Journal of Antimicrobial Chemotherapy (2008) **62**, 184–188
doi:10.1093/jac/dkn141
Advance Access publication 4 April 2008

JAC

Predicting pathogens causing ventilator-associated pneumonia using a Bayesian network model

Stefan Visscher[1], Elize M. Kruisheer[1], Carolina A. M. Schurink[1], Peter J. F. Lucas[2] and Marc J. M. Bonten[1,3,4]*

[1]Department of Internal Medicine and Infectious Diseases, University Medical Center Utrecht, Utrecht, The Netherlands; [2]Institute for Computing and Information Sciences, Radboud University, Nijmegen, The Netherlands; [3]Department of Medical Microbiology, University Medical Center Utrecht, Utrecht, The Netherlands; [4]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands

Received 30 January 2008; returned 2 March 2008; revised 7 March 2008; accepted 10 March 2008

***Background*: We previously validated a Bayesian network (BN) model for diagnosing ventilator-associated pneumonia (VAP). Here, we report on the performance of the model to predict microbial causes of VAP and to select antibiotics.**

***Methods*: Pathogens were grouped into seven categories based upon the antibiotic susceptibility and epidemiological characteristics. Colonization of the upper respiratory tract was modelled in the BN and depended—in additional steps—on (i) duration of admission and ventilation, (ii) previous culture results and (iii) previous antibiotic use. A database with 153 VAP episodes and their microbial causes was used as reference standard. Appropriateness of antibiotic prescription, with fixed choices for pathogens predicted, was determined.**

***Results*: One hundred and seven VAP episodes were monobacterial and 46 were caused by two pathogens. Using duration of admission and ventilation only, areas under the receiver operating curve (AUC) ranged from 0.511 to 0.772 for different pathogen groups, and model predictions significantly improved when adding information on culture results, but not when adding information on antibiotic use. The best performing model (with all information) had AUC values ranging from 0.859 for *Acinetobacter* spp. to 0.929 for *Streptococcus pneumoniae*. With this model, 91 (85%) and 29 (63%) of all pathogen groups were correctly predicted for monobacterial and polymicrobial VAP, respectively. With fixed antibiotic choices linked to pathogen groups, 92% of all episodes would have been treated appropriately.**

***Conclusions*: The BN models' performance to predict pathogens causing VAP improved markedly with information on colonization, resulting in excellent pathogen prediction and antibiotic selection. Prospective external validation is needed.**

Keywords: decision support, ICUs, appropriate antibiotic treatment

Introduction

Ventilator-associated pneumonia (VAP) occurs in a considerable number of critically ill patients.[1] Delayed administration of appropriate antimicrobial treatment is associated with higher mortality and longer duration of mechanical ventilation.[2] Therefore, it is important to identify infected patients accurately and rapidly.

Diagnosing VAP remains a challenge as no gold standard exists. Usually, the combination of systemic signs of infection, abnormalities on chest roentgenogram and culture results of endotracheal secretions is used. However, each of these criteria has a low specificity for VAP.[1] Although invasive diagnostic techniques, such as broncho-alveolar lavage (BAL), may have higher specificity,[1] they are not commonly used in ICUs. As a consequence, many antibiotics are prescribed for presumed VAP, which may contribute to the emergence of resistant pathogens. Furthermore, current methods for bacterial identification and susceptibility

*Correspondence address. Department of Medical Microbiology, University Medical Center Utrecht, Utrecht, The Netherlands. Tel: +31-88-755-7676; Fax: +31-30-252-3741; E-mail: mbonten@umcutrecht.nl

testing bare a considerable diagnostic delay. Therefore, real-time decision-support systems may provide diagnostic benefits.

VAP is preceded by colonization of the upper respiratory tract in almost all patients.[3] Bacterial colonization depends, among others, on the duration of mechanical ventilation and hospitalization and on previous antibiotic use. In daily clinical practice, physicians base their judgement on the most likely cause of VAP on these variables and on the results of microbiological cultures. Durations of hospitalization and mechanical ventilation, information on previous culture results and previous antibiotic use were, therefore, modelled in the previously described Bayesian network (BN) model.[4,5]

Methods

We used a previously described cohort of 157 episodes of VAP in 140 patients.[5] The bacteria isolated from respiratory tract samples were considered the aetiological cause of VAP (Table 1; Enterobacteriaceae comprised multiple species; hence, they were subdivided into two groups depending on the capacity to produce β-lactamase). These episodes and pathogens were considered the reference standard in the current study. As no intervention was evaluated, the Institutional Review Board waived the necessity of informed consent.

Pathogens were divided into early onset pathogens (*Streptococcus pneumoniae*, *Haemophilus influenzae* and *Staphylococcus aureus*) and late onset pathogens (Enterobacteriaceae group 1, Enterobacteriaceae group 2, *Pseudomonas aeruginosa* and *Acinetobacter* spp.). Previous colonization was defined as one or more positive culture of endotracheal aspirate in the 3 days prior to the day VAP was diagnosed for the early onset pathogens and in the 7 days prior to the day VAP was diagnosed for the late onset pathogens. Obviously, if no cultures had been performed, previous colonization was considered unknown. Furthermore, if more than one culture was performed, only the results of the most recently performed culture were selected.

Previous antibiotics were considered effective when both the following conditions were fulfilled: (i) the pathogen causing VAP was, based on *in vitro* susceptibility testing, susceptible; and (ii) the antibiotics were administered during at least 2 out of 4 days preceding VAP. In all other cases (including when no antibiotics were given), ineffective treatment was assumed.[5]

Each of the seven groups of pathogens was modelled as a single node in the BN, as the presence of a certain pathogen does not imply the absence of other pathogens. As acquisition of pathogens depends on the duration of hospital stay and on mechanical ventilation, these two time-related variables were modelled as parents of the pathogen-nodes. In addition, for each pathogen group, a parent-node representing whether effective or non-effective treatment was previously administered[6] and a parent-node indicating whether previous colonization had been demonstrated were added [Figure S1, available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/)].

The BN model predicts the likelihood (0% to 100%) for a certain pathogen to cause VAP. To denote either the presence or absence of a pathogen as a cause of VAP, this likelihood was dichotomized based upon the point on the receiver operating curve (ROC) that resulted in the optimal trade-off between sensitivity and specificity (points above being positive, i.e. the model predicts that specific pathogen should be considered as causative for VAP). Naturally, these thresholds differ for each model.

The diagnostic accuracy of the model to predict pathogens causing VAP was assessed by successively adding information. Analysis 1: only information on duration of mechanical ventilation and duration of hospital stay; analysis 2: information on endotracheal culture results was added to analysis 1; analysis 3: information on previous antibiotics was added to analysis 2; and analysis 4: all information (previous antibiotics and culture results) was added simultaneously to analysis 1.

Table 1. Reference standard: frequency of VAP-causing pathogens

	Episodes of VAP		
Causative pathogens	monobacterial $n = 107$ episodes (70%)	polymicrobial $n = 46$ episodes (30%)	total $n = 153$ episodes
P. aeruginosa	19	11	30
Acinetobacter spp.	6	8	14
Enterobacteriaceae group 1	29	17	46
Escherichia coli	17	7	24
Klebsiella pneumoniae	11	4	15
Klebsiella spp.	1	2	3
Proteus mirabilis	0	4	4
Enterobacteriaceae group 2	17	15	32
Serratia spp.	5	4	9
Morganella spp.	0	2	2
Citrobacter spp.	3	2	5
Enterobacter spp.	2	0	2
Enterobacter cloacae	7	7	14
S. aureus	25	16	41
H. influenzae	8	14	22
S. pneumoniae	3	11	14
Total number of pathogens	107	92	199

Appropriateness of antibiotic therapy was pragmatically analysed assuming a standard antibiotic prescription for each pathogen group predicted by the model, using the following fixed choices (the absence of multiresistant pathogens causing VAP was assumed): amoxicillin for *S. pneumoniae*, amoxicillin/clavulanic acid for *H. influenzae* and Enterobacteriaceae group 1, flucloxacillin for *S. aureus*, ciprofloxacin for Enterobacteriaceae group 2, and ceftazidime for *P. aeruginosa* and *Acinetobacter* species. Appropriateness was determined upon *in vitro* susceptibilities of the reference pathogens.

The performance of the BN model was analysed with receiver operating curve (ROC) characteristics. Diagnostic test accuracy was further assessed by calculating the sensitivity, specificity and positive and negative predictive values for all episodes of VAP. The output of the best performing model was then used to analyse how well the model predicted polymicrobial VAP episodes. The sum of log-likelihood scores, expressing how well the model, in terms of underlying structure and parameters, fits the data, was used to assess the quality of predicting each pathogen. The closer the sum is to zero, the better the model fits to the data.

Results

One hundred and five VAP episodes were monobacterial and 52 episodes were polymicrobial. *Stenotrophomonas maltophilia* was considered causative in four monobacterial and six polymicrobial VAP episodes and these were excluded as *S. maltophilia* had not been incorporated as a pathogen group. In two polymicrobial episodes, both pathogens belonged to the same group (Enterobacteriaceae group 1). Thus, in total, 199 pathogens were considered causative [153 episodes in 140 patients: 107 monobacterial and 46 polymicrobial (in all cases caused by two pathogens)]. The largest group of pathogens (23%) was Enterobacteriaceae group 1 and the smallest were *Acinetobacter* spp. and *S. pneumoniae* (both 7%) (Table 1).

Previous colonization ranged from 46% of *S. aureus* to 70% of *P. aeruginosa* episodes. Proportions of patients that had received effective antibiotics ranged from 9% for *H. influenzae* to 47% for Enterobacteriaceae group 2 (Table 2).

In analysis 1 (information on duration of hospitalization and mechanical ventilation only), the threshold for positivity was 27.8% for *P. aeruginosa*, yielding an AUC for predicting *P. aeruginosa* as a cause of VAP of 0.718 [95% confidence interval (CI): 0.626–0.809] (Table 3). The highest AUC was obtained for *S. pneumoniae* [0.772 (95% CI: 0.64–0.905)] and the lowest for the two Enterobacteriaceae groups, both with an AUC of 0.511.

In analysis 2 (information on previous culture results added), performance improved for all pathogens. AUCs were now 0.916 (95% CI: 0.846–0.987) for *P. aeruginosa* (cut-off now 13.7%) and 0.916 (95% CI: 0.85–0.982) for *S. pneumoniae* (cut-off now 3.4%). The lowest AUC [0.831 (95% CI: 0.681–0.981)] was obtained for *Acinetobacter* species. The CIs of the AUCs of the second analysis did not overlap with those of the first analysis for *P. aeruginosa*, Enterobacteriaceae group 1, Enterobacteriaceae group 2 and *S. aureus*, indicating that model predictions improved statistically significantly for these pathogens.

Adding information on previous antibiotic use to analysis 1 hardly changed model performances (analysis 3: data not shown), and adding previous antibiotic exposure to analysis 2 only increased the model performance slightly, but not significantly (analysis 4). The sum of log-likelihood scores increased with adding information (from analysis 1 to 3; $P < 0.05$), indicating improved fit of the BN model to the data.

The model predicted VAP to be monobacterial in 67 cases (107 episodes according to reference), which was correct in 60 episodes (90%) with the correct pathogen predicted in 52 episodes (78%). In 86 episodes, the model predicted VAP to be polymicrobial (46 according to reference): 43 times by 2 pathogens and 43 times by >2–6 pathogens. In all, 91 of the 107 pathogens (85%) causing monobacterial VAP were correctly predicted.

In 46 episodes, the model incorrectly predicted polymicrobial VAP. The two pathogens causing polymicrobial VAP (according to reference) were correctly identified as the only two pathogens in 17 of 46 (37%) episodes and as part of more pathogens in another 12 episodes [total correct being 29 of 46 (63%) episodes]. Combined accuracy for predicting monobacterial and polymicrobial VAP was 78% (91 + 29/153 of all VAP episodes). With a fixed antibiotic choice linked to the pathogen(s) predicted, 92% (140 of 153) of all episodes of VAP would have received appropriate therapy.

Table 2. Previous colonization and previous antibiotic use for all 153 episodes of VAP

		Previous colonization (%)			Previous antibiotic use (%)	
Pathogen	*n*	yes	no	Unknown	effective	ineffective (none)
P. aeruginosa	30	70	27	3	13	87 (37)
Acinetobacter spp.	14	64	36	0	36	64 (14)
Enterobacteriaceae group 1	46	67	20	13	44	56 (39)
Enterobacteriaceae group 2	32	59	25	16	47	53 (47)
S. aureus	41	46	27	27	15	85 (78)
H. influenzae	22	55	18	27	9	91 (77)
S. pneumoniae	14	50	21	29	21	79 (79)

Previous colonization status was considered unknown when culture data were not available.

Table 3. Predictive performance of the BN model using information on duration of hospitalization and mechanical ventilation

Group	AUC	95% CI	T	Sens	Spec	PPV	NPV	∑LL
Analysis 1: without information of previously performed cultures and without information previous antibiotic use								
P. aeruginosa	0.718	0.626–0.809	27.8	0.900	0.472	0.293	0.951	−71.6
Acinetobacter spp.	0.603	0.469–0.737	12.3	0.857	0.424	0.130	0.967	−46.7
Enterobacteriaceae group 1	0.511	0.416–0.606	33.3	0.848	0.252	0.328	0.794	−92.7
Enterobacteriaceae group 2	0.511	0.391–0.631	18.7	0.906	0.058	0.203	0.700	−78.4
S. aureus	0.633	0.532–0.733	17.1	0.976	0.080	0.280	0.900	−85.9
H. influenzae	0.768	0.666–0.870	6.6	0.818	0.627	0.295	0.957	−60.3
S. pneumoniae	0.772	0.640–0.905	4.3	0.786	0.662	0.190	0.968	−45.4
Analysis 2: with information on previously performed cultures, but without information on previous antibiotic use								
P. aeruginosa	0.916	0.846–0.987	13.7	0.833	0.837	0.591	0.963	−34.5
Acinetobacter spp.	0.831	0.681–0.981	1.4	0.786	0.655	0.385	0.969	−30.8
Enterobacteriaceae group 1	0.877	0.816–0.938	29.7	0.783	0.776	0.607	0.902	−63.7
Enterobacteriaceae group 2	0.887	0.830–0.944	17.9	0.781	0.777	0.524	0.910	−52.4
S. aureus	0.861	0.794–0.927	37.2	0.805	0.812	0.447	0.909	−7.7
H. influenzae	0.893	0.823–0.963	8.9	0.818	0.824	0.378	0.954	−43.7
S. pneumoniae	0.916	0.850–0.982	3.4	0.857	0.799	0.476	0.970	−30.5
Analysis 4: with information on previously performed cultures and with information on previous antibiotic use								
P. aeruginosa	0.921	0.854–0.989	28.9	0.833	0.959	0.641	0.956	−33.9
Acinetobacter spp.	0.859	0.739–0.980	1.3	0.786	0.698	0.526	0.970	−29.9
Enterobacteriaceae group 1	0.879	0.818–0.939	27.1	0.783	0.766	0.569	0.863	−63.5
Enterobacteriaceae group 2	0.890	0.835–0.946	21.5	0.781	0.793	0.328	0.876	−54.5
S. aureus	0.873	0.809–0.937	27.2	0.805	0.812	0.493	0.907	−64.9
H. influenzae	0.899	0.833–0.965	12.0	0.818	0.832	0.375	0.962	−39.3
S. pneumoniae	0.929	0.875–0.983	5.8	0.857	0.827	0.224	0.971	−28.4

AUC, area under the ROC; CI, confidence interval; T, threshold; Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value; ∑LL, sum of log-likelihood scores.

Discussion

The BN model accurately predicted the most likely cause(s) of VAP. Combining information on the time of intubation and on previous culture results from respiratory tract samples appeared essential, supporting the usefulness of regular surveillance as a means to assist physicians in choosing appropriate antibiotics. If confirmed in prospective studies in other settings, this BN model might offer a reliable and valuable tool in the management of critically ill patients. Our findings suggest that decision-support systems could enhance patient management. Appropriateness of antimicrobial therapy in 92% of the episodes would be much higher than reported rates from international studies that have been as low as 32%[7] and 46%.[8]

Despite the positive results of the previous[5] and the present study, some aspects preclude widespread use of this model in daily clinical practice, at this stage. The model has been tested only retrospectively in a single cohort and external validation, with the ultimate proof of clinical usefulness evaluation in a randomized study, is, therefore, warranted.

Funding

This study was supported by a grant from NWO (634.000.026) for the TimeBayes project.

Transparency declarations

None to declare.

Supplementary data

Figure S1 is available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

References

1. Chastre J, Fagon JY. Ventilator-associated pneumonia. *Am J Respir Crit Care Med* 2002; **165**: 867–903.

2. van Nieuwenhoven CA, Buskens E, Bergmans DC *et al.* Oral decontamination is cost-saving in the prevention of ventilator-associated pneumonia in intensive care units. *Crit Care Med* 2004; **32**: 126–30.

3. Bonten MJM, Bergmans CJJ. Risk factors for pneumonia, and colonization of respiratory tract and stomach in mechanically ventilated ICU patients. *Am J Respir Crit Care Med* 1996; **154**: 1339–46.

4. Lucas PJF, Bruijn de NC, Schurink CAM *et al.* A probabilistic and decision-theoretic approach to the management of infectious disease at the ICU. *Artif Intell Med* 2000; **19**: 251–79.

5. Schurink CAM, Visscher S, Lucas PJF *et al*. A Bayesian decision-support system for diagnosing ventilator-associated pneumonia. *Intensive Care Med* 2007; **33**: 1379–86.

6. Visscher S, Schurink CAM, Melsen WG *et al*. Effects of systemic antibiotic therapy on bacterial persistence in the respiratory tract of mechanically ventilated patients. *Intensive Care Med* 2008; **34**: 692–9.

7. Luna CM, Aruj P, Niederman MS *et al*. Appropriateness and delay to initiate therapy in ventilator-associated pneumonia. *Eur Respir J* 2006; **27**: 158–64.

8. Teixeira PJ, Seligman R, Hertz FT *et al*. Inadequate treatment of ventilator-associated pneumonia: risk factors and impact on outcomes. *J Hosp Infect* 2007; **65**: 361–7.