An Algorithm Using Twelve Properties of Antibiotics to Find the Recommended Antibiotics, as in CPGs

R. Tsopra, MD[123], A. Venot, MD, PhD[123], C. Duclos, PharmD, PhD[123]
[1]INSERM, U1142, LIMICS, F-75006, Paris;
[2]Université Paris 13, Sorbonne Paris Cité, F-93000, Bobigny;
[3]Sorbonne Universités, Univ Paris 06, F-75006, Paris, France.

Abstract

Background. Clinical Decision Support Systems (CDSS) incorporating justifications, updating and adjustable recommendations can considerably improve the quality of healthcare. We propose a new approach to the design of CDSS for empiric antibiotic prescription, based on implementation of the deeper medical reasoning used by experts in the development of clinical practice guidelines (CPGs), to deduce the recommended antibiotics. Methods. We investigated two methods ("exclusion" versus "scoring") for reproducing this reasoning based on antibiotic properties. Results. The "exclusion" method reproduced expert reasoning the more accurately, retrieving the full list of recommended antibiotics for almost all clinical situations. Discussion. This approach has several advantages: (i) it provides convincing explanations for physicians; (ii) updating could easily be incorporated into the CDSS; (iii) it can provide recommendations for clinical situations missing from CPGs.

Introduction

The first Clinical Decision Support Systems (CDSS) were developed in the 1960s. Many were expert systems, designed to provide support for diagnosis and/or treatment decisions in a particular medical domain. Their development required collaboration between a medical expert and a computer scientist[1], with the medical knowledge and reasoning of the expert captured and implemented by the computer scientist. For example, INTERNIST-I[2] was a rule-based expert system providing support for multiple, complex diagnoses in general internal medicine. MYCIN[1] was a rule-based expert system developed for the diagnosis and treatment of infectious diseases.

In the 1990s, the concept of "Evidence-Based Medicine" was introduced and defined as "the integration of best research evidence with clinical expertise and patient values"[3]. This new paradigm led to the production and diffusion of Clinical Practice Guidelines (CPGs) by national health authorities[4]. CPGs are documents written by a group of experts for a particular domain, recommending diagnostic and therapeutic strategies on the basis of a systematic review of the available clinical evidence. However, CPGs are long, complex, textual documents that are difficult to use in daily clinical practice[5]. Many CDSSs were then designed to implement CPGs[6], rather than the medical knowledge of a single medical expert, to overcome these limitations and to take the concept of "evidence-based medicine" into account. Several formalisms were developed to facilitate and standardize the implementation of CPGs (e.g. Arden Syntax, EON, GLIF). These formalisms made it possible to associate "actions" (e.g. amoxicillin should be prescribed) to "patient conditions" (e.g. patient allergic to penicillin) in different ways: as Medical Logic Modules (MLMs) in Arden Syntax[7], an arborescence of the different clinical situations for a particular disease in Decision trees[8], a graph focusing on patient states in EON[9], or a flowchart of structured steps in GLIF[10].

However, there are two main problems associated with the implementation of CPGs in CDSSs. First, many clinical situations are not described in CPGs and are therefore not considered[11,12]. For instance, in some CPGs , experts give recommendations for uncomplicated cystitis, but not for cystitis in a woman with renal impairment. Second, CPG updating lags behind advances in medical knowledge[13], because updating takes time and it can be difficult to determine when an update is actually required[14]. For instance, in France, general practitioners have continued to prescribe amoxicillin-potassium clavulanate combinations for adult patients with sinusitis, as recommended in the CPGs written in 2005, but the frequency of acquired resistance to amoxicillin in *Haemophilus influenzae* has actually decreased considerably, making it possible to prescribe amoxicillin alone rather than the amoxicillin-potassium clavulanate combination. Physicians did not receive this information until 2011.

It may be possible to overcome these limitations by implementing the medical reasoning used to deduce medical "actions" from patient "conditions", rather than implementing "conditions"-"actions" combinations. In this approach, the CDSS should be able to retrieve the recommended drugs without expert intervention. For example, for women with cystitis, CPGs recommend fosfomycin trometamol treatment.

(i) The usual approach is based on superficial associative medical reasoning, often involving the implementation of expert conclusions: i.e. the association "woman cystitis → fosfomycin trometamol" (e.g.: "if cystitis in a woman, then prescribe fosfomycin trometamol");
(ii) In our approach, we use a deeper reasoning: we try to implement the arguments used by the experts who wrote the CPGs to recommend one antibiotic, i.e. "In cystitis, the recommended antibiotic should have the following properties: it must be naturally active against *E. coli*, it must reach sufficiently high concentrations in the bladder, it must not be contraindicated in the patient, etc.". By taking these properties into account, the CDSS should be able to deduce that fosfomycin trometamol should be preferred over other choices for women with cystitis.

The use of this deeper medical reasoning should make it possible to retrieve the recommended treatment from patient and disease conditions. This should make it easier to cover a larger number of clinical situations, and should facilitate updating of the knowledge base.

We used the empiric prescription of antibiotics in primary care as a case study. In this domain, it is particularly important to update recommendations frequently, in accordance with advances in medical knowledge (e.g. the frequency of acquired resistance), because of the risk of bacterial resistance emerging[15]. For the testing of our approach, we needed to understand the deeper medical reasoning used by the experts to recommend a particular antibiotic over others in CPGs for a given clinical situation. We carried out a literature review, but found no accurate description of this deeper medical reasoning. However, we hypothesized that such medical reasoning could be extracted from CPGs and formalized.

The goals of our study were:

(i) To extract from CPGs the deeper medical reasoning on which experts based their recommendations concerning the antibiotics suitable for given clinical situations;
(ii) To implement this reasoning by two different methods and then to select the method giving the best automatic retrieval of the antibiotics recommended in CPGs.

We will first describe the two methods for reproducing the deeper medical reasoning of experts. We then present the study design for their evaluation and the results obtained.

Methods

An analysis of CPGs showed that the deeper medical reasoning used by the experts to recommend a particular antibiotic over others in CPGs was based on the use of the antibiotic properties. We began by identifying these properties and then investigated two methods for reproducing the medical reasoning taking these properties into account. Finally, we implemented and tested the two methods.

Extraction of the properties of antibiotics on which expert recommendations are based

We first extracted from the CPGs the properties of antibiotics used by the experts writing these CPGs to argument the recommendation of a particular antibiotic over others .

We analyzed seven CPGs: five were provided by French health authorities, one by the European Society of Clinical Microbiology and Infectious Diseases and one by both the Infectious Diseases Society of America and the European Society of Clinical Microbiology. They concerned 21 clinical situations relating to various diseases (cystitis, pyelonephritis, prostatitis, pharyngitis, otitis, sinusitis and pneumonia). We manually extracted all the expressions linked to the properties of antibiotics used to argument the preference of one antibiotic over others. Similar expressions were then grouped into categories of properties. For example, "natural sensitivity" and "natural activity" were grouped into the category "natural activity".

For each category of properties, we then added a question to determine whether the antibiotic considered displayed the property concerned. For example, the property "natural activity" was associated with the question "Does the antibiotic have sufficient microbiological activity against wild-type strains of the causal bacterium?" The response to the question, obtained from CPGs, was used to determine whether a given antibiotic had the property considered: if the response to the question was "yes" or, "no", then the considered antibiotic was considered to "have" or "not have" the property concerned, respectively, and if the response was "not available", then we considered that there was "no information available".

We then differentiated between:

(i) The "necessary" properties that an antibiotic must have to be usable in a patient, and to treat the infection. These properties ensure that an antibiotic is both safe for the patient, and able to cure the infection. These properties were used to obtain a list of appropriate antibiotics;

(ii) The "preference" properties that an appropriate antibiotic must have for that antibiotic to be preferred from a list of appropriate antibiotics, in a given clinical situation. These properties make it possible to choose one antibiotic through a list of antibiotics that could be prescribed to cure a patient. These properties were used to generate a list of recommended antibiotics.

Use of antibiotic properties to reproduce the deeper medical reasoning used by experts to generate a list of recommended antibiotics

We then tried to reproduce the deeper medical reasoning used by the experts writing CPGs, to generate a list of appropriate and recommended antibiotics, taking into account the properties of these drugs. We investigated two methods.

<u>Constructing a list of appropriate antibiotics</u>

For each clinical situation, we began with an initial list of antibiotics, all of which were potential candidates for recommendation. This initial list of candidate antibiotics differs between clinical situations and corresponds to all antibiotics described for the situation concerned in CPGs.

For each antibiotic on the list, we searched for answers to questions about necessary properties in CPGs. We excluded from the list all antibiotics for which there was at least one "no" or "not available" answer to the questions about necessary properties. The remaining antibiotics were considered to be appropriate.

<u>Generating a list of recommended antibiotics by method 1</u>

Method 1 involved calculating a score expressing the extent to which a particularly antibiotic satisfied the preference properties. The antibiotics with the highest scores were identified as those to be recommended by this method.

For each antibiotic from the list of appropriate antibiotics, we attributed a value according responses to questions about preference properties: if the response to the question was "yes", "no" or "not available", we attributed scores of "1", "-1" or "0", respectively, for the property concerned.

For each appropriate antibiotic, we then calculated the sum of the values attributed for all the preference properties. We retained the antibiotics with the highest scores and discarded the others from the list. The final list obtained with method 1 contained the antibiotics with the highest scores and should correspond to the list of antibiotics recommended in CPGs.

<u>Generating a list of recommended antibiotics by method 2</u>

In method 2, we excluded an antibiotic as soon as a property for preference was not satisfied. The antibiotics remaining in the list after the series of questions depended on the order of the questions in the sequence. The antibiotics remaining in the list, or if none remained, those excluded in response to the last question, were considered to be the recommended antibiotics according to this method.

For each successive question relating to preference properties, we excluded the antibiotic from the list if the answer was "no", but retained the antibiotic in the list if the response to the question was "yes" or "not available".

The list was, thus, progressively reduced after each question. The final list of antibiotics to be recommended corresponded to the antibiotics remaining in the list, or if there were no antibiotics remaining, those excluded by the last question. The final list should correspond to the list of antibiotics recommended in the CPGs.

As the final list depends on the order in which the questions are asked, we tested all possible sequences of questions for the 21 clinical situations, and selected the sequences that retrieved the list of antibiotics recommended in the CPGs for the largest number of clinical situations.

Implementation and evaluation of the two methods for reproducing the deeper medical reasoning used by experts in CPGs

We compared the two methods, by creating a database containing all the clinical situations and antibiotics described in CPGs (34 substances and 11 classes of antibiotics), the properties of which were extracted from CPGs. We implemented both methods in PHP.

We then tested each method as follows. First, for each clinical situation, we established:

- An initial list of candidate antibiotics for the testing of both methods, corresponding to all antibiotics described for the situation in CPGs (about 13 antibiotics per clinical situation);
- A list of the antibiotics recommended in CPGs, which we took as the gold standard.

For each clinical situation, we then applied the method to the initial list of candidate antibiotics and obtained a final list of antibiotics. This final list was then compared with the gold standard. If the final list of antibiotics obtained with the method corresponded exactly to the full list of antibiotics recommended in CPGs, then the method was considered "satisfactory" for the clinical situation.

We then calculated the total number of clinical situations for which the method was considered "satisfactory".

Finally, we compared the numbers of clinical situations for which a "satisfactory" result was obtained between the two methods. The method with the largest number of situations for which a "satisfactory" result was obtained was considered to be the best method for reproducing the deeper medical reasoning of experts for the empiric prescription of antibiotics.

Results

Properties of antibiotics used by the experts to formulate recommendations

Twelve antibiotic properties were retrieved in CPGs, in one or more clinical situations (e.g.: "natural activity" was retrieved for all clinical situations, whereas "availability" was retrieved for only one clinical situation). Two kinds of properties could be distinguished:

(i) "Necessary" properties (A to F, Table 1). Two of these properties related to the use of the antibiotic ("availability", "contraindication"). Four related to its potential efficacy ("natural activity", "likely activity", "concentration", "evidence of clinical efficacy"). Any antibiotic with all six necessary properties was considered "appropriate". For instance, amoxicillin, ampicillin, and penicillin V were all considered appropriate for pharyngitis;

(ii) "Preference" properties (G to L, Table 2). These properties related to the efficacy of the antibiotic ("level of efficacy", "protocol characteristics"), tolerance ("side effects") or ecological risk ("class characteristics", "spectrum of activity", "ecological adverse effects"). For instance, amoxicillin is recommended over ampicillin and penicillin for pharyngitis, because of the characteristics of its treatment protocol (shorter duration of treatment, favoring compliance).

Information about the properties described in CPGs was obtained from various resources:

(a) Results of clinical trials (properties: "evidence of clinical efficacy", "protocol characteristics", "level of efficacy");

(b) Clinical data (property: "contraindication");

(c) Microbiological data (properties: "natural activity", "likely activity", "spectrum of activity");

(c) Pharmacokinetics data (properties: "concentration in the infected organ");

(d) Pharmacovigilance (properties: "side effects");

(e) Drug marketing (property: "availability);

(f) Expert knowledge (properties: "class characteristics", "ecological adverse effects").

Table 1. Necessary properties used in expert medical reasoning as the basis for recommendations concerning antibiotic use. The frequency of use of the properties is the number of clinical situations in which the property is mentioned.

	Property	Questions relating to the property concerned, with examples of responses indicated in italics	Frequency of use (%)
A	Market availability	Is the antibiotic commercially available in the country? *No, pivmecillinam is not available in North America*	1/21 (5)
B	Natural activity against etiologic bacteria	Does the antibiotic have sufficient microbiological activity against wild-type strains of the causal bacterium? *Yes, amoxicillin is naturally active against Streptococcus pyogenes*	21/21 (100)
C	Concentration in the infected organ	Does the antibiotic reach sufficiently high concentration in the infected organ? *No, nitrofurantoin does not reach high concentrations in the kidney*	16/21 (76)
D	Evidence of clinical efficacy	Has clinical efficacy been proven in the clinical situation? *Yes, fluoroquinolones have been shown to be effective for acute pyelonephritis in a randomized controlled trial*	20/21 (95)
E	Likely activity against etiologic bacteria	Is the frequency of acquired resistance to the antibiotic low in the etiologic bacterium? *Yes, the frequency of acquired resistance to amoxicillin in Streptococcus pyogenes is less than 10%*	21/21 (100)
F	Contraindication in the patient	Is the antibiotic not contraindicated in the patient? *No, telithromycin is contraindicated in children under the age of 12 years*	17/21 (81)

Table 2. Preference properties used in the deeper medical reasoning of experts for antibiotic recommendations. The frequency of use of the properties corresponds to the number of clinical situations for which the property is mentioned.

	Property	Questions relating to the properties, with examples of responses given in italics	Frequency of use (%)
G	Protocol characteristics	Does the protocol for the use of the antibiotic favor compliance? *Yes, fosfomycin trometamol is prescribed as a single dose for uncomplicated cystitis*	17/21 (81)
H	Class characteristics	Does the antibiotic belong to a class that is not precious? *No, levofloxacin belongs to a precious class of antibiotics that should be reserved for serious indications*	6/21 (29)
I	Side effects	Is the antibiotic known to have (no serious or no frequent) side effects? *No, cefixime is associated with a high risk of pseudomembranous colitis caused by Clostridium difficile*	13/21 (62)
J	Level of efficacy (high, middle, low)	Is the antibiotic very effective? *Yes ciprofloxacin is highly effective in women with uncomplicated cystitis (clinical cure: 90% [85;98])*	17/21 (81)
K	Activity spectrum	Is the spectrum of activity of the antibiotic narrow? *No, levofloxacin has a broad spectrum of activity*	4/21 (19)
L	Ecological adverse effects	Does the antibiotic have a low risk of collateral damage? *No, first-generation quinolones promote the emergence of bacterial resistance*	14/21 (67)

Number of clinical situations for which a satisfactory result was obtained with each method

Method 1: Attribution of a relative score to antibiotics (illustration, Table 3)

With method 1, we obtained satisfactory results for 16 of a total of 21 situations (Table 4). The five clinical situations for which satisfactory results were not obtained were “uncomplicated pyelonephritis in women”, “uncomplicated cystitis in women”, “pharyngitis in adults without allergy”, “maxillary sinusitis in adults without allergy” and “pneumonia in adults”.

Method 2: Exclusion of antibiotics through a sequence of questions (illustration, Figure 1)

Permuting the questions about the six preference properties resulted in 720 sequences of questions (6!=720). We tested all 720 sequences for the 21 clinical situations, and tried to identify the most generic sequences (those giving satisfactory results in the largest number of clinical situations). Ten such sequences were identified:

“G, H, I, J, L, K” / “G, H, J, I, L, K” / “G, I, H, J, L, K”
“H, I, J, G, L, K” / “H, I, G, J, L, K” / “H, G, I, J, L, K” / “H, G, J, I, L, K”
“I, G, H, J, L, K” / “I, H, G, J, L, K” / “I, H, J, G, L, K”

The qualitative analysis of the 10 sequences showed that:

- In the 1st and 2nd positions of the sequence, we always found questions relating to properties “G” (Protocol characteristics), “H” (Class characteristics) or “I” (Side effects);
- In the 3rd position of the sequence, we always found questions relating to the properties “G” (Protocol characteristics), “H” (Class characteristics), “I” (Side effects) or “J” (Level of efficacy);
- In the 4th position of the sequence, we always found questions about property “G” (Protocol characteristics), “I” (Side effects) or “J” (Level of efficacy);
- In the 5th position of the sequence, we always found questions about property “L” (Ecological adverse effects);
- In the 6th position of the sequence, we always found questions about property “K” (Activity spectrum).

Method 2 gave a satisfactory response in 20 of the 21 clinical situations (Table 4), for these 10 sequences of questions. The only clinical situation for which a satisfactory result was not obtained was “uncomplicated cystitis in women”.

Table 3. Method 1 – Attributing a relative score to antibiotics. (See the correspondence of properties A to L in Tables 1 and 2). Example of seven antibiotics, for pharyngitis in adults with penicillin allergy and without a contraindication for beta-lactams. All seven antibiotics were present in the initial list of candidate antibiotics. Two antibiotics did not have all the necessary properties, and were therefore excluded from the list (“amoxicillin” for property F, and “azithromycin” for property E). The five remaining antibiotics were considered appropriate. For each of these antibiotics, we attributed a relative value to each preference property. The sum of these values was maximal for three antibiotics (“cefuroxime axetil’, “cefotiam hexetil”, and “cefpodoxime proxetil”), which were therefore considered to be recommended by method 1. As they corresponded to the gold standard (i.e. the list of antibiotics recommended in CPGs), method 1 was considered “satisfactory” for this clinical situation.

	Necessary properties Responses to questions *(Y: Yes, N: No)*						**Preference properties** Attribution of a score						**Sum for G to L**	**Conclusion**
	A	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**	**L**		
Amoxicillin	Y	Y	Y	Y	Y	N	-	-	-	-	-	-	-	Inappropriate
Azithromycin	Y	Y	Y	Y	N	Y	-	-	-	-	-	-	-	Inappropriate
Cefaclor	Y	Y	Y	Y	Y	Y	-1	0	0	0	0	-1	-2	Appropriate
Cefuroxime axetil	Y	Y	Y	Y	Y	Y	1	0	0	0	0	-1	**0**	Recommended
Cefotiam hexetil	Y	Y	Y	Y	Y	Y	1	0	0	0	0	-1	**0**	Recommended
Cefpodoxime proxetil	Y	Y	Y	Y	Y	Y	1	0	0	0	0	-1	**0**	Recommended
Pristinamycin	Y	Y	Y	Y	Y	Y	0	0	0	-1	0	0	-1	Appropriate

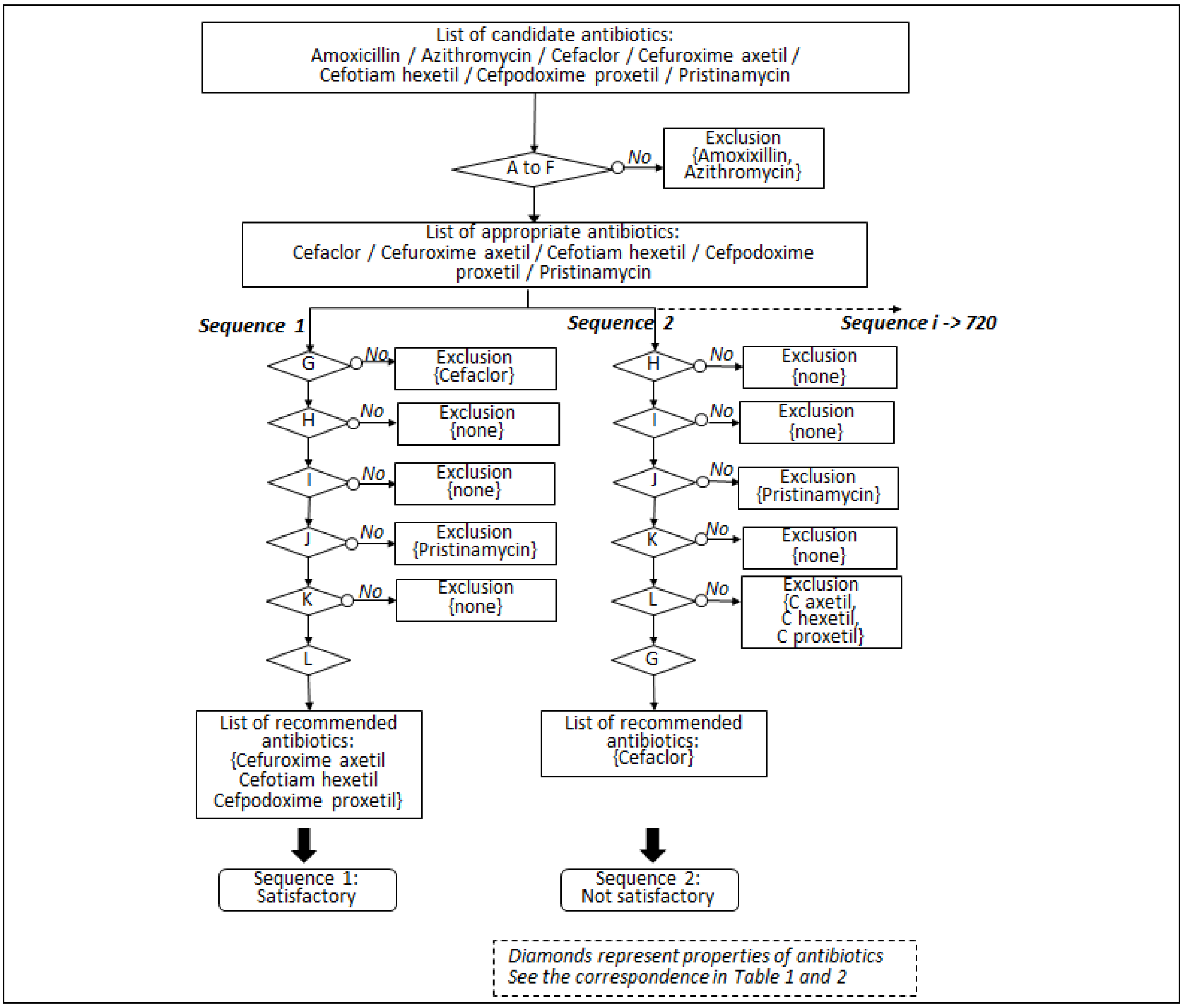

Figure 1. Method 2 – Exclusion of antibiotics according to a sequence of questions (see the correspondence of properties A to L in Tables 1 and 2). Example of seven antibiotics, for pharyngitis in adults with penicillin allergy and without a contraindication for beta-lactams. All seven antibiotics were present in the initial list of candidate antibiotics. Two antibiotics did not have all the necessary properties and were excluded from the list ("amoxicillin" for property F, and "azithromycin" for property E). The other five antibiotics were considered appropriate. For the six preference properties, 720 sequences of questions are possible by permutation of the properties. The final list of antibiotics obtained depends on the order of questions in the sequence. We illustrate the results for two sequences: sequence 1 generated a list of three antibiotics ("cefuroxime axetil', "cefotiam hexetil", and "cefpodoxime proxetil"), whereas sequence 2 yielded one antibiotic ("cefaclor"). As the list obtained with sequence 1 corresponds to the gold standard (i.e. the list of antibiotics recommended in CPGs), sequence 1 of method 2 is considered "satisfactory" for this clinical situation, whereas sequence 2 is not.

Table 4. Comparison of methods 1 and 2. Method 2 gives satisfactory results for a larger number of clinical situations than method 1.

	Method 1 – Attribution of a relative score to antibiotics	Method 2 – Exclusion of antibiotics through a sequence of questions
Number of clinical situations for which the result was considered "satisfactory"	16	20
Number of clinical situations for which the result was considered "not satisfactory"	5	1
Total	21	21

Discussion and Conclusion

We extracted the deeper medical reasoning underlying the CPGs, from the arguments used by the experts formulating recommendations concerning antibiotic use. We used this reasoning in two ways: "attribution of a relative score to antibiotics" and "exclusion of antibiotics through a sequence of questions". The "exclusion" method reproduced expert reasoning more accurately, as it retrieved the full list of recommended antibiotics for nearly all clinical situations (20 clinical situations, versus 16 for the "scoring" method). Furthermore, the only situation for which the "exclusion" method did not give a satisfactory result (uncomplicated cystitis) cannot really be considered a failure. In this situation, the experts produced a CPG that can be divided into several nation-specific recommendations, with a broad list of antibiotics that could be recommended in various countries, the final choice depending on local levels of acquired resistance. We gave equal weighting to all the properties of antibiotics considered. This approach yielded a highly satisfactory score, and we would have been unlikely to obtain a better result by weighting the properties differently.

Our approach is different from that of MYCIN[1] because (i) we used the arguments of a group of experts based on evidence-based medicine rather than the knowledge of a single expert; (ii) our method did not require interaction with the clinician; (iii) our method is simple and can generate recommendations very rapidly; (iv) our method can provide clinicians with an overview of the deeper medical reasoning underlying recommendations. This is not the case for MYCIN, for which the underlying reasoning is too complex to be presented in full to clinicians.

Our approach can be used to design a CDSS reproducing the deeper medical reasoning used by the experts writing CPGs. CDSSs generally implement the conclusions of the medical reasoning, i.e. the "actions" recommended for a particular clinical situation (e.g.: "*Amoxicillin is recommended for childhood pharyngitis*"). In our approach, we tried to implement the arguments underpinning the reasoning behind the recommendation, to make it possible to deduce the recommended antibiotics automatically (e.g.: "*for prescription for childhood pharyngitis, an antibiotic should have properties A to F, then, successively, properties G, H, I, J, L and K (see the correspondence in table 1 and 2)*"). The implementation of deeper medical reasoning, rather than its conclusions, has several advantages:

Recommendations can be justified and explained to physicians. As the deeper medical reasoning is based on the properties of the antibiotics, it can easily be understood by physicians. For example, a physician can easily understand that an antibiotic that has proved to be clinical effective and well tolerated by patients is preferred over an antibiotic that is effective but poorly tolerated. The provision of convincing and understandable explanations to physicians should increase their confidence in the CDSS, increasing the chances of its adoption[16]. Such explanations also help to provide physicians with up-to-date knowledge[17] and to develop their critical analysis capacities[17].

Recommendations may be easier to update. As the deeper medical reasoning is separate from the knowledge base containing the properties of antibiotics, it should be easier to update recommendations, and this process should be instantaneous[18]. The properties of antibiotics could be updated through various resources. For example, microbiological properties ("natural activity", "likely activity"; "activity spectrum") could be extracted from microbiological observatories. Properties relating to clinical data ("contraindication"), pharmacokinetics ("concentration"), or market availability ("availability") could be recuperated from drug databases[19]. The "side effects" property could be updated from pharmacovigilance databases. Properties relating to expert knowledge ("class characteristics", "ecological adverse effects") could be extracted from reference sources in infectious diseases. Similarly, evidence-based properties ("evidence of clinical efficacy", "protocol characteristics", "level of efficacy") could be extracted from previous publications (e.g.: Medline). The incorporation of evidence-based medicine into CDSSs can considerably improve healthcare quality[14,20].

Recommendations could be given for clinical situations not described in CPGs. For example, the clinical situations described in CPGs for pharyngitis are: {adult; child < 6; child 6-12; child > 12} AND {without beta-lactam allergy; with penicillin allergy without cephalosporin contraindication; with beta-lactam contraindication}. The clinical situation "pharyngitis in pregnant women" is not described. With our approach, the system could deduce the antibiotics that should be recommended, by excluding all antibiotics contraindicated in pregnant women. Furthermore, the list of appropriate antibiotics could be used by physicians when they do not wish to prescribe the recommended antibiotics. For example, in uncomplicated cystitis in women, if the physician prefers not to prescribe the recommended antibiotic (fosfomycin trometamol) because it has been poorly tolerated by the patient in the past, he or she can select an alternative from the list of appropriate antibiotics. The provision of recommendations that can be adjusted to any clinical situation is likely to increase the compliance of physicians with recommendations[21].

This work now needs to be taken forward in several ways:

Confirmation of the robustness of our approach by expanding the evaluation to other clinical situations and to all the antibiotics available on the market. Both methods were assessed for urinary and respiratory infections, and only for the antibiotics described in CPGs. These methods should now be tested in other clinical situations (e.g. sexually transmitted infections, clinical situations specific to hospitals, etc.) and for all the antibiotics available on the market.

Confirmation of the validity of the recommendations generated by this method for clinical situations not described in CPGs, and for the updating of CPGs. Our approach was tested only for clinical situations described in CPGs, and not for other clinical situations. It will be necessary to test this method for clinical situations not described in CPGs, by taking the opinions of experts specializing in antibiotic treatment as the gold standard (because these situations are not described in CPGs).

Checking of the completeness of the list of the properties of the antibiotics identified in CPGs. We extracted, from CPGs, the properties of antibiotics most important for medical reasoning. It would be useful to collect the opinions of clinicians specialized in the domain of infectious diseases, to ensure that this list is complete.

Evaluation of the extent to which our approach could be extrapolated to other medical domains. The use of a deeper reasoning based on the arguments of the experts writing in CPGs, is particularly appropriate in the domain of antibiotic treatment, because arguments are explicit and related to the properties of drugs, including patient safety (contraindication), efficacy for curing the disease, and pharmaceutical properties (e.g. side effects). In other domains, other arguments would probably need to be taken into account, relating to temporal reasoning in chronic diseases, or to combinations of drugs. The possible extrapolation of this approach to other medical domains should therefore be investigated.

In conclusion, we propose a method for reproducing the deeper medical reasoning used by experts drawing up CPGs and underpinning the arguments used to justify the choices made. The robustness of this method should be assessed in a larger study before its implementation in a CDSS[22,23], to assist physicians in the empiric prescription of antibiotics in primary care. This CDSS will be assessed in clinical practice.

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