Journal of Antimicrobial Chemotherapy (2009) **63**, 400–404
doi:10.1093/jac/dkn504
Advance Access publication 17 December 2008

JAC

Performance of the TREAT decision support system in an environment with a low prevalence of resistant pathogens

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Received 29 June 2008; returned 29 August 2008; revised 11 October 2008; accepted 19 November 2008

***Objectives*: To evaluate a decision support system (TREAT) for guidance of empirical antimicrobial therapy in an environment with a low prevalence of resistant pathogens.**

***Methods*: A retrospective trial of TREAT has been performed at Copenhagen University, Hvidovre Hospital. The cohort of patients included adults with systemic inflammation and suspicion of community-acquired bacterial infection. The empirical antimicrobial treatment recommended by TREAT was compared with the empirical antimicrobial treatment prescribed by the first attending clinical physician.**

***Results*: Out of 171 patients recruited, 161 (65 with microbiologically documented infections) fulfilled the inclusion criteria of TREAT. Coverage achieved by TREAT was significantly higher than that by clinical practice (86% versus 66%, $P = 0.007$). There was no significant difference in the cost of future resistance between treatments chosen by TREAT and those by physicians. The direct expenses for antimicrobials were higher in TREAT when including patients without antimicrobial treatment, while there was no significant difference otherwise. The cost of side effects was significantly lower using TREAT.**

***Conclusions*: The results of the study suggest that TREAT can improve the appropriateness of antimicrobial therapy and reduce the cost of side effects in regions with a low prevalence of resistant pathogens, however, at the expense of increased use of antibiotics.**

Keywords: computerized decision support system, empirical antimicrobial therapy, severe infections

Introduction

Bacterial infections and sepsis are major causes of morbidity and mortality in hospitals.[1,2] Although new treatment modalities have been recently introduced, prompt appropriate antimicrobial treatment is of utmost importance in order to reduce the overall fatality rate of severe infections.[3] However, 20% to 50% of patients are given inappropriate empirical antimicrobial treatment.[4–6] Concurrently, hospitals are facing a grave and increasing problem of antimicrobial-resistant infections driven by excessive and inappropriate antimicrobial use.[7]

We have previously shown in a randomized controlled trial that a computerized decision support system (DSS, TREAT) based on a causal probabilistic network significantly improves antimicrobial treatment of inpatients in settings with an intermediate to high prevalence of resistant pathogens.[4] However, so far TREAT has not been tested in an environment with a low prevalence of resistant pathogens, as is seen in Denmark where it is often possible to use inexpensive antimicrobials with relatively low impact on the ecosystem.

To assess whether TREAT can improve antimicrobial treatment in an environment with a low prevalence of resistant pathogens, we conducted a non-interventional cohort study in Denmark. We aimed to compare TREAT's advice with physicians' performance regarding appropriate empirical antimicrobial treatment and antimicrobial costs.

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Methods

DSS

TREAT is a computerized system for the diagnosis and treatment of severe infections. The input data include the patient's demographic characteristics, background conditions, previous antimicrobial treatment, devices, radiological and laboratory test results, signs and symptoms of sepsis and local infection, and microbiological results (if available). The system predicts diagnosis and recommends antimicrobial treatment if needed, based on local infection prevalences and antimicrobial resistance as well as a cost–benefit analysis. The benefit components are the increase in survival and reduction in bed-days; the cost components associated with each antimicrobial agent are the direct cost, the cost of expected side effects and the cost of future resistance. Direct cost includes the cost of purchasing a drug, disposables and administration costs. The cost of side effects for each antimicrobial agent was abstracted from the literature using a systematic approach[8] and expressed as hospital days and quality-adjusted life years. The cost of future resistance is the sum of three components: individual patient cost, for the probability of infection and antibiotic failure in the ensuing months; costs to the eco-system, for loss of antibiotic efficacy within the department; and a penalty for drugs of last resort (e.g. carbapenems). Results are presented as ranking of diagnoses, pathogens, treatments (including 'no treatment'), their coverage and their cost-benefit as detailed elsewhere.[4,9] A screen print of the advice page of TREAT is available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

Calibration of TREAT

Administrative factors that were calibrated included department names, locally available antimicrobials, local units of measurement and other information to adapt the interface to the hospital. Administrative costs that were calibrated included purchasing costs of antimicrobials, disposables and the labour of drug administration. The bed-day component of side effects was converted into Euros by multiplying the number of bed-days with the local average cost of a bed-day, 536 Euros/day. The life-year component of side effects was converted into Euros using a rate of 50 000 Euros/quality-adjusted life-year. The same rate was used to convert benefit related to survival into Euros, assuming an average life expectancy of 5 years.[10] Total cost of future resistance was estimated by a local clinical microbiologist (G. L.) and an infectious disease specialist (O. A.), summing up the three components mentioned earlier. Table 1 gives examples of the cost components for the treatments considered by TREAT.

The local/national prevalence of background conditions, e.g. alcoholism, chronic obstructive pulmonary disease (COPD) and liver cirrhosis, and the incidences of community-acquired infections, e.g. pneumonia, urinary tract infections and gastrointestinal infections, were found by searching the National Patient Registry, local health reports and published literature.

To calibrate local antimicrobial susceptibilities and pathogen distribution by place of acquisition, we used all clinically significant bloodstream infections recorded at the Department of Microbiology from January 2005 to March 2007. A total of 1826 patient-unique cultures were included.

Patients

The cohort of patients used in the present study was prospectively collected as part of a sepsis biomarker study.[11,12] Data were collected between February 2005 and March 2006 at Hvidovre Hospital, an 800 bed university hospital in Copenhagen, Denmark. All consecutive newly admitted (<24 h) adult patients (≥18 years) who fulfilled at least two criteria of systemic inflammatory response syndrome (SIRS)[13] or were suspected of meningitis and were admitted to the Department of Infectious Diseases or the infectious disease unit of the Medical Emergency Department were asked to participate. We excluded patients with travel-related infections or suspected tuberculosis. Patients were included only once in the study.

For the present study, all patient records were examined retrospectively for data used by the TREAT system. The Scientific Ethical Committee of Copenhagen and Frederiksberg Municipalities approved sample collection on the basis of informed written consent (KF01-108/04).

All available data were entered into the TREAT DSS and TREAT's first recommendation for antimicrobial treatment (or no treatment) was recorded.

Table 1. Cost components (in Euros) for a selection of treatments considered by TREAT

Treatment	Route of administration	Direct cost	Cost of side effects	Cost of future resistance
None		0	0	0
Ampicillin	intravenous	56	157	200
Cefotaxime	intravenous	50	58	800
Cefuroxime	intravenous	90	58	300
Ciprofloxacin	oral	12	24	1000
Ciprofloxacin	intravenous	53	55	1000
Clarithromycin	intravenous	150	23	700
Ertapenem	intravenous	157	85	1200
Penicillin	intravenous	41	149	0
Vancomycin	intravenous	228	155	1200

Outcomes and analysis

The primary outcome was appropriate empirical antimicrobial treatment, defined as the percentage of antimicrobial treatment matching the *in vitro* susceptibility of subsequently isolated pathogen(s), and was assessed among all patients with microbiologically documented infections. Empirical antimicrobial treatment was defined as treatment commenced before any pathogen was isolated and within 24 h of admission. Secondary outcomes were assessed for all patients and included the types of antimicrobials used and their costs. Coverage and costs of treatment for physicians versus TREAT were compared using the McNemar test and the *t*-test (two-tailed), respectively. Results regarding treatment/no treatment were compared using the χ^2 test.

Results

Overall, 171 patients were recruited. Ten were subsequently excluded due to suspicion of travel infections or tuberculosis. Baseline characteristics of the 161 patients are shown in Table 2. Culture-based microbiologically documented infections were documented in 65 patients (40%). Of these, a microorganism was isolated from the blood in 25 patients (16%) and from local cultures in the remaining 40 patients (25%).

Table 2. Baseline patient characteristics, $n = 161$

Characteristic	
Age, median years (range)	55 (20–94)
Gender	
male	80 (50.0)
female	81 (50.0)
Co-morbidity[a]	72 (44.7)
solid tumours and haematological malignancies	14 (8.7)
HIV infection	15 (9.3)
diabetes	12 (7.5)
COPD and asthma	17 (10.6)
drug or alcohol abuse	12 (7.5)
other diseases[b]	19 (11.8)
Medication prior to admission	
bacterial antimicrobials	42 (26.1)
immunosuppressives[c]	10 (6.2)
Disease severity	
Simplified Acute Physiology Score II, median (5th–95th percentiles)	18 (6–35)

Data are given as no. of patients (%), unless otherwise indicated.
[a]Several patients had more than one co-morbidity.
[b]Inflammatory bowl disease, rheumatoid arthritis, disseminated sclerosis, chronic adrenal insufficiency, viral hepatitis, cardiovascular diseases and diseases of the thyroid gland.
[c]Steroids, methotrexate, azathioprine and monoclonal TNF-α antibodies.

Overall, physicians prescribed appropriate empirical treatment to only 66% (43/65) of patients with a clinically significant pathogen, compared with 86% (56/65 patients) for TREAT ($P = 0.007$). The pathogen/treatment combinations of inappropriate therapy of physicians (22 cases) and TREAT (9 cases) are shown in Table 3. TREAT advised appropriate empirical treatment to 92% (23/25) of patients with bacteraemia, while treatment prescribed by the physicians covered 76% (19/25) ($P = 0.22$) of these patients.

TREAT advised 15 different antimicrobial regimens while physicians used 30 regimens. TREAT advised no empirical antimicrobial treatment to 14 patients (8.7%), significantly less than the physicians who did not prescribe empirical antimicrobials to 40 patients (25%) ($P < 0.001$). In the 65 cases with a clinically significant pathogen, nine patients (14%) did not receive empirical treatment with physicians, while TREAT advised empirical treatment for all but one (1.5%) patient ($P = 0.005$).

The mean expenses per patient using TREAT versus clinical practice are shown in Table 4. If averaged over all patients in the cohort, the total cost using TREAT is not significantly different from the total cost incurred by using the physician, while there is a tendency towards lower total cost using TREAT if calculations are made only for the patients who were recommended (by TREAT) or given (by physicians) antibiotic treatment.

Discussion

In the present study, we demonstrate that in an area with a low prevalence of resistant pathogens, TREAT's advice provided significantly better antimicrobial coverage than physicians' empirical choices. TREAT used a narrower antimicrobial formulary. TREAT recommended empirical antimicrobial treatment to more patients than did physicians, but this seemed appropriate: judging from patients in whom a clinically significant pathogen had been isolated, TREAT was significantly better at advising timely empirical treatment. TREAT successfully identified patients with severe infections, as reflected by the non-significant higher rate of appropriate empirical treatment given by the system to patients with bacteraemia.

TREAT has previously been tested in areas with intermediate to high levels of resistant pathogens (Israel, Italy and Germany). In a similar observational study, TREAT recommended appropriate antimicrobial treatment to 70% of patients, compared with

Table 3. The pathogen/treatment combinations of inappropriate therapy of physicians (22 cases) and TREAT (9 cases)

Physician		TREAT	
pathogen(s)	treatment	pathogen(s)	treatment
Campylobacter sp.	none, ciprofloxacin	*Campylobacter jejuni*	ampicillin
Escherichia coli	none (2 cases), penicillin (2 cases)	*Campylobacter* spp.	ampicillin
E. coli and *Enterococcus faecalis*	penicillin	*E. faecalis*	cefuroxime
E. faecalis	none	*Enterococcus* spp.	cefuroxime
Haemophilus influenzae	penicillin	*H. influenzae*	penicillin
H. influenzae and *Streptococcus pneumoniae*	penicillin	*Legionella pneumophila*	cefotaxime
Moraxella catarrhalis	penicillin	*P. aeruginosa*	cefuroxime (2 cases)
M. catarrhalis and *S. pneumoniae*	penicillin	*S. pneumoniae*	none
Mycoplasma pneumoniae	penicillin, cefuroxime		
Pseudomonas aeruginosa	none, penicillin		
Salmonella enteritidis	none		
Salmonella typhi	ciprofloxacin		
Streptococcus agalactiae	none		
S. agalactiae and *S. pneumoniae*	ciprofloxacin		
Streptococcus pyogenes	none (2 cases)		

Table 4. Costs (in Euros) of antibiotic treatment by physicians versus TREAT

	Physician	TREAT	*P* value[a]
Costs per patient ($n = 161$)			
direct cost, mean (SD) per patient	54 (51)	76 (56)	0.0003
cost of side effects, mean (SD) per patient	126 (201)	96 (103)	0.05
cost of future resistance, mean (SD) per patient	289 (458)	310 (294)	0.6
total cost, mean (SD) per patient	469 (534)	482 (313)	0.77
Costs per treatment given by physician or recommended by TREAT ($n = 121$ for physician and $n = 147$ for TREAT)			
direct cost, mean (SD) per patient	72 (46)	84 (53)	0.07
cost of side effects, mean (SD) per patient	168 (216)	105 (103)	0.002
cost of future resistance, mean (SD) per patient	384 (492)	339 (291)	0.36
total cost, mean (SD) per patient	624 (532)	528 (288)	0.06

[a]*t*-test (two-tailed).

57% by physicians.[4] The higher coverage was achieved at a lower total cost than that of the treatment chosen by physicians, mainly by recommending narrower spectrum antibiotics with low cost of future resistance. There was, however, a tendency towards higher side effect costs due to TREAT's use of aminoglycosides for urinary tract infections.[4] In contrast, in the present study, there was no reduction in total cost and cost of future resistance, while the costs for side effects decreased significantly. Comparison of treatment cost per patient with treatment cost per treatment (Table 4) shows that TREAT actually tended to recommend treatments with lower total cost and cost of future resistance but for more patients. The difference between cost per patient and cost per treatment is due to TREAT being significantly better at advising timely empirical treatment for patients with a clinically significant pathogen. This indicates some degree of under-utilization of antimicrobials by physicians, which may be due to a high awareness in Denmark of the impact of antimicrobials on the ecosystem and a tradition of a rather restricted use of antimicrobials. TREAT appears to trade in a slightly higher direct cost ($P = 0.07$) for a lower total cost ($P = 0.06$) and a 20% higher coverage. The tradition of restricted use of antimicrobials results in low levels of bacterial resistance in Denmark: most common bacterial infections are still susceptible to relatively cheap antibiotics (e.g. >95% of *Streptococcus pneumoniae* are still susceptible to penicillin)[14] and this makes it difficult to further reduce the direct cost of treatment. Local attitudes towards this balance between side effects, direct costs and future ecological costs for any given antibiotic are reflected in the local choice of the cost of future resistance. As part of the calibration process, the study physicians were offered the opportunity to adjust the cost of future resistance to mimic physicians' behaviours in Denmark. However, confronted with the results shown, the study physicians in Hvidovre Hospital accepted the costs of future resistance given in Table 1, since this provided a substantially improved rate of appropriate empirical antimicrobial treatment.

The 'correct' balance between different costs is debatable, given the lack of a quantitative understanding of the factors that influence the rate of development of future resistance. The actual effects of TREAT on resistance development in Denmark must be assessed in an interventional study of longer duration.

It needs to be seen how well clinicians in Denmark will receive TREAT's advice. This study only assessed the performance of TREAT in guiding antimicrobial therapy in patients with SIRS suspected of a community-acquired infection. The performance of the system in other patient groups in Denmark, especially in nosocomial infections, should be further assessed.

In summary, in Denmark, the antimicrobial coverage achieved by TREAT was significantly higher than coverage achieved by the physician and the cost of side effects was lower. These results suggest that TREAT can improve appropriateness of antimicrobial therapy in regions with a low prevalence of resistant pathogens.

Acknowledgements

We would like to thank study nurse Jan Olsen for the reading of patient records and typing in data, as well as the staff at the Emergency Department and the Department of Infectious Diseases for their support that made recording of clinical data possible.

Funding

This study was supported by grants from the NABIIT programme (2106-05-0026), the research foundation at Copenhagen University Hospital, Hvidovre, and the H:S Research Foundation.

Transparency declarations

None to declare.

Supplementary data

A screen print of the advice page of TREAT is available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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