparison with other antibiotics in the list (Figure 1). We tested all 720 possible sequences for 21 clinical situations. For one clinical situation, none of the sequences retrieved the full list of recommended antibiotics. For the other 20 clinical situations, 10 sequences were considered "satisfactory", as they retrieved the full list of recommended antibiotics:

"H, G, J, I, L, K"--- "H, G, I, J, L, K"--- "H, I, G, J, L, K"--- "H, I, J, G, L, K" ---
"I, G, H, J, L, K"--- "I, H, G, J, L, K"--- "I, H, J, G, L, K"
"G, I, H, J, L, K"---"G, H, J, I, L, K"--- "G, H, I, J, L, K"

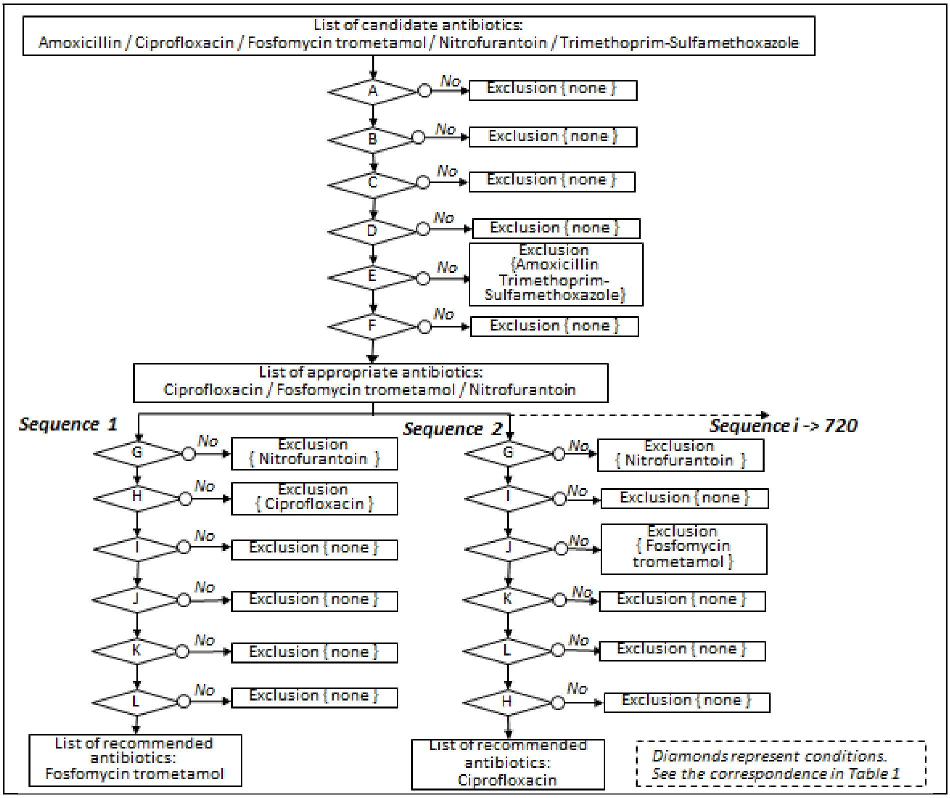

Figure 1. Example of 5 antibiotics for uncomplicated cystitis. At the beginning of the algorithm, all five antibiotics are candidates for recommendation. After the first six questions relating to essential conditions, the list of antibiotics is reduced to 3 (2 antibiotics being excluded by condition E). For the next six conditions, 720 sequences are possible and result in different lists of antibiotics (e.g.: fosfomycin for sequence 1 vs. ciprofloxacin for sequence 2).

3. Discussion

We propose a new approach based on the implementation of evidence-based medical reasoning, to generate a list of the antibiotics recommended in CPGs. We analyzed CPGs for empirical antibiotic treatment, to generate a set of 12 antibiotic properties accounting for the choices made by experts. These properties were included in an algorithm, which retrieved the recommended antibiotics in 95% of clinical situations. In one situation, the recommended antibiotics were not retrieved because the experts proposed a broader list of antibiotics, depending on the level of acquired resistance in the country of application of the CPG. This approach presents several advantages. First, it can be applied to all clinical situations, including those absent from CPGs (e.g. if the CPG does not deal with the case of renal impairment, drug properties relating to contraindications can be applied to exclude some antibiotics). Second, an explanation of the rationale for recommending a subset of antibiotics can easily be derived and given to the physician. This is an important feature for increasing confidence in the CDSS [7]. Third, this approach should facilitate the updating of knowledge, by making it possible to retrieve data concerning antibiotic properties from different resources [8] (e.g. drug databases, microbial observatories).

Further developments are required. For example, this algorithm was not assessed for all infectious diseases (e.g. sexually transmitted infections), or for all the antibiotics available on the market. The next step in this work will involve a more detailed evaluation of this formalization of expert reasoning, and its implementation in a CDSS for antibiotic treatment [9] to help experts drawing up CPGs.

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