

## Rapid identification and antimicrobial susceptibility testing reduce antibiotic use and accelerate pathogen-directed antibiotic use

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**Introduction:** Rapid bacterial identification and susceptibility tests can lead to earlier microbiological diagnosis and pathogen-directed, appropriate therapy. We studied whether accelerated diagnostics affected antibiotic use and patient outcomes.

**Patients and methods:** A prospective randomized clinical trial was performed over a 2-year period. Inpatients were selected on the basis of a positive culture from normally sterile body fluids and randomly assigned to either a rapid intervention arm or the control arm. The intervention arm used the Vitek 2 automated identification and susceptibility testing device, combined with direct inoculation of blood cultures. In the control arm, the Vitek 1 system inoculated from subcultures was used. Follow-up was 4 weeks after randomization.

**Results:** A total of 1498 patients were randomized: 746 in the intervention arm and 752 in the control arm. For susceptibility testing, the rapid arm was 22 h faster than the control arm, and for identification, it was 13 h faster ( $P < 0.0001$ ). In the rapid arm, antibiotic use was 6 defined daily doses lower per patient than in the control arm ( $P = 0.012$ ). Whereas antibiotics were switched more in the rapid group on the day of randomization ( $P = 0.006$ ), in the control group they were switched more on day two ( $P = 0.02$ ). Mortality rates did not differ significantly between the two groups (17.6% versus 15.2%).

**Conclusions:** While rapid bacterial identification and susceptibility testing led to earlier changes and a significant reduction in antibiotic use, they did not reduce mortality.

Keywords: diagnostics, antimicrobial management, antibiotic usage

### Introduction

Initially, most infections are treated empirically until the causative agents and their susceptibility profile are known. As soon as results of determination and susceptibility tests become available, the antibiotic regimen can be streamlined. Since administration of appropriate antimicrobial agents is correlated with a decrease in mortality<sup>1,2</sup> shortening the period in which empirical therapy is given may result in a better outcome for the patient. Hospitalized individuals, as well as those in the community, may benefit from the prudent use of antibiotics.<sup>3–7</sup>

Determination and susceptibility testing of microorganisms usually takes 24–48 h after initial growth in a routine laboratory setting. With the newest diagnostic methods, however, identification and susceptibility testing can now be performed within one working day. It is to be expected that modification of antibiotic therapy to narrow spectrum antibiotics or to adequate antibiotics can be made earlier using these rapid techniques, and that these techniques will contribute to improved patient management. Only a few studies have addressed the impact of these rapid techniques on patient outcomes.<sup>8–11</sup>

Our hypothesis was that rapid diagnostics could improve patient outcomes and reduce antibiotics use. Therefore, the aim

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of the present randomized controlled clinical trial was to assess the impact of rapid identification and susceptibility results of organisms causing severe bacterial infections, on antibiotic use and patient outcome.

### Patients and methods

#### Setting

The Erasmus MC is a 1200-bed tertiary-care university medical centre, located in Rotterdam, the Netherlands. The Department of Medical Microbiology and Infectious Diseases has an integrated laboratory and an active consultation service by medical microbiologists and infectious diseases specialists. In addition to consultations on request, this consultation service actively generates consultations after growth from a blood, or CSF culture or other clinical specimens suggesting a severe infection.

The consultation service operates 24 h every day. The laboratory is open on weekdays from 07:30 am until 5 pm and on Saturdays and Sundays from 8:30 am until 1 pm. During the weekend days, all blood and CSF specimens are processed as well as samples deemed important by the consultation service. During the evening and night shift, a technician is on call for emergency purposes.

#### Inclusion criteria

Included were patients hospitalized or seen at the emergency department, older than 18 years, and who had a specimen from a usually sterile bodily fluid (excluding urine) that showed bacterial or fungal growth in blood culture bottles or on agar plates. Otherwise, no patient was excluded. Patients were followed-up for 28 days. The inclusion period was from February 2001 until March 2003.

#### Power calculation

It was calculated that 1500 patients were needed to demonstrate a 6% absolute reduction in mortality (power of 80% and a two-sided  $\alpha$  of 0.05) from 25% in the control group to 18% in the rapid group (Sample Power, SPSS, Chicago, USA). The study was approved by the Medical Ethics Committee of the Erasmus MC and no informed consent was required.

#### Randomization

The randomization was carried out in computer-generated, permuted blocks of variable size stratified on the department where the specimen was collected. Personnel of the biostatistics department, who had no direct contact with the study investigators, prepared opaque, sealed envelopes. Patients were randomized by the laboratory technician handling the cultures. Randomization was carried out before patients' medical data were obtained. Final eligibility was assessed by the study investigator who checked if the patients were alive at the time of randomization and met the predefined inclusion criteria. Only these patients were included in the intention-to-treat analyses. All clinical wards and the emergency department of the hospital participated in this study. Patients were included only once. Subsequent cultures of an already randomized patient were processed by the same method as the index culture. Concealing turn around time (TAT) is

impossible, therefore no formal blinding was attempted. However, the treating physician was not informed that the patient was included in the trial.

#### Intervention

Patients randomized to the rapid (intervention) arm had their positive culture specimens processed using rapid methods during the follow-up period of 4 weeks. Patients randomized to the control group had their positive culture specimens processed in the conventional manner during the follow-up period.

Rapid testing was achieved by combining three methods. First, the Vitek 2 system (bioMérieux, Marcy-l'Étoile, France) was used for identification (2–3 h) and antibiotic susceptibility testing (6–12 h). Secondly, positive blood cultures were tested directly, without subculturing, with the Vitek 2<sup>12</sup> and, thirdly, the use of remote access to the Vitek 2 system in the evening hours by the study investigator and reporting the results to the infectious disease consultation service by telephone immediately. Specimens from the control group were analysed by the overnight (21 h) Vitek 1 system (bioMérieux). Organisms not suitable to be analysed by either the Vitek 1 or 2 system (e.g. *Corynebacterium* sp. and *Haemophilus influenzae*) were handled by conventional methods in both arms.

The TAT of the specimen used to randomize the patient (=index specimen) was determined. Specimen collection, transport and culture methods were identical in both arms. The time period in which the laboratory results were reported by the laboratory technician to the infectious disease consultation service was from 10:30 am to 5.00 pm for the conventional arm. For the rapid arm, this period was from 10:30 am to 11 pm.

#### Outcomes and data collection

The primary outcome was mortality during the follow-up period. Secondary outcome parameters were antibiotic use and changes in antibiotic therapy, total duration of hospital stay and number of intensive care unit (ICU) days. Of all included patients, microbiological culture data, age, sex, duration and department of stay and mortality data were collected from the hospital information system. Mortality after discharge was assessed by contacting the Dutch municipal population register for all patients with unknown status of life/death at the end of the follow-up period.

Due to the labour-intensive data collection from patient (paper) medical files, the following data were collected in a sub-cohort consisting of the first consecutive 1000 patients included (March 2001–July 2002): (severity of) underlying diseases, the use of immunosuppressive drugs, antibiotic use and infections during the hospital stay. The severity of underlying diseases was classified according to a modified McCabe score<sup>10</sup> by a medical microbiologist (M. C. V.), who was unaware of the patient's assigned trial arm. The collection of the other objective clinical data was not blinded.

Start and stop dates and dosage regimens of all systemic antibacterial and antifungal agents were collected manually from the patient's medical files. Antibiotics used for surgical prophylaxis were not included. Days of antibiotic use were calculated including both the day on which therapy was started and the day on which it was stopped. Defined daily doses (DDDs) were calculated according to the WHO 2006 definitions<sup>13</sup> with the exception of the DDD for intravenous amoxicillin and flucloxacillin;

these were changed from 1000 and 2000 mg to 4000 and 6000 mg, respectively. As DDDs of the lipid formulations of amphotericin B are not defined, 5 times the DDD of the deoxycholate formulation was used. Antibiotic switch was defined as a change to a different antibiotic agent. The date of the first dose of the new antibiotic was defined as the switch date. Changes in the route of administration of the same antibiotic and the addition of an antibiotic were not scored as switches. Antibiotics given for prophylactic indications were disregarded in counting switches.

Infections were classified using the CDC definitions of nosocomial infections.<sup>6</sup>

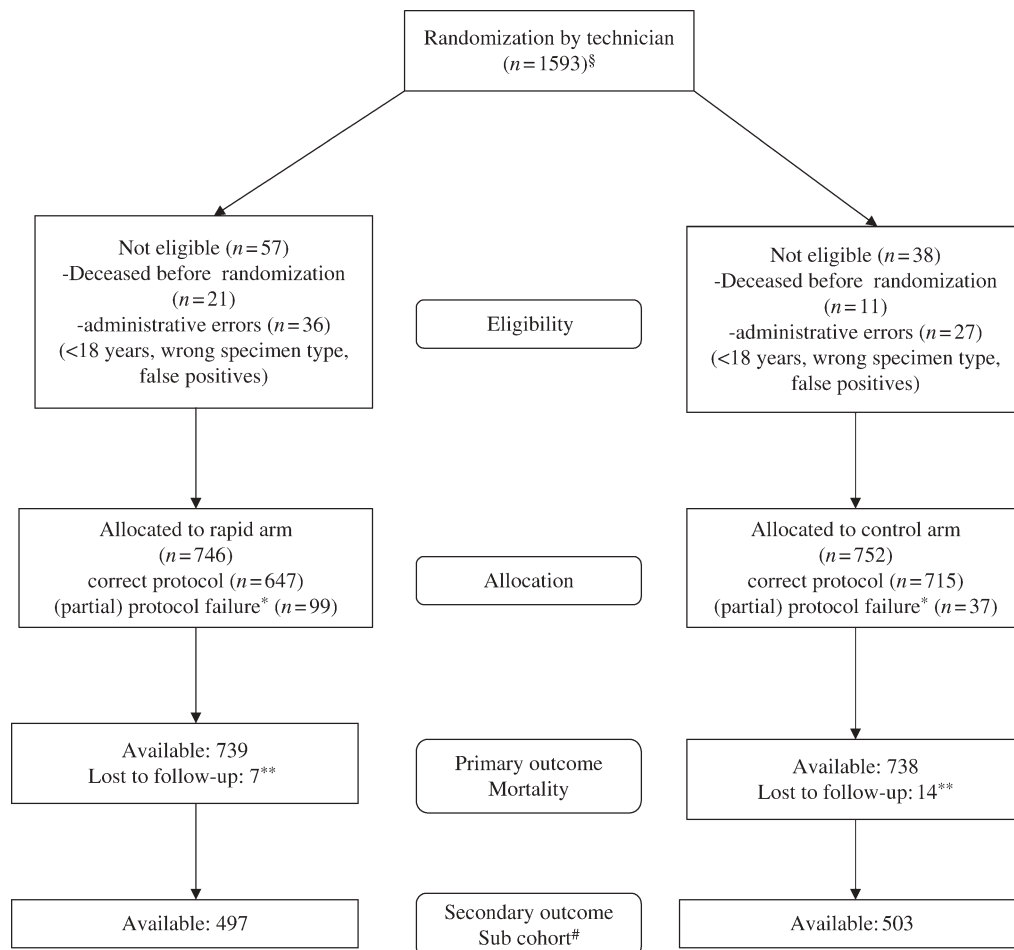
Cultures were defined as contaminated if they did not meet the criteria for infection (e.g. coagulase-negative staphylococci in a single blood culture) or were considered not clinically relevant (e.g. skin flora from cerebral spinal fluid from a patient suspected of community-acquired meningitis). Nosocomial infections were defined as infections acquired two or more days after admission, or those infections linked to a medical procedure or admission.<sup>14</sup>

### Statistical analysis

All patients randomized who met the eligibility criteria were analysed on their assigned trial arm (intention-to-treat). Patient characteristics, culture isolates and infections at baseline were analysed by  $\chi^2$  tests and *t*-tests. Differences in TAT were analysed using *t*-tests. A  $\chi^2$  test was used to compare switches of antibiotic therapy with total number of switches per day as counter and with total number of subjects as denominator. Differences in DDDs of antibiotics were analysed with the Mann–Whitney test. A *P* value <0.05 was considered statistically significant. Planned interim analyses were carried out after observing the outcomes of 40%, 60% and 80% of the included number of patients; no significant differences in mortality were observed.

### Results

In total 1498 patients were enrolled, 746 in the rapid arm and 752 in the control arm (Figure 1). In the rapid arm, 7 patients were lost to follow-up, and in the control arm, 14 were lost. In



**Figure 1.** Flow chart of the randomized patients. <sup>§</sup>Patients were randomized by a technician when a culture became positive; clinical data were not available at the time of opening the envelope. \* (Partial) protocol failure: culture not handled according to assigned protocol. For example, the technician used wrong instrument; the patient was not put on the remote access list; if the first identification failed and not promptly repeated in rapid arm. \*\* Patients not registered in a Dutch municipal population register: foreign nationals or unregistered homeless people. <sup>#</sup>The subcohort consisted of the first 1000 consecutive patients. Outcomes and demographic data collected were: (severity of) underlying diseases, the use of immunosuppressive drugs, antibiotic use, and infections during the hospital stay.

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**Table 1.** Patient characteristics at baseline

	Rapid	Control
Age ( $\pm$ SD)	56.0 (16.8)	55.8 (17.0)
Male sex: no./total (%)	457/746 (61)	455/752 (61)
Ward: no./total (%)		
medical	238/746 (32)	244/752 (32)
general surgery	157/746 (21)	174/752 (23)
neurology and neurosurgery	46/746 (6)	49/752 (7)
cardiology and thorax surgery	46/746 (6)	46/752 (6)
emergency department	79/746 (11)	72/752 (10)
ICU	180/746 (24)	167/752 (22)
Specimen type: no./total no (%)		
blood	522/746 (70)	526/752 (70)
cerebral spinal fluid	26/746 (3)	35/752 (5)
ascites	37/746 (5)	20/752 (3)
other	161/746 (22)	171/752 (23)
Major clinical syndromes and signs: no./total (%)		
diabetes mellitus	88/495 (18)	78/493 (16)
haematological malignancy	51/495 (10)	48/499 (10)
solid malignancy	95/495 (19)	109/496 (22)
central nervous system	107/496 (22)	109/501 (22)
cardiovascular	194/491 (40)	212/489 (43)
solid organ transplantation	45/495 (9)	34/499 (7)
HIV+	12/489 (2)	12/500 (2)
immunosuppressive drugs	87/449 (19)	87/448 (19)
neutropenia <sup>a</sup>	26/494 (5)	31/499 (6)
ventilator support	89/485 (18)	83/499 (17)
McCabe score		
non-fatal	199/497 (40)	223/503 (44)
possibly fatal	216/497 (43)	206/503 (41)
ultimately fatal	60/497 (12)	55/503 (11)
rapidly fatal	22/497 (4)	19/503 (4)

Demographic data (age, sex, ward and specimen type) were available for all 1498 included patients. Detailed clinical data were collected for the first 1000 consecutive patients. There were no significant differences ( $\chi^2$ ) present at baseline.

<sup>a</sup>Neutrophils  $<0.5 \times 10^9$ .

the rapid arm, 130 of 739 patients (17.6%) died within the 4-week follow-up period; in the control arm, 112 out of 738 patients (15.2%) died ( $P = 0.21$ ). The 95% confidence interval (CI) for this 2.4% difference in mortality is  $-1.6\%$  to  $6.1\%$ .

Table 1 gives the baseline patient characteristics at baseline; there were no significant differences between the two groups. In both arms, the majority of patients (70%) were included based on a positive blood culture.

The microorganisms isolated from the index culture are given in Table 2. No significant differences were observed in the distribution of pathogens. Table 3 shows the origin of the infections as defined by the index culture in the subcohort: 21% of index cultures in the rapid arm and 26% in the control arm were considered not to represent a true infection but a contamination.

Compared with the control arm, the mean reduction in TAT in the rapid arm was 13 h for identification results and 20 h for susceptibility testing ( $P < 0.001$ ) (Figure 2). Same-day identification results were available in 413 of 746 (55%) patients in the

**Table 2.** Number of microorganisms isolated from index culture

	Rapid (n)	Control (n)
Gram-positive		
CoNS*	240	264
<i>Staphylococcus aureus</i> *	120	109
<i>Streptococcus pneumoniae</i> *	28	27
enterococci*	45	34
other Gram-positive	118	138
Gram-negative		
Enterobacteriaceae*	284	273
non-fermenter*	59	42
other Gram-negative	34	25
Yeast	22	23
Total	950	935

Number of microorganisms isolated from the index culture (rapid group,  $n = 746$  patients; control group,  $n = 752$  patients); in both arms, 80% of index/inclusion cultures yielded one isolate only. There were no significant differences between both groups. Microorganisms marked with an asterisk were tested with the Vitek 2 instrument in the rapid group and with the Vitek 1 instrument in the control group. For isolates not testable with a Vitek system, conventional laboratory methods were used. CoNS, coagulase negative staphylococci.

rapid arm, in 71 of 752 (9%) patients the control arm ( $P < 0.001$ ). Same-day susceptibility results were available in 393 of 746 (53%) patients in the rapid arm and in 2 of 752 ( $<1\%$ ) in the control arm ( $P < 0.001$ ). Limiting the TAT calculation to index cultures of patients with isolates testable by either Vitek 1 or 2, the TAT reduction increased to 14.8 h for identification and 22.3 h for susceptibility ( $P < 0.001$ ). There was no significant

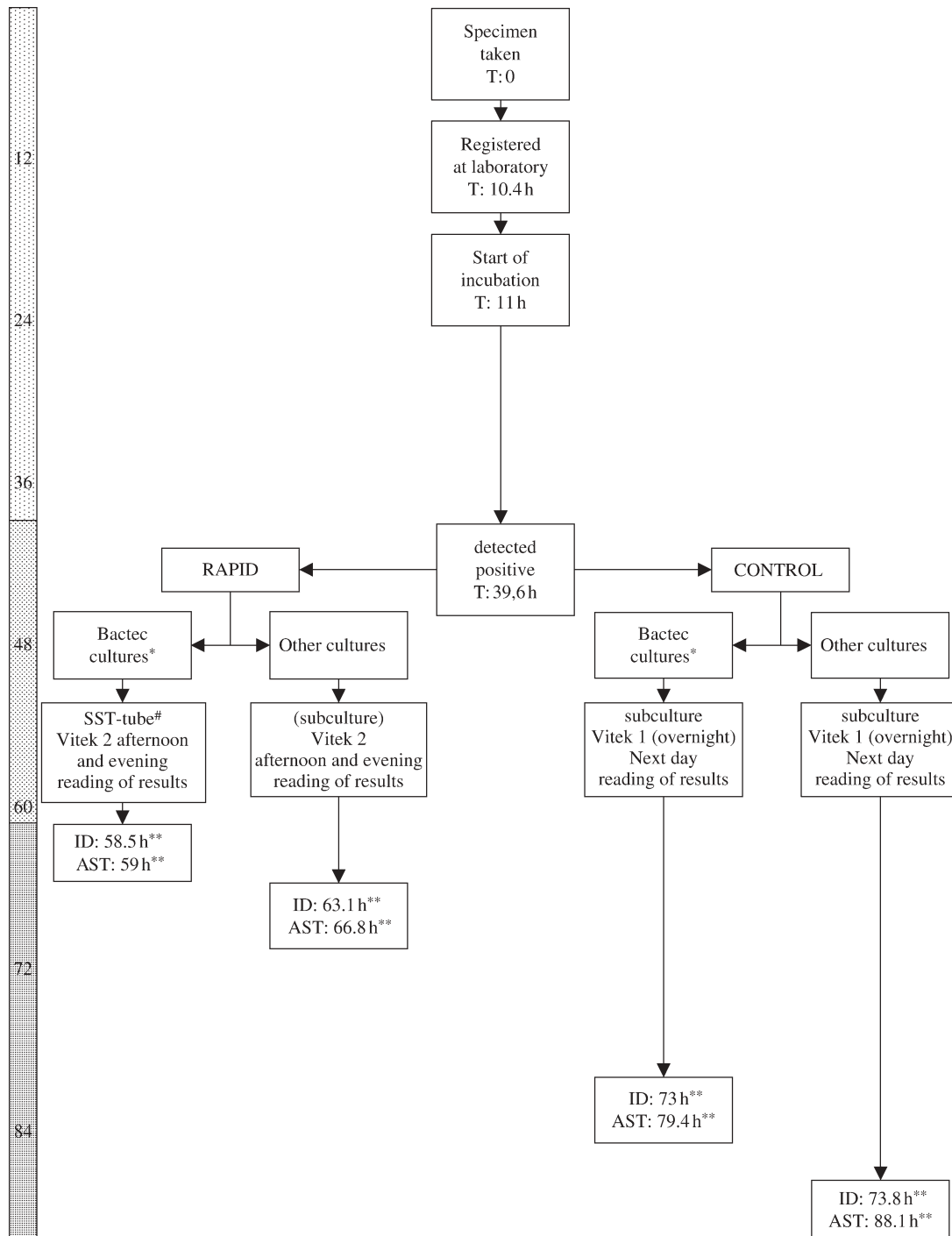
**Table 3.** Distribution of infections as indicated by index cultures in the secondary outcome subcohort

	Rapid n (%) bacteraemia	Control n (%) bacteraemia
Urinary tract	45 (100)	48 (97.9)
IV-catheter related	81 (100)	57 (100)
Respiratory tract	39 (69.2)	40 (45.0)
Intra-abdominal	87 (43.7)	88 (59.1)
Skin <sup>a</sup>	44 (29.5)	39 (23.1)
Central nervous system	19 (15.8)	24 (20.8)
Bloodstream of unknown origin	53 (100)	50 (100)
Other	25 (44.0)	26 (57.7)
Total infections	393 (69)	372 (68)
nosocomial infections	292 (74)	280 (75)
(% of total)		
Contamination <sup>b</sup>	104 (82.7)	131 (73.3)
Total	497 (71.8)	503 (69.4)

Distribution of infections indicated by the index cultures. Index cultures are cultures from specimens of usually sterile body fluids, excluding urine. There were no significant differences in type of inclusion infection.

<sup>a</sup>Including non-organ space surgical site infection.

<sup>b</sup>Cultures not fulfilling the CDC criteria and/or organism not considered clinically relevant.



**Figure 2.** Flow chart showing the turn-around-time in the study. Laboratory flow before randomization in the rapid and control arms was identical. Randomization was carried out by a technician after a culture was detected positive. Time points before randomization were only available from Bactec cultures. \*Bactec cultures, cultures grown in Bactec bottles, e.g. blood, ascites and cerebrospinal fluid. #SST, serum separator tube (SST, Becton–Dickinson Vacutainer, USA). \*\*ID, identification of microorganism; AST, antimicrobial susceptibility testing,  $P < 0.0001$  for the difference between rapid arm and control arm for Bactec® cultures. Difference between rapid and control arms for other cultures: identification,  $P = 0.043$ ; susceptibility,  $P < 0.0001$ .

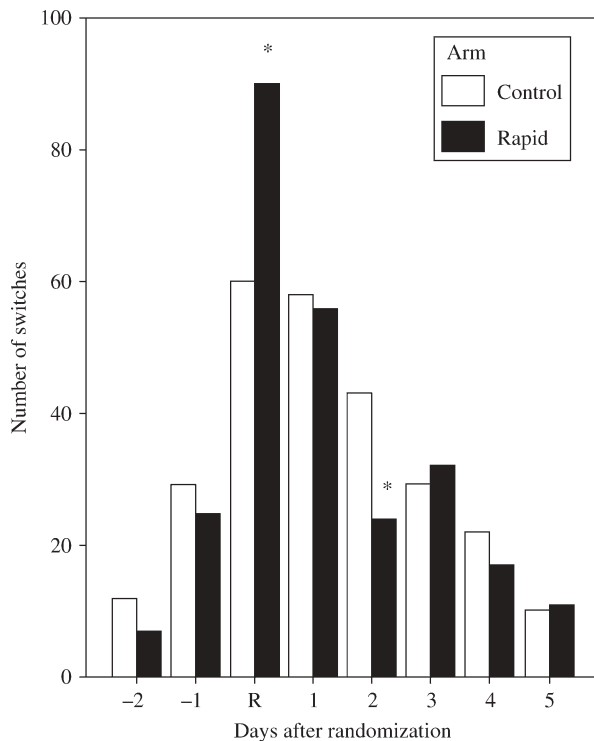
difference in admission period to the ICU or general ward between both arms.

Figure 3 shows data on antibiotic switches in the subcohort. There were significantly more changes on the day of randomization in the rapid group ( $P = 0.006$ ) and significantly more changes on day two after randomization in the control group

( $P = 0.02$ ). On the day of randomization, the number of antibiotic switches in the rapid arm, compared with the control arm, increased by 50% (from 60 to 90). On that day, in 267 out of 497 patients in the rapid arm, susceptibility results were available compared with 1 out of 503 patients in the control arm. There were no significant differences between both arms in total



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**Figure 3.** Total antibiotic switches per group in the secondary outcome subcohort. \*On the day of randomization (R) and on day two after randomization the differences between the two arms are significant ( $P = 0.006$  and  $P = 0.019$ , respectively).

numbers of starting, stopping or adding antibiotics during the follow-up period.

Table 4 presents the total antibiotic use in both arms in the subcohort. Total antibiotic use was reduced with 4 DDDs (95% CI: 1.2–6.9) in the rapid arm ( $P = 0.020$ ). Furthermore, there was a significant difference of 2 DDDs (95% CI: 0.5–3.9) in the use of antifungal drugs ( $P = 0.050$ ).

## Discussion

This study has shown that it is possible to significantly reduce the TAT of both identification and susceptibility testing of bacteria. In the rapid arm, the mean TAT of susceptibility testing was reduced by 20 h and same-day susceptibility results were available in 53% of patients. This reduction in TAT led to an earlier switch of antibiotics and a reduction in total DDDs of antibiotics used; however, the reduction in TAT did not lead to a lower mortality rate. Switches were correlated with the timing of laboratory results used by our active infection diseases service line to streamline and change antibiotic therapy. The reduction in antibiotic use could not be attributed to a single (class of) antibiotic(s). Possible explanations for this reduction are that antibiotic therapy was stopped when a contaminant organism was identified, or that combination therapy was streamlined to one agent earlier. The physicians of the infectious disease service were not blinded for the assigned study arm, because they received the results of the rapid group earlier. However, we do not think that they acted differently regarding the two groups

**Table 4.** Antibiotic use in average DDDs per patient in the secondary outcome subcohort

Antibiotic group	DDDs (SD)		<i>P</i> value*
	rapid arm ( <i>n</i> = 497)	control arm ( <i>n</i> = 503)	
Penicillins <sup>a</sup>	5.7 (13.0)	6.6 (14.7)	0.27
Penicillin and β-lactamase inhibitor <sup>b</sup>	4.5 (8.7)	5.0 (10.7)	0.32
Cephalosporins <sup>c</sup>	1.9 (4.6)	1.9 (5.2)	0.83
Carbapenems + monobactam <sup>d</sup>	1.1 (5.2)	1.3 (5.2)	0.053
Aminoglycosides <sup>e</sup>	1.2 (4.2)	1.1 (3.4)	0.85
Macrolides/lincosamides <sup>f</sup>	1.4 (5.5)	2.3 (8.1)	0.373
Quinolones <sup>g</sup>	5.7 (10.3)	6.1 (11.2)	0.67
Glycopeptides <sup>h</sup>	0.9 (3.6)	1.2 (4.4)	0.26
Other <sup>i</sup>	1.7 (5.6)	2.6 (7.9)	0.022
Total antibacterials	23.9 (21.5)	27.9 (24.7)	0.020
Antifungals <sup>j</sup>	2.7 (9.9)	4.9 (16.5)	0.050
Total antibacterials + antifungals	26.6 (24.5)	32.9 (31.9)	0.012

DDDs, defined daily doses. Antibiotic usage over 4 weeks after randomization excluding surgical prophylaxis. *t*-tests were used for statistical analysis. Only patients included in the secondary analysis were available for analysis.

<sup>a</sup>Penicillin, amoxicillin, piperacillin and flucloxacillin.

<sup>b</sup>Amoxicillin/clavulanic acid and piperacillin/tazobactam.

<sup>c</sup>Cefazolin, cefuroxime, ceftriaxone, ceftazidime and cefotaxime.

<sup>d</sup>Imipenem/cilastatin, meropenem and aztreonam.

<sup>e</sup>Amikacin, gentamicin and tobramycin.

<sup>f</sup>Erythromycin, clarithromycin, azithromycin and clindamycin.

<sup>g</sup>Ciprofloxacin, norfloxacin and levofloxacin.

<sup>h</sup>Vancomycin and teicoplanin.

<sup>i</sup>Doxycycline, trimethoprim/sulfamethoxazole and rifampicin.

<sup>j</sup>Fluconazole, amphotericin B (deoxycholate, lipid complex and liposomal) and itraconazole.

\*Mann–Whitney  $P < 0.05$  considered significant.

except that they could change, stop or start antibiotics at an earlier time.

Reductions in antibiotic use after reducing TAT have been reported previously. Bouza *et al.*<sup>15</sup> showed that rapid direct susceptibility testing of respiratory specimens of patients with ventilator-associated pneumonia led to a reduction of antibiotic use with 10 DDDs. Trenholme *et al.*<sup>11</sup> showed that rapid identification and susceptibility testing of blood culture isolates lead to a significant reduction of antibiotic use. They reported that treatment recommendations made by an infectious disease specialist based upon a rapid susceptibility test result were more likely to be followed compared with the control group; they attributed this to the reluctance of physicians to change therapy after 2 or 3 days in patients with improving status. This could also have contributed to the reduction in antibiotic use found in the present study.

In addition to lowering costs, reduction in antibiotic use will lead to less side effects such as nephrotoxicity or selection of resistant bacteria.<sup>5,16</sup> There is overwhelming evidence that antibiotic use is the main driver of antibiotic resistance both in the hospital and general population.<sup>3</sup>

We could not demonstrate a decrease in mortality. Three earlier studies have reported on the effect of rapid diagnostics on mortality.<sup>8–10</sup> The main difference between our study and theirs is that they included all types of clinical specimens, whereas we limited our study to include only blood specimens and other usually sterile body fluids (excluding urine). In our study, the percentage of bloodstream infections was 70%, whereas in the aforementioned studies this percentage ranged from 10% to 15%. Doern *et al.*,<sup>10</sup> in their randomized trial, demonstrated a significant decrease in mortality. The decrease in TAT in their study, however, was 7 h less in determination and 8 h less in susceptibility results, compared with our results. Explanations as to why we could not confirm their findings are the following. Reduction in mortality can only be explained if a significant proportion of the empirical therapy was inadequate. In our patient population, inadequate empirical therapy is highly unlikely as the level of resistance in our hospital is low. During our 2-year study period, only three patients with a MRSA bloodstream infection were included and no vancomycin-resistant enterococci were isolated. Furthermore, all positive cultures of clinically relevant specimens are judged by a physician of our infectious disease service whereupon treatment options are advised to the treating physician. Of the included patients, 81% had already received infectious diseases consultations at or before inclusion. Therefore, in most cases, the treating physician prescribed empirical treatment in both arms after an infectious disease expert had given advice. It has been shown that infectious disease consultations lead to a reduction of inadequate antibiotic therapy.<sup>17–19</sup> In the study of Doern *et al.*,<sup>10</sup> it is not clear what the activity of an infection disease service was; there have also been some comments on the validity of their study.<sup>20</sup>

Bruins *et al.*<sup>9</sup> conducted a randomized trial including patients growing bacteria in all types of specimens. They also failed to demonstrate a reduction in mortality and found no difference in antibiotic use between their two groups. In 40% of their patients, lower urinary tract infections were diagnosed. In this group, empirical antibiotic therapy is mostly adequate and of short duration.

In conclusion, we have shown that rapid identification and susceptibility testing results in significantly earlier switches in antibiotic therapy and thus to a change in the narrowest spectrum providing adequate coverage and a reduction in total antibiotic

consumption. Rapid bacterial diagnostics are therefore recommended to be implemented in the clinical laboratory. However, in a setting where infectious disease consultations are involved early in the process of the infectious disease, together with a low level of antibiotic resistance, this does not lead to a reduction in mortality.

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## Transparency declarations

None to declare.

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