Antibiotic usage and antimicrobial resistance in indonesia

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Chapter VII

Optimizing antibiotic usage in adult admitted with fever by a multifaceted intervention in an Indonesian governmental hospital

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Abstract

Antibiotic use in hospitalized patients in Indonesia is high and often inappropriate, leading to unnecessary side effects, extra costs, and unwanted selective pressure of resistant bacteria. The present study aims to optimize antimicrobial treatment of patients with fever upon admission to the department of Internal Medicine of Dr. Soetomo Hospital in Surabaya, Indonesia.

Method. A prospective intervention study. The intervention was multifaceted including the development of a consensus guideline, an official declaration of the guideline by the head of department, the distribution of a guideline pocketbook, the carrying out of blood cultures free of charge, teaching sessions and refresher courses. The outcome was measured with reference to (1) percentage of patients with fever started on antibiotic therapy, (2) amount of antibiotics used expressed as defined daily doses (DDD)/100 patient-days, (3) percentage of appropriate prescriptions and of prescriptions without indication as assessed by independent reviewers, (4) percentage of treatments in accordance with guidelines, (5) percentage of patients in whom blood cultures were taken before starting antimicrobial therapy, (6) percentage of treatments appropriately stopped on re-evaluation of the patients at 72 hours, and (7) mortality.

Results. The study involved 501 patients, 95 residents and 60 specialists. A comparison of the period before the declaration of the guideline and the period after showed an absolute decrease of 17% points for patients treated with antibiotics upon admission and a decrease from 99.8 to 73 DDD/100 patient-days. The percentage of patients with sepsis and dengue treated in accordance with the guideline increased by 23 and 30 % points, respectively. The percentage of appropriate therapies, therapies without indication and mortality did not change significantly. The percentage of patients for whom a blood culture was taken upon admission increased from 3 to 81%, however almost all were taken after they commenced antibiotic therapy. Therapy was not adjusted after 72 hours in any of the cases. Interrupted time series analysis showed that the start of development of the guideline and the declaration of the guideline were the interventions with the greatest impact.

Conclusion. The multifaceted intervention had limited success. A very important drawback to the prudent use of antibiotics was the absence of adequate microbiological diagnostics.

Introduction

Antibiotic use in hospitalized patients in Indonesia, as in many other countries, is high and often inappropriate (Hadi *et al*. 2006). We surveyed two hospitals in Surabaya and Semarang and showed that depending on the type of department between 67% (Internal Medicine) and 90% (Surgery and Paediatrics) of patients who are hospitalized for at least 5 days are treated with antibiotics during their stay in hospital. Only 21% of prescriptions were considered appropriate, for 42% there was no indication for treatment and 15% were inappropriate regarding choice, dosage or duration. Fever was often the trigger for starting antimicrobial therapy, even when no obvious signs or symptoms of bacterial infection were present or even a viral infection was likely. The presumed diagnosis in a patient with fever without a focal infection was often sepsis, without applying strict criteria for this diagnosis.

Prudent use of antibiotics is characterized by using narrow spectrum antibiotics on strict indication, adequately dosed, and for no longer than necessary. Initial therapy may have a broad spectrum but should be adapted as soon as results of microbiological tests are known. For several reasons, these tests were not done in the Indonesian hospitals surveyed by us or the results were not available in good time. Therefore, tailoring of antibiotic therapy rarely occurred.

Inappropriate use of antibiotics is a particular concern because it promotes the selection of resistant bacteria such as methicillin-resistant *Staphylococcus aureus,* vancomycin-resistant *enterococci*, multiresistant *Mycobacterium tuberculosis,* etc. Because these (multi)resistant bacteria are difficult to treat, they are associated with increased morbidity and mortality, and treatment with second or even third choice antibiotics that often result in more side effects and higher costs is required.

For this reason it is important to promote the prudent use of antibiotics by doctors.

Few intervention studies to improve the performance of prescribers of antibiotics have been carried out in low income and developing countries. In a study carried out in Colombia, the introduction of an antibiotic order form and educational activities led to a decrease in incorrect prescriptions for aminoglycosides, ceftazidime, cefotaxime and surgical prophylaxis (Perez *et al*. 2003). Another Colombian study showed a decrease in wound infections by improving prophylaxis for caesarean section by the introduction of a

protocol and making the antibiotics available in the operating theatre. A third study from Pakistan diminished the use of broad spectrum antibiotics in an intensive care unit by introducing restricted usage for 72 hours (Siddiqui *et al*. 2007).
Our observations of antibiotic treatment in hospitalized patients in Indonesia and our concerns about inappropriate antibiotic treatment led us to initiate a multifaceted intervention to improve the prudent use of antibiotics in patients with fever on admission to the department of Internal Medicine of the Dr. Soetomo hospital in Surabaya. We analyzed whether the multifaceted intervention was effective in its entirety, and whether the components as such were effective.

Methods

Study design

The study is a prospective intervention study carried out in the five wards of the Internal Medicine department of Dr. Soetomo teaching hospital, in the city Surabaya, on the island of Java, Indonesia. Surabaya is the second largest city of Indonesia with around 5 million inhabitants. The hospital has 1432 beds for approximately 60,000 admissions per year. Ninety-five residents and 60 specialists work in the Internal Medicine department. Residents primarily see the patients and prescribe antibiotic treatment. Specialists supervise their activities.
The study consisted of 4 periods: (1) a baseline period in which data were collected without intervening in routine practice, (2) a post-declaration period after the official proclamation of a new guideline that was prepared by a small group of staff members during the last 3 months of the baseline period, (3) a post-teaching period that began with teaching sessions for the residents, and (4) a post-refresher period that started after repetition of teaching sessions for the residents.

Inclusion and exclusion of patients

Patients were included if they had fever on admission or in the first 24 hours after admission. Informed consent was not required because patients received standard treatment. Fever was defined as rectal temperature $\geq 38\ ^{0}$C or axillary temperature $\geq 37.8\ ^{0}$C. Data collectors checked the temperature lists and medical records on a daily basis.

The highest temperature recorded was used as a criterion for inclusion. Patients were excluded if they had neutropenia due to chemotherapy or when they were known to be HIV positive because of the specific infectious problems occurring in these patients.

Data collection

The period of observation of a patient was 6 days, or shorter if the patient was discharged earlier. Information from the medical records about sex, age, ward, diagnosis, signs and symptoms was noted down. Results of laboratory tests (haemoglobin, white blood cell count, platelet count, urine sediment, stool examination for leucocytes and parasites), radiological investigations and serological tests were followed up for the first 2 days after admission. Data with regard to the use of antibiotics during the first six days of admission were extracted from the medical records on the day the patients were discharged from the hospital.
Data collection was always carried out by one of the four trained data collectors.

Intervention

The intervention consisted of six activities, i.e. the development of a guideline, the declaration of the guideline, the distribution of a guideline pocket book, the carrying out of blood cultures free of charge, teaching sessions and refresher courses. These activities took place at four different times during the study.

Development of guideline

The first activity that was carried out was the development of a guideline. Consensus about the management of patients admitted with fever was reached by staff members appointed by the head of the department. The team consisted of representatives of all divisions in the Internal Medicine department, i.e. tropical and infectious diseases, rheumatology, nephrology, haematology and oncology, immunology, geriatric medicine and gastroenterology. The team held weekly meetings, during which international and national publications on diagnostics and treatments of patients with fever were discussed. Existing guidelines dated back to 1992 and were considered during the discussions. Results of the discussions were not communicated.

Declaration of the guideline

The second intervention, which was the first public activity, was the official declaration of the guideline. The head of the department officially declared the obligatory use of the guideline, during a meeting that was attended by all staff members and residents. In the declaration meeting, the guideline in the form of a pocket book was given to all attendees. From this intervention onwards all blood cultures taken were free of charge to the patients. The declaration was designed as an intervention in itself, because we hypothesized that in a society in which authority and seniority play an important role, the official proclamation by the head of the department could be an effective intervention.

Teaching session

The second public intervention was a teaching session for the residents in the Internal Medicine department. Three sessions were organised to give all residents the opportunity to attend the teaching. Attending one of the teaching sessions was obligatory.
Lectures were given and cases were discussed interactively. Residents were educated about rational antibiotic use and the emergence of antimicrobial resistance, and the use of the guideline was explained. A teaching session lasted eight hours.

Refresher course

The third public intervention was a refresher course. Two months after the teaching sessions, two refresher courses of each 8 hours were given, in which cases that had been seen after the declaration of the guideline were discussed with the residents. For residents, attending one of the refresher courses was obligatory.

Outcome measures

Quantity of antibiotic use

Antibiotic use was quantified by calculating the percentages of patients treated with antibiotics within 24 hours after admission, and Defined Daily Doses (DDD)/100 patient-days. The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults (World Health Organization 1996). For example, WHO has defined the DDD for amoxicillin as 1 g. A patient who is treated with three doses of 500 mg per day, uses 1.5 DDD per day. If this patient is treated for four days, the total amount of amoxicillin used is 6 DDD. The DDD/100 patient-days of a study period were calculated by dividing the sum of DDD used during this period by the number of patient-days of this period. Because the study restricted itself to antibiotic use during the first 6 days of admission, the maximum number of patient days a patient could contribute was 6 days, even when the patient was admitted for a longer period.

Quality of antibiotic use

The quality of antibiotic use was assessed using a validated assessment tool (Gyssens *et al*. 1992) and expressed as the percentage of prescriptions assessed to be appropriate and assessed to have no indication. For each study period, 40 cases were reviewed and were selected in proportion to the frequency of the admission diagnoses. To prevent selection bias, the required number from each diagnosis was obtained by taking the first and the last case, then the middle case, then the middle case of the first half and the second half and so on. Information regarding the use of antibiotics and clinical symptoms and signs was collected from the medical records and summarized in a case record form. Two independent reviewers individually assessed the prescriptions by means of the case record forms and original medical records. Discrepancies were discussed, in order to reach consensus about the assessment.

Adherence to the guideline

Adherence to the guideline was expressed as: (1) the percentage of patients treated according to the guideline, (2) the percentage of patients in whom empirical antibiotic treatment was stopped correctly after 72 hours, (3) the percentage of patients in whom blood cultures were taken on admission, and (4) the percentage of patients in whom blood cultures were taken before antibiotics were started.

Mortality

Percentage of patients that died during the first six days of admission

Statistical analysis

Comparisons were made by calculating differences and 95% confidence intervals according to the Bonferroni method using SPSS version 12. For outcome measures for which interrupted time series (ITS) analysis was feasible, i.e. percentages of patients treated with antibiotics within 24 hours after admission, DDD/100 patient-days and percentages of patients treated according to the guideline, ITS analysis was done according to Wagner *et al*. (2002) . The equation for linear regression analysis was: $Y = b + a_1*t_1 + a_2* aftert_1 + a_3*t_2 + a_4*aftert_2 + a_5*t_3 + a_6*aftert_3 + a_7*t_4 + a_8*aftert_4$, in which b is the constant, t_1 the moment that development of the guideline was started, t_2 the time of the declaration of the guideline, t_3 the time of the teaching sessions, t_4 the time of the refresher course, $aftert_1$, $aftert_2$,$aftert_3$, $aftert_4$ the periods after t_1, t_2, t_3 and t_4, respectively, and a_1 to a_8 the coefficients. When the results of calculations of differences with 95% confidence intervals and ITS analysis did not correlate, what could be the case because these results are based on different calculations and comparisons, conclusions were based on the ITS analysis, this being the strongest statistic method.

Results

From July 2003 to August 2004, 501 patients were enrolled. During the four study periods, the proportion of patients admitted with fever varied between 23 and 30% of the total number of patients admitted (Table 1). Ninety-three to 100% of the patients with fever were included. Equal numbers of male and female patients participated in the study. Significant differences in age were found between the four periods with the lowest mean (T test, $p = 0.01$) and median age in the post-declaration period. The duration of fever before admission and duration of admission were equal for the four periods. The most prevalent clinical diagnoses on admission were sepsis syndrome, acute gastroenteritis, dengue fever and typhoid fever. During the post-declaration period, in 45% of the patients included, dengue fever was diagnosed, compared to 10% during the other periods. The post-declaration period coincided with the dengue fever season on Java. The frequencies of the other diagnoses were similar throughout the study periods (Table 1).

Baseline period

The baseline period lasted 7 months until the first public intervention activity. In the first 16 weeks, no other activities took place other than patient enrolment. In the last 14 weeks of the baseline period, members of the medical staff developed the consensus guideline. In the meantime, patient inclusion went on as before.

Eighty-eight percent of the patients with fever upon admission were treated with antibiotics (Table 2). The amount of antibiotics used was 99.8 DDD/100 patient-days. The reviewers assessed 16% of the prescriptions to be completely correct and 53% not to be indicated. In retrospect, 87% of the antimicrobial treatments were according to the decision tree (Fig. 1) that was published at the same time as the declaration of the guideline. For gastroenteritis and typhoid fever, therapy was in line with the recommendations of the guideline in the majority of patients. This was not the case for sepsis syndrome and dengue fever (Table 2).

The guideline recommended taking blood cultures immediately after admission of patients with fever and prior to the administration of antibiotics. This was not routine practice, as the results of the baseline period show: blood cultures were taken from 6 of the 212 patients, and half of these were taken after antibiotics had been started.

During the baseline period, 14 patients (6.6%) died during the first 6 days of admission that were the focus of the present study. In 12 patients, sepsis was indicated as the cause of death.

Guideline

During the last 14 weeks of the baseline period, the staff of the Internal Medicine department developed a guideline for the management of patients with fever on admission. The recommendations were summarized in a decision tree as an easy bed-side tool for the doctors to identify patients who did and did not need empirical antibiotic therapy (Fig. 1). All patients underwent a physical examination. A chest X-ray was done on indication. Routine laboratory tests of blood, urine and faeces were performed. Blood cultures were required from all patients before the start of antibiotics. To remove the most important obstacle to taking blood cultures the costs were paid from the study budget as from the declaration of the guideline.

The first question that the attending physician had to answer was whether there were signs of systemic inflammatory response syndrome (SIRS) (Bone *et al*. 1992) . SIRS was diagnosed when two or more of the following criteria were present: (1) hyperthermia or hypothermia (>38° C or < 36° C), (2) tachycardia > 90/min, (3) tachypnoea >20/min, and (4) leucocytosis or leucopoenia (> 12,000 cell /cmm or <4000 cell/cmm). Usually SIRS is diagnosed when three or more criteria are present. However, consensus among the staff members was that for the purpose of managing of patients admitted with fever, they should stay on the safe side.

The second question to be answered was whether there were signs of infection. When one of the specified infections, e.g. typhoid fever, gastroenteritis, urinary tract infection (Fig. 1), was suspected, antibiotics were given depending on the clinical diagnosis, irrespective of the presence or absence of SIRS criteria (Dellinger *et al*. 2004). In case of two or more signs of SIRS in the absence of one of the specified infections, empirical antibiotic therapy was given, unless a viral infection was suspected, such as dengue fever, morbilli or varicella.

Treatment with antibiotics was not commenced for patients without SIRS and no obvious signs of an infection. Patients not started on antibiotics were followed up daily to check for signs and symptoms of infection. Patients on antibiotic therapy were evaluated 72 hours after start of the antibiotics to decide whether therapy should be stopped, e.g. because blood cultures remained negative or no other proof of infection was obtained.

Post-declaration period

The second study period started with the official proclamation of the consensus guideline by the head of the department of Internal Medicine. From that moment on, doctors were considered to follow the guideline every time a patient with fever was admitted. The post-declaration period lasted for 2 months, during which 103 patients were enrolled (Table 1). The proportion of patients treated with antibiotics decreased from 88 to 54% (effect size -34% points, 95% confidence interval (CI) -25 to -43%) (Table 2). The amount of antibiotics used almost halved from 99.8 to 53 DDD/100 patient-days.

The number of completely appropriate prescriptions increased from 16 to 27% (effect size 11% points, 95% CI -10 to 32%), and the number of treatments without indication

decreased from 53 to 36 % (effect size -17% points, 95% CI -43 to 9%). The percentage of treatments in agreement with the guideline, already high during the first period, remained the same (effect size -1.4% points, 95% CI -7 to10%) For sepsis syndrome and dengue fever, about one and a half to twice as many of the therapies were in accordance with the guideline than during the baseline period (effect size 44% points, 95% CI 17 to 72%, and 29% points, 95% CI 8 to 48%, respectively). Treatment for typhoid fever and gastroenteritis did not change after the declaration of the guideline.
Blood cultures were taken in 71 patients, however, in only 3 patients was this done before starting antibiotics in accordance with the guideline. In none of the patients did evaluation at 72 hours as required by the guideline lead to a decision to stop treatment. Mortality during the first 6 days of admission was 7.8%. Six patients died under the diagnosis of sepsis syndrome and 3 patients of suspected dengue fever, based on clinical grounds, and only one of the three patients was given antibiotics. According to the guideline for treatment of Dengue Fever/Dengue Haemorrhagic Fever from WHO 1999 the mortality rate should be less than 1%(World Health Organization 1999). Data from Dr. Soetomo Hospital in Surabaya showed that the mortality rate was 3/742 (0.4%) in the year 2002, 6/283 (2%) in the year 2003, 12/289 (4%) in the year 2004, and 15/1044 (1.4%) in the year 2005.

Post-teaching period.

Two months after the declaration of the guideline, teaching sessions were held that were attended by 74 of 95 internal medicine residents (78%). The residents were divided into three groups and each group received one teaching session. During a two-month period after the teaching sessions, 110 patients with fever were included in the study. The percentage of patients treated upon admission with antibiotics increased with respect to the post-declaration period from 54 to 82%, and decreased from 88 to 82 % compared to the baseline period (effect size -6% points, 95% CI -14 to 2%) (Table 2). The amount of antibiotics prescribed also increased in respect of the post-declaration period to the level of the baseline period. The percentage of prescriptions assessed as completely correct came back almost to the baseline level. The percentage of treatments without indication remained at the same lower level as in the post-declaration period (Table 2). As before,

the guideline was followed in a very high proportion of the cases. For example, during the post-declaration period, patients with dengue fever were treated less often with antibiotics than in the base line period (effect size 35% points, 95% CI 5 to 64%). However, with regard to the treatment of sepsis syndrome adherence to the guideline decreased to a level no longer significantly different to that during the baseline period (effect size 14% points, 95% CI -10 to 37%).
After the teaching sessions, the taking of blood cultures upon admission increased further to 98% of the patients, however, 97% of these cultures were taken after starting antibiotic therapy. Evaluation at 72 hours did not result in decisions to stop antibiotic treatment. Mortality during the post-teaching period was 6.4%. All patients died under the diagnosis of sepsis.

Post-refresher course period.
The last period of the study started with a refresher course that was attended by 83 of 95 residents (87%). They were divided into two groups. Each group had one session during which cases from the previous study periods were discussed. Seventy-six patients were included during the 2 months that this study period lasted, of whom 79% were treated with antibiotics, effect size compared to baseline period -9% points (95% CI -0.01 to -18%) (Table 2). The amount of antibiotics prescribed that had been back at baseline level during the post-teaching period decreased to 64 DDD/100 patient-days The percentage of completely appropriate treatments increased from 19% in the post-teaching period to 32% (effect size 13% points, 95% CI -6 to 32%) and was twice that in the baseline period (effect size 16% points, 95% CI -3 to 34%). The guideline was followed in 83% of cases, which is in the same order of magnitude as before. In 71% of patients, sepsis treatment was according to the guideline (effect size compared to baseline period 22% points, 95% CI -7 to 50%). During the last period, only 7 cases of dengue fever were observed. The cases were too few to assess the agreement with the guideline reliably. Blood cultures were taken in 56 out of 76 patients. Two blood cultures were taken before starting antibiotic therapy. No therapy was stopped on the basis of the evaluation at 72 hours after starting antimicrobial therapy. Mortality during this period was 3.9%. Two of the three

patients died under the diagnosis of sepsis. The third patient was diagnosed as having diabetes mellitus with complications of acute lung oedema.

Pre-post comparison

A comparison of the 7 months before the declaration of the guideline (baseline period) with the 6 months after the declaration (post-declaration period, post-teaching period and post-refresher period together) showed a decrease from 88 to 71 % (effect size -17% points; 95% CI -10 to -24%) in patients with fever in whom antibiotic therapy is started within 24 hours after admission (Table 2). The amount of antibiotics used expressed as DDD/100 patient-days decreased from 99.8 to 73.

Therapies assessed by the reviewers as appropriate increased from 16 to 25% (effect size 9% points; 95% CI -6 to 24%), and therapies without indication decreased from 53 to 40% (effect size -13% points; 95% CI 4 to -32%). The percentage of therapies in agreement with the guideline was the same before and after the interventions. For sepsis and dengue fever, therapy in agreement with the guideline increased from 49 to 72% (effect size 23% points, 95% CI 4 to 41%) and from 58 to 88% (effect size 30% points, 95% CI 12 to 48%), respectively. No significant differences were found for therapy of gastro-enteritis and typhoid fever. Taking blood cultures increased from 3 to 81%. Only 3% of the blood cultures taken in the post-intervention period were taken before starting antibiotic treatment. Treatment was not stopped after 72 hours based on the evaluation of culture results in any cases. Mortality in the post period was the same as in the baseline period

Dengue fever

The post-declaration period coincided with the dengue season, which is from February to April in Surabaya. The declaration of the guideline led to a significant decrease in patients with dengue fever who were treated with antibiotics (Table 2, therapy according to guideline for dengue fever). To see to what extent the seasonal variation of dengue fever influenced the results, we calculated the outcome measures, excluding the patients with dengue fever. This made a difference for the outcome measures ‘antibiotic therapy on admission’ and ‘therapy according to guideline’. A decrease of 34% points in patients treated with antibiotics on admission was observed comparing the baseline and post-declaration period. However, leaving out the dengue patients, the percentage of patients with antibiotics decreased from 94 to 88, a decrease of 6 % points, indicating that the decrease in patients treated with antibiotics on admission is largely due to adherence to the guideline that recommends not treating patients with dengue fever with antibiotics. The comparisons between baseline and the post-teaching and post-refresher course periods were less influenced by leaving out the dengue patients: baseline versus post-teaching period 6 % points versus 1 % point decrease; baseline versus post-refresher course period 9 % points versus 10 % points decrease.

Throughout the study, antibiotic therapy was in accordance with the guideline in 83 to 95% of the cases. Analysis of the data omitting the patients with dengue fever showed a decrease of 11 % points in therapy according to the guideline, compared with the baseline period, whereas for all patients this decrease was 2 % points, reflecting good adherence to the instruction to treat patients with dengue fever not with antibiotics. For the other periods, differences were small whether the analyses were done for all patients or without dengue patients.

Interrupted time series analysis

The interrupted time series analysis showed that the development of the guideline, although not meant to be a public intervention, had an influence on the prescription of antibiotics (Table 3, Figures 2a and 2b). Immediately after the start of the discussions about the guideline, the amount of prescribed antibiotics and the percentage of treatments in agreement with the guideline decreased significantly. After the declaration of the guideline, a further decrease in the amounts of antibiotics used was observed, although not statistically significant. The decrease in percentage of patients treated with antibiotics upon admission was borderline significant. After the teaching sessions, a significant countermovement was observed, with an increase in patients treated with antibiotics upon admission and in the amount of antibiotics used. After the refresher course, these outcome measures moved again in the opposite direction. Only the decrease in the percentage of patients treated with antibiotics upon admission was significant.

Discussion

A multifaceted intervention was carried out in an Indonesian hospital to improve the treatment of patients admitted with fever to the Internal Medicine department. We used a multifaceted approach as this has been advocated as the most effective way to bring about changes in healthcare, although a recent systematic review challenged this opinion, because no relationship was found between the size of the effect and number of interventions (Grol and Grimshaw 2003, Rowe *et al*. 2005, Grimshaw *et al*.2004). The intervention lasted 58 weeks. The first 16 weeks were used to collect baseline data for the outcome measures. Then staff members started to develop a consensus guideline. Efforts were undertaken to secure the broad involvement of the staff in the department in order to ensure support for the recommendations. Essential changes to the existing policies were the use of strict clinical criteria for the diagnosis of sepsis, taking blood cultures before the start of antibiotic therapy, the evaluation of treatment at 72 hours when culture results are available and not prescribing antibiotics to patients with dengue fever. Although the discussions among the staff members developing the guideline were not made public, the interrupted time series analysis showed significant effects immediately after this activity began. There was a decrease in the amount of antibiotics used as reflected in DDD/100 patient-days, although applying the not yet available guideline retrospectively on the antibiotic treatments of this period showed a decrease in the percentage of treatments that agree with the guideline.

In week 30 of the study, a meeting was organized for all staff members and residents in which the head of the department declared the official status of the guideline as a compulsory standard for the treatment of patients with fever. The guideline was provided as a pocketbook and it was announced that blood cultures could be done free of charge for the patients. After the declaration, there was an immediate drop in DDD/100 patient-days, followed by a sustained negative trend, although not statistically significant. The percentage of patients treated with antibiotics upon admission decreased and treatment of patients with sepsis and dengue fever was more often in line with the guideline than before. After the teaching sessions, a remarkable increase in the percentage of patients treated with antibiotics upon admission and the amounts of antibiotics prescribed occurred, nullifying the positive effects that had been seen since the development of the guideline began. After the refresher course, the direction of these outcome measures changed again.

In conclusion, overall the intervention had limited effect on the prescription behaviour of the doctors of the Internal Medicine department. The improvements observed for the percentage of patients treated with antibiotics upon admission, the amount of antibiotics used and the percentage of patients with sepsis or dengue fever treated in agreement with the guideline had absolute effect sizes that are in the order of magnitude frequently achieved by intervention studies (Grimshaw *et al.*2004). No favourable effects were seen on the other outcome measures. The development of the guideline and the official declaration of the guideline by the head of the department had the greatest impact, indicating that our hypothesis about the culture in which authority and seniority play an important role, might be true. However, this conclusion is debatable. The first two months after the declaration of the guideline coincided with the rainy season in which many more cases of dengue fever were admitted. The large impact on antibiotic use that was seen directly after introduction of the guideline is at least partially also explained by the fact that more patients with dengue fever were seen and in this respect, doctors adhered to the guideline very well, i.e. by not prescribing antibiotics for dengue fever.

In retrospect, adherence to the guideline and the decision tree about management of patients with fever upon admission was high during the baseline period when this guideline did not yet exist. This indicates that the guideline mainly reflected what was already common practice in the department. Two exceptions were the management of patients with dengue fever and sepsis. The guideline emphasized that antibiotics should not be prescribed for dengue fever and delivered clear clinical criteria for the diagnosis of sepsis. The intervention achieved an improvement in antibiotic usage with regard to both of these topics.

The implementation of the guideline failed with regard to the introduction of blood cultures and the evaluation of patients at 72 hours after starting antibiotic therapy. On the one hand, this failure is due to the inadequate taking of blood cultures by the clinicians and on the other hand by the lack of adequate functioning microbiology. It is not common practice in Indonesia to take blood cultures from patients with fever, among others because many patients can not afford the costs of blood cultures. Furthermore, clinicians have a low opinion of microbiology because culture results are often reported late, contrary to what is good common practice, and have no consequences for management of patients. The guideline tried to remedy this deficiency by requiring blood cultures for every patient admitted with fever and by stipulating that after 72 hours, antibiotic therapy should be evaluated in the light of the results of these cultures. The financial barrier was eliminated because during the project, blood cultures were paid from the investigational budget. In this way, the investigators hoped to demonstrate to the clinicians that blood cultures are useful and can lead to adjustments of antimicrobial therapy. The project was successful regarding the numbers of blood cultures taken on admission but only very few of these blood cultures were taken before antibiotics were administered as the guideline explicitly stated. On the other hand, the microbiology laboratory was not able to produce culture results in time, despite mutual agreement. At 72 hours after admission, the clinician had no information about the culture results, which were essential for the evaluation of the empirically started antibiotic therapy. There therefore exists a vicious circle of clinicians who fail to take microbiological diagnostics seriously and of microbiologists who receive inadequate materials and are not able to provide the clinicians with useful information at the right time. This is a very serious drawback to the promotion of prudent use of antibiotics in Indonesia and should be addressed with high priority.

The present study has several limitations. An intervention study with a control group deserves preference but was, for several reasons, not a feasible proposition in the context of the internal medicine department. Residents move around between wards and divisions within the department, making it impossible to have control wards without intervention activities. Initial decisions about antibiotic therapy are often taken in the emergency department by the internal medicine residents, before patients go to a ward. We used interrupted time series analysis as the best alternative for a controlled study, in so far as the data were suitable for this type of analysis. The study does not give information about

costs and cost-effectiveness of the intervention. The study was not designed as such, due to the fact that because the primary objective of our study was to evaluate the effectiveness of a multifaceted intervention and to compile an inventory of impeding factors in the setting of an Indonesian hospital.
Data were collected from the medical records by trained data collectors. We could assure completeness of data by collecting data while patients were present in the department and for antibiotic use on the day of discharge. In this way, medical records were always available. We did not check for accuracy of data collection by having data extracted by two independent data collectors.

Our multifaceted intervention study to improve the treatment of patients admitted with fever to an internal medicine department had varying success. In contrast with teaching activities, the development of a guideline by discussions among staff members and the official declaration of the guideline by the head of the department seem to have had some impact on treatment behaviour of the doctors. Further studies should elaborate these findings to see what is the best way to use these activities in interventions. A very important drawback to the prudent use of antibiotics was the absence of adequate microbiological diagnostics. Removing the cost barrier for blood cultures did not result in better use of this diagnostic test, which therefore meant that we were unable to supply proof of the principle that blood cultures are essential for optimizing antibiotic treatment. This problem requires remediation at an organizational level that is higher than that of the doctors working in clinical wards.

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Transparency declaration
None to declare

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Table 1. Population characteristics

	Baseline	Post-declaration	Post-teaching	Post-refresher course	Post - baseline*
Duration (months)	7	2	2	2	6
Patients admitted (n)	767	427	402	332	1161
Patients admitted with fever (n)	227	106	113	76	295
Patients included (n)	212	103	110	76	289
Female/male (n/n)	111/101	41/62	58/52	38/38	137/152
Age (years; mean/ median (range))	41/38 (13-82)	35/31 (13-84)	40/37 (13-79)	44/47 (14-82)	40/35 (13-84)
Duration of fever before admission (days; mean/median (range))	6/3 (1-60)	5/4 (1-30)	6/3 (1-90)	12/4 (1-180)	7/4 (1-180)
Duration of admission (days; mean/median (range))	7/6 (1-47)	7/6 (1-39)	8/6 (1-31)	8/7 (1-34)	8/6 (1-39)
Patient-days (n)	1018	525	561	388	1474
Diag. on adm n(%)					
- sepsis syndrome	43 (20)	15 (14)	32 (29)	17 (22)	64 (22)
- acute gastro-enteritis	53 (25)	7 (7)	25 (23)	15 (20)	47 (16)
- dengue fever					
- typhoid fever	24 (11)	46 (45)	14 (13)	7 (9)	67 (23)
- other	44 (21)	12 (12)	16 (14)	9 (12)	37 (13)
	48 (23)	23 (22)	23 (21)	28 (37)	74 (22)

* Post-baseline is combined data of post-declaration, post-teaching and post-refresher course

Table 2. Outcome measures.

	Baseline	Post-declaration	Post-teaching	Post-refresher course	Post-baseline*
Antibiotic therapy upon admission n/n included (%)	187/212 (88)	56/103 (54)	90/110 (82)	60/76 (79)	206/289 (71)
DDD/100 patient-days	99.8	53	91.4	64	73
Appropriate therapy n/ n assessed prescriptions** (%)	7/43 (16)	6/22 (27)	8/43 (19)	12/38 (32)	26/103 (25)
No indication n/ n assessed prescriptions ** (%)	23/43 (53)	8/22 (36)	15/43 (35)	18/38 (47)	41/103 (40)
Therapy according to guideline n/n included (%)	184/212 (87)	88/103 (85)	104/110 (95)	63/76 (83)	255/289 (88)
Therapy according to guideline for - n/n sepsis (%) - n/n gastroenteritis - n/n dengue - n/n typhoid fever	 21/43 (49) 51/53 (96) 14/24 (58) 38/44 (86)	 14/15 (93) 6/7 (86) 40/46 (87) 11/12 (92)	 20/32 (63) 24/25 (96) 13/14 (93) 14/16 (88)	 12/17 (71) 13/15 (87) 6/7 (86) 6/9 (67)	 46/64 (72) 43/47 (91) 59/67 (88) 31/37 (84)
Blood cultures taken n/n (%)	6/212 (3)	71/103 (70)	108/110 (98)	56/76	235/289 (81)
Blood cultures taken before start antibiotics n/n (%)	3/6 (50)	2/71 (3)	3/108 (3)	2/56 (4)	7/235 (3)
Antibiotic treatment was correctly stopped after 72 hours n/n	0/212 (0)	0/103 (0)	0/110 (0)	0/76 (0)	0/289
Mortality n/n (%) (first 6 days of admission)	14/212 (6.6)	8/103 (7.8)	7/110(6.4)	3/76 (3.9)	18/289 (6.2)

* Post-baseline is combined data of post-declaration, post-teaching and post-refresher course.

** Selected medical records assessed by independent reviewers

Table 3. Results of interrupted time series analysis

	Antibiotics upon admission		Therapy according to guideline		DDD/100 patient-days		DDD/100 patient-days (dengue excluded)	
	Co-efficient	p-value	Co-efficient	p-value	Co-efficient	p-value	Co-efficient	p-value
Baseline period	0.833	0.412	2.417	0.042	1.009	0.526	-1.053	0.479
Development of guideline								
Immediate effect	-3.756	0.666	-23.067	0.026	-31.859	0.030	-34.211	0.014
Trend after	-0.776	0.714	0.126	0.957	2.146	0.522	4.579	0.152
Declaration of guideline								
Immediate effect	-12.476	0.268	2.143	0.862	-29.193	0.107	-15.134	0.358
Trend after	-8.057	0.053	-4.743	0.288	-9.508	0.138	-6.047	0.304
Teaching session								
Immediate effect	27.000	0.029	7.300	0.572	38.220	0.047	25.725	0.141
Trend after	12.600	0.018	4.700	0.396	10.002	0.207	3.888	0.592
Refresher course								
Immediate effect	10.600	0.317	-4.500	0.699	-2.429	0.883	-10.690	0.489
Trend after	-11.400	0.014	-5.900	0.223	-9.845	0.154	-7.152	0.262

Legends

Figure 1.

Decision tree for the management of patients with fever upon admission. The decision tree forms part of the consensus guideline that was developed during the last 14 weeks of the baseline period.

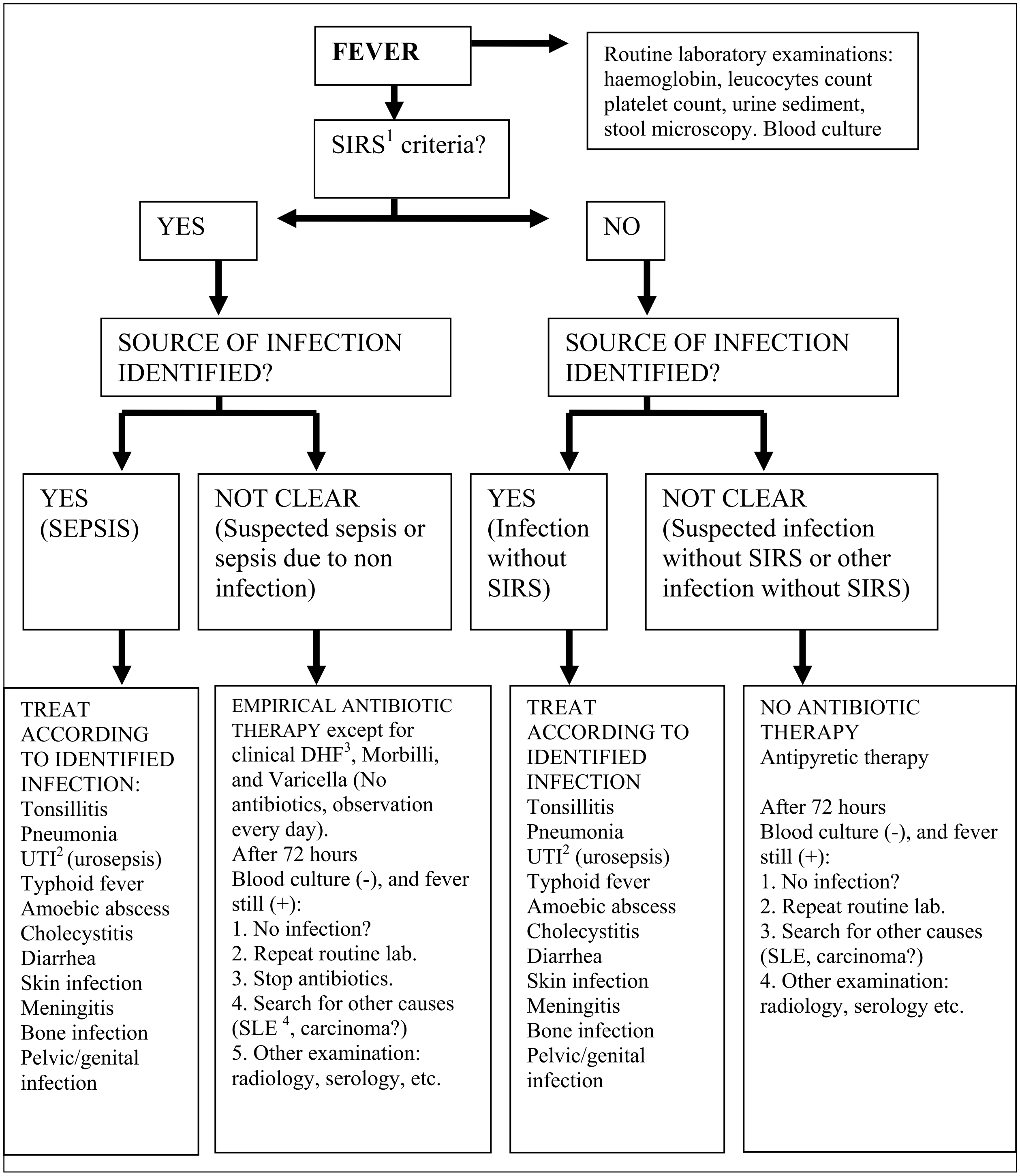
Figure 2a.

Antibiotic consumption expressed as defined daily doses (DDD)/100 patient-days for all patients. Study time was divided up into two-week periods and DDD/100 patient-days calculated for each period. The lines represent the regression lines from the interrupted time series analysis. t_1 = time that development of guideline started, t_2 = time of declaration of the guideline, t_3 = time of teaching session, t_4 = time of refresher course.

Figure 2b.

Antibiotic consumption expressed as defined daily doses (DDD)/100 patient-days omitting patients with dengue fever. Study time was divided up into two-week periods and DDD/100 patient-days calculated for each period. The lines represent the regression lines from the interrupted time series analysis. t_1 = time that development of guideline started, t_2 = time of declaration of the guideline, t_3 = time of teaching session, t_4 = time of refresher course.

Figure 1.



[1] SIRS: Systemic Inflamatory Response Syndrome
[2] UTI: Urinary Tract Infection
[3] DHF: Dengue Haemorrhagic Fever
[4] SLE: Systemic Lupus Erythematosus

Figure 2a. DDD/100 patient-days by two-week periods

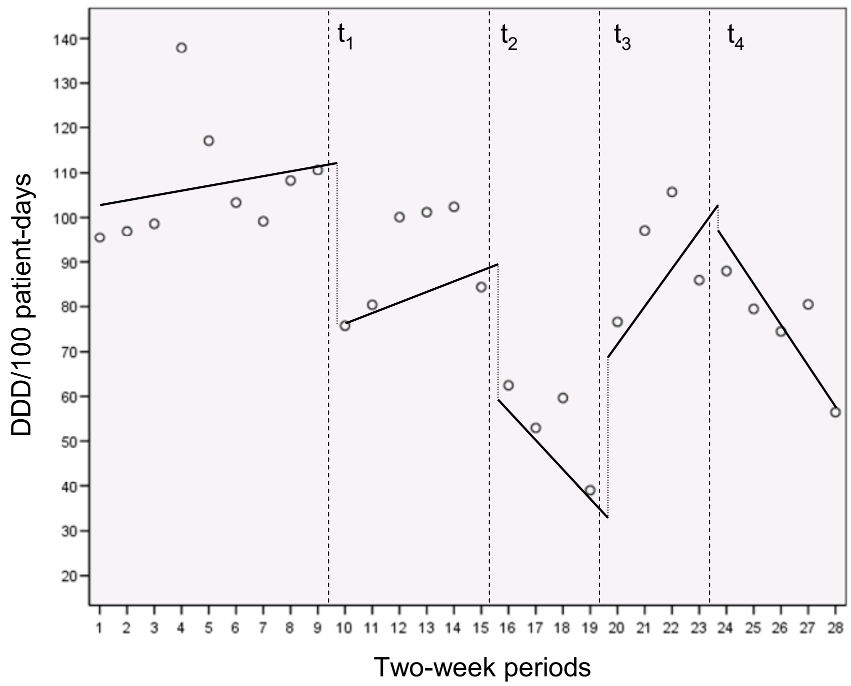


Figure 2b. DDD/100 patient-days by two-week periods (Dengue patients excluded))