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Improving empirical antibiotic treatment using TREAT, a computerized decision support system: cluster randomized trial

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***Background*: Appropriate antibiotic treatment decreases mortality, while superfluous treatment is associated with antibiotic resistance. We built a computerized decision support system for antibiotic treatment (TREAT) targeting these outcomes.**

***Methods*: Prospective cohort study comparing TREAT's advice to physician's treatment followed by a cluster randomized trial comparing wards using TREAT (intervention) versus antibiotic monitoring without TREAT (control). We included patients suspected of harbouring bacterial infections in three hospitals (Israel, Germany and Italy). The primary outcome, appropriate antibiotic treatment, was assessed among patients with microbiologically documented infections (MDI). Length of hospital stay, adverse events, mortality (interventional trial) and antibiotic costs (both studies), including costs related to future antibiotic resistance, were compared among all included patients.**

***Results*: Among 1203 patients included in the cohort study (350 with MDI), TREAT prescribed appropriate empirical antibiotic treatment significantly more frequently than physicians (70% versus 57%, $P < 0.001$) using less broad-spectrum antibiotics at half physicians' antibiotic costs. The randomized trial included 2326 patients, 570 with MDI. The rate of appropriate empirical antibiotic treatment was higher in intervention versus control wards [73% versus 64%, odds ratio (OR): 1.48, 95% confidence interval (CI): 0.95–2.29, intention to treat, adjusted for location and clustering]. For patients treated according to TREAT's advice in intervention wards, the difference with controls was highly significant (OR: 3.40, 95% CI: 2.25–5.14). Length of hospital stay, costs related to future resistance and total antibiotic costs were lower in intervention versus control wards.**

***Conclusions*: TREAT improved the rate of appropriate empirical antibiotic treatment while reducing antibiotic costs and the use of broad-spectrum antibiotic treatment.**

Keywords: appropriate antibiotic treatment, antibiotic resistance, ecological antibiotic costs, decision support system

Introduction

Antibiotic treatment for suspected infections is initiated empirically, before identification of the causative pathogen. Appropriate treatment, that is matching the *in vitro* susceptibilities of subsequently isolated pathogens, reduces the overall fatality rate of severe infections with adjusted odds ratios (ORs) varying between 1.6 and 6.9.[1–9] However, 20–50% of patients are given inappropriate empirical antibiotic treatment.[1–9] Concurrently, hospitals are facing a grave problem of antibiotic-resistant infections driven by excessive and inappropriate antibiotic use.[10] One-sided interventions, such as antibiotic restriction or cycling, frequently result in unintended increases in consumption of other antibiotics, triggering further resistance.[11,12]

We developed a computerized decision support system (DSS) (TREAT) based on a causal probabilistic network (CPN) to

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improve antibiotic treatment of inpatients. The aims of the system were to improve the rate of appropriate antibiotic treatment, thereby reducing mortality, and to route antibiotic use towards ecologically economical antibiotics as determined by local resistance profiles. The system can be calibrated to different locations.

We evaluated TREAT in two phases. We firstly assessed the performance and safety of the system in three countries in a non-interventional cohort study. We then assessed the effect of TREAT on the management of inpatients in these sites in a cluster randomized controlled trial.

Methods

Decision support system

The TREAT core model is based on a CPN, in which causal relations are drawn reflecting knowledge, and the magnitudes of the relations are given as conditional probabilities. The basic units of TREAT are pathogens, whose probabilities are determined by the place of acquisition and underlying conditions of the patient. Pathogens are linked to sites of infection (e.g. pneumonia) causing local signs, symptoms and laboratory and radiological findings. All sites cause sepsis and bacteraemia.[13–15]

The system can be used at any decision point during the course of antibiotic therapy. The current trial addressed only empirical treatment. Input to the system includes variables that significantly influence pathogen probabilities (either infection probability or pathogen distribution) and are available at the time empirical treatment is prescribed. These include patient demography, background conditions, devices (e.g. presence of catheter), vital signs, laboratory tests, symptoms and signs relevant to infection, and available radiological (e.g. chest X-ray) and microbiological (e.g. Gram stain) results. TREAT's output includes the probability of infection and its severity, source of infection, pathogen distribution, mortality and antibiotic coverage. TREAT recommends treatment by highlighting the three top-rank antibiotic regimens, with the highest cost-benefit difference, including no antibiotic treatment [Appendix 1, available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/)].

Antibiotics' benefit comprises the 30 day survival gain and reduction in hospital stay associated with appropriate empirical antibiotic treatment.[16] Antibiotic costs include three components: direct drug and administration, adverse event and ecological costs. Adverse event rates for each antibiotic were abstracted from the literature using a systematic approach[17] and assigned costs in hospital days and quality-adjusted life years. To assign ecological costs, we used a model similar to the one proposed to deal with optimal use of non-renewable resources.[18,19] We used local data and data available from the literature to draw a curve relating consumption to rise in resistance for each antibiotic. Ecological costs summed three components: individual patient costs, for the probability of infection and antibiotic failure in the ensuing month; costs to the eco-system, for loss of antibiotic efficacy within the department; and a penalty cost for drugs of last resort (e.g. carbapenems). All components of the cost-benefit equations may be calibrated, as well as pre-specified probabilities within the CPN (e.g. pathogen probabilities, coverage). The full cost-benefit model is described in Appendix 2 (available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

Setting and patients

Both studies were conducted in Israel (6 wards of internal medicine, 240 beds) at Rabin Medical Center, Beilinson Campus; Germany (2 gastroenterology, 2 nephrology, 2 intensive care wards, 94 beds) at University Hospital of Freiburg; and Italy (3 infectious disease wards, 90 beds) at Universitá Cattolica del Sacro Cuore School of Medicine, Gemelli Hospital in Rome. All hospitals are university affiliated primary and tertiary care centres.

Included were (i) patients from whom blood cultures were drawn; (ii) patients prescribed antibiotics (not for prophylaxis); (iii) patients fulfilling criteria for the systemic inflammatory response syndrome;[20] (iv) patients with a focus of infection; (v) patients with shock compatible with septic shock; and (vi) patients with febrile neutropenia.[21] We excluded HIV-positive patients with a current (suspected or identified) opportunistic disease and/or AIDS-defining illness currently or within the past 6 months, organ or bone marrow transplant recipients, children <18 years, suspected travel infections or tuberculosis, and pregnant women. Patients were included only once in the interventional study.

Objectives

In the cohort study we aimed to compare TREAT's advice with physician performance as regards appropriate empirical antibiotic treatment and antibiotic costs, to show the potential of TREAT to improve treatment. In the interventional randomized trial we assessed whether TREAT improved physician performance and patient-related outcomes.

Outcomes

We selected appropriate antibiotic treatment as primary outcome, since *in vitro* testing provides an objective comparator and appropriate empirical antibiotic treatment has been shown to correlate with reduced mortality. Empirical antibiotic treatment was defined as appropriate if it commenced within 24 h of admission (community-acquired infections) or infection presentation (hospital-acquired infections) and matched *in vitro* susceptibility of subsequently isolated pathogens. The primary outcome was assessed among patients with microbiologically documented infections (MDI) deemed clinically significant [Appendix 3, available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/)]. Secondary outcomes were compared for all patients and included the type of antibiotics used and their costs. In the interventional trial we compared costs of observed side effects, duration of hospital stay, fever and overall 30 day mortality. Outcome data were collected 30 days following patients' recruitment.

Prospective cohort study

The cohort study was conducted between 1 July 2002 and 1 January 2003 in Israel and Germany, and between 1 March 2003 and 30 September 2003 in Italy. Patients fulfilling inclusion criteria were prospectively identified by daily chart review. Relevant data were collected within 24 h of empirical treatment. Physicians' empirical antibiotic treatment was compared with that of TREAT's single top-rank treatment selection.

Appropriateness of treatment for physicians versus TREAT's top-rank advice were compared using McNemar's test for each site and the Mantel–Haenszel statistic for the combined analysis adjusting for the three recruitment sites. Continuous variables were compared using the Mann–Whitney *U*-test.

Interventional cluster randomized trial

The interventional trial was conducted between May 2004 and November 2004 at the three sites. Within each site, wards were

randomly allocated to intervention or control by drawing a random code from a closed opaque box. In Germany, pairs were matched by ward specialty. Evaluators were blinded to patient assignment.

The TREAT system was installed in intervention wards and its use was offered to physicians at the time of empirical antibiotic treatment. Physicians were asked to inspect TREAT's result interface, but the final choice of antibiotic treatment was theirs. To avoid selection bias, we performed daily chart review in intervention wards to identify and include patients fulfilling inclusion criteria that were not entered by physicians to the TREAT system. In control wards, patients' data were prospectively collected through daily chart review. To prevent the Hawthorne effect,[22] data collection in control wards was open with the intention that physicians be aware of a monitoring process.

Within each site, dichotomous outcomes were compared using the Pearson χ^2 test. Combined analysis was performed using the Mantel–Haenszel statistic, when appropriate, adjusting for the three recruitment sites. Costs, duration of fever and hospital stay within each site were compared using the Mann–Whitney *U*-test. Multivariate analysis for the appropriateness of antibiotic treatment was conducted using a generalized estimating equation (GEE) approach, constructing a logistic regression model with exchangeable correlations adjusting for medical centre and accounting for clustering by ward. ORs with 95% confidence intervals (CIs) were calculated. Analysis was performed using STATA version 8 (StataCorp, College Station, TX, USA, XTGEE command).[23] Continuous outcomes were compared using a general linear model.

The planned sample of 1500 patients in 15 wards had a power of >99% to detect a 15% reduction in inappropriate antibiotic treatment (from 35% to 20%), for a two-tailed test, assuming cluster randomization of wards stratified within three hospitals by a two-way analysis of variance and a between-ward variance of 0.0005. We chose a sample size that would allow us to detect a difference even if two wards defaulted. Owing to the grant time limits the trial was stopped before attaining the planned sample size. The primary analysis of the interventional trial was performed by intention to treat, including all patients recruited, regardless of physician's compliance with TREAT. Per protocol analysis was performed including patients in intervention wards for whom physicians prescribed one of the antibiotics advised by the three top-ranking treatments suggested by TREAT.

Ethical considerations

The research ethics committees at the three sites approved both study protocols. Informed consent for the interventional trial (ClinicalTrials.gov Identifier: NCT00233376) was waived by the committee in Israel and Germany, given that clinicians retained the prerogative on antibiotic treatment, and obtained for patients in Italy.

Results

Cohort study

Overall, 1203 patients were recruited [Appendix 4, available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/)]. Physicians prescribed appropriate treatment to 57% (199/350) of patients with an identified bacterial pathogen, compared with 70% (245/350 patients) for TREAT, $P = 0.0001$, a relative increase of 23% (Table 1). TREAT performed better than physicians in each location, reaching statistical significance in Israel and overall.

Among all patients, TREAT advised fewer different antibiotic regimens than those used by physicians (30 versus 79 in Israel, 24 versus 105 in Germany, and 10 versus 53 in Italy, for TREAT versus physician, respectively). TREAT advised no antibiotic treatment to 274 patients (23%), compared with physicians (232 patients, 19%).

Table 1. Cohort study: appropriate antibiotic treatment

	Patients	Physician[a]	TREAT[a]	*P* value[b]
Israel	164	87 (53.0)	121 (73.8)	<0.001
Germany	105	62 (59.0)	71 (67.6)	0.108
Italy	81	50 (61.7)	53 (65.4)	0.690
Overall	350	199 (56.9)	245 (70.0)	<0.001

Data given as numbers of patients with percentages in parentheses.
[a]Physician's coverage undetermined for 8 patients in Freiburg and 6 in Rabin; TREAT's coverage undetermined for 9 and 12 patients, respectively. Undetermined coverage counted as inappropriate treatment.
[b]McNemar test for the comparison within each site; Mantel–Haenszel stratified by location for the overall analysis. Mantel–Haenszel OR of 4.12 (2.53–6.69) for the overall comparison.

All cost components, except those related to expected adverse events, were significantly lower for the treatments suggested by TREAT compared with those used by physicians (Appendix 4). Total antibiotic costs were 289 Euros lower per patient for TREAT compared with physicians, a relative decrease of 48%.

TREAT performed differently in the three locations, reflecting local calibrations. The system drove for improved coverage while containing costs in Israel and Germany. In Italy, it mainly lowered costs while maintaining coverage.

Randomized controlled trial

The trial flow diagram is detailed in Figure 1. The three sites recruited 2326 patients, 1245 to intervention and 1081 to control (Table 2). Infections were mainly community-acquired and the leading outcome diagnosis was pneumonia. Among patients with MDI, evaluated for the primary outcome, the percentage of hospital-acquired infections was higher and urinary tract infections were the major diagnosis [Appendix 5, available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/)].

Primary outcome (Table 3). The rate of appropriate empirical antibiotic treatment improved from 64% (176/273) in control to 73% (216/297) in intervention wards (intention to treat analysis). The difference was statistically significant: Mantel–Haenszel OR: 1.48 (95% CI 1.03–2.11). Multivariate logistic regression model, adjusting for medical centre and accounting for clustering by ward, yielded an OR of 1.48 (95% CI: 0.95–2.29). The latter model adjusts both standard errors and parameter estimates to allow for clustering within wards. Both models account for the variability between the sites.

Per protocol analysis, restricting the intervention to cases in which physicians prescribed an antibiotic identical to TREAT advice, showed a highly significant advantage to the intervention. The improvement was evident at each site. Overall, appropriate antibiotic treatment in intervention wards was 85% (114/134). The combined OR for appropriate antibiotic treatment in intervention versus control wards per protocol adjusted for location and clustering in the multivariate model was 3.40 (95% CI: 1.96–5.90).

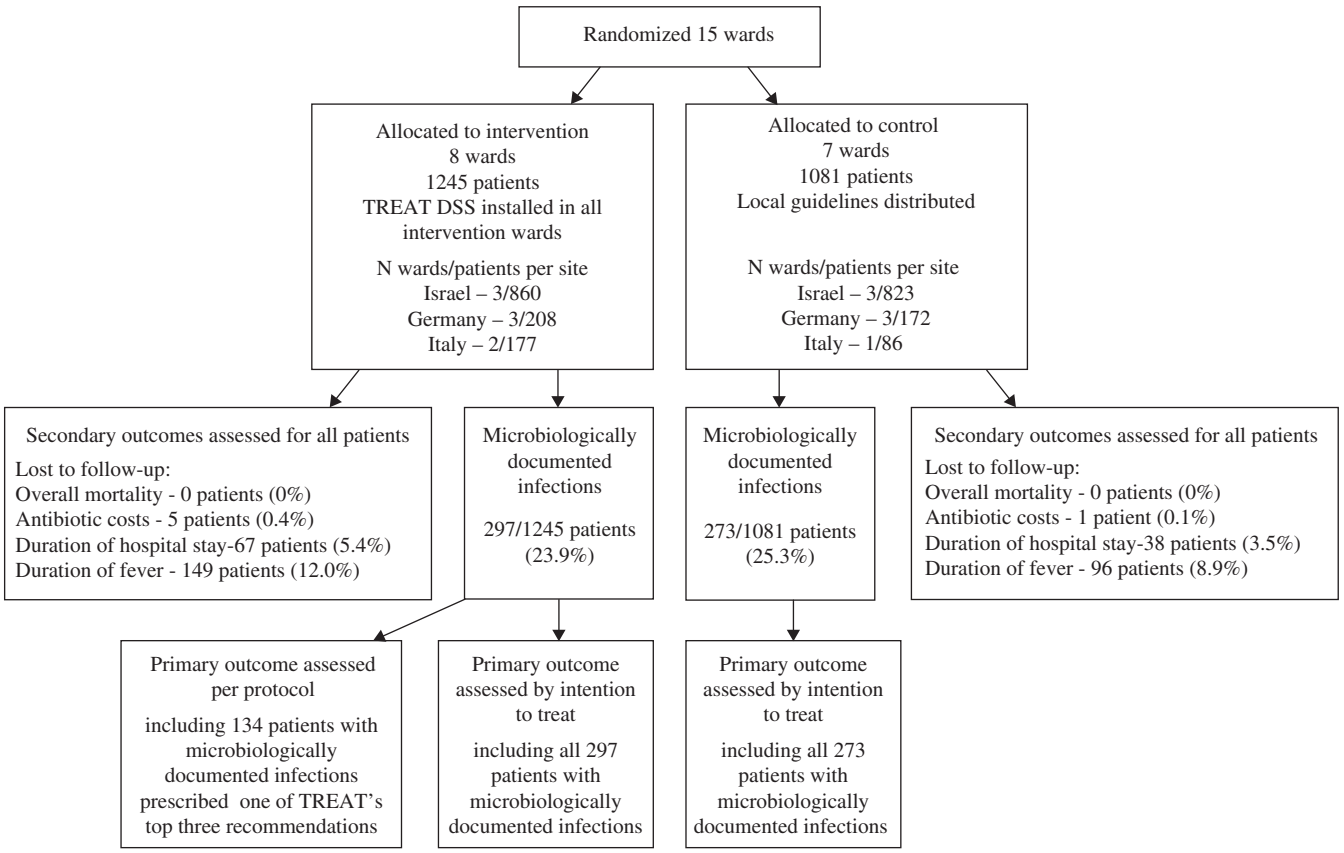

Figure 1. Flow diagram for patients and clusters: cluster randomized trial.

To examine whether the difference originated from baseline departmental heterogeneity, we used the cohort database and compared the appropriateness of empirical antibiotic treatment for wards subsequently randomized to intervention versus control. No significant difference existed before the intervention (OR: 0.97, 95% CI: 0.62–1.52).

Secondary outcomes. In Israel and Italy, intervention wards used significantly less broad-spectrum cephalosporins and more penicillins, quinolones and aminoglycosides (Table 4).

Accordingly, the use of TREAT resulted in significantly lower antibiotic costs in intervention versus control wards, the difference originating from lower ecological costs in intervention wards in Israel and Italy. Direct antibiotic costs, as well as costs incurred by observed adverse events, were similar (Table 5).

Duration of hospitalization shortened significantly in intervention wards in Israel and Germany, both among all patients and among those surviving 30 days. The crude costs of one hospital day, the average reduction in length of stay in intervention wards, varied between 350 and 467 Euros at the three sites. Mean fever duration was shorter in intervention wards.

No significant difference in 30 day overall mortality was observed overall and within each site, for all patients, those with infectious diagnoses and among patients with MDI (Table 5 and Appendix 5).

TREAT performance. The appropriateness of TREAT advice did not decline in the intervention period. TREAT's single top-rank antibiotic advice was appropriate in 76% (414/548) of patients: 75% (305/405) of patients in Israel, 86% (63/73) in Germany and 65% (46/70) in Italy. Total projected costs for these TREAT regimens were lower than physician's treatment by 262 Euros per patient, a relative decrease of 44%, with the reduction originating mainly from lower ecological costs.

Discussion

The TREAT DSS advises antibiotic therapy for inpatients using data available at the time of empirical antibiotic treatment. We firstly conducted a cohort study showing that TREAT's advice surpassed physicians' performance. TREAT prescribed appropriate antibiotic treatment to 70% of patients, compared with 57% treated appropriately by physicians. TREAT used a narrower antibiotic formulary and at lower costs, mainly lowering costs assigned by the model to future resistance. The system performed well in three different countries.

We then proceeded to an interventional cluster randomized trial at the three locations. This is the first multicentre trial of an antibiotic DSS. The trial included 2326 patients. Intervention wards using TREAT achieved a higher rate of appropriate empirical antibiotic treatment while reducing overall antibiotic costs. The mean length of stay was shortened by about 1 day.

A major achievement attained was a reduction in ecological antibiotic costs among all patients in intervention wards (–12%, $P = 0.002$). These are costs assigned by TREAT's calibration

Table 2. Patient characteristics

	Israel		Germany		Italy	
	control	intervention	control	intervention	control	intervention
Number of wards	3	3	3	3	1	2
Number of patients	823	860	172	208	86	177
Age, mean (range)	68 (18–104)	68 (18–104)	66 (20–92)	64 (18–93)	50 (22–83)	48 (17–91)
Sex (female)	49%	49%	49%	49%	42%	46%
HIV-positive	1 (0.1)	0	0	0	15 (17.4)	25 (14.1)
Place of acquisition						
community	701 (85)	730 (85)	113 (67)	158 (76)	74 (86)	155 (88)
nursing home	31 (4)	48 (6)	1 (1)	2 (1)	0	1 (1)
medical/surgical	90 (11)	80 (9)	51 (30)	35 (17)	9 (10)	16 (9)
intensive care unit	0	1	7 (4)	13 (6)	0	0
unknown	1	1	0	0	3 (4)	5 (3)
Major final diagnoses at discharge						
urinary tract infection	137 (16.6)	158 (18.4)	30 (17.4)	26 (12.5)	11 (12.8)	13 (7.3)
pneumonia	192 (23.3)	158 (18.4)	67 (39.0)	85 (40.9)	35 (40.7)	74 (41.8)
skin/soft tissues	94 (11.4)	90 (10.5)	6 (3.5)	6 (2.9)	5 (5.8)	11 (6.2)
abdominal	23 (2.8)	27 (3.1)	22 (12.8)	31 (14.9)	2 (2.3)	0
other infections	281 (34.1)	307 (35.7)	42 (24.4)	55 (26.4)	26 (30.2)	60 (33.9)
non-infectious	96 (11.7)	120 (14.0)	5 (2.9)	5 (2.4)	7 (8.1)	19 (10.7)
Microbiologically documented infections						
total	206 (25)	203 (23.6)	43 (25)	44 (21.2)	24 (27.9)	50 (28.3)
bacteraemia	75 (9.1)	104 (12.1)	19 (11.0)	22 (10.6)	1 (1.2)	12 (6.8)
local isolates	131 (15.9)	99 (11.5)	24 (14.0)	22 (10.6)	23 (26.7)	38 (21.5)
Microbiology (% of total patients with documented infections)						
Escherichia coli	76 (28)	92 (34)	14 (27)	13 (21)	10 (37)	14 (21)
Klebsiella spp.	39 (14)	23 (8)	5 (10)	7 (11)	0	1 (2)
Proteus spp.	20 (7)	25 (9)	4 (8)	2 (3)	0	1 (1)
Pseudomonas spp.	27 (10)	14 (5)	3 (6)	1 (2)	0	2 (3)
Salmonella spp.	2 (1)	3 (1)	0	0	2 (7)	1 (1)
Acinetobacter spp.	11 (4)	11 (4)	0	2 (3)	1 (4)	0
Staphylococcus aureus	21 (8)	25 (9)	5 (10)	6 (10)	0	14 (19)
coagulase-negative staphylococci	2 (1)	11 (4)	0	0	1 (4)	1 (1)
Streptococcus pneumoniae	7 (3)	4 (1)	0	3 (5)	1 (4)	4 (5)
other streptococci	21 (8)	16 (6)	3 (6)	6 (10)	1 (4)	1 (2)
Enterococcus spp.	20 (7)	26 (9)	7 (13)	10 (16)	1 (4)	2 (3)
others	27 (10)	23 (8)	11 (21)	11 (18)	10 (37)	28 (41)

Patient numbers with percentages in parentheses.

Table 3. Primary outcome, appropriate antibiotic treatment

	Control	Intervention intention to treat	OR (95% CI), *P* value[a]	Intervention per protocol	OR (95% CI), *P* value[a]
Israel, *n*/*N* (%)	131/206 (63.6)	140/203 (69.0)	1.27 (0.84–1.92), 0.251	74/87 (85.1)	3.26 (1.69–6.27), <0.001
Germany	32/43 (74.4)	38/44 (86.4)	2.18 (0.72–6.54), 0.160	18/19 (94.7)	6.19 (0.74–51.91), 0.062
Italy	13/4 (54.2)	38/50 (76.0)	2.68 (0.95–7.52), 0.057	22/28 (78.6)	3.10 (0.93–10.39), 0.061
Overall	176/273 (64.5)	216/297 (72.7)	1.48 (1.03–2.11), 0.033[b]	114/134 (85.1)	3.42 (1.97–5.96), 0.001[b]
			1.48 (0.95–2.29), 0.082[c]		3.40 (1.96–5.90), 0.001[c]

[a]Intervention versus control, Pearson's χ^2 test for the comparison within each site.
[b]Mantel–Haenszel odds ratio stratified by location and Cochran's significance for the overall analysis.
[c]Generalized estimating equations, family: logistic, correlation structure: exchangeable, accounting for clustering by ward and adjusting for location. Intention to treat analysis: Italy versus Israel OR: 1.05, 95% CI: 0.59–1.75; Germany versus Israel OR: 2.11, 95% CI: 1.14–3.94. Wald χ^2 for the significance of the model: 8.51, $P = 0.037$. Per protocol analysis: Italy versus Israel OR: 0.65, 95% CI: 0.33–1.28; Germany versus Israel OR: 1.81, 95% CI: 0.91–3.62.

Table 4. Empirical antibiotics prescribed by physicians in control versus intervention wards for all 2326 patients

	Control	Intervention
No antibiotic treatment		
Israel	172 (21)	173 (20)
Germany	3 (2)	4 (2)
Italy	8 (9)	28 (16)
Narrow-spectrum penicillins[a]		
Israel	85 (10)	92 (11)
Germany	26 (15)	36 (17)
Italy	8 (9)	44 (25)
Piperacillin/tazobactam or sulbactam		
Israel	17 (2)	26 (3)
Germany	13 (8)	14 (7)
Italy	3 (3)	11 (6)
First-generation cephalosporin		
Israel	11 (1)	29 (3)
Germany	0	0
Italy	0	0
Broad-spectrum cephalosporins[b]		
Israel	405 (49)	333 (39)
Germany	84 (49)	108 (52)
Italy	37 (43)	32 (18)
Fluoroquinolones		
Israel	98 (12)	144 (17)
Germany	29 (17)	29 (14)
Italy	28 (32)	68 (38)
Aminoglycosides		
Israel	15 (2)	33 (4)
Germany	8 (5)	6 (3)
Italy	1 (1)	3 (2)
Glycopeptides		
Israel	21 (3)	26 (3)
Germany	8 (5)	9 (4)
Italy	6 (7)	5 (3)
Carbapenems		
Israel	3 (0.4)	5 (0.6)
Germany	6 (3)	9 (4)
Italy	3 (3)	6 (3)

Patient numbers with percentages in parentheses.
[a]Penicillin, ampicillin, amoxicillin/clavulanate, ampicillin/sulbactam, penicillinase-resistant penicillins.
[b]Second- to fourth-generation cephalosporins.

database to the personal and environmental effect of antibiotic use on future resistance. We have shown that ecological costs can be part of an antibiotic DSS and that such a system can improve physician's performance by the standards incorporated in it.

DSS to diagnose or treat infections have previously shown merit, somewhat singularly among DSS in medicine.[24] 'MYCIN', a rule-based expert system for treating bloodstream infections was evaluated against clinicians using infectious diseases experts as reference.[25] The system outperformed clinicians from students to senior physicians. We have previously developed a DSS for antibiotic treatment using local microbiological data and relying on clinician's opinion for the site of infection.[26] The DSS was tested against clinical isolates showing significant improvement

Table 5. Costs of antibiotic treatment prescribed by physicians and secondary outcomes for all 2326 patients

	Control	Intervention	*P* value
Direct costs in Euros, mean (SD) per patient[a]			
Israel	25.5 (30.9)	25.2 (33.2)	0.079
Germany	73.5 (85.4)	68.9 (75.6)	0.674
Italy	84.9 (83.9)	79.1 (87.7)	0.302
Overall	37.9 (54.2)	40.2 (57.6)	0.473
Observed side effects costs in Euros, mean (SD) per patient[a]			
Israel	88.5 (1046.9)	98.3 (1048.6)	0.163
Germany	189.8 (1765.5)	129.2 (1294.4)	0.526
Italy	24.4 (159.2)	74.6 (992.2)	0.819
Overall	99.5 (1154.0)	100.1 (1085.1)	0.960
Ecological costs in Euros, mean (SD) per patient[a]			
Israel	511.7 (439.9)	445.9 (404.7)	<0.001
Germany	503.8 (336.7)	517.8 (374.6)	0.870
Italy	372.2 (248.3)	317.2 (282.2)	0.030
Overall	499.3 (414.1)	439.5 (388.4)	0.002
Total antibiotic costs in Euros, mean (SD) per patient[a]			
Israel	612.5 (507.7)	546.0 (476.7)	0.001
Germany	716.1 (522.1)	712.1 (532.6)	0.960
Italy	540.0 (371.5)	487.5 (419.5)	0.135
Overall	623.2 (502.2)	565.4 (483.4)	0.007
Duration of hospital stay, median/mean (SD)[a,b]			
Israel	5/8.04 (11.1)	4/7.21 (9.7)	0.014
Germany	14/16.3 (12.0)	10/13.6 (11.2)	0.016
Italy	7/11.3 (10.7)	8/12.13 (15.7)	0.600
Overall	6/9.45 (11.52)	6/8.83 (11.29)	0.055
Duration of hospital stay among patients surviving 30 days (N = 1837)			
Israel	5/7.9 (11.6)	4/7.1 (10.2)	0.032
Germany	16/19.9 (13.8)	11/16.4 (13.2)	0.040
Italy	7/11.4 (10.7)	8/12.2 (15.9)	0.586
Overall	5/9.4 (12.2)	5/8.8 (11.9)	0.128
Duration of fever, median/mean (SD)[a,c]			
Israel	1/2.5 (4.7)	1/2.2 (4.1)	0.014
Germany	1/2.1 (3.0)	1/1.9 (2.7)	0.487
Italy	3/3.8 (4.3)	3/4.0 (3.4)	0.024
Overall	1/2.5 (4.5)	1/2.4 (3.9)	0.253
Overall 30 day mortality intention to treat, n/N (%)[d]			
Israel	128/823 (15.6)	113/860 (13.1)	0.158
Germany	16/172 (9.3)	26/208 (12.5)	0.322
Italy	1/86 (1.2)	10/177 (5.6)	0.109
Overall	145/1012 (14.3)	149/1153 (12.9)	0.611
Overall 30 day mortality per protocol, n/N (%)[d]			
Israel	38/301 (12.6)	35/344 (10.2)	0.327
Germany	6/53 (11.3)	9/69 (13.0)	0.774
Italy	0/42 (0)	5/120 (4.2)	0.328
Overall	44/371 (11.9)	49/503 (9.7)	0.719

[a]Mann–Whitney U-test for the comparison within each site; general linear models adjusted for location for the overall analysis.
[b]Data unavailable for 30/1683 (2%) of patients in Israel and 75/380 patients in Germany (20%). All patients included in Italy.
[c]Data unavailable for 133/1683 (8%) of patients in Israel; 76/380 patients in Germany (20%); 36/263 (14%) in Italy.
[d]χ^2 test for the comparison within each site. Mantel–Haenszel ORs and significance adjusted for location for the overall analysis. Intention to treat OR of 0.93 (95% CI: 0.73–1.19) including all 2326 patients. Per protocol OR of 0.90 (95% CI: 0.58–1.39) including all patients who received one of the antibiotics advised by the three top-ranking treatments suggested by TREAT.

compared with clinicians both with regard to better appropriate and less superfluous antibiotic treatment. A DSS developed and tested at 'LDS hospital' in USA uses patient's diagnosis merged with data available from the hospital's information systems, including microbiological data or patient-matched local microbiological data from the preceding 5 years.[27,28] The system suggests antibiotic therapy and provides information on infections, therapy, dosing adjustment, drug–drug interactions and direct costs. The DSS was shown to outperform clinicians with regard to appropriate treatment, improve clinicians' empirical antibiotic selections and dosing and decrease adverse events rates, and was liked by its users. The system suggested appropriate antibiotic treatment for 94% of isolates, but used superfluous broad-spectrum antibiotics.

In TREAT we aimed to overcome the difficulties experienced with previous systems. The need for temporal and local calibration was addressed by differentiating between universal and local factors (e.g. sensitivity and specificity of diagnostic tests versus distribution of pathogens and susceptibilities). The system assigns explicit costs to antibiotic resistance. These can be calibrated, assigning higher costs to ecologically 'expensive' antibiotics as viewed locally to curb their use. Overall antibiotic costs are balanced against the benefit of appropriate antibiotic treatment. This balance may be calibrated, as well, to match local requirements from the system. Finally, we believe that the CPN core of TREAT is best suited to tackle complex situations such as those involved in the diagnosis of infections. The system was calibrated to three different sites and formally tested in a randomized controlled trial in three countries.

While an advantage to intervention wards was observed, TREAT did not fulfil its full potential in the interventional trial. The first treatment suggested by TREAT was appropriate significantly more often than the treatment actually prescribed to patients by physicians in intervention wards. When the system's recommendations were followed (per-protocol analysis), results were highly significant with an adjusted OR of 3.4 for appropriate antibiotic treatment. Results for the intention to treat population were thus affected by incomplete acceptance of the system's recommendations.

We used a cluster randomization design mainly because the system is highly educative.[29] The result interface provides the clinician with data regarding local pathogen distribution and antibiotic susceptibilities, as well as treatment advice. Randomization of patients would have resulted in contamination through physicians treating patients in both study groups. We believe that contamination was minimized by our design. Cluster randomization results in reduced statistical efficiency,[30] as shown by the larger CIs when our analysis was adjusted for clustering. We cannot rule out the possibility that we measured inherent differences between wards rather than changes introduced by the system. However, this is highly unlikely in light of lack of pre-trial differences in appropriate antibiotic treatment and patterns of antibiotic use. During the cohort study, no significant differences between participating wards in antibiotic use or appropriateness of empirical treatment were evident. During the trial, the antibiotic use patterns in intervention wards changed, reflecting advice generated by TREAT, and a difference in appropriateness of the empirical treatment emerged. The intervention continued for 7 months and we cannot be sure how the use of the system would fare over a longer period. The short duration did not permit us to calibrate the system after installation. Although TREAT has explicit mechanisms to calibrate for secular changes, they were not tested in this trial.

Future efforts should be invested in integrating TREAT into an electronic patient file with a drug module. Input data from electronic sources can serve as a trigger alerting physicians to incorrect decisions or for the need to activate the system, thereby circumventing the major difficulty encountered thus far with TREAT—physician's compliance. In the trial we were careful to point out that the final decision is in the hands of the physician. In practice, more efforts can be directed in convincing physicians to adopt TREAT's recommendations. Its actual effects on resistance development must be assessed in studies of longer duration, within the timeframe of antibiotic-resistance development.

In summary, TREAT improved the rate of appropriate empirical antibiotic treatment in intervention wards while reducing hospital stay and antibiotic costs, mainly the costs assigned by the model to future resistance. The increase in appropriate antibiotic treatment was highly significant when the system's recommendations were followed. The system can be calibrated to different locations. It can serve as one of the solutions for the antibiotic crisis we are facing.

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L. L. and S. A. conceived the project and basic concepts. M. P., L. L., Brian Kristensen, Elad Goldberg, A. D. N., Alina Zalounina and S. A. built the model. Leif E. Kristensen, Karsten Falborg, Alina Zalounina and A. D. N. built the interface, database and

supporting software. L. L., U. F., E. T., M. P., N. A., S. A. and R. C. planned the clinical study. M. P., N. A., E. T., Adriana Cataldo, Liat Vidal, Monika Strehlein, Michal Cohen, Elisheva Pokroy, Rita Citton, Anat Gafter-Gvili, Dafna Yahav, Erez Skapa and Sara Borok collected data. M. P., A. D. N., E. T., N. A., U. F., Abigail Fraser and L. L. did data analysis. M. P., S. A., E. T., A. D. N., N. A., U. F., R. C. and L. L. wrote the article. M. P. and L. L. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Transparency declarations

Should TREAT be developed into a commercial system, all participating organizations might profit from it.

Supplementary data

Appendices 1–5 are available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

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