Computer-assisted decision support for the diagnosis and treatment of infectious diseases in intensive care units

C A M Schurink, P J F Lucas, I M Hoepelman, M J M Bonten

Lancet Infect Dis 2005; 5: 305–12

CAMS, IMH, and MJMB are consultants in internal medicine at the Department of Medicine, Division of Acute Medicine and Infectious Diseases, University Medical Centre, Utrecht, Netherlands; PJFL is a senior lecturer at the Institute for Computing and Information Sciences, Radboud University Nijmegen, Nijmegen, Netherlands; IMH and MJMB are also at the Division of Medical Microbiology, Eijkman-Winkler Institute, University Medical Centre, Utrecht; MJMB is also at the Julius Center for Epidemiology and Primary Care Medicine, University Medical Centre, Utrecht.

Correspondence to:
Dr C A M Schurink, Department of Medicine, Division of Medicine and Infectious Diseases, F02-126, University Medical Centre, PO Box 85500, Utrecht, Netherlands.
Tel +31 30 2506228; fax +31 30 2523741;
K.Schurink@umcutrecht.nl

Diagnosing nosocomial infections in critically ill patients admitted to intensive care units (ICUs) is a challenge because signs and symptoms are usually non-specific for a particular infection. In addition, the choice of treatment, or the decision not to treat, can be difficult. Models and computer-based decision-support systems have been developed to assist ICU physicians in the management of infectious diseases. We discuss the historical development, possibilities, and limitations of various computer-based decision-support models for infectious diseases, with special emphasis on Bayesian approaches. Although Bayesian decision-support systems are potentially useful for medical decision making in infectious disease management, clinical experience with them is limited and prospective evaluation is needed to determine whether their use can improve the quality of patient care.

Introduction

The management of infectious diseases is complex, especially in an intensive care unit (ICU) setting, because many patients have concomitant diseases. In daily practice, considerable clinical expertise is required to establish the correct diagnosis, to choose appropriate antimicrobial treatment, and to balance optimal patient care with possible undesirable negative aspects, such as the development of antibiotic resistance, the risk of adverse events, and health-care costs. Although computerised patient records—when properly linked to hospital information systems—provide physicians with the information they need for clinical decision making, some form of computer-based decision support would assist clinicians in this process.

Computer-based decision-support systems for daily patient care have been developed. Decision-support systems based on models of expert knowledge are called expert systems.[1] We review the development of such models applied to infectious disease management. We use the diagnosis of ventilator-associated pneumonia (VAP) to illustrate the differences and similarities between the various methods, in particular regarding their clinical use.

Conventional clinical approach to diagnosis and treatment of infectious diseases

Any diagnosis, including that of an infectious disease, is based on evidence—eg, the various clinical signs and symptoms obtained by history taking, physical examination, and laboratory investigations. Using this information, clinicians decide whether to initiate empirical anti-infective therapy, even in the absence of precise information about the causative organisms. Local ecology and antimicrobial-resistance patterns must be taken into account when selecting appropriate empirical treatment, which should be tailored as much as possible, taking the immunocompetence of the host, the virulence of suspected pathogens, and the possible side-effects of the chosen antibiotics into consideration. Depending on culture results and the evolution of clinical signs and symptoms, clinicians then need to decide whether to continue, adjust, or discontinue the selected therapy.

In principle, the antibiotic used should be as specific as possible and discontinued when there is no microbiological evidence of infection. However, in practice, physicians frequently administer, or continue to administer, antibiotics even when objective criteria of infection are scarce or absent. Although the dangers of unnecessary antibiotic use are recognised, sometimes a patient's clinical condition is so poor that antibiotics have to be administered even though culture results remain negative. Because there is no diagnostic gold standard for most infectious diseases, in many situations little is known about the predictive value of specific signs and symptoms.

Probability-based methods for diagnosing and treatment of infectious diseases

With decision-support systems, patients are classified into categories, such as either having or not having a specific disease. Different systems use different methods (or so-called classifiers) to achieve this classification.

Early probabilistic and decision analytical approaches

The first attempts in computer-based decision support in medicine date back to the early 1960s and mostly concerned the use of Bayes' theorem, with subsequent addition of sequential gathering of information and the use of graphics for conveying diagnostic information to the user.[2–4] Bayes' theorem enables computation of the probability of the presence (and absence) of a disease on the basis of a set of clinical criteria and the prior probability (or prevalence) of the disease. To limit the amount of information needed and the number of computation steps required, it was assumed that each piece of evidence was independent (actually "conditionally independent" given the presence or absence of the disease; panel 1). The outcome was the product of the sensitivity of individual signs and

Panel 1: **Definition of terms**

Bayesian approach: knowledge is updated using a statistical rule that uses observed evidence from data.
Bayesian network: graphical network representation of a multivariate probability distribution, where arrows between variables represent statistical dependence, and absence of an arrow represents statistical independence.
Bayes' theorem: also known as Bayes' rule. The computation rule allows computing reverse probabilities such as *P*(VAP|fever)—ie, the probability that VAP is present after having observed fever in a patient, is based on *P*(fever|VAP) and the prior probability *P*(VAP). In its general form, Bayes' theorem allows computation of the probability of any combination of events, assuming any other combination of events.
Black-box method: method that produces results that are difficult to explain in terms of the underlying model—eg, because mathematical arguments are required instead of arguments that are easy to understand by computer users.
Classification: assignment of a patient to a particular class—eg, a patient with signs and symptoms of an infection to the class of patients with pneumonia. Diagnosis and treatment selection can often be cast as classification tasks.
Conditionally (in)dependent: (in)dependence of variables given the disease. Assuming that VAP (the condition) is present, the pieces of evidence (eg, fever, radiological signs) are independent (not related) and when VAP is absent, the pieces of evidence are dependent (related).
Decision-support system: computer program that is able to assist users in making a decision for a particular problem, such as establishing a diagnosis in a patient with an infectious disease.
Decision variable: variable that represents a choice that must be made using decision theory—eg, treatment.
Dependence: correlation between statistical variables.
Evidence: observed information—eg, signs and symptoms in a patient.
Expert system: decision-support system that is based on the subjective knowledge of one or more experts about a problem.
If-then rule: rule of the form "if certain conditions are true then certain conclusions are true". If-then rules are used in rule-based systems to represent problem-solving knowledge.
Independence: lack of correlation between variables.
Linear function: function of the form f(x)=ax + b, where x is an numeric quantity, and a and b represent weights.
Logistic regression: linear function that approximates a probability distribution taking into account conditional independence of the evidence variables given the class variable.
Medical decision analysis: medical discipline studying the application of decision theory to clinical problems.
Model-based method: method using models that produce output that can be explained in terms of the underlying model, such that the user understands the output.
Naive Bayes' theorem: special form of Bayes' theorem, where the probability of a disorder D is computed based on evidence E, and where the items in the set of evidence are assumed to be conditionally independent given the disorder. This assumption facilitates the acquisition of probabilities and eases the computation of the relevant probabilistic information.
Neural network: function that includes threshold values that can be used to approximate any function, such as a probability function underlying patient data.
Overfitting: lack of generalisation capabilities of a model in comparison with the knowledge underlying data. As a consequence, the model will perform poorly with new data.
Rule-based method: method based on logic which uses if-then rules to represent medical knowledge; rule-based systems supports a logical type of reasoning, of the form: if A is true and we have the rule "if A then B", then B is also true.
Uncertainty calculus: method that provides rule for the representation and reasoning (computing) with uncertain knowledge.
Utility variable: variable that is used in decision theory to represent preferences.
Weight: multiplier of an evidence variable, which is used to increase or decrease the role of a variable, for example, in classification.

symptoms multiplied by the prior probability of the disease, converted to a number between 0 and 1. However, the assumption that signs and symptoms are independent is rarely justified in medicine, and thus the calculated probability is not clinically realistic. These models have since been called naive Bayesian classifiers. Although such models perform reasonably well in certain circumstances,[5] they are not adequate when it comes to choosing a treatment.

As a fictitious example, let us assume that the prevalence of VAP among ICU patients is 20%, that 75% of patients with VAP and 12% of patients without VAP have signs of consolidation on chest radiograph, and that 75% of patients with VAP and 23% of patients without VAP have fever. Assuming that fever has been observed in a patient and that a chest radiograph has not yet been done, then:

Certainty of having VAP=$0{\cdot}75 \times 0{\cdot}20=0{\cdot}15$
Certainty of not having VAP=$0{\cdot}23 \times 0{\cdot}80=0{\cdot}184$.

To turn these certainties into probabilities, with the probabilities of having VAP and of not having VAP summing to 1, we have to multiply the numbers 0·15

and 0·184 by 3; thus, the probability of having VAP is 0·45 and the probability of not having VAP is 0·55.

Since the a priori probability of having VAP was 0·20, the likelihood of VAP more than doubled by observing fever. The ultimate decision whether VAP is present or not depends on the chosen threshold probability. For example, if we take a threshold probability of 0·5, then it would be concluded that this patient does not have VAP. It is possible to use a naive Bayesian classifier without taking all possible evidence (eg, chest radiograph results) into account.

Logistic regression, developed in the 1960s, is closely related to the naive Bayesian approaches (table 1). Logistic regression models the interactions among signs and symptoms as a linear function, weighing their contribution to the probability of disease presence. A logistic regression prediction rule depends on an existing database. Disadvantages of this technique are the frequent inclusion of variables that cannot be justified by the opinion of experts[6] and the inability to make a prediction for a specific patient if one or more variables are missing. There are several logistic regression models for infectious diseases. For example, Leibovici and colleagues[7,8] developed a logistic regression model containing five variables to diagnose urinary tract infection in women. The model had a sensitivity of 95%, a specificity of 85%, and a positive predictive value of 98%.

For a logistic regression model with two variables (ie, fever and radiological signs) and with a VAP prevalence similar to that used in the previous example, the probability of VAP can be calculated as follows:

$P(\text{VAP})=1/(1+\exp -[0\cdot6*\text{V1}+0\cdot8*\text{V2}-1\cdot39])$

where V1=fever; V2=radiological signs.

The figures 0·6 and 0·8 are weights for the variables V1 and V2 computed by the logistic regression model. V1 is 1·18 if fever is present (probability of fever in case of VAP/probability of fever in case of not having VAP=75/23=3·26 [ln 3·26=1·18]) and V2 is 1·83 for the presence of radiological signs of pneumonia (probability of radiological signs in case of VAP/probability of radiological signs in case of not having VAP=75/12=6·25 [ln 6.25=1·83]). The probability of VAP would be 0·69. As with the naive Bayesian models, it is necessary to define a probability threshold to distinguish between patients with and without VAP. With a threshold of 0·5, this particular patient would be considered to have VAP.[9–11]

Rule-based methods

An entirely different, non-statistical method for building computer-based decision-support programs was proposed in the 1970s by Shortliffe and colleagues.[1,12] The basic idea was to collect a large number of if-then rules from experienced clinicians and to use these rules, together with data on patients' signs and symptoms, in a logical reasoning computer program to classify a patient's condition into diagnostic and therapeutic categories. However, a drawback of this approach was the difficulty in dealing with missing information.[13] For this reason, rule-based methods have largely been abandoned. MYCIN, one of the first rule-based expert systems, proved able to identify the microbiological cause of septicaemia and meningitis, and to determine the appropriate anti-infective treatment.[12,14–16] Unfortunately, the system has never been tested in clinical practice, because of the immature state of the clinical information infrastructure in the 1980s.[17]

For diagnosing VAP with rule-based methods, two rules (concerning fever and radiological signs) need to be defined:

IF fever is present, THEN VAP has a likelihood of 0·7 and:

IF radiological signs of pneumonia are present, THEN VAP has a likelihood of 0·8.

If both fever and radiological signs are observed, then the so-called certainty-factor calculus determines that the likelihood of VAP is $0\cdot7+0\cdot8*(1-0\cdot7)=0\cdot94$.[1] Although it is possible to take available clinical evidence into account, rule-based methods are based on a very restrictive type of probability theory, making it impossible to express correlations between signs and symptoms.[13]

Modern methods

New computational techniques (model-based methods and black-box methods) developed in the past two decades are better at detecting patterns hidden in biomedical data and have better statistical techniques to represent and manipulate uncertainties. Model-based methods are understandable to the user and can often be used in the absence of data, whereas black-box methods cannot be explained in terms of logical relationships among variables and are almost solely based on data.

Artificial neural networks and related black-box methods

Artificial neural networks are powerful mathematical functions, often represented by a network diagram with input nodes, output nodes, and internal, or

Method	Theoretical basis	Model-based or Black-box	Possibility of incorporation of expert opinion	Use for data analysis
Logistic regression	Probability theory and function approximation	Black-box	No	Yes
Rule-based	Logic	Possibly model-based	Yes	No
Neural networks	Function approximation and optimisation	Black-box	No	Yes
Bayesian networks	Probability theory	Model-based	Yes	Yes

Table 1: **Comparison of various methods underlying decision-support systems**

hidden, layers.[18] Input nodes are connected by links to hidden layers and these are in turn connected to output nodes. Individual links are weighted and are used to calculate the output at the next layer. As the neural network learns from a dataset, the weighting of the links is continuously adjusted: important links are given a heavier weighting and unimportant links a lighter weighting. Figure 1 shows an example of a three-layer neural network, able to classify patients as having or not having VAP on the basis of the signs "(body) temperature" and "PO_2/F_1O_2".[19]

Neural networks are black-box models that function reasonably well when it comes to problems of pattern recognition, for example in medical image analysis.[20] However, because they need a lot of training data to perform well, they are less suitable for the construction of clinical classification and prediction models. The fact that clinical data are often limited and modelled relations are hidden and, therefore, not readily understood or explained, further limits the use of neural networks to compensate for the lack of data.[21]

Bayesian networks and influence diagrams

Bayesian networks are built on the probability distributions of multiple variables, taking information about dependence and independence between individual variables into account. These probability distributions can be based on subjective estimates, information from the literature, patient data, or a mixture of these. A diagram representing a Bayesian network consists of arrows that connect variables (panel 2). Variables linked to each other by an arrow are assumed to be dependent—ie, if we have information about one of the variables (eg, leucocytosis) we also have some information about another variable (eg, fever). If variables are not directly connected by an arrow, they are assumed to be independent. The direction of an arrow signifies causality, so the arrow "pneumonia→fever" is simply read as "pneumonia may cause fever". If two or more arrows point to the same variable, this can be interpreted clinically as a consequence of these two or more causes. For example, "mechanical ventilation→sputum" and "pneumonia→sputum" represent two separate, but interacting, causes of increased sputum production.

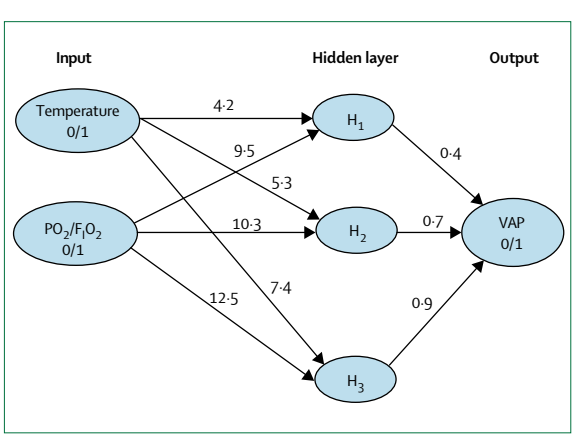
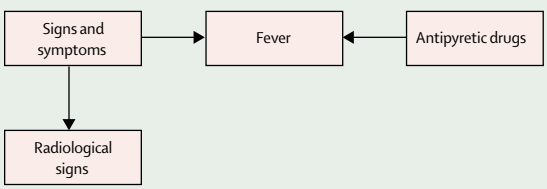


Figure 1: **Fictitious three-layer neural network with two input variables**
Input variables are "Temperature" (value 0 for ⩽38·5°C and 1 for >38·5°C) and "PO_2/F_1O_2", (value 0 for >240 and 1 for ⩽240). H_1, H_2, and H_3 represent three hidden units, and there is one output variable (VAP, where 0 means VAP is absent and 1 that VAP is present). The weights given to each variable are given on the arrows that connect the variables and hidden units.

Panel 2: **Bayesian network representation of the simplified VAP problem**



Knowledge about fever is determined by information about whether the patient has VAP or not, and whether antipyretic drugs have been prescribed. The observation of radiological signs depends only on the presence or absence of VAP. Patient-based observations can be used for any subset of the four variables and any resulting probability can be computed. For example, even if it is not known whether a patient has received antipyretic drugs and a chest radiograph has not been done yet, it is possible to compute the probability of VAP on the basis of the patient having a fever. Moreover, it is also possible to predict how often fever and radiological signs are observed in patients with VAP.

Figure 2 illustrates a more complex example of a simple Bayesian network for diagnosing VAP.[22] Here, VAP is causally related to six variables, such as leucocytosis, radiological signs, changes in body temperature, PO_2/F_1O_2 ratio, and number of leucocytes in sputum. Thus, information about the probability distribution of each variable and patient data is needed as input. If new patient information is added, the resulting probability distributions are automatically updated. For example, if we add patient data about the duration of mechanical ventilation (24–48 h), the presence (yes) and colour of sputum (purulent), and the PO_2/F_1O_2 ratio (decreased) to the model, then the probability of VAP changes from 10% if nothing is known about the patient, to 92% (figure 2). The probability distribution of the variable "temperature", is shown in table 2.

A Bayesian network can be extended with decision and utility variables. Decision variables represent the various decisions the user can take, such as the prescription of antibiotics. Utilities are assessments of outcomes of diagnostic and treatment decisions, taking

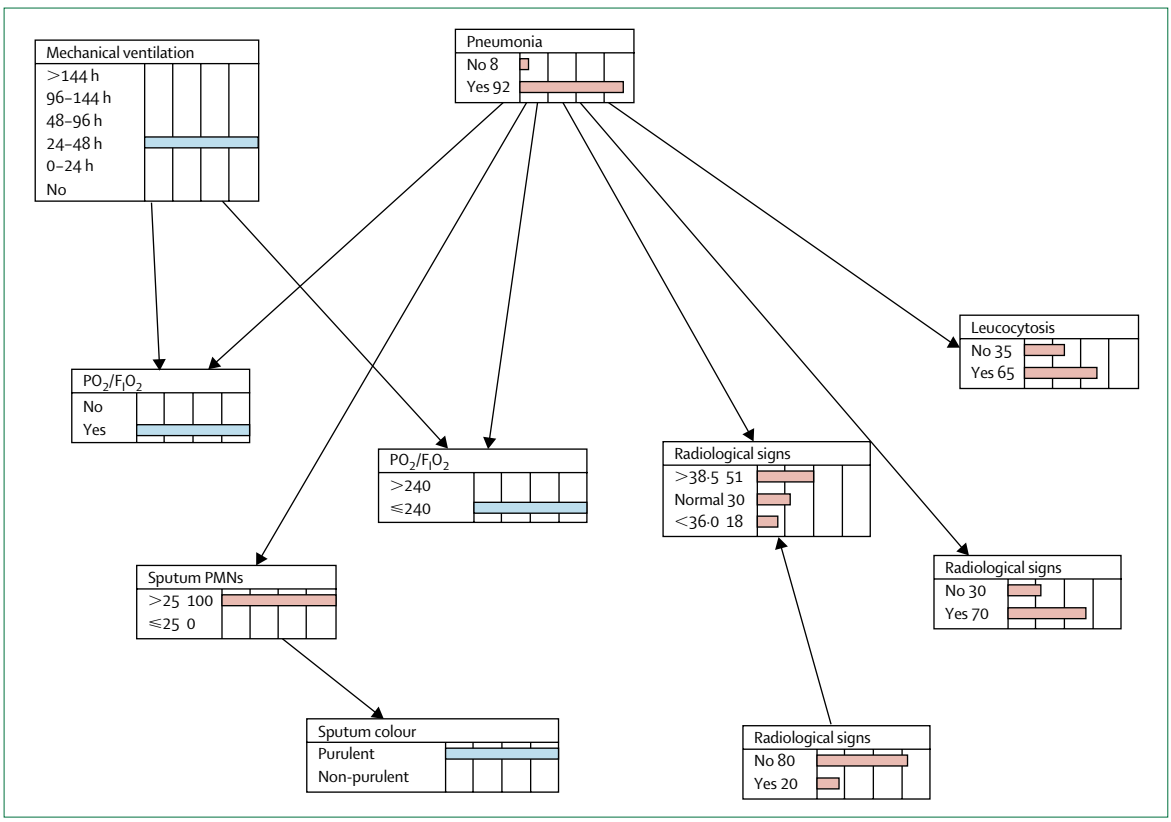


Figure 2: **Fragment of a Bayesian network of ventilator-associated pneumonia with variables "mechanical ventilation", "sputum", "PO_2/F_IO_2", and "sputum colour" filled in with patient data**

The bar graphs show the probability distribution of each individual variable, given the patient findings concerning these four variables.

into account the patient's condition, cost of treatment, side-effects, etc. For example, the choice of antibiotics for VAP can be categorised so that relatively narrow-spectrum agents are chosen first, instead of broad-spectrum antibiotics.[23] Bayesian networks can be also used for simulations, to determine the characteristics of patient groups and to investigate what will happen if a (potentially inappropriate) drug is prescribed.[24]

Clinical experience with decision-support systems

Probably the best-known medical decision support system for the treatment of nosocomial infections is the Health Evaluation by Logical Processing (HELP) system developed in the early 1970s in the LDS hospital in Salt Lake City, Utah, USA, and continuously improved since then.[25] The system combines data from multiple medical services, such as emergency, pharmacy, radiology, surgery, pathology, nursing, and respiratory therapy, as well as clinical laboratories, including microbiology, within computerised medical records connected with Bayesian networks.[25] This system has been used to register and analyse hospital-acquired infections and to identify patients at high risk of developing a nosocomial infection.[26,27] Over the years, many of the techniques of model development for decision-support systems have been explored with the HELP system. For example, the rule-based method has been integrated to suggest alternatives for patients receiving inappropriate anti-infective therapy,[28,29] to improve the timing of antibiotic prophylaxis in surgery,[30–32] to limit unnecessarily prolonged prophylaxis,[33] and to survey[34,35] and prevent adverse drug events.[36] Computerised surveillance of adverse drug events, as reflected by sudden medication stop orders, and the ordering of antidote and specific laboratory tests (such as elevated eosinophil counts, elevated serum potassium levels, and low white blood cell counts), has increased the

Antipyretic drugs	Pneumonia	Temperature >38·5°C	Temperature ⩾36·0°C and ⩽38·5°C	Temperature <36·0°C
No	No	0·03	0·95	0·02
No	Yes	0·6	0·2	0·2
Yes	No	0·02	0·95	0·03
Yes	Yes	0·4	0·4	0·2

The chance of having fever when the patient has pneumonia and the patient is using antipyretic drugs: *P*(temperature|pneumonia, antipyretic drugs); eg, *P*(temperature>38·5|pneumonia=yes, antipyretic drugs=yes)=0·4.

Table 2: **Conditional probability distribution associated with the variable "temperature"**

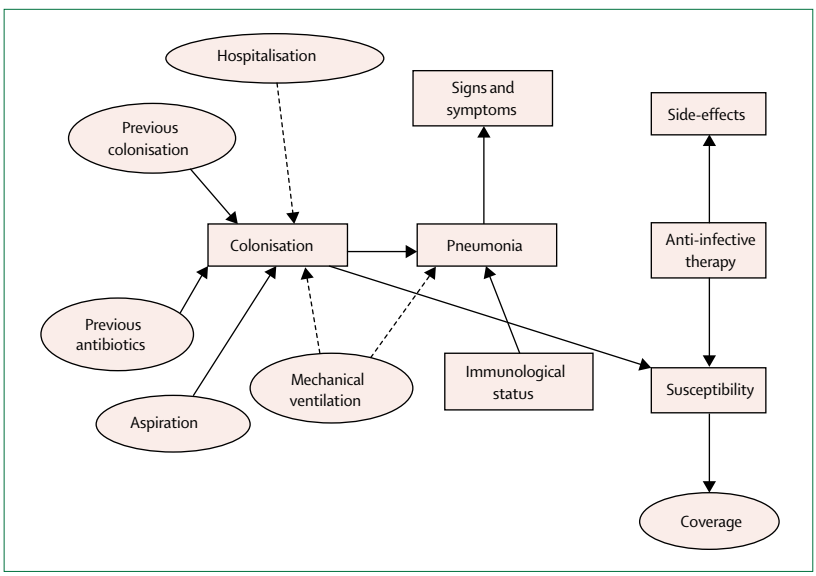


Figure 3: **Schematic representation of the VAP Bayesian network model**
Each box represents a collection of similar variables. For example, the box labelled "colonisation" represents colonisation of the patient by organisms such as *Pseudomonas aeruginosa* or *Haemophilus influenzae*; colonisation by each of these organisms is modelled by a separate variable, indicating that it is possible to be colonised by more than one organism at the same time (ie, they are not mutually exclusive). A dotted arrow indicates that the variable (hospitalisation or mechanical ventilation) has time-related states, reflecting temporal effects of duration of hospitalisation and mechanical ventilation on likelihood of colonisation and pneumonia.

detection and reporting of such events 60-fold.[34] In a prospective study, the use of an expert model to advise on anti-infective drugs for prophylaxis, empirical therapy, and microbiologically confirmed infections improved the quality of patient care (reflected by reductions in drug allergies, excess drug dosages, and antibiotic-susceptibility mismatches) and reduced costs.[37] Integration of a Bayesian network model to diagnose patients with community-acquired pneumonia in the emergency room was prospectively compared with diagnoses made by emergency room physicians.[38–40] During a 9-week period, 4361 patients entered the emergency room, of whom 112 had pneumonia. The area under the receiver operating characteristic (ROC) curve of the model was 0·93 (CI 0·91, 0·95), with a sensitivity of 95% and a specificity of 68·5%.[40]

Leibovici and colleagues developed a logistic regression model incorporated into a decision-support system to predict the presence of a broad range of infections, including urinary tract infections[41] and bacteraemia.[42] In retrospective evaluation this decision-support system predicted the causative pathogen in 78% of the infections and advised appropriate anti-infective treatment in about 77% of the episodes. By comparison, treating physicians predicted the causative pathogen in 55% of the infections and advised appropriate anti-infective treatment in about 58% of the episodes.[43] If a blood culture tested positive, the microbiologist used the decision-support system to provide the treating physician with an initial antibiotic advice. This advice was compared with that suggested by a guideline and with the empiric treatment prescribed by the physicians.[44–46] Causative microorganisms were covered by empirical therapy in 94·6% of the cases when the advice was based on decision-support systems, in 92·7% of the cases when it was based on guidelines, but only in 60·7% of the cases when it was prescribed by the physicians. However, the probabilistic information in these models was based only on the presence of bacteraemia. Clinical, laboratory, or radiographic signs of infections were not incorporated, and the decision-support system was not integrated into a clinical information system, which hampers its use in daily clinical practice.

We have developed a Bayesian network to assist in the diagnosis and treatment of VAP (figure 3).[21] The model covers progression from bacterial colonisation to infection of the lungs. The variables "hospitalisation" and "mechanical ventilation" and signs and symptoms of pneumonia are used to adjust the likelihood that a patient is colonised or infected by particular hospital-specific bacteria. The choice of optimal anti-infective treatment is then based on the most likely causative organisms, taking into account their susceptibility and the potential side-effects of the treatment. An extra variable (called "utility") has been added to prevent the prescription of only very broad-spectrum antibiotics for all patients with VAP. The model has been incorporated in a decision-support system, which has been implemented in the ICUs of the Utrecht Medical Centre. We evaluated our decision-support system using a database of 883 patients that were mechanically ventilated for more than 48 hours (9422 patient-days) over a 3-year period.[22] There were 157 episodes of VAP based upon a diagnostic flowchart. Median likelihood predictions of the decision-support system were 98% (interquartile range [IQR] 61–100%) for the 157 VAP-days and 20% (IQR 1–87%; p<0·001) for the 9265 non-VAP-days. The optimal cut-off point for this decision-support system was 74·5%, resulting in a sensitivity and a specificity of 70%, a positive predictive value of 3·8%, and a negative predictive value of 99·3%. The area under the ROC curve for decision-support system predictions and presence of absence of VAP was 0·76.[47,48]

Search strategy and selection criteria

Data for this review were identified by searches of Medline, PubMed, and references from relevant articles, using the search terms "computer-assisted decision report", "computer model", or "expert systems", and "infection". Only papers published from 1960 to 2004 were chosen. Studies were selected and references from relevant articles were retrieved.

Conclusions

We have described several computer models that may be used in clinical practice in the near future. Some clinicians believe that the use of decision-support systems in medicine will improve the quality of patient care through better treatment choices and by achieving a better balance between costs (both financial and medical, such as side-effects of drugs) and benefits. In the past, the lack of a suitable electronic information infrastructure in many hospitals was seen as a major obstacle to the use of decision-support systems;[17] however, most hospitals have started—or will start—to use electronic systems for patient management within the next 10 years. Clinicians are generally reluctant to use computerised guidelines that require additional data entry and time and effort.[39] As a result, decision-support systems still lack clinical credibility.[49] Yet, a few decision-support systems have actually been shown to improve the care process. Therefore, as for any other new diagnostic technique or therapy, prospective trials are needed to provide the necessary evidence on which implementation and wide-scale use of decision-support systems can be based.

Conflicts of interest

We declare that we have no conflicts of interest and sources of funding to disclose.

References

1 Lucas PJF, van der Gaag LC. Principles of expert systems. Wokingham: Addison-Wesley, 1991.
2 Martin WB, Apostolakos PC, Roazen H. Clinical versus acturial prediction in the differential diagnosis of jaundice. A study of the relative accuracy of predictions made by physicians and by a statistically derived formula in differentiating parenchymal and obstructive jaundice. *Am J Med Sci* 1960; **240:** 571–78.
3 Carlstrom E, Edlund Y, Hansen HA, Hugosson K, Wedinius N. Hepatic tests in the differential diagnosis of jaundice. *Scand J Clin Lab Invest* 1963; **15:** 338–41.
4 Gorry GA, Barnett GO. Experience with a model of sequential diagnosis. *Comput Biomed Res* 1968; **1:** 490–507.
5 Domingos P, Pazzani M. On the optimality of the simple Bayesian classifier under zero-one loss. *Machine Learning* 1997; **29:** 103–30.
6 Steyerberg EW, Eijkemans MJ, Harrell FEJ, Habbema JD. Prognostic modelling with logistic regression analysis: a comparison of selection and estimation methods in small data sets. *Stat Med* 2000; **19:** 1059–79.
7 Leibovici L, Alpert G, Kalter-Leibovici O, Danon YL. Risk factors for recurrence of symptomatic urinary tract infection in young women. *Isr J Med Sci* 1989; **25:** 110–11.
8 Leibovici L, Arav-Boger R, Danon YL. A clinical model for diagnosis of urinary tract infection in young women. *Arch Intern Med* 1993; **153:** 1011–15.
9 Sox HC, Blatt MA, Higgins MC, Marton KI. Medical decision making. Boston, MA: Butterworth-Heinemann, 1988.
10 Stamm WE, McKevitt M, Counts GW, Wagner KF, Turck M, Holmes KK. Is antimicrobial prophylaxis of urinary tract infections cost effective? *Ann Intern Med* 1981; **94:** 251–55.
11 van Nieuwenhoven CA, Buskens E, Bergmans DC, van Tiel FH, Ramsay G, Bonten MJ. Oral decontamination is cost-saving in the prevention of ventilator-associated pneumonia in intensive care units. *Crit Care Med* 2004; **32:** 126–30.
12 Buchanan BG, Shortliffe EH. Rule-based expert systems: the MYCIN experiments of the Stanford heuristic programming project. Reading: Addison-Wesley, 1984.
13 Lucas PJF. Certainty-factor-like structures in Bayesian networks. *The Knowledge-based Systems Journal* 2001; **14:** 327–35.
14 Shortliffe EH. Computer-based medical consultations: MYCIN. New York: Elsevier, 1976.
15 Yu VL, Buchanan BG, Shortliffe EH, et al. Evaluating the performance of a computer-based consultant. *Comput Programs Biomed* 1979; **9:** 95–102.
16 Yu VL, Fagan LM, Wraith SM, et al. Antimicrobial selection by a computer. A blinded evaluation by infectious diseases experts. *JAMA* 1979; **242:** 1279–82.
17 Shortliffe EH. Knowledge-based systems in medicine. Berlin: Springer-Verlag, 1991.
18 Bose NK, Liang P. Neural network fundamentals with graphs, algorithms, and applications. New York: McGraw-Hill, 1996.
19 Hastie T, Tibshirani R, Friedman J. The elements of statistical learning: data mining, inference, and prediction. New York: Springer-Verlag, 2001.
20 Doornewaard H, van de Seijp H, Woudt JM, van der Graaf Y, van den Tweel JG. Negative cervical smears before CIN 3/carcinoma. Reevaluation with the PAPNET testing system. *Acta Cytol* 1997; **41:** 74–78.
21 Hanson CW 3rd, Marshall BE. Artificial intelligence applications in the intensive care unit. *Crit Care Med* 2001; **29:** 427–35.
22 Lucas PJ, de Bruijn NC, Schurink K, Hoepelman A. A probabilistic and decision-theoretic approach to the management of infectious disease at the ICU. *Artif Intell Med* 2000; **19:** 251–79.
23 Shachter RD. Evaluating influence diagrams. *Operation Research* 1986; **34:** 871–82.
24 Lucas PJF, Boot H, Taal BG. A decision-theoretic network approach to treatment management and prognosis. *Knowledge-based Systems* 1998; **11:** 321–30.
25 Burke JP, Classen DC, Pestotnik SL, Evans RS, Stevens LE. The HELP system and its application to infection control. *J Hosp Infect* 1991; **18** (suppl A)**:** 424-31.
26 Evans RS, Larsen RA, Burke JP, et al. Computer surveillance of hospital-acquired infections and antibiotic use. *JAMA* 1986; **256:** 1007–11.
27 Jacobson JT, Johnson DS, Ross CA, Conti MT, Evans RS, Burke JP. Adapting disease-specific isolation guidelines to a hospital information system. *Infect Control* 1986; **7:** 411–18.
28 Pestotnik SL, Evans RS, Burke JP, Gardner RM, Classen DC. Therapeutic antibiotic monitoring: surveillance using a computerized expert system. *Am J Med* 1990; **88:** 43–48.
29 Evans RS, Classen DC, Pestotnik SL, Lundsgaarde HP, Burke JP. Improving empiric antibiotic selection using computer decision support. *Arch Intern Med* 1994; **154:** 878–84.
30 Larsen RA, Evans RS, Burke JP, Pestotnik SL, Gardner RM, Classen DC. Improved perioperative antibiotic use and reduced surgical wound infections through use of computer decision analysis. *Infect Control Hosp Epidemiol* 1989; **10:** 316–20.
31 Classen DC, Evans RS, Pestotnik SL, Horn SD, Menlove RL, Burke JP. The timing of prophylactic administration of antibiotics and the risk of surgical-wound infection. *N Engl J Med* 1992; **326:** 281–86.
32 Pestotnik SL, Classen DC, Evans RS, Burke JP. Implementing antibiotic practice guidelines through computer-assisted decision support: clinical and financial outcomes. *Ann Intern Med* 1996; **124:** 884–90.
33 Evans RS, Pestotnik SL, Classen DC, Burke JP. Evaluation of a computer-assisted antibiotic-dose monitor. *Ann Pharmacother* 1999; **33:** 1026–31.
34 Classen DC, Pestotnik SL, Evans RS, Burke JP. Computerized surveillance of adverse drug events in hospital patients. *JAMA* 1991; **266:** 2847–51.
35 Lazarus HM, Fox J, Evans RS, et al. Adverse drug events in trauma patients. *J Trauma* 2003; **54:** 337–43.
36 Evans RS, Pestotnik SL, Classen DC, Horn SD, Bass SB, Burke JP. Preventing adverse drug events in hospitalized patients. *Ann Pharmacother* 1994; **28:** 523–27.
37 Evans RS, Pestotnik SL, Classen DC, et al. A computer-assisted management program for antibiotics and other antiinfective agents. *N Engl J Med* 1998; **338:** 232–38.

38 Aronsky D, Haug PJ. Diagnosing community-acquired pneumonia with a Bayesian network. *Proc AMIA Symp* 1998; 632–36.

39 Aronsky D, Haug PJ. An integrated decision support system for diagnosing and managing patients with community-acquired pneumonia. *Proc AMIA Symp* 1999; 197–201.

40 Aronsky D, Haug PJ. Automatic identification of patients eligible for a pneumonia guideline. *Proc AMIA Symp* 2000: 12–16.

41 Leibovici L, Alpert G, Laor A, Kalter-Leibovici O, Danon YL. A clinical model for diagnosis of urinary tract infection in young women. *Arch Intern Med* 1989; **149:** 2048–50.

42 Leibovici L, Greenshtain S, Cohen O, Mor F, Wysenbeek AJ. Bacteremia in febrile patients. A clinical model for diagnosis. *Arch Intern Med* 1991; **151:** 1801–06.

43 Leibovici L, Gitelman V, Yehezkelli Y, et al. Improving empirical antibiotic treatment: prospective, nonintervention testing of a decision support system. *J Intern Med* 1997; **242:** 395–400.

44 Andreassen S, Riekehr C, Kristensen B, Schonheyder HC, Leibovici L. Using probabilistic and decision-theoretic methods in treatment and prognosis modeling. *Artif Intell Med* 1999; **15:** 121–34.

45 Kristensen B, Andreassen S, Leibovici L, Riekehr C, Kjaer AG, Schonheyder HC. Empirical treatment of bacteraemic urinary tract infection. Evaluation of a decision support system. *Dan Med Bull* 1999; **46:** 349–53.

46 Kristensen B, Andreassen S, Leibovici L, Kjaer AG, Schønheyer HC. A cost-benefit analysis of three strategies for selection of empirical antibiotic therapy for bacteraemia: the TREAT decision support system compared with a guideline and clinical practice (PhD thesis). Aalborg University, Denmark, 2003.

47 Schurink CAM, de Bruijn N, Buskens E, Lucas P, Bonten MJM, Hoepelman IM. Construction of a Baysian model for the diagnosis of ventilator associated pneumonia in intensive care unit. 41st International Conference on Antimicrobial Agents and Chemotherapy; Chicago, IL, USA; December 16–19, 2001. Abstract K1471.

48 Schurink CAM, Lucas P, Hoepelman IM, Bonten MJM. A Bayesian decision-support system (BDSS) to reduce unnecessary antibiotic prescriptions for suspected ventilator associated pneumonia (VAP). 44th International Conference on Antimicrobial Agents and Chemotherapy; Washington, DC, USA; October 30–November 2, 2004. Abstract K 416/A.

49 Wyatt JC, Altman DG. Commentary: prognostic models: clinically useful, or quickly forgotten? *BMJ* 1995; **311:** 1539–41.