Clinical Microbiology and Infection xxx (2017) 1.e1–1.e8

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

Effect of an antibiotic checklist on length of hospital stay and appropriate antibiotic use in adult patients treated with intravenous antibiotics: a stepped wedge cluster randomized trial

F.V. van Daalen [1,*], J.M. Prins [1], B.C. Opmeer [2], M.A. Boermeester [3], C.E. Visser [4], R.M. van Hest [5], J. Branger [6], E. Mattsson [7], M.F.M. van de Broek [8], T.C. Roeleveld [9], A.A. Karimbeg [10], E.A.F. Haak [11], H.C. van den Hout [12], M.A. van Agtmael [13], M.E.J.L. Hulscher [14], S.E. Geerlings [1]

[1] Department of Internal Medicine, Division of Infectious Diseases, Centre for Infection and Immunity Amsterdam, The Netherlands
[2] Clinical Research Unit, Academic Medical Centre, Amsterdam, The Netherlands
[3] Department of Surgery, Academic Medical Centre, Amsterdam, The Netherlands
[4] Department of Microbiology, Academic Medical Centre, Amsterdam, The Netherlands
[5] Department of Pharmacy, Academic Medical Centre, Amsterdam, The Netherlands
[6] Department of Internal Medicine, Flevoziekenhuis, Almere, The Netherlands
[7] Department of Medical Microbiology, Reinier de Graaf, Delft, The Netherlands
[8] Department of Internal Medicine, Antoniusziekenhuis, Nieuwegein, The Netherlands
[9] Department of Internal Medicine, Spaarnegasthuis, Hoofddorp, The Netherlands
[10] Department of Internal Medicine, Westfriesgasthuis, Hoorn, The Netherlands
[11] Department of Hospital Pharmacy, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands
[12] Department of Internal Medicine, Spaarnegasthuis, Haarlem, The Netherlands
[13] Department of Internal Medicine, Division of Infectious Diseases, VU Medical Centre, Amsterdam, The Netherlands
[14] Department of Scientific Institute for Quality of Healthcare (IQ healthcare), Radboud University Medical Centre, Nijmegen, The Netherlands

ARTICLE INFO

Article history:
Received 23 November 2016
Received in revised form
24 January 2017
Accepted 25 January 2017
Available online xxx

Editor: C. Pulcini

Keywords:
Antibiotic checklist
Antibiotic stewardship
Appropriate antibiotic use
Cluster randomized trial
Quality improvement
Quality indicators

ABSTRACT

Objectives: Quality indicators (QIs) have been developed to define appropriate antibiotic use in hospitalized patients. We evaluated whether a checklist based on these QIs affects appropriate antibiotic use and length of hospital stay.

Methods: An antibiotic checklist for patients treated with intravenous antibiotics was introduced in nine Dutch hospitals in a stepped wedge cluster randomized trial. Prophylaxis was excluded. We included a random sample before (baseline), and all eligible patients after (intervention) checklist introduction. Baseline and intervention outcomes were compared. Primary endpoint was length of stay (LOS), analysed by intention to treat. Secondary endpoints, including QI performances, QI sum score (performance on all QIs per patient), and quality of checklist use, were analysed per protocol.

Results: Between 1 November 2014 and 1 October 2015 we included 853 baseline and 5354 intervention patients, of whom 993 (19%) had a completed checklist. The LOS did not change (baseline geometric mean 10.0 days (95% CI 8.6–11.5) versus intervention 10.1 days (95% CI 8.9–11.5), p 0.8). QI performances increased between +3.0% and +23.9% per QI, and the percentage of patients with a QI sum score above 50% increased significantly (OR 2.4 (95% CI 2.0–3.0), $p < 0.001$). Higher QI sum scores were significantly associated with shorter LOS. Discordance existed between checklist-answers and actual performance.

Conclusions: Use of an antibiotic checklist resulted in a significant increase in appropriateness of antibiotic use, but not in a reduction of LOS. Low overall checklist completion rates and discordance between checklist-answers and actual provided care might have attenuated the impact of the checklist. **F.V. van Daalen, Clin Microbiol Infect 2017;■:1**

© 2017 European Society of Clinical Microbiology and Infectious Diseases. Published by Elsevier Ltd. All rights reserved.

* Corresponding author. F.V. van Daalen, Department of Internal Medicine, Division of Infectious Diseases, Academic Medical Centre, University of Amsterdam, Room F4-132, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.
E-mail address: f.v.vandaalen@amc.nl.

http://dx.doi.org/10.1016/j.cmi.2017.01.019
1198-743X/© 2017 European Society of Clinical Microbiology and Infectious Diseases. Published by Elsevier Ltd. All rights reserved.

Download van SWAB.nl | 2026-02-06 00:27

ARTICLE IN PRESS

Introduction

Better use of antibiotic agents is necessary to control antimicrobial resistance (AMR) [1,2]. There is considerable room for improvement in antibiotic use, as 30-50% of antibiotic prescriptions in hospitals are indicated to be unnecessary or inappropriate [3]. Appropriate antibiotic use has been associated with better outcomes at the patient level, such as a decreased length of hospital stay [4–8] which is an important outcome measure to reflect recovery time of patients and to define hospital costs [8].

Antibiotic Stewardship Programs (ASP) have been introduced in hospitals to measure and improve appropriate use of antibiotics [9]. Most ASP interventions are performed during antibiotic treatment, with few focusing on prescribers at the moment of antibiotic prescribing [4,9,10]. An antibiotic checklist could be functional to embed appropriate antibiotic use in daily practice, as checklists have been shown to be useful tools for improving health care in different settings [11,12].

In previous studies we developed generic quality indicators (QI) to define and measure appropriate antibiotic treatment in adult patients with a suspected bacterial infection [13,14]. Treatment according to these QIs was associated with a shorter length of hospital stay [8]. Based on these QIs we developed an antibiotic checklist [15]. Our aim was to analyse the effect of the introduction of this antibiotic checklist on outcomes at the patient level, including length of hospital stay, admission to ICU, and mortality, and on appropriate antibiotic treatment defined by the generic QIs.

Methods

Study design and participants

We evaluated the introduction of the antibiotic checklist in a multicentre stepped wedge cluster randomized trial, comparing outcomes before and after its introduction. The full study protocol is reported elsewhere [16]. Fig. 1 presents the study design in detail. The stepped wedge design was considered to be the most suitable because of the cross-sectional control between, and the longitudinal control within, hospitals, and because in the end all hospitals used the checklist, which was favourable as the checklist was unlikely to cause harm [8,17,18]. Clusters were defined by hospitals. Hospitals were eligible if they were willing to be randomly assigned to a time point of checklist introduction, and if at least one surgical, one non-surgical, and the emergency department (ED) were willing to participate. The ICU and the paediatric department were excluded, as the QIs do not apply to these populations. Twelve hospitals were approached by the researchers (SG, FVD) to take part in the study. Two university hospitals and seven teaching hospitals agreed to participate. The size of the hospitals ranged between 347 and 1000 beds. Since 1 January 2014, an antibiotic stewardship team is mandatory in each hospital in The Netherlands. In all nine hospitals such a team was present at the start of our study.

Eligible patients were hospitalized adults (≥18 years old), or adults at the ED who were admitted to a participating ward, with a suspected bacterial infection, who were to be treated with intravenous (IV) antibiotics. We excluded patients with orally initiated antibiotic therapy, as we aimed to test the intervention in patients in whom all checklist-items could be checked. The item IV-oral switch is not possible in patients starting with oral antibiotics. Patients were excluded in cases of a hospital stay of less than 24 hours, antibiotics used as prophylaxis or treatment less than 24 hours, transfer from another hospital, or inclusion in another study on antibiotic use.

The Medical Ethics Research Committee of the Academic Medical Centre confirmed that the Medical Research Involving Human Subjects Act did not apply to this study. As the study involved a quality improvement intervention introduced at the hospital level with negligible risk of harming patients, individual informed consent was waived for all participating hospitals. Each hospital's board of directors approved the study protocol. This trial was registered with the Dutch Trial Registry, number NTR4872.

Randomization and masking

Participating hospitals were randomly allocated to four sequential time points by an independent data manager using ALEA software version release 4.0 for randomization in clinical trials. Masking of physicians and researchers was not possible. Patients were unaware of the study.

Procedures

Baseline measurement (baseline group). Eligible patients admitted between 1 November 2014 and 1 month before introduction of the checklist at that hospital were considered as baseline patients. For each hospital we determined a minimum number of patients that should be included, based on the power calculation and the randomization order of the hospital in the stepped wedge trial.

To identify eligible patients, in each hospital a list was generated by the local hospital pharmacy from the computerized medication ordering system of all patients treated with IV antibiotics. This list was structured by date, and we included every second or every third eligible patient—depending on the number of patients required for inclusion relative to the number of patients on the list.

Introduction of the antibiotic checklist. The antibiotic checklist is based on generic QIs that define appropriate antibiotic use in the treatment of bacterial infections in the hospital [13,14]. We determined the barriers towards the uptake of this checklist among physicians and used their comments to adapt it [15]. The antibiotic checklist is divided into two bundles (Fig. S1, supporting information). The first bundle (five items) has to be completed at the moment of prescribing IV antibiotics. The second bundle (two items) has to be completed during the course of treatment, at the latest after 72 hours of treatment.

During the transition period, which took place 1 month preceding the start of checklist use in each hospital, introduction of the antibiotic checklist was prepared and no data were collected. The checklists were displayed in printed form at all working places at the participating departments. Other interventions were organized to stimulate use of the checklist, such as education, feedback on current antibiotic use showing baseline data from the department's own hospital, and reminders (Table S1, supporting information) [15]. The education material was sent by email to all participating physicians at the start of the intervention period. These interventions were organized by a project team consisting of the study coordinator (FVD) and at least two physicians per hospital.

Physicians were asked to complete checklists for all eligible patients during the intervention period. If the first bundle was completed at the ED, the checklist was to be taken to the ward with the patient. It was the physicians' responsibility to use the checklist each time an antibiotic was started. The project team visited the participating departments weekly to supply the checklists and to remind the physicians to use the checklist. In one university hospital the start of the intervention coincided with the rotation of residents, and an extra presentation was given on their first working day. In other hospitals these rotations occurred during the intervention period and new residents were informed by email and during the weekly visits of the project team.

Please cite this article in press as: van Daalen FV, et al., Effect of an antibiotic checklist on length of hospital stay and appropriate antibiotic use in

Download van SWAB.nl | 2026-02-06 00:27

Post introduction measurement (intervention group). Eligible patients admitted after introduction of the checklist and before 1 October 2015 were considered as the intervention group. Likewise, we used the list of all patients with prescribed IV antibiotics per hospital, but for the intervention group we included all eligible patients. In this way we were able to perform both an intention-to-treat analysis (including the complete intervention group) and a per-protocol analysis (including only those patients in the intervention group with a completed checklist), as illustrated in Fig. 2. If eligible patients were hospitalized more than once during the intervention period, we included all admissions.

Data collection

Case notes and electronic medical records were reviewed to collect the data, which were entered into a certified online data entry system (OpenClinica). Two researchers collected the data in all hospitals, using a logbook that was developed before start of data collection. We distinguished the following four patient groups:

- Baseline group (1)
- Intervention group, consisting of:
  - Eligible patients with a completed checklist; (2)
  - Eligible patients with a partially completed checklist; (3)
  - Eligible patients without a checklist. (4)

For all patients, we recorded length of stay and patient characteristics, including age, sex, Charlson comorbidity index [19], clinical condition as assessed by the Modified Early Warning System [20], current use of anti-cancer chemotherapy, use of antibiotics during the previous 30 days, type of diagnosis, community- or hospital-acquired infection, ward of admission, and location of start

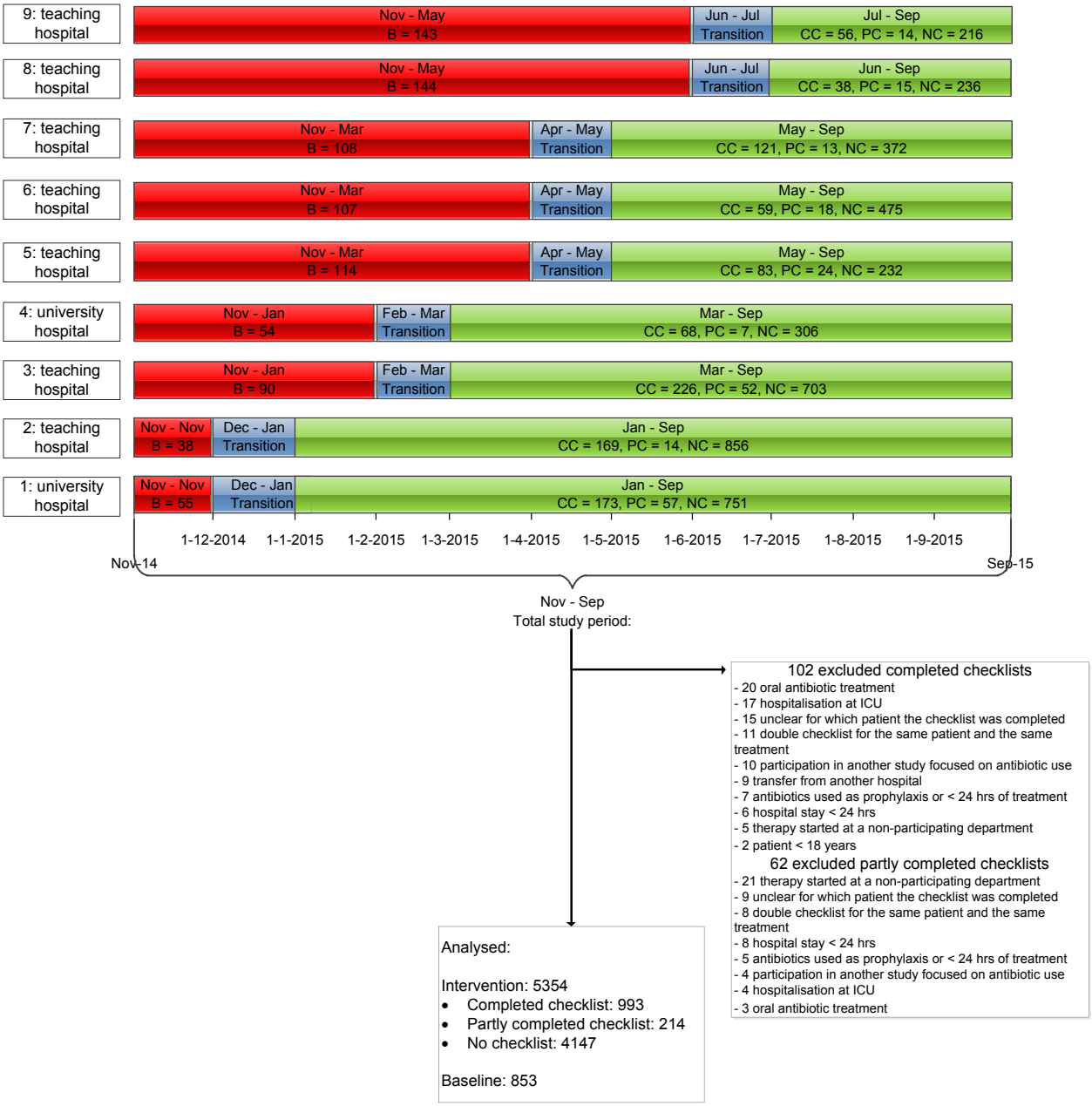

Fig. 1. Study design and trial profile. Red colour indicates baseline period, green colour indicates intervention period. B = number of baseline patients, CC = number of patients with completed checklist, PC = number of patients with partially completed checklist, NC = number of patients without a checklist.

Download van SWAB.nl | 2026-02-06 00:27

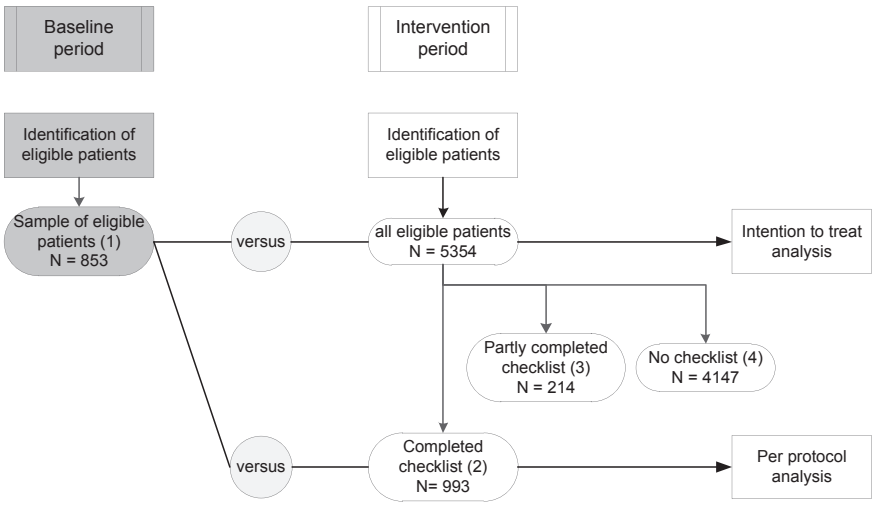

Fig. 2. Procedure of patient inclusion and length of stay analysis. 1 = Baseline group, 2 = Eligible patients with a completed checklist in the intervention group, 3 = Eligible patients with a partially completed checklist in the intervention group, 4 = Eligible patients without a checklist in the intervention group.

of antibiotic treatment (ED or ward), as these characteristics were suggested to be potential confounders for length of stay in our previous studies [7,8].

Data concerning secondary outcomes, including data to calculate QI performance [16], total antibiotic use (both IV and oral treatment), admission and duration of ICU stay, mortality, and readmission, were only collected for all baseline patients (1) and for patients with a (partially) completed checklist (2 and 3). For patient groups 2 and 3 we documented the answers to all items on the checklists.

Outcomes

Primary endpoint was length of hospital stay (LOS) per patient in days. LOS in community-acquired infections was defined as the number of days between admission and discharge. In hospital-acquired infections, LOS was defined as the number of days between start of antibiotic treatment and discharge.

Secondary endpoints were appropriate antibiotic treatment according to the generic QIs, defined by a score per QI (yes/no per QI) and a sum score of all QIs per patient [7,8], and total antibiotic use defined by days of therapy (DOT) per single antibiotic agent. Other secondary endpoints at patient level were ICU admission, duration of ICU stay in days, in-hospital mortality, mortality in the first 30 days after discharge, and readmission within 30 days with an infection.

To investigate the quality of checklist use, secondary endpoints at implementation level were the completion rate of checklists [21,22] and discordance between 'YES'-answers on the checklist indicating appropriate care and actual provided care, as ticking the 'YES'-box might not always mean actual performance of that checklist-item [23].

Statistical analysis

To adjust for the time steps of the stepped wedge and for clustering in the data, we used mixed models to compare the primary outcome, LOS, before and after introduction of the checklist. The core model included the clusters (hospitals) as a random effect and the time in months as a fixed effect. To adjust the estimated (difference in) LOS for other factors associated with LOS, for each analysis several covariates were considered and selected as follows: the core model was extended with each single covariate. Covariates with a significant univariate effect ($p < 0.1$) on the outcomes were included in the multivariate model. Thereafter we excluded covariates without an effect ($p > 0.1$) in the multivariate model (backward selection). Tested covariates included the potential confounders mentioned in the 'data collection' section. We also explored whether clinically relevant subgroups of patients were associated with a longer or shorter LOS and, if so, interaction variables were included in the model to account for these differences. We used the Akaike's Information Criterion as a parameter for the goodness-of-fit for the model. According to the intention-to-treat principle, we compared the geometric mean of LOS of the baseline group (1) with the geometric mean of the total intervention group (2, 3, and 4). In addition, the baseline group (1) was compared with the intervention group with a completed checklist (2), reflecting a per protocol approach (Fig. 2).

For secondary outcomes we evaluated differences between the baseline group (1) and the checklist groups (2 and 3). QI performance was calculated for each patient by algorithms [14]. We used mixed models to compare the proportions of appropriate antibiotic treatment according to the generic QIs. The patient's QI sum score was calculated by the performance on all QIs for a patient according to the information from the electronic medical records, divided by the number of QIs that applied to that specific patient. In a mixed model analysis we compared the percentage of patients with a QI sum score >50% in the baseline and the checklist group [8]. Furthermore, we determined whether the association between a higher QI sum score and a reduced length of stay—as described previously [8]—also existed in our baseline and checklist patients with a mixed model analysis.

Mixed models were also used to compare the DOTs per 100 patient-days and per 100 admissions. For outcomes with a relatively low incidence that varies between hospitals (including ICU admission, duration of ICU stay, in-hospital mortality, mortality in the first 30 days after discharge, and readmission within 30 days), we could not use mixed model analyses, as groups have been compared and adjusted for hospitals. Therefore descriptive statistics assessed those secondary outcomes.

To evaluate the quality of checklist use we also used descriptive measures. The completion rate was expressed as the percentage of eligible patients for whom the checklist was fully completed. Discordance between 'YES'-answers indicating appropriate care

Download van SWAB.nl | 2026-02-06 00:27

and actual provided care was expressed by the percentage of 'YES'-answers on the checklists that could not be confirmed by information from the electronic medical records.

Sample size

Previous studies showed that appropriate antibiotic use reduces LOS by approximately 10-15% [7,8]. We performed extensive simulation analyses, where hypothetical data were generated according to the stepped wedge design, by varying macro parameters for baseline values and before/after differences for LOS, intra-class correlation coefficients, number of clusters, and number of patients per cluster. Each simulated dataset was analysed with a mixed effects model. We estimated that 1620 patients would be needed to show a 13% reduction in LOS, assuming a type I error of 0.05, a type II error of 0.2, and an intra-cluster correlation coefficient of 0.2. To identify a significant difference in LOS in the per protocol analysis (Fig. 2), a minimum of 810 patients was required in both the baseline group and the complete checklist group.

For the power analysis we used SAS version 9.3. All other analyses were done using IBM SPSS Statistics, version 23.0.

Results

Between 1 November 2014 and 1 June 2015, 853 patients were included in the baseline group. Between 1 January and 1 October 2015, 5354 patients were enrolled in the intervention group: 19% had a completed checklist, 4% had a partially completed checklist, and 77% had no checklist (Fig. 1). Baseline, transition, and intervention periods took place as planned in all hospitals (Fig. 1). Patient characteristics are listed in Table 1.

In an intention-to-treat analysis 853 baseline patients were compared with 5354 intervention patients. Three subgroups of patients with a completed checklist were associated with a longer LOS: patients admitted to a university hospital, those hospitalized at a surgical ward, and those currently treated with anti-cancer chemotherapy (Table S2, supporting information). Independently, these three factors did not affect LOS, but as an interaction variable with a completed checklist, they all had a significant effect on LOS (Table S3, supporting information). The geometric mean of LOS was 10.0 days in the baseline group (95% CI 8.6–11.5) versus 10.1 days in the total intervention group (95% CI 8.9–11.5) (p 0.8), while adjusting for age, comorbidity, type of diagnosis, community- or hospital-acquired infection, antibiotics started at ED or ward, and the interaction variables.

In a per-protocol analysis we compared LOS of 853 baseline patients and 993 intervention patients with a completed checklist. Adjusted for the same covariates and interaction variables as in the intention-to-treat analysis, the geometric mean of LOS of the baseline group was 10.1 days (95% CI 8.5–12.0), which is similar to the LOS of the checklist group (10.4 days (95% CI 9.1–12.0), p 0.6).

For the secondary outcomes we compared the baseline group with the patients with a (partially) completed checklist ($n = 1207$). Scores per QI and QI sum scores were higher in the patients with a checklist compared with baseline (Table 2). The increase of QI performance varied between +3.0% and +23.9%, and this was significant for five of the seven QIs. The percentage of patients with a QI sum score above 50% was also significantly higher in the checklist group compared with the baseline group (OR 2.4 (95% CI 2.0–3.0), $p < 0.001$). In the baseline group and the patients with a (partially) completed checklist together ($n = 2060$), a higher QI sum score was significantly associated with a shorter length of hospital stay (Fig. 3).

DOTs, admission to- and LOS at the ICU, mortality, and readmission rates were similar across the study groups (Table 3).

For 23% of all eligible patients a checklist was used, of whom 19% had a fully, and 4% had a partially completed checklist. The percentage of patients with a (partially) completed checklist per hospital varied between 18.3% and 31.6%. The total number of checklist-items answered with 'YES' was 5020. In 32% the 'YES'-answer (1628/5020) was discordant with information on actual care provided from the electronic medical records.

Discussion

In the present study the use of an antibiotic checklist for in-hospital antibiotic treatment did not result in a shorter length of

Table 1
Patient characteristics

Characteristics	Baseline $N = 853$[a]	Intervention $N = 5354$[b]			
		Completed checklists $N = 993$	Partially completed checklist $N = 214$	No checklist $N = 4147$	Overall $N = 5354$
Sex, male	445 (52.2)[c]	557 (56.1)[c]	120 (56.1)[c]	2265 (54.6)[c]	2942 (54.9)[c]
Age, mean (SD)	69.1 (17)	66.9 (17)	66.4 (17)	66.0 (17)	66.2 (17)
Infection, community-acquired/ hospital-acquired	656 (76.9)/197 (23.1)	742 (74.8)/251 (25.2)	163 (76.2)/51 (23.8)	2890 (69.7)/1257 (30.3)	3795 (70.9)/1559 (29.1)
Type of diagnosis					
Respiratory tract infection	221 (25.9)	233 (23.5)	45 (21.0)	945 (22.8)	1223 (22.8)
Urinary tract infection	133 (15.6)	174 (17.5)	34 (15.9)	608 (14.7)	816 (15.2)
Skin and soft tissue infection	99 (11.6)	85 (8.6)	13 (6.1)	351 (8.5)	449 (8.4)
Intra-abdominal infection	95 (11.1)	80 (8.0)	26 (12.1)	629 (15.1)	735 (13.7)
Other infections	108 (12.7)	184 (18.5)	38 (17.8)	701 (16.9)	923 (17.2)
Two diagnoses	82 (9.6)	106 (10.7)	24 (11.2)	331 (8.0)	461 (8.6)
More than two possible diagnoses/ diagnosis not covered by guideline	115 (13.5)	131 (13.2)	34 (15.9)	582 (14.0)	747 (14.0)
Charlson comorbidity index, median (IQR)	1·0 (0-2)	1·0 (0-2)	2·0 (0-3)	1·0 (0-2)	1·0 (0-2)
Received antibiotics <30 days before start of treatment	306 (36.0)	424 (42.7)	79 (36.9)	1592 (38.4)	2095 (39.2)
Antibiotic started at the emergency department	369 (43.3)	525 (52.9)	125 (58.4)	1707 (41.2)	2357 (44.0)

[a] Missing data in ≤3 patients.
[b] Missing data in ≤6 patients.
[c] Numbers are *n* (%) unless otherwise indicated. Percentages were calculated with the denominator excluding missing cases.

Download van SWAB.nl | 2026-02-06 00:27

Table 2
Score per quality indicator (QI) and QI sum score

QI	Baseline $N = 853$	Checklist $N = 1207$	Comparison			
	Score %	Score %	Difference %	OR[a]	95% CI	p
1. Blood cultures	46.5	70.4	+ 23.9	3.2[b]	2.6 to 4.0	<0.001
2. Cultures of suspected site of infection	46.6	50.5	+ 3.9	1.2[c]	0.9 to 1.5	0.3
3. Guideline adherence	45.6	55.8	+ 10.2	1.5[d]	1.2 to 1.8	<0.001
4. Adjustment to renal function	34.0	44.6	+ 10.6	1.4[e]	0.8 to 2.3	0.2
5. Documented antibiotic plan	87.0	90.0	+ 3.0	1.6[f]	1.1 to 2.1	0.006
6. Adapt therapy when culture results become available	33.7	41.8	+ 8.1	1.5[g]	1.0 to 2.1	0.03
7. IV-oral switch	56.2	66.8	+ 10.6	1.5[h]	1.2 to 2.0	0.003
QI sum score >50%	48.8	67.5	+ 18.7	2.4[i]	2.0 to 3.0	<0.001

[a] Based on generalized linear mixed models, taking covariates into account.
[b] Adjusted for sex, Modified Early Warning Score, type of diagnosis, antibiotics started at emergency department vs. ward.
[c] Adjusted for type of diagnosis.
[d] Adjusted for antibiotic use in last 30 days, type of diagnosis, community- vs. hospital-acquired infection.
[e] Adjusted for sex.
[f] Adjusted for type of diagnosis, community- vs. hospital-acquired infection.
[g] Adjusted for community- vs. hospital-acquired infection.
[h] Adjusted for age, type of diagnosis, community- vs. hospital-acquired infection, antibiotics started at emergency department vs. ward.
[i] Adjusted for community- vs. hospital-acquired infection, antibiotics started at emergency department vs. ward.

stay (LOS). However, antibiotics were used more appropriately according to generic quality indicators (QIs) after introduction of the antibiotic checklist. In addition, a higher QI sum score was associated with a shorter LOS, which is in line with previous results [7,8]. Further analysis showed a first probable reason for these conflicting conclusions, as 32% of the checklist-answers indicating appropriate care were not in line with actual provided care. The checklists with discordant answers might have disrupted the impact of the checklist on LOS, as it is obviously not ticking the 'YES'-boxes that leads to reduction in length of stay, but performance according to the QIs.

Few other studies report exact numbers of discordance between indicated appropriate care and actual provided care [23]. The most successful checklist studies do not discuss discordance at all [11,12,24], but it has previously been suggested as an explanation for the absence of effects [25,26]. In 101 hospitals in Canada, for example, use of the WHO surgical safety checklist did not have the expected effect on comorbidity and mortality rates [25]. The most likely explanation was that the actions on the checklist were not actually performed [25,26]. While this explanation is only a suggestion in the Canadian study, we actually measured it in the current project.

A second explanation for the absence of effect on LOS in the group with a completed checklist might be indication bias, as the checklist seemed to be predominantly used in more complicated cases. The geometric mean of LOS in patients with a completed checklist and admitted to a university hospital, hospitalized at a surgical ward, or currently treated with anti-cancer chemotherapy, was more than 3 days longer than in patients without a checklist (Tables S2 and S3). We have statistically corrected for this and for

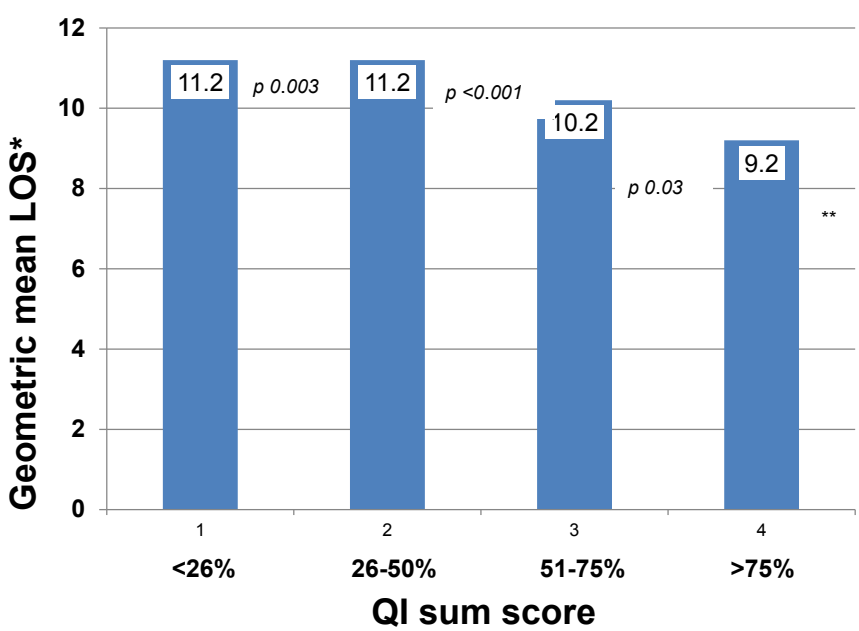

Fig. 3. Association between quality indicator sum score and length of stay. *Adjusted for age, comorbidity, type of diagnosis, community- vs. hospital-acquired infection, antibiotics started at emergency department vs. ward, and interaction variables checklist+anti-cancer chemotherapy, checklist+admission at a University Medical Centre, checklist+surgical ward. **The upper quartile is the reference quartile.

Download van SWAB.nl | 2026-02-06 00:27

ARTICLE IN PRESS

Table 3
Other secondary endpoints

Endpoints	Baseline $N = 853$[a]	Checklists $N = 1207$[b]
Days of therapy per 100 patient-days without adjustment for covariates	84	79
Days of therapy per 100 patient-days with adjustment for covariates[c]	99	98
Days of therapy per 100 admissions without adjustment for covariates	827	837
Days of therapy per 100 admissions with adjustment for covariates[d]	951	941
ICU admission	31 (3.6)	50 (4.1)
Geometric mean of LOS at ICU (95% CI)[e]	2.32 (1.5-3.5)	2.61 (1.8-3.8)
In-hospital mortality[e]	54 (6.3)	64 (5.3)
Mortality <30 days after discharge	33 (4.2[f])	39 (3.4[f])
Readmission <30 days after discharge	98 (12.3[f])	123 (10.8[f])

Numbers are *n* (%) unless otherwise indicated. Percentages were calculated with the denominator excluding missing cases.
[a] Missing data on IC admission in three patients, on mortality <30 days after discharge in 10 patients, and on readmission <30 days after discharge in three patients.
[b] Missing data on IC admission in two patients, on mortality <30 days after discharge in eight patients, and on readmission <30 days after discharge in six patients.
[c] Adjusted for comorbidity, type of diagnosis, community- vs. hospital-acquired infection, antibiotics started at emergency department vs. ward.
[d] Adjusted for sex, MEWS, type of diagnosis, community- vs. hospital-acquired infection, antibiotics started at emergency department vs. ward.
[e] No correction for covariates.
[f] The percentages are calculated after exclusion of the patients who died in hospital.

several other potential confounders, but residual confounding is possible.

Our study has several strengths. To our knowledge, this study is the first large multicentre randomized trial including both surgical and medical wards in the evaluation of an antibiotic stewardship intervention focused on prescribers at the moment of prescribing [9,10,27–29]. The patients included in the study were representative of all patients treated with IV antibiotics in those hospitals, as for patients in the baseline group a random sample, and in the intervention group all eligible patients were included. The collection of data from 4147 eligible patients without a checklist in the intervention period enabled identification of indication bias in the checklist group. Finally, we demonstrated the importance of evaluating parameters as completion and discordance between checklist-answers and actual performance.

Our study has some limitations. The checklist was only tested in Dutch hospitals. Although the generic QIs included in the checklist were developed with an international panel [13], our results may not be completely generalizable to all other hospitals. Moreover, only teaching and university hospitals participated. Furthermore, the low rate of checklist completion is remarkable. Our implementation strategy appeared to have important limitations, such as the lack of a reminder each time an antibiotic was started. During the weekly visits by the project team the physicians often acknowledged they had forgotten the checklist 'in the heat of the moment'. Also logistic barriers, such as the transport of checklists from the ED to the ward and the checklists not being available electronically, might have discouraged prescribers from using them. As the importance of supporting activities added to the introduction of a checklist has been stressed [26,29,30], for example a checklist for reassessing intravenous antibiotic therapy after 3 days in combination with advice from an infectious disease specialist had much more impact than simply distributing the checklist [29], additional activities might have resulted in higher completion scores. However, our completion score of 19% is comparable with the measured score of 20% in the first period of a surgical safety checklist implementation study [21]. Other studies mentioned completion scores that are self-reported by hospitals, which appear to be much higher than real-life completion [22,25] or do not present completion rates at all [12,24].

In future, the checklist could be included in the electronic medical record with links to digital antibiotic guidelines and to instructions for adjustment to renal function and IV-oral switch. Further analysis of discordant 'YES'-answers per QI could illustrate where to focus for further implementation. Also the economic perspective of the antibiotic checklist introduction should be considered.

In conclusion, introduction of the antibiotic checklist resulted in significantly improved quality of IV antibiotic use in the hospital as defined by the generic QIs. Unfortunately, LOS was not affected, presumably as a result of indication bias, low overall checklist completion rates, and high discordance rates between checklist-answers indicating appropriate care and actual provided care. Improving the quality of checklist use is necessary to conclude whether implementation of the antibiotic checklist is the most optimal way to improve the quality of antibiotic use among prescribers of antibiotics in the hospital.

Transparency declaration

The authors declare no competing interests. This trial was funded by ZonMw, the Netherlands Organisation for Health Research and Development grant 836021001. The funder had no role in the study design, data collection, data analysis, data interpretation or writing of the manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Acknowledgments

We thank all physicians who participated in this trial, including the staff and residents of the Antonius ziekenhuis, Flevoziekenhuis, Onze Lieve Vrouwe Gasthuis, Reinier de Graaf, Spaarnegasthuis Hoofddorp, Spaarnegasthuis Haarlem, VU Medical Centre, Westfriesgasthuis, and the Academic Medical Centre. We also wanted to give a special thanks to Jolien Janzen for the coordination of the data collection.

Appendix A. Supporting information

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.cmi.2017.01.019.

References

[1] World Health Organization (WHO). Antimicrobial resistance: global report on surveillance 2014. http://www.who.int/drugresistance/documents/surveillancereport/en/ (accessed 14 July 2016).

Download van SWAB.nl | 2026-02-06 00:27

ARTICLE IN PRESS

[2] The Review on Antimicrobial Resistance. Tackling drug-resistant infections globally: Final report and recommendations. 2016. http://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf (accessed 5 September 2016).
[3] Centers for Disease Control and Prevention (CDC). Get Smart for Healthcare. http://www.cdc.gov/getsmart/healthcare/ (accessed 14 July 2016).
[4] Davey P, Brown E, Charani E, Fenelon L, Gould IM, Holmes A, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev 2013;4:CD003543.
[5] Schuts EC, Hulscher ME, Mouton JW, Verduin CM, Stuart JW, Overdiek HW, et al. Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis. Lancet Infect Dis 2016;16:847–56.
[6] McCabe C, Kirchner C, Zhang H, Daley J, Fisman DN. Guideline-concordant therapy and reduced mortality and length of stay in adults with community-acquired pneumonia. Arch Intern Med 2009;169:1525–31.
[7] Spoorenberg V, Hulscher ME, Akkermans RP, Prins JM, Geerlings SE. Appropriate antibiotic use for patients with urinary tract infections reduces length of hospital stay. Clin Infect Dis 2014;58:164–9.
[8] van den Bosch CM, Hulscher MEJL, Akkermans RP, Wille J, Geerlings SE, Prins JM. Appropriate antibiotic use reduces length of hospital stay. J Antimicrob Chemother 2016 Dec 20. http://dx.doi.org/10.1093/jac/dkw469. pii: dkw469. [Epub ahead of print].
[9] Barlam TF, Cosgrove SE, Abbo LM, MacDougall C, Schuetz AN, Septimus EJ, et al. Implementing an Antibiotic Stewardship Program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis 2016;62:e51–77.
[10] Hamilton KW, Gerber SJ, Moehring R, Anderson DJ, Calderwood MS, Han JH, et al. Point-of-prescription interventions to Improve Antimicrobial stewardship. Clin Infect Dis 2015;60:1252–8.
[11] De Vries EN, Prins HA, Crolla RM, den Outer AJ, van Andel G, van Helden SH, et al. SURPASS Collaborative Group. Effect of a comprehensive surgical safety system on patient outcomes. N Engl J Med 2010;363:1928–37.
[12] Pronovost P, Needham D, Berenholtz S, Sinopoli D, Chu H, Cosgrove S, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. N Engl J Med 2006;355:2725–32.
[13] Van den Bosch CM, Geerlings SE, Natsch S, Wille J, Prins JM, Hulscher ME. Quality indicators to measure appropriate antibiotic use in hospitalized adults. Clin Infect Dis 2015;60:281–91.
[14] van den Bosch CM, Hulscher ME, Natsch S, Wille J, Prins JM, Geerlings SE. Applicability of generic quality Indicators for appropriate antibiotic use in daily hospital practice: a cross-sectional point-prevalence multicenter study. Clinical Microbiol Infect 2016;22. 888.e1-e9.
[15] Van Daalen FV, Geerlings SE, Prins JM, Hulscher ME. A survey to identify barriers of implementing an antibiotic checklist. Eur J Clin Microbiol Infect Dis 2016;35:545.
[16] Van Daalen FV, Prins JM, Opmeer BC, Boermeester MA, Visser CE, van Hest RM, et al. A cluster randomized trial for the implementation of an antibiotic checklist based on validated quality indicators: the AB-checklist. BMC Infect Dis 2015;15:134.
[17] Hemming K, Haines TP, Chilton PJ, Girling AJ, Lilford RJ. The stepped wedge cluster randomised trial: rationale, design, analysis, and reporting. BMJ 2015;350:h391.
[18] Brown CA, Lilford RJ. The stepped wedge trial design: a systematic review. BMC Med Res Methodol 2006;6:54.
[19] Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 2005;43:1130–9.
[20] Subbe CP, Kruger M, Rutherford P, Gemmel L. Validation of a modified early warning score in medical admissions. QJM 2001;94:521–6.
[21] Van Klei WA, Hoff RG, van Aarnhem EE, Simmermacher RK, Regli LP, Kappen TH, et al. Effects of the Introduction of the WHO 'Surgical Safety Checklist' on in-hospital mortality: a cohort study. Ann Surg 2012;255:44–9.
[22] Pickering SP, Robertson ER, Griffin D, Hadi M, Morgan LJ, Catchpole KC, et al. Compliance and use of the World Health Organization checklist in UK operating theatres. Br J Surg 2013;100:1664–70.
[23] Sparks EA, Wehbe-Janek H, Johnson RL, Smythe WR, Papaconstantinou HT. Surgical safety checklist compliance: a job done poorly! J Am Coll Surg 2013;217:867–73.
[24] Haynes AB, Weiser TG, Berry WR, Lipsitz SR, Breizat AH, Dellinger EP, et al., Safe Surgery Saves Lives Study Group. A surgical safety checklist to reduce morbidity and mortality in a global population. N Engl J Med 2009;360:491–9.
[25] Urbach DR, Govindarajan A, Saskin R, Wilton AS, Baxter NN. Introduction of Surgical Safety Checklists in Ontario, Canada. N Engl J Med 2014;370:1029–38.
[26] Leape LL. The checklist conundrum. N Engl J Med 2014;370:1063–4.
[27] Lee TC, Frenette C, Jayaraman D, Green L, Pilote L. Antibiotic Self-stewardship: Trainee-led structured antibiotic time-outs to improve antimicrobial use. Ann Intern Med 2014;161:s53–8.
[28] Pulcini C, Dellamonica J, Bernardin G, Molinari N, Sotto A. Impact of an intervention designed to improve the documentation of the reassessment of antibiotic therapies in an intensive care unit. Med Mal Infect 2014;41:546–52.
[29] Lesprit P, Landelle C, Girou E, Brun-Buisson C. Reassessment of intravenous antibiotic therapy using a reminder or direct counselling. J Antimicrob Chemother 2010;65:789–95.
[30] Bosk CL, Dixon-Woods M, Goeschel CA, Pronovost PJ. Reality check for checklists. Lancet 2009;374:444–5.

Please cite this article in press as: van Daalen FV, et al., Effect of an antibiotic checklist on length of hospital stay and appropriate antibiotic use in

Download van SWAB.nl | 2026-02-06 00:27