STICHTING WERKGROEP ANTIBIOTICABELEID

# SWAB Guidelines for Antimicrobial Stewardship


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**Contents**

## 1 Summary of recommendations

| Recommendation | Strength | Quality of Evidence[1] |
|---|---|---|
| The Guideline committee recommends to prescribe empirical antibiotic therapy for community-acquired pneumonia according to the guidelines.<br><br>The Guideline committee recommends to prescribe empirical antibiotic therapy according to the guideline also for other infections. | Strong<br><br>Strong | Low<br><br>Low |
| It is recommended to take blood cultures and cultures from the site of infection before starting systemic antibiotic therapy. | Strong | * |
| It is recommended to change empirical antibiotics to pathogen-directed therapy as soon as culture results become available. | Strong | Very low |
| It is recommended to adapt the dose and dosing interval of antibiotics to renal function. | Strong | Very low |
| It is recommended to switch systemic antibiotic therapy from intravenous to oral antibiotic therapy after 48 -72 hours on the basis of the clinical condition and when oral treatment is adequate | Strong | Very low |
| It is recommended to document an antibiotic plan in the case notes at the start of systemic antibiotic treatment. | Strong | * |
| It is recommended to perform therapeutic drug monitoring (TDM) in patients treated with aminoglycosides, glycopeptides, posaconazole or voriconazole. | Strong | Very low |
| It should be considered to discontinue empirical antibiotic therapy for presumed bacterial infection based on the lack of clinical or microbiological evidence of infection. | Weak | Very low |
| It is recommended to have a local antibiotic guide present in the hospital.<br><br>The Guideline committee also recommends that the local antibiotic guide corresponds to the national antibiotic guidelines. | Strong<br><br>Strong | Low<br><br>* |
| It is recommended to use a list of restricted antibiotics. The A-teams should update their hospital antimicrobial restriction list regularly. | Strong | Very low |

| | | |
|---|---|---|
| It is recommended to perform a bedside consultation in patients with *S. aureus* bacteremia. | Strong | Very low |
| The Guideline committee recommends to perform a bedside consultation in patients with bacterial endocarditis or (intra)vascular infections. | Weak | * |
| The Guideline committee is of the opinion that a multidisciplinary consultation for patients with prosthetic joint infections is acceptable and that a bedside consult will not always be necessary for this particular patient group. | Strong | * |
| The Guideline committee cannot make any recommendation for assessing the patient's compliance with the antibiotic prescription in the hospital setting. | NA | * |
| The Guideline committee is of the opinion that tailored application of guideline recommendations for the hospital setting may be considered in the LTCF setting | Strong | * |
| The Guideline committee cannot make recommendations which Stewardship strategy should be used to achieve the Stewardship objectives. | NA | Low |
| Procalcitonin-guided antibiotic treatment discontinuation should be considered in the ICU setting. | Weak | High |
| The Guideline committee does not recommend the use of procalcitonin for guiding treatment duration of respiratory tract infections. | Weak | High |

* no evidence obtained from the literature

## 2 Introduction

The Dutch Working Party on Antibiotic Policy (SWAB), established by the Dutch Society for Infectious Diseases , the Dutch Society for Medical Microbiology and the Dutch Association of Hospital Pharmacists, coordinates activities in the Netherlands aimed at optimization of antibiotic use, containment of the development of antimicrobial resistance, and limitation of the costs of antibiotic use. By means of the evidence-based development of guidelines, SWAB offers local antibiotic and formulary committees a guideline for the development of their own, local antibiotic policy. SWAB yearly reports on the use of antibiotics and on trends in antimicrobial resistance in The Netherlands in NethMap (available from www.swab.nl), in collaboration with the National Institute for Public Health and the Environment (RIVM-CIb).

### Purpose and scope of the SWAB Guidelines for Antimicrobial Stewardship

Although the benefits of antibiotic use are indisputable, misuse and overuse of antibiotics have contributed to the growing problem of antibiotic resistance, which has become a serious and growing threat to public health.[2,3] Patients with infections caused by resistant bacteria generally have an increased risk of worse clinical outcomes and death, and consume more healthcare resources than patients infected with the same bacteria not demonstrating the resistance pattern in question.[3] In addition, antibiotics can have serious adverse events, including adverse drug reactions and *Clostridium difficile* infection (CDI).

Of all antibiotics prescribed in acute care hospitals, 20-50% are inappropriate.[4-8] Over the recent years there has been a worldwide trend to incorporate Antimicrobial Stewardship in hospitals with the goal to improve the quality of antimicrobial use. The primary goal of Antimicrobial Stewardship is to optimize clinical outcomes and ensure cost-effective therapy while minimizing unintended consequences of antimicrobial use, including toxicity, the selection of pathogenic organisms and the emergence of resistance.[9] The characteristics of Antimicrobial Stewardship programs (ASP) vary[10] and consist of a variety of interventions that can be designed and adapted to fit the infrastructure of any hospital.[11]

In stewardship programs, two sets of interventions should be distinguished. The first set of interventions describes recommended care at the patient level, i.e., 'Stewardship

objectives'. Examples of such objectives are: 'treat according to the guidelines', 'take blood cultures and cultures from the site of infection', or 'de-escalate therapy after culture results have become available'. A second set of interventions describes recommended strategies how to achieve the Stewardship objectives as mentioned in the first set. These include restrictive (e.g. formulary restriction) and persuasive strategies (e.g. education, feedback) to improve appropriate antimicrobial use in patient care.
The SWAB Guideline committee has systematically reviewed the yield of each Stewardship objective – these systematic reviews have been published separately.[12] The evidence for the various improvement strategies to achieve these ASP objectives was systematically reviewed in a Cochrane review.[11] In addition, the use of procalcitonin (PCT) as Stewardship strategy has recently been systematically assessed.[13]

Although Stewardship for patients in the ambulatory setting is of equal importance, the aim of this SWAB guideline is to summarize, for patients in the hospital setting, the current state of evidence of the effects of the various Antimicrobial Stewardship objectives in adults[12] and of the effects of various Stewardship improvement strategies.[11,13] Effectiveness is assessed on patient outcomes (e.g., mortality, length of stay), adverse events, costs and bacterial resistance. It is important to emphasize that for some objectives, like IV to oral switch, not showing harm (equivalence) is an important outcome. Some outcomes may also be more relevant for one objective than for another. For example, switching a patient from IV to oral therapy may decrease the likelihood of catheter-related events, but we would not expect this stewardship intervention to impact mortality or bacterial resistance. Based on this information, recommendations are formulated for clinicians and members of hospital Stewardship teams. We additionally investigated which recommendations could be made for the Long Term Care Facility (LTCF) setting.

Complementary to this guideline is the 'Practical Guide Antimicrobial Stewardship in the Netherlands' (www.ateams.nl). This is intended as a resource for A-teams in setting up an Antimicrobial Stewardship Programme in their hospital. It is not a guideline, but a guide containing suggestions on how the different elements of a stewardship programme can be designed and what the conditions are for a properly functioning A-team taking into account the local situation.

## 3 Stewardship objectives and strategies: systematic literature review

### 3.1 Stewardship objectives: Definitions of good quality antibiotic use

Using a RAND-modified Delphi procedure among international experts, we previously developed a set of 11 quality indicators (QIs) that can be used to measure appropriateness of antibiotic use in the treatment of all bacterial infections in hospitalized adult patients.[14] As these QIs were designed to be used in ASPs to determine for which aspects of antibiotic use there is room for improvement, we considered them as a set of Stewardship objectives.

The Antimicrobial Stewardship objectives are: (1) prescribe empirical antibiotic therapy according to the local guideline, (2) take at least two sets of blood cultures before starting systemic antibiotic therapy, (3) take cultures from suspected sites of infection before starting systemic antibiotic therapy, (4) change empirical to pathogen-directed therapy as soon as culture results become available, (5) adapt dose and dosing interval of systemic antibiotics to renal function, (6) switch systemic antibiotic therapy from intravenous (IV) to oral antibiotic therapy after 48 -72 hours on the basis of the clinical condition and when oral treatment is possible, (7) document the antibiotic plan in the case notes at the start of systemic antibiotic treatment, (8) perform therapeutic drug monitoring, and (9) discontinue antibiotic therapy if infection is not confirmed. Two additional QIs describe recommended care at the hospital level: (10) a local antibiotic guide should be present in the hospital, and (11) these local guides should be in agreement with the national antibiotic guidelines.

Three additional objectives were mentioned in the 2007 IDSA guidelines on Antimicrobial Stewardship[9] and/or were identified during a consensus meeting with the Antimicrobial Stewardship guideline development group representing the professional societies most involved in establishing ASPs in the Netherlands. These additional objectives were: (12) use a list of restricted antimicrobials (through formulary limitation or by the requirement of preauthorization and justification), (13) perform a bedside consultation for patients with certain infectious conditions, and (14) measure patient's compliance with the antibiotic prescription. All 14 Antimicrobial Stewardship objectives and the corresponding structured clinical questions are presented in Table 1.

We performed a search of all relevant studies published until April 2014 in the Embase, OVID MEDLINE and PubMed databases, for each of the above-mentioned 14 objectives, i.e., we performed 14 separate systematic searches. To be eligible, at least one of the following four primary outcomes had to be mentioned in the abstract: patient outcome (i.e. mortality, length of stay), adverse events, costs or antimicrobial resistance. We included studies that compared patients in whom the targeted Antimicrobial Stewardship objective was met (the intervention group) with patients in whom the targeted objective was not met (the control group). For example, patients in whom empirical treatment was prescribed in accordance with the guideline as compared to patients in whom it was not. For all systematic reviews we followed the PRISMA criteria and the study protocol was registered at PROSPERO.[1,15]

For a further description of the Methodology, the description of the retrieved studies, and the Systematic review of each Stewardship Objective we refer to the published paper.[16] In Chapter 5, Recommendations, the main findings will be summarized for each Stewardship Objective separately.

### 3.2 Stewardship strategies: summary of Cochrane review 'Interventions to improve antibiotic prescribing practices for hospital inpatients'

Having defined the set of Antimicrobial Stewardship objectives, it is also important to define the various strategies how to achieve these ASP objectives. Recently, a Cochrane review systematically reviewed the evidence for the various strategies.[11] The objective of this review was to estimate the effectiveness of professional interventions that, alone or in combination, are effective in Antimicrobial Stewardship for hospital inpatients, to evaluate the impact of these interventions on reducing the incidence of antimicrobial-resistant pathogens or *Clostridium difficile* infection (CDI) and to evaluate their impact on clinical outcome. The main comparison was between interventions with a restrictive element and those that were purely persuasive. Restrictive interventions were implemented through restriction of the freedom of prescribers to select some antibiotics. Persuasive interventions used one or more of the following methods for changing professional behaviour: dissemination of educational resources, reminders, audit and feedback, or educational outreach.

Restrictive interventions had significantly greater impact on prescribing outcomes at one month and on microbial outcomes at 6 months, but there were no significant differences at 12 or 24 months. Interventions intended to decrease excessive prescribing were associated with reduction in CDI and colonization or infection with aminoglycoside- or cephalosporin-resistant gram-negative bacteria, methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecium*. Four interventions intended to increase effective prescribing for pneumonia were associated with significant reduction in mortality, whereas nine interventions intended to decrease excessive prescribing were not associated with significant increase in mortality.[11]

Overall, the results of the Cochrane review showed that interventions to reduce excessive antibiotic prescribing to hospital inpatients can reduce antimicrobial resistance or hospital-acquired infections, and interventions to increase effective prescribing can improve clinical outcome. The use of restrictive interventions showed more immediate impact, but persuasive and restrictive interventions were equally effective after six months.

In addition to this Cochrane review, more systematic reviews have been published evaluating Stewardship strategies.[7,10,11,17-25] These Stewardship strategies will be summarized in an update of this Cochrane review foreseen for 2017.

Table 1. Structured Clinical Questions: Population[1], Intervention, Comparator, Outcome (PICO)

| Intervention | Comparator | Outcome | Methodology | Definitions |
|---|---|---|---|---|
| **Empirical therapy according to the guidelines** | Empirical therapy not according to the guidelines | Clinical outcome and adverse events<br>Costs<br>Resistance rates | Randomized controlled trials<br>Observational studies | Empirical systemic antibiotic therapy prescribed according to local guide or national guidelines[2] |
| **Blood cultures** | Not taking blood cultures | Clinical outcome and adverse events<br>Costs<br>Resistance rates | Randomized controlled trials<br>Observational studies | Take at least two sets of blood cultures before starting systemic antibiotic therapy |
| **Cultures from the site of infection** | Not taking cultures from the site of infection | Clinical outcome and adverse events<br>Costs<br>Resistance rates | Randomized controlled trials<br>Observational studies | Take cultures from suspected sites of infection, preferably before starting systemic antibiotic therapy |
| **De-escalation of therapy** | Therapy not de-escalated | Clinical outcome and adverse events<br>Costs<br>Resistance rates | Randomized controlled trials<br>Observational studies | Change to narrow-spectrum antibiotic or stop antibiotics as soon as culture results are available[14,26-28] |
| **Adjustment of therapy to renal function** | Therapy not adjusted to renal function | Clinical outcome and adverse events<br>Costs<br>Resistance rates | Randomized controlled trials<br>Observational studies | Adjustment of dose and dosing interval of systemic antibiotics |
| **Switch from intravenous to oral therapy** | Not switching intravenous to oral | Clinical outcome and adverse events<br>Costs<br>Resistance rates | Randomized controlled trials<br>Observational studies | Switch after 48–72 h, when the clinical condition of the patient is stable, oral intake and gastrointestinal absorption are adequate, and when sufficiently high concentrations in blood with a suitable oral antibiotic can be achieved[14,29,30] |

1 Population for all searches: patients treated with antibiotics in a hospital or long-term care facility

2 All results extracted if both reported

| | | | | |
|---|---|---|---|---|
| **Documented antibiotic plan** | Not documenting the antibiotic plan | Clinical outcome and adverse events<br>Costs<br>Resistance rates | Randomized controlled trials<br>Observational studies | Documented antibiotic plan should include indication, drug name and dose, and administration route and interval, and should be included in the case notes at the start of systemic antibiotic treatment |
| **Therapeutic drug monitoring (TDM)** | Not performing TDM | Clinical outcome and adverse events<br>Costs<br>Resistance rates | Randomized controlled trials<br>Observational studies | NA |
| **Discontinuation of antibiotic therapy if infection is not confirmed** | Not discontinuing antibiotic therapy if infection is not confirmed | Clinical outcome and adverse events<br>Costs<br>Resistance rates | Randomized controlled trials<br>Observational studies | Discontinuation of empirical treatment based on lack of clinical or microbiological evidence of infection[3] |
| **Presence of a local antibiotic guide** | No local antibiotic guide present | Clinical outcome and adverse events<br>Costs<br>Resistance rates | Randomized controlled trials<br>Observational studies | Local antibiotic guide present in the hospital and assessed for update every 3 years |
| **Local antibiotic guide in agreement with national antibiotic guidelines** | Local antibiotic guide not in agreement with national antibiotic guidelines | Clinical outcome and adverse events<br>Costs<br>Resistance rates | Randomized controlled trials<br>Observational studies | Corresponds for all features but can deviate on the basis of local resistance patterns |
| **List of restricted antibiotics** | Not using a list of restricted antibiotics | Clinical outcome and adverse events<br>Costs<br>Resistance rates and use of antibiotics | Randomized controlled trials<br>Observational studies | Removal of specific antibiotics from the formulary or restriction of use by requiring preauthorisation by a specialist (infectious diseases or medical microbiology) or allowing use for only 72 h with mandatory approval for further use; studies in outbreak settings excluded |

[3] Studies only reporting on differences between discontinuing and continuing treatment were included, whereas those including more general reports on de-escalation of therapy (broad to narrower spectrum or stopping treatment based on culture results) were included in the review of de-escalation of therapy

| | | | | |
|---|---|---|---|---|
| **Bedside consultation** | Not performing bedside consultation | Clinical outcome and adverse events<br>Costs<br>Resistance rates | Randomized controlled trials<br>Observational studies | Formal consultation by an infectious disease specialist leading to written comments and advice on treatment based on physical examination and review of medical records (informal consultation, for example by telephone, does not count as bedside consultation) |
| **Assessment of patients' adherence** | Not assessing patients' compliance | Clinical outcome and adverse events<br>Costs<br>Resistance rates | Randomized controlled trials<br>Observational studies | NA |

## 4 Methodology of developing this guideline

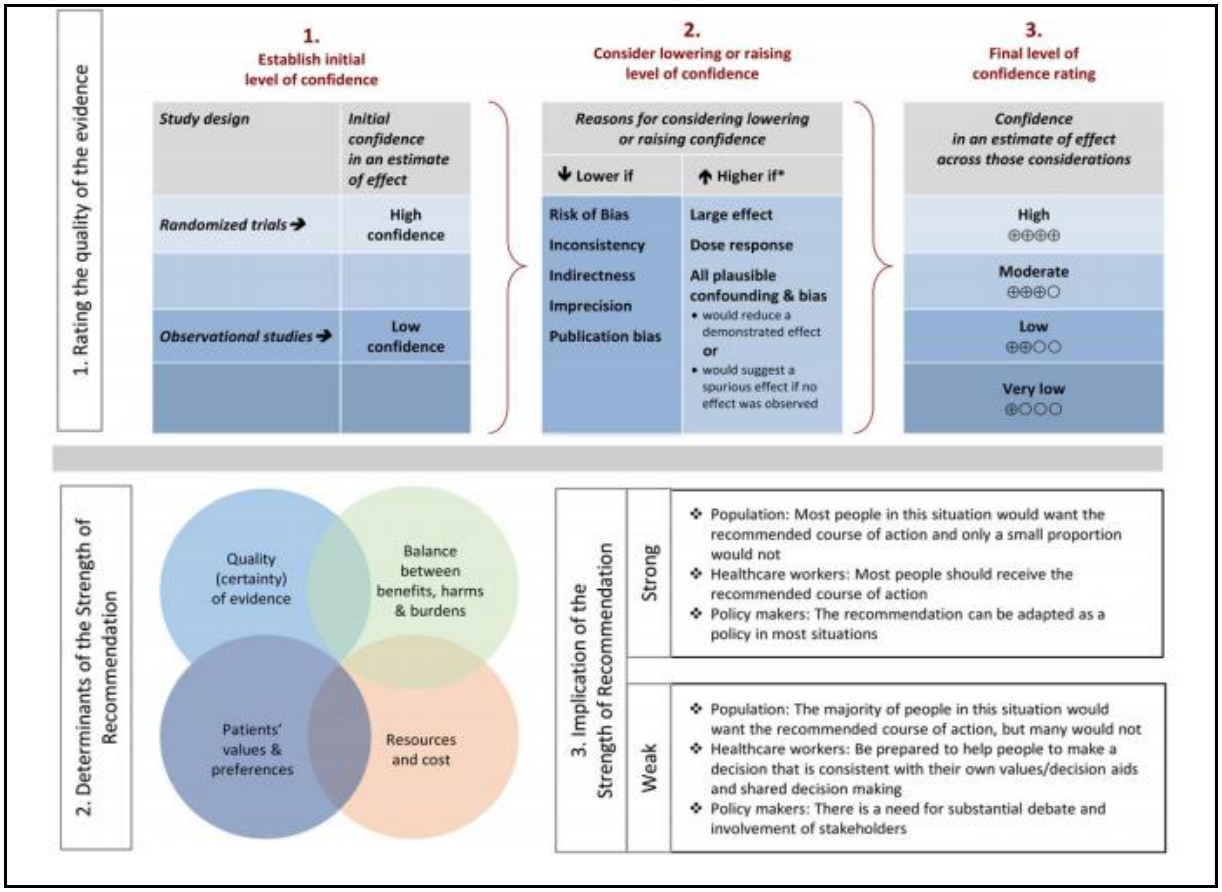
The guideline was written according to the Appraisal of Guidelines for Research & Evaluation (AGREE) instrument.[31] The recommendations in this guideline are based on the conclusions from the systematic reviews of the literature on the 14 Stewardship objectives and the Cochrane review on Stewardship strategies.[6,12,16] Conclusions from the literature are divided into conclusions regarding mortality, length of stay (LOS), cost and resistance rates. In addition, when at least three papers in a specific search reported results on other variables (e.g. Treatment failure), these conclusions are also reported. For full text and the remaining outcomes we refer to the appendix of the original paper.[12]
In addition to the AGREE instrument, the Guideline committee followed a guideline development process comparable to that of the Infectious Diseases Society of America (IDSA), which includes a systematic method of grading both the quality of evidence (very low, low, moderate, and high) and the strength of the recommendation (weak or strong).[32]

The quality of evidence per outcome variable is graded according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system, adopted by SWAB. Quality of evidence is determined by several factors, the most important of these being study design (Table 2)[1]. The remaining factors (e.g. Risk of Bias) can downgrade or upgrade the quality of evidence based on design. For example, a observational study with a serious risk of bias is considered to have a very low quality of evidence. The quality of evidence is indicated with an asterisk (*) when no evidence was obtained from the literature.
In the final step of the process recommendations are made. The strength of recommendations is graded as Strong or Weak, taking the quality of evidence, patients' values, resources and costs, and the balance between benefits, harms and burdens into account (Table 2)[33]. The SWAB Stewardship Guideline committee and for example the WHO are of the opinion that a low quality of evidence does not necessarily lead to a weak recommendation[32,34]: for example, little evidence supports taking blood cultures or cultures from suspected sites of infection, but the Guideline committee nevertheless strongly recommends to take cultures. Likewise, strong evidence for a certain intervention can sometimes nevertheless result in a weak recommendation. The reasons for the guideline committee to give strong or weak recommendations are discussed for each

recommendation in the section: Other considerations, where applicable divided into patients' values, resources and costs, and the balance between benefits, harms and burdens. When scientific verification could not be found, recommendations were formulated on the basis of the opinions and experience of the members of the Guideline committee. Notably, conclusions regarding costs had to be carefully approached. Since cost is a variable that is highly subjective to the setting and time of research, it is difficult to translate the effects of the included studies to the current healthcare environment in the Netherlands. The Guideline committee is of opinion that an increase in costs should not prevent the A-teams from pursuing Stewardship objectives.

Preparation of the guideline text was carried out by a multidisciplinary committee consisting of experts delegated from the professional societies for Infectious Diseases (VIZ), Internal Medicine (NIV), Medical Microbiology (NVMM), Intensive Care (NVIC), Hospital Pharmacy (NVZA), Pediatrics (NVK), Elderly Care Medicine (Verenso), and a methodologist and quality of care expert. After consultation with the members of these professional societies, the definitive guideline was drawn up by the delegates and approved by the board of SWAB.

Table 2. Approach and implications to rating the quality of evidence and strength of recommendations using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology[1,32]



## 5 Recommendations

5.1 Should empirical therapy be prescribed according to the guideline?

### Search strategy

| *Empirical antibiotic therapy according to the guideline* | |
|---|---|
| MEDLINE | 489 hits (14/10/14) |
| Embase | 489 hits (14/10/14) |
| PubMed not MEDLINE | 48 hits (14/10/14) |
| Total titles screened after removing all duplicates | 760 |
| Full-text articles assessed | 110 |
| Studies included in qualitative synthesis | 40 |

### Literature overview

40 studies were identified, originating from over 10 countries spanning five continents. Patient populations across studies were diverse, but the vast majority (32) of studies was on lung infections (Community-Acquired Pneumonia (CAP), Hospital-Acquired Pneumonia (HAP) and Ventilator-Associated Pneumonia (VAP)). A large number of studies (21) were multicenter studies, others were exclusively set in university (9), tertiary care (6) and community hospitals (4). Most studies reported data from both Intensive Care Unit (ICU) and hospital wards, but eight showed data exclusively from the ICU setting. All studies were observational and the risk of bias was mostly serious. Therefore, the quality of research was judged to be poor.

Of 37 studies reporting the effect on mortality, the majority (31)[5,35-64] showed that having empirical therapy prescribed according to the guideline resulted in a lower mortality rate, with 14 studies showing a significant difference[35-38,42-44,46,52,53,56,58,60,62]. One study reported no effect on mortality[65] and five studies reported a higher mortality rate[66-70], one being significant[66]. A significant Relative Risk Reduction (RRR) of 35% (Relative Risk (RR) 0.65, 95% Confidence Interval (CI) 0.54 – 0.80, $p<0.0001$) was found across all studies reporting on mortality, with moderate heterogeneity ($I^2$ 65%). Since the majority of studies looked at pulmonary infections, mainly CAP, we performed a sensitivity analysis which did not reveal a different impact on mortality. All four studies reporting on treatment failure showed a significant difference in favor of guideline adherence[52,55,61,71]. Of the 24 studies assessing the

impact on hospital LOS, 17 reported a lower length of stay in case of adherence to the guideline[5,35,38,39,42,46,47,50,51,56,58-61,63,68,72], and in eight of those studies the difference was significant[35,38,39,42,47,56,60,72]. Notably, this effect was not so clear for ICU length of stay. The remaining seven studies showed a non-significant longer length of stay for guideline-adherent patients in four[40,49,64,66] and no effect on LOS in the other three studies[41,48,57]. All studies reporting data on costs (4) reported that expenditures can be saved when adhering to guidelines[48,51,60,72], with the savings in two of these studies being highly significant[60,72].

**Conclusions**

| Outcome[4] | Quality of evidence | Conclusion |
|---|---|---|
| **Mortality** | Very low | Pooled data show a significant decrease of mortality. |
| **Length of hospital stay** | Very low | The majority of studies reports a decrease in length of hospital stay. |
| **Length of ICU stay** | Very low | Insufficient data to draw a conclusion. |
| **ICU admission** | Very low | Insufficient data to draw a conclusion. |
| **Readmission** | | Insufficient data to draw a conclusion. |
| **Treatment failure** | Very low | All studies report a consistent and significant effect: a decrease of treatment failure rates. |
| **Cost** | Very low | All studies report a consistent effect: a decrease of expenses, with two studies reporting a significant decrease. |
| **Resistance** | Very low | One study reports a significantly higher |

[4] Given here are the outcomes reported in three studies or more. For full text and the remaining outcomes we refer to the appendix of the original paper[12]

| | | |
|---|---|---|
| | | percentage of resistant bacteria in non-adherent with a positive culture |

**Other considerations**

The Guideline committee is of the opinion that there are no reasons to assume that prescribing empirical therapy according to the guideline wouldn't hold true for other infections than CAP.

| Recommendation | Strength | Quality of evidence |
|---|---|---|
| The Guideline committee recommends to prescribe empirical antibiotic therapy for community-acquired pneumonia according to the guidelines. | Strong recommendation | Low |
| The Guideline committee recommends to prescribe empirical antibiotic therapy according to the guideline also for other infections. | Strong recommendation | Low |

5.2 Should blood cultures or cultures from the site of infection be taken before starting systemic antibiotic therapy?

**Search strategy**

| *Blood cultures* | |
|---|---|
| MEDLINE | 1027 hits (17/04/2014) |
| Embase | 1673 hits (17/04/2014) |
| PubMed not MEDLINE | 64 hits (17/04/2014) |
| Total titles screened after removing all duplicates | 1921 |
| Full-text articles assessed | 9 |
| Studies included in qualitative synthesis | 0 |

| *Cultures from the site of infection* | |
|---|---|
| MEDLINE | 696 (17/04/2014) |
| Embase | 1169 (17/04/2014) |
| PubMed not MEDLINE | 90 (17/04/2014) |
| Total titles screened after removing all duplicates | 1352 |
| Full-text articles assessed | 14 |
| Studies included in qualitative synthesis | 0 |

**Literature overview**

No papers were found on performing blood cultures or taking culture samples from the site of infection. A recently presented study reported that performing blood cultures reduces the length of hospital stay.[73] This study was not included since it was not yet published at the time of our search.

**Conclusions**

No conclusions can be drawn since no published literature was found for this objective.

**Other considerations**

In a RAND-modified Delphi procedure among international experts, performing (blood) cultures was considered an important Quality indicator describing appropriate antibiotic use in hospitalized adults.[14] Although we did not find direct evidence that performing a (blood) culture is beneficial for the patient, the indirect evidence is obvious. De-escalation of antibiotic therapy and IV-oral switch have positive effects on clinical outcome, adverse

events and costs, and performing a (blood)culture is a prerequisite for de-escalating and switching. Also, (blood) culture results are important for monitoring local resistance data, which are necessary to guide the empiric therapy recommended in the local antibiotic guides.

**Recommendation**

| Recommendation | Strength | Quality of evidence |
|---|---|---|
| The Guideline committee recommends to take blood cultures and cultures from the site of infection before starting systemic antibiotic therapy. When performing a (blood)culture is not possible or desirable, this should be documented in the patient's file. | Strong recommendation | * |

* no evidence obtained from the literature

5.3 Should empirical antibiotics be changed to pathogen-directed therapy as soon as culture results become available?

**Search strategy**

| *De-escalation of therapy based on culture results* | |
|---|---|
| MEDLINE | 929 hits (24/02/2014) |
| Embase | 1756 hits (24/02/2014) |
| PubMed not MEDLINE | 123 hits (24/02/2014) |
| Total titles screened after removing all duplicates | 2726 |
| Full-text articles assessed | 121 |
| Studies included in qualitative synthesis | 25 |

**Literature overview**

We identified 25 studies meeting our inclusion criteria, originating from 12 countries on three continents (Europe, North America, Asia), with most studies being performed in the United States (9). Patient populations were very diverse, varying from pulmonary infections (CAP, HAP, VAP and Health Care Associated Pneumonia (HCAP)) to bacteremia and sepsis. Nine of 25 were multicenter studies, and nine were solely in ICU patients. There was one good quality Randomized Controlled Trial (RCT), but most studies scored having a serious risk of bias, resulting in poor quality evidence.

The hypothesis of these studies is usually to demonstrate non-inferiority of de-escalating therapy. Nevertheless, of the 19 observational studies reporting data on mortality rates, 17 studies showed a beneficial effect of de-escalation[74-90], with six of those showing significant results[76,79,80,83,85,87]. The two remaining studies reported a higher mortality rate[28,91], although the difference was not significant. A significant RRR of 56% (RR 0.44, 95% CI 0.30 – 0.66, p<0.0001) was found across all studies reporting on mortality, with moderate heterogeneity ($I^2$ 59%). A sensitivity analysis of observational studies did not reveal a different impact on mortality. Ten studies assessed the impact of de-escalation on length of stay, with eight observational studies showing a trend for decreasing hospital stay[28,74,80-83,87,91], two being significant[80,87]. One observational study reported a non-significant increase in length of stay[76]. The only RCT reported a non-significant longer length of hospital and ICU stay[26]. All

four observational studies showed a reduced number of days spend in the ICU[28,74,80,83], with two of those studies showing a significant difference[74,80].

Of the 13 studies reporting on costs, 11 studies showed savings when comparing de-escalation to unmodified therapy[74,75,81,82,87,89,91-95], with five studies reporting a significant difference[74,81,82,87,89]. Two studies claim higher cost due to de-escalation[90,96], with one study reporting higher cost due to culturing specimens[96] and one study reporting significantly higher median daily antimicrobial costs[90].

**Conclusions**

| Outcome | Quality of evidence | Conclusion |
|---|---|---|
| **Mortality** | Very low | Pooled data shows a significant decrease of mortality. |
| **Length of hospital stay** | Very low | The majority of the studies reports a decrease in length of hospital stay. |
| **Length of ICU stay** | Very low | All studies report a consistent effect: a decrease in length of ICU stay. |
| **Cost** | Very low | The majority of the studies reports a decrease of expenses. |

**Other considerations**

The hypothesis of these studies was usually to demonstrate non-inferiority of de-escalating therapy. Indeed, non-inferiority was demonstrated for all outcomes reported. Moreover, meta-analysis showed a significant beneficial effect on mortality.

| Recommendation | Strength | Quality of evidence |
|---|---|---|
| The Guideline committee recommends to change empirical antibiotics to pathogen-directed therapy as soon as culture results become | Strong recommendation | Very low |

| | | |
|---|---|---|
| available. | | |

5.4 Should dose and dosing interval of systemic antibiotics be adapted to renal function?

**Search strategy**

| *Adapting dose and dosing interval of antibiotics to renal function* | |
|---|---|
| MEDLINE | 531 hits (11/04/2014) |
| Embase | 846 hits (11/04/2014) |
| PubMed not MEDLINE | 15 hits (11/04/2014) |
| Total titles screened after removing all duplicates | 1087 |
| Full-text articles assessed | 24 |
| Studies included in qualitative synthesis | 5 |

**Literature overview**

Five studies were identified, originating from the Netherlands (1 study), France (1), the United States (2) and Japan (1). Patient populations across studies were very diverse, but in general most patients had renal impairment or were treated with medication that needs careful monitoring. All five were single-center studies, in university-affiliated hospitals (2), tertiary care centers (2) and one general hospital. Three studies were performed in the hospital setting and two studies were solely ICU based. The study design was observational for all five studies, resulting in a serious risk of bias. Therefore, the quality of studies can be considered poor.

Very few data on our pre-defined endpoints were reported in these studies. One study noted a non-significant positive effect on mortality of adjusting therapy to renal function[97]. A significant effect on reducing ICU length of stay was shown by the same study[97]. Three studies looking at adverse effects claimed a beneficial effect of adjusting according to renal function[97-99], with two of three being significant[97,99].

Most studies (4) looked at the effects on costs. All four studies showed cost savings by adjusting therapy according to renal function[97-101], but no significance levels were mentioned.

**Conclusions**

| Outcome | Quality of | Conclusion |
|---|---|---|

| | evidence | |
|---|---|---|
| **Mortality** | Very low | One study reports a non-significant positive effect on mortality. |
| **Length of ICU stay** | Very low | One study reports significant benefits with regard to length of ICU stay. |
| **Adverse Drug Events** | Very low | All studies report a consistent effect: a decrease of adverse drug events. |
| **Cost** | Very low | All studies report a consistent effect: a decrease of expenses. |

**Other considerations**

We were able to identify only five studies in which in all patients doses were adapted to renal function by the study team. Nevertheless, adapting the dose consistently appeared to decrease toxicity. In clinical practice, physicians adjust in only 50 % of the cases where adjustment is needed.[102] Therefore, the Guideline committee has decided that recommendations concerning dose adaptation in case of renal failure should be followed and the renal function of the patient should be monitored. As this applies to all medication but applies to only a small minority of patients (9%) treated with antibiotics,[103] the Guideline committee considers adapting the dose and dosing interval of antibiotics to renal function an Antimicrobial Stewardship objective that should not be a priority of the A-team.

**Recommendation**

| Recommendation | Strength | Quality of evidence |
|---|---|---|
| The Guideline committee recommends to adapt the dose and dosing interval of antibiotics to renal function. | Strong recommendation | Very low |

5.5 Should systemic antibiotic therapy be switched from intravenous to oral antibiotic therapy after 48 -72 hours on the basis of the clinical condition and when oral treatment is feasible?

**Search strategy**

| *Switch antibiotic therapy from intravenous to oral therapy* | |
|---|---|
| MEDLINE | 1247 hits (11/04/2014) |
| Embase | 603 hits (11/04/2014) |
| PubMed not MEDLINE | 27 hits (11/04/2014) |
| Total titles screened after removing all duplicates | 1499 |
| Full-text articles assessed | 112 |
| Studies included in qualitative synthesis | 18 |

**Literature overview**

18 studies were identified, originating from 13 countries on four continents (Europe, North America, South America, Asia). The majority of studies (12) were multicenter and patient populations were very diverse, varying from CAP to pyogenic liver abscess. 13 studies were RCTs and five were observational studies. Quality of evidence was generally low due to small size of patient groups and a serious risk of bias.

There were five RCTs reporting data on mortality, with four showing a non-significant beneficial effect[104-107] and one showing a non-significant negative effect[108]. One observational study reported a non-significant lower mortality rate in the IV to oral switch group[109]. A sensitivity analysis of RCTs only did not reveal a different impact on mortality. There were 11 studies reporting data on cure/resolution, none showed a significant result. Seven studies reported a positive effect on cure/resolution[106,110-115], three studies reported a negative effect[105,116,117] and one study did not show any effect[107]. Both observational studies[5,109] and five RCTs[104,108,114,117,118] showed a significant effect on reducing hospital length of stay. Three observational[75,95,109] and eight RCTs[104,106-108,110,114,117,118] showed that switching therapy from IV to oral leads to cost savings, with two RCTs[104,108] and one observational study[95] reporting a significant difference.

**Conclusions**

| Outcome | Quality | Conclusion |
|---|---|---|
| **Mortality** | Very low | Pooled data show a non-significant decrease of mortality. |
| **Length of hospital stay** | Very low | The majority of the studies report a decrease in length of hospital stay. |
| **Failure and relapse** | Very low | Insufficient data to draw a conclusion. |
| **Cure/Resolution** | Very low | The majority of the studies report a beneficial effect on cure/resolution. |
| **Adverse events** | Very low | Insufficient data to draw a conclusion. |
| **Cost** | Very low | All studies consistently report a decrease of expenses. |

**Other considerations**

No other considerations.

**Recommendation**

| Recommendation | Strength | Quality of evidence |
|---|---|---|
| The Guideline committee recommends to switch systemic antibiotic therapy from intravenous to oral antibiotic therapy after 48 -72 hours on the basis of the clinical condition and when oral treatment is feasible | Strong recommendation | Very low |

5.6 Should the antibiotic plan be documented in the case notes at the start of systemic antibiotic treatment?

**Search strategy**

| *Documenting an antibiotic plan* | |
|---|---|
| MEDLINE | 109 hits (24/04/2014) |
| Embase | 205 hits (24/04/2014) |
| PubMed not MEDLINE | 13 hits (24/04/2014) |
| Total titles screened after removing all duplicates | 234 |
| Full-text articles assessed | 2 |
| Studies included in qualitative synthesis | 0 |

**Literature overview**

No studies were found on documenting an antibiotic plan in the case notes at the start of systemic antibiotic treatment.

**Conclusions**

No conclusions can be drawn, since no literature was found for this objective.

**Other considerations**

In a RAND-modified Delphi procedure among international experts, documenting an antibiotic plan in the case notes at the start of systemic antibiotic treatment was considered an important quality indicator describing appropriate antibiotic use in hospitalized adults.[14] Although we did not find direct evidence that documenting an antibiotic plan in the case notes at the start of systemic antibiotic treatment is beneficial for the patient, the Guideline committee considers documentation of great importance. Also, documenting an antibiotic plan is part of most hospital quality assurance programs and should therefore be pursued as an important Stewardship objective by the hospital's A-team.

**Recommendation**

| Recommendation | Strength | Quality of evidence |
|---|---|---|

| | | |
|---|---|---|
| The Guideline committee recommends to document an antibiotic plan in the case notes at the start of systemic antibiotic treatment. | Strong recommendation | * |

* no evidence obtained from the literature

5.7 Should therapeutic drug monitoring (TDM) be performed?

**Search strategy**

| *TDM* | |
|---|---|
| MEDLINE | 868 hits (14/04/2014) |
| Embase | 1842 hits (14/04/2014) |
| PubMed not MEDLINE | 16 hits (14/04/2014) |
| Total titles screened after removing all duplicates | 2250 |
| Full-text articles assessed | 64 |
| Studies included in qualitative synthesis | 17 |

**Literature overview**

16 unique studies were identified, originating from the United States (11 studies), Spain (1), Japan (1), France (1), South Korea (1) and the Netherlands (1). Populations were patients treated with aminoglycosides (11 studies), vancomycin (4) and voriconazole (1). Only two studies were multicenter studies. Single-center settings included university hospitals (2), tertiary care centers (7) and community hospitals (5). Out of 16 studies we identified seven RCT/non-randomized controlled trials (NRCT) and nine observational studies. A NRCT is an experimental study in which people are allocated to different interventions using allocation methods that are not random.

Mortality rates were presented in six RCT/NRCTs. No significant differences were found, but there was a tendency towards lower mortality rates for patients with TDM in four studies[119-122] and higher mortality rates in two[123,124]. Three observational studies reported data on mortality, with one showing no effect[125] and two studies reporting a significant reduction when using TDM. A sensitivity analysis revealed a significant effect on mortality in observational studies (3), but no significant effect in RCTs (6).

Four of five RCT/NRCT reported a decreased length of hospital stay for patients receiving TDM compared to those not receiving TDM[119,120,123,124], with two studies showing a significant difference[119,123]. One RCT reported a non-significantly prolonged length of stay[79]. In the observational studies, four of six studies reported a reduced length of stay[125-128], with three of four reporting significant differences[125-127]. The remaining two observational studies reported a non-significantly longer length of stay[129,130]. Thirteen studies, four NRCTs and

nine observational studies, reported on nephrotoxicity. A significant RRR of 50% (RR 0.50, 95% CI 0.29 – 0.88, p<0.02) was found across all studies reporting on nephrotoxicity, with moderate heterogeneity ($I^2$ 45%).

The data regarding costs using TDM show a wide variation, but overall the data seem in favor of TDM, with two of three RCT/NRCTs reporting non-significant cost savings[123,124] and one RCT reporting non-significant higher costs[121]. All five observational studies report cost savings[125,126,129-131], with one study showing a significant difference[126].

**Conclusions**

| Outcome | Quality | Conclusion |
|---|---|---|
| **Mortality** | Very low | Pooled data show a non-significant decrease of mortality. |
| **Length of hospital stay** | Low | The majority of the studies reports a decrease in length of hospital stay. |
| **Failure** | Very low | The majority of the studies reports a decrease of treatment failure rates. |
| **Nephrotoxicity** | Very low | Pooled data show a significant decrease of nephrotoxicity in studies related to TDM of aminoglycosides. |
| **Cost** | Very low | The majority of the studies report lower expenses. |
| **Resistance** | Very low | One study reports non significant changes in susceptibility of the bacterial organisms to gentamicin. |

**Other considerations**

All evidence found for this objective is on aminoglycosides, glycopeptides or voriconazole. The Guideline committee considers performing TDM in patients treated with posaconazole to be useful and supported by the literature. Compelling arguments can be made for TDM of colistin, but this is at present not possible in most Dutch hospitals.

**Recommendation**

| Recommendation | Strength | Quality of evidence |
|---|---|---|
| The Guideline committee recommends to perform therapeutic drug monitoring (TDM) in patients treated with aminoglycosides, glycopeptides, posaconazole or voriconazole. | Strong recommendation | Very low |

5.8 Should empirical antibiotic therapy for presumed bacterial infection be discontinued based on the lack of clinical or microbiological evidence of infection?

**Search strategy**

| *Discontinue therapy* | |
|---|---|
| MEDLINE | 148 hits (24/04/2014) |
| Embase | 393 hits (24/04/2014) |
| PubMed not MEDLINE | 27 hits (24/04/2014) |
| Total titles screened after removing all duplicates | 447 |
| Full-text articles assessed | 19 |
| Studies included in qualitative synthesis | 3 |

**Literature overview**

Only three studies were identified, all originating from the United States. All studies addressed patients with pulmonary infections, two specifically VAP. All were single-center ICU studies, in one university-affiliated teaching hospital, one tertiary care hospital and one university-affiliated tertiary care veterans medical center. Two of three studies were low-quality randomized controlled trials and one study was observational with a low risk of bias, making the overall quality of the evidence very low to moderate. One RCT and the observational study included fewer than 50 patients per group.

Clinical endpoints were comparable. One observational study reported a positive effect on mortality[132] and the two RCTs also reported a non-significant favourable difference in mortality rates[133,134]. A sensitivity analysis of RCTs did not reveal a different impact on mortality. A decrease in ICU length of stay was reported by both RCTs[133,134], with one study showing a significant effect[133]. One RCT also reported that discontinuing therapy led to lowering expenditures and reported a significant beneficial effect on resistance rates[133].

**Conclusions**

| Outcome | Quality | Conclusion |
|---|---|---|
| **Mortality** | Low | Pooled data show a non-significant decrease of mortality. |

| | | |
|---|---|---|
| **Length of hospital stay** | Moderate | Insufficient data to draw a conclusion. |
| **Subsequent infection and superinfection** | Low | Insufficient data to draw a conclusion. |
| **Cost** | Very low | One study reports lower expenses. |
| **Resistance** | Low | One study reports a decrease in antimicrobial resistance and/or superinfection |

**Other considerations**

Very little evidence was found for this objective and studies were mainly on VAP. These studies reported a beneficial effect on clinical outcome, indicating that discontinuation of antibiotic therapy is a safe option if infection is not confirmed. Also, this objective can be considered part of Antimicrobial Stewardship objective 'de-escalation', which is strongly recommended in this guideline. In addition, in a practice test this objective was difficult to operationalize. Study results showed a kappa value of 0.24, indicating that agreement between investigators was very low, partly because the impossibility to design a good algorithm for 'lack of clinical evidence of infection' left it subject to personal interpretation. Given the absence of evidence for this objective and the difficulties in operationalization of this objective, the Guideline committee does not consider discontinuation of antibiotic therapy an Antimicrobial Stewardship objective that should be actively pursued by the A-team.

**Recommendation**

| Recommendation | Strength | Quality of evidence |
|---|---|---|
| The Guideline committee recommends to discontinue empirical antibiotic therapy for presumed bacterial infection based on the lack of clinical- or microbiological evidence of infection. | Weak recommendation | Very low |

5.9 Should a current local antibiotic guide be present in the hospital and should the local antibiotic guide correspond to the national antibiotic guidelines?

**Search strategy**

| *Local guide present* | |
|---|---|
| MEDLINE | 421 hits (15/04/2014) |
| Embase | 826 hits (15/04/2014) |
| PubMed not MEDLINE | 31 hits (15/04/2014) |
| Total titles screened after removing all duplicates | 946 |
| Full-text articles assessed | 4 |
| Studies included in qualitative synthesis | 1 |

| *Local guide in agreement with the national guideline* | |
|---|---|
| MEDLINE | 116 hits (24/04/2014) |
| Embase | 275 hits (24/04/2014) |
| PubMed not MEDLINE | 8 hits (24/04/2014) |
| Total titles screened after removing all duplicates | 295 |
| Full-text articles assessed | 8 |
| Studies included in qualitative synthesis | 0 |

**Literature overview**

Only one study met our inclusion criteria for having a local antibiotic guide present. This was a multicenter study on ICU patients performed in France. The only pre-defined outcome reported in this study was mortality. The data showed that the availability of a local antibiotic therapy protocol in the ICU for community-acquired infections, nosocomial infections and postoperative intra-abdominal infections was associated with a decrease in mortality[135]. The observational design makes the quality of evidence low.

**Conclusions**

| Outcome | Quality | Conclusion |
|---|---|---|
| **ICU Mortality** | Low | One study reports a significant decrease of ICU mortality. |

**Other considerations**

Very little evidence was found for these objectives. However, in a RAND-modified Delphi procedure among international experts, having a local antibiotic guide present in the hospital and having this guide corresponding to the national antibiotic guidelines were considered important structure quality indicators for appropriate antibiotic use in hospitalized adults.[14] Also, empirical therapy prescribed according to the guideline has been shown to have beneficial effects on clinical outcome, adverse events and costs. Therefore, it is essential to have an antibiotic guide with recommendations for empirical therapy, regardless whether this is a local guide or a version of the national guideline.

Local resistance data should guide the recommendations in the local antibiotic guides. However, NethMap 2016 shows that, in the Netherlands, minimal variations exist in local resistance rates, which are not sufficient to explain the differences between policies in the antimicrobial guides.[136] Therefore, the Guideline committee is of the opinion that in the Dutch healthcare setting, local resistance rates are only by exception a reason to deviate from the national guidelines. The Guideline committee therefore recommends that deviations from the national guidelines should be explained explicitly.

**Recommendation**

| Recommendation | Strength | Quality of evidence |
|---|---|---|
| The Guideline committee recommends to have a local antibiotic guide present in the hospital. | Strong recommendation | Low |
| The Guideline committee also recommends that the local antibiotic guide corresponds to the national antibiotic guidelines and that deviations from the national guidelines should be explained explicitly. | Strong recommendation | * |

* no evidence obtained from the literature

5.10 Should a list of restricted antibiotics be used in the hospital?

**Search strategy**

| *A list of restricted antibiotics* | |
|---|---|
| MEDLINE | 761 hits (14/04/2014) |
| Embase | 1126 hits (14/04/2014) |
| PubMed not MEDLINE | 45 hits (14/04/2014) |
| Total titles screened after removing all duplicates | 1231 |
| Full-text articles assessed | 140 |
| Studies included in qualitative synthesis | 30 |

**Literature overview**

30 studies were identified, originating from 15 countries spanning four continents (North America, South America, Asia and Europe). Patient populations across studies were diverse, a.o. studies focusing on hospitalized patients (6), gram-negative bacteria (4) and MRSA prevalence (1). Only two studies were multicenter studies. Other settings included university hospitals (4), tertiary care centers (16) and community hospitals (8). Seven of 30 studies reported data from the ICU setting. We found one non-blinded randomized trial and 29 observational studies. Most studies were subject to a high risk of bias and the general quality of evidence was therefore low.

LOS was reported in five studies: in two studies, restrictive use was associated with a significant shorter LOS[137,138], in two studies with a non-significant shorter LOS[139,140] and in one with a non-significant longer LOS. Identical results were obtained for studies reporting LOS in the ICU[141-146]. Effects on mortality were reported in nine observational studies and one RCT. Pooled data shows a non-significant decrease of mortality. For the observational studies, two reported a non-significant increase in mortality[139,147] and seven reported a decrease in mortality[138,141,142,144-146,148], with one study showing a significant difference[142]. The RCT reported a non-significant increase in mortality[137]. A sensitivity analysis of observational studies did not reveal a different impact on mortality. The effect on nosocomial infection rates was reported in five observational studies. Three studies reported a decrease[142,145,147] with one significant difference[147] and two studies reported an increase[144,148], also with one significant difference[144]. The effect on costs were reported in 11

observational studies and one RCT. Ten observational studies[138-140,146-152] and one RCT[137] reported lower costs, with four studies showing a significant effect[137,140,146,152].

The impact of restrictive programs on the prevalence of resistant micro-organisms in hospitals was evaluated in 26 of the 30 studies. In 4 of the 26 studies (17%), no significant effect of the restrictive program on resistance rates was observed[139,151,153,154]. In addition, in 17 of the 24 studies[141-150,155-162] (71%), no consistent correlations were observed between antibiotic use and prevalence of resistance. The absence of a consistent correlation between antibiotic use and nosocomial resistance rates in those studies may be explained by transmission of resistance micro-organisms, which may occur independent of antibiotic use. As changes in resistance rates during stewardship programs result from both transmission or introduction of resistant bugs and antibiotic selection, strain-typing should be performed to determine the relative contribution of both mechanisms. However, typing was not done in any of the abovementioned studies. Well-designed studies that include strain-typing are therefore required to determine the impact of restrictive programs on resistance rates.

**Conclusions**

| Outcome | Quality | Conclusion |
|---|---|---|
| **Mortality** | Very low | Pooled data shows a non-significant decrease of mortality. |
| **Length of hospital stay** | Low | The majority of the studies reports a decrease in length of hospital stay. |
| **Length of ICU stay** | Very low | The majority of the studies reports a decrease in length of ICU stay. |
| **Nosocomial infection rate** | Very low | Insufficient data to draw a conclusion. |
| **Cost** | Very low | All studies consistently report a decrease of |

| | | |
|---|---|---|
| | | expenses. |
| **Resistance** | Very low | Inconsistent effects on resistance rates, and influence of transmission on resistance rates not investigated. |

**Other considerations**

The Guideline committee refers to the Handbook on Antimicrobial Stewardship ('Praktijkgids Stewardship') for the list of antibiotics for which restriction is recommended.

**Recommendation**

| Recommendation | Strength | Quality of evidence |
|---|---|---|
| The Guideline committee recommends to use a list of restricted antibiotics. The A-teams should update their hospital antimicrobial restriction list regularly. | Strong recommendation | Very low |

5.11 Should a bedside consultation be performed by an infectious diseases specialist for specific patient groups?

**Search strategy**

| *Bedside consultation* | |
|---|---|
| MEDLINE | 252 hits (14/04/2014) |
| Embase | 642 hits (14/04/2014) |
| PubMed not MEDLINE | 14 hits (14/04/2014) |
| Total titles screened after removing all duplicates | 684 |
| Full-text articles assessed | 24 |
| Studies included in qualitative synthesis | 7 |

**Literature overview**

Seven studies were identified, originating from four countries, including the United States (3 studies), Finland (1), Germany (2) and Italy (1). Four of the study populations involved patients with S. *aureus* bacteremia. All studies reported data from a single center, with four university, one community and one tertiary care hospital, including both the ICU and hospital wards. Two studies reported data exclusively on the ICU, one of those being a neurological ICU. All studies were observational and the risk of bias was high in most studies. Therefore, quality of research was generally poor. Studies with multiple interventions, e.g., an infectious diseases consultation combined with a Positron Emission Tomography (PET) scan, were not included.

All studies assessed the impact of performing a bedside consultation on mortality (7), with five of seven studies showing a decrease of mortality rates[163-167], of which three were statistically significant[164-166]. Two observational studies reported a non-significant increase in mortality[168,169], with one study reporting a 7% increase in mortality when a bedside consultation was performed[168]. In this study, the possibility that bedside consultations were performed because of more severe illness was cited as a source of bias. This study has a very high risk of bias. The overall effect on mortality was not significant, but the four studies on bedside consultations for patients with S. *aureus* bacteremia consistently showed a significant beneficial effect on mortality, with an overall 66% RRR (RR 0.34, 95% CI 0.15 – 0.75, p=0.008). Three studies reported the effect on hospital LOS. One study reported a

decrease in LOS[164] and two reported an increase[165,168], with one study showing a significant increase[165]. One study showed a significant increase in identification of deep infection foci, for instance mediastinitis, endocarditis, or deep-seated abscesses[165].

Only two of seven studies reported data on costs. One study, previously mentioned as being seriously biased, reported a non-significant increase in expenses[168] and the other study reported significant cost savings in the group where bedside consultations were performed[169].

**Conclusions**

| Outcome | Quality | Conclusion |
|---|---|---|
| **Mortality – overall** | Very low | Pooled data show a non-significant decrease of mortality |
| **Mortality - S.*aureus* bacteremia** | Very low | Pooled data show a significant decrease of mortality |
| **Length of hospital stay** | Very low | Insufficient data to draw a conclusion. |
| **Length of ICU stay** | Very low | The majority of the studies reports a decrease in length of ICU stay. |
| **Cost** | Very low | Insufficient data to draw a conclusion. |

**Other considerations**

The majority of studies included for this objective is on patients with *S. aureus* bacteremia. However, the Guideline committee is of the opinion that the same principle of performing a bedside consult is applicable in patients with bacterial endocarditis or (intra)vascular infections. For prosthetic joint infections a bedside consultation will not always be necessary, and the Guideline committee considers a multidisciplinary consultation in most cases to be acceptable in this specific patient group.

**Recommendation**

| Recommendation | Strength | Quality of evidence |
|---|---|---|
| It is recommended to perform a bedside consultation in patients with *S. aureus* bacteremia. | Strong recommendation | Very low |
| The Guideline committee recommends to perform a bedside consultation in patients with bacterial endocarditis or (intra)vascular infections. | Weak recommendation | * |
| The Guideline committee is of the opinion that a multidisciplinary consultation for patients with prosthetic joint infections is acceptable and that a bedside consult will not always be necessary for this particular patient group. | Strong recommendation | * |

* no evidence obtained from the literature

5.12 Should the patient's compliance to antimicrobial drug prescriptions be monitored?

**Search strategy**

| *Patient compliance* | |
|---|---|
| MEDLINE | 429 hits (15/04/2014) |
| Embase | 678 hits (15/04/2014) |
| PubMed not MEDLINE | 4 hits (15/04/2014) |
| Total titles screened after removing all duplicates | 868 |
| Full-text articles assessed | 18 |
| Studies included in qualitative synthesis | 0 |

**Literature overview**

No papers were found for measuring patient's compliance with the antibiotic prescription.

**Conclusions**

No conclusions can be drawn since no literature was found for this objective.

**Other considerations**

Monitoring the patient 's compliance is probably more important in the outpatient setting, where oral drugs are prescribed and used without professional supervision.

**Recommendation**

| Recommendation | Strength | Quality of evidence |
|---|---|---|
| The Guideline committee cannot make any recommendation for assessing the patient's compliance with the antibiotic prescription in the hospital setting. | NA | * |

* no evidence obtained from the literature

5.13 Long Term Care Facility (LTCF) setting

**Search strategy**

in all searches performed for the 14 Antimicrobial Stewardship objectives studies pertaining to the LTCF setting was included.

**Literature overview**

No studies were found on the yield of Stewardship objectives in the LTCF setting.

**Conclusions**

No conclusions can be drawn since no literature was found for this particular setting.

**Other considerations**

Results obtained in the hospital setting cannot automatically be applied in the LTCF setting, because of the specific patient population and the limited diagnostic resources available here. The lack of available evidence for the LTCF setting is a concern and therefore an area where further research is urgently needed.[170,171] Nonetheless, provided that the characteristics of the (institutional) environment, the patient population and the available diagnostic and therapeutic procedures are taken into account, recommendations in this guideline can be of relevance for the LTCF setting, especially the recommendations regarding empirical therapy, de-escalation, documentation of antibiotic plans, using a local guide and a list of restrictive antibiotics. Although we found no direct evidence, we neither found counter-evidence.[172]

**Recommendation**

| Recommendation | Strength | Quality of evidence |
|---|---|---|
| The guideline committee is of the opinion that tailored application of guideline recommendations for the hospital setting should be considered in the LTCF setting. | Strong recommendation | * |

* no evidence obtained from the literature

5.14 Use of procalcitonin

Sufficient data are available for adult patients in the ICU and for patients with a respiratory tract infection. Results from a systematic review published by Soni et al (2013)[13] are presented below.

**ICU patients**

**Search strategy**

| *Search performed as and published by to Soni et al (2013)[13]* | |
|---|---|
| Total titles screened after removing all duplicates | 1967 (01/01/1990-16/12/2011) |
| Full-text articles assessed | 909 |
| Studies included in qualitative synthesis | 18 |

**Literature overview**

In total, 18 RCTs were identified. Data were pooled for clinically similar patient populations and the quality of evidence varied per population.

In adult ICU patients, PCT-guided discontinuation of antibiotics reduced antibiotic treatment duration by 2.05 days (95% CI 22.59 – 21.52) without increasing morbidity (including length of ICU stay) or mortality. In 2016, a large Dutch RCT performed in 15 ICUs including 1575 patients was published online.[27,28] This study showed that PCT-guided discontinuation of antibacterial therapy in the ICU resulted in a significant decrease in consumption of antibiotics, a significantly shorter duration of treatment and a significant decrease in mortality at 28 days.

**Conclusions – ICU patients**

| Outcome | Quality | Conclusion |
|---|---|---|
| **Mortality** | High | Procalcitonin-guided antibiotic discontinuation does not increase mortality rates. |
| **Length of ICU stay** | High | Procalcitonin-guided antibiotic discontinuation does not increase ICU length of stay. |

| | | |
|---|---|---|
| **Antibiotic use** | High | Procalcitonin-guided antibiotic discontinuation reduces antibiotic treatment duration and total antibiotic exposure. |

**Other considerations**

Several serum biomarkers have been identified in recent years that have the potential to guide patient treatment: help diagnose infections, differentiate bacterial and fungal infections from viral syndromes or noninfectious conditions, and manage antibiotic therapy. Among these, PCT is the most extensively studied biomarker.

PCT guidance in the adult ICU reduces duration of antibiotic therapy and antibiotic usage when used to discontinue antibiotic therapy, and appears to be safe. The Dutch SAPS trial[159,173] is the largest PCT-guided antibiotic intervention trial in the adult ICU setting thus far. The Guideline committee is of the opinion that the benefits of procalcitonin-guided discontinuation of antibiotic treatment in the ICU have convincingly been demonstrated. The cost implications have not been studied, and procalcitonin measurements are at present not universally available in Dutch hospitals. This has to be addressed before a class 1 recommendation can be made.

**Recommendation**

| Recommendation | Strength | Quality of evidence |
|---|---|---|
| Procalcitonin-guided antibiotic treatment discontinuation should be considered in the ICU setting. | Weak recommendation | High |

Use of Procalcitonin

**Respiratory tract infections**

**Search strategy**

| *Search performed as and published by Soni et al (2013)*[13] | |
|---|---|
| Total titles screened after removing all duplicates | 1967 (01/01/1990-16/12/2011) |
| Full-text articles assessed | 909 |
| Studies included in qualitative synthesis | 18 |

**Literature overview**

Eight studies addressed initiation and/or discontinuation of antibiotics in adult patients with acute upper and lower respiratory tract infections.

In adult patients with respiratory tract infections, PCT guidance significantly reduced antibiotic prescription rate by 22% (95% CI 241% – 24%), antibiotic treatment duration by 2.35 days (95% CI 24.38 – 20.33) and total antibiotic exposure, without affecting morbidity or mortality.

**Conclusions**

Conclusions reported as published by Soni et al (2013).[13]

| Outcome | Quality | Conclusion |
|---|---|---|
| **Mortality – Respiratory tract infection** | Moderate | Procalcitonin-guided antibiotic discontinuation does not increase mortality rates. |
| **Morbidity – Respiratory tract infection** | Moderate | Procalcitonin-guided antibiotic discontinuation does not increase hospital length of stay and ICU admission rates. |
| **Antibiotic use – Respiratory tract** | High | Procalcitonin guidance reduces antibiotic treatment duration and total antibiotic exposure. |

| | | |
|---|---|---|
| **infection** | | |

**Other considerations**

For guiding the treatment duration of respiratory tract infections the Committee notes that the recommended antimicrobial therapy duration in Dutch hospitals is already short (five days), and the Guideline committee is therefore of the opinion that in the Netherlands guiding patient treatment duration of RTIs based on PCT will have very little effect on patient outcomes (e.g., mortality, length of stay), adverse events, costs and bacterial resistance.

**Recommendation**

| Recommendation | Strength | Quality of evidence |
|---|---|---|
| For guiding treatment duration of respiratory tract infections, the Committee sees in the Dutch situation no role for procalcitonin. | Strong recommendation | High |

## 6 Recommendations regarding stewardship strategies: interventions to reach good quality antibiotic use

Many different interventions -like educational meetings, the provision of a formulary, prospective or retrospective audit and feedback, reminders- can be applied to reach good quality antibiotic use. These behavioural change interventions target the professional and, overall, restrict or guide towards appropriate use of antibiotics. In their 2013 updated Cochrane review Davey and colleagues evaluated the impact of professional interventions that, alone or in combination, effectively improve antibiotic prescribing practices for hospital inpatients (e.g. choice of drug, dose, route or duration of treatment), the impact of these interventions on reducing the incidence of antimicrobial-resistant pathogens or Clostridium difficile infection, and their impact on clinical outcome (e.g. mortality, length of hospital stay). The search performed by the Cochrane working party on Stewardship strategies will be used as the foundation for this guideline chapter.

### Search strategy

| *Search performed as and published by to Davey et al (2013)*[11] | |
|---|---|
| Total titles screened after removing all duplicates | 5463 (2006) |
| Full-text articles assessed | 507 |
| Studies included in qualitative synthesis | 118 |
| Studies included in quantitative synthesis (meta-analysis) | 70 |
| Studies listed in 'Characteristics of included studies' table | 89 |

### Literature overview

Fifty-two studies were from North America. The remaining 37 were from Europe (29), the Far East (3), South America (3) and Australia (2). There were 56 Interrupted Time Series (ITS), 20 RCTs, 5 Controlled Before Afters (CBA), 2 Controlled Clinical Trials (CCT), 1 cluster-CCT and 5 cluster-RCTs. The 89 studies reported 95 interventions with reliable data about at least one outcome. Two studies reported two interventions and one study reported five interventions. Eighteen of the studies had low risk of bias, 31 studies had medium risk of bias and 40 had high risk of bias. Therefore, quality of research was generally poor.

The study distinguished three types of interventions: persuasive, restrictive and structural interventions. Restrictive interventions were implemented through restriction of the

freedom of prescribers to select some antibiotics. Persuasive interventions used one or more of the following methods for changing professional behaviour: dissemination of educational resources, reminders, audit and feedback, or educational outreach. Restrictive interventions could contain persuasive elements. Structural interventions included changing from paper to computerized records, rapid laboratory testing, computerized decision support systems and the introduction or organization of quality monitoring mechanisms.

Most (80/95) of the interventions targeted the antibiotic prescribed (choice of antibiotic, timing of first dose and route of administration). The remaining 15 interventions aimed to change exposure of patients to antibiotics by targeting the decision to treat or the duration of treatment. Reliable data about impact on antibiotic prescribing data were available for 76 interventions (44 persuasive, 24 restrictive and 8 structural). For the persuasive interventions, the median change in antibiotic prescribing, in the direction of the intended effect, was 42,3% for the ITSs, 31,6% for the controlled ITSs, 17,7%for the CBAs, 3,5% for the cluster-RCTs and 24,7% for the RCTs. The restrictive interventions had a median effect size of 34,7% reduction in antibiotic prescribing for the ITSs, 17,1% for the CBAs and 40,5% for the RCTs. The structural interventions had a median effect of 13,3% reduction in antibiotic prescribing for the RCTs and 23,6% for the cluster-RCTs. Data about impact on microbial outcomes were available for 21 interventions but only 6 of these also had reliable data about impact on antibiotic prescribing. However, large differences in improvement were reported between the various studies that tested similar stewardship interventions. Meta-analysis of 52 ITS studies was used to compare restrictive vs. purely persuasive interventions. Restrictive interventions had significantly greater impact on prescribing outcomes at one month (Effect size 32%, 95% CI 2% – 61%, p = 0.03) and on microbial outcomes at 6 months (Effect size 53%, 95% CI 31% – 75%, p = 0.001), but there were no significant differences in prescribing or microbiological outcomes at 12 or 24 months.

Interventions intended to decrease excessive prescribing were associated with reduction in *Clostridium difficile* infections and colonization or infection with aminoglycoside- or cephalosporin-resistant gram-negative bacteria, methicillin-resistant *S.aureus* and vancomycin-resistant *Enterococcus faecalis*. Meta-analysis of clinical outcomes showed that four interventions intended to increase effective prescribing for pneumonia were associated

with significant reduction in mortality (RR 0,89, 95% CI 0,82 – 0,97), whereas nine interventions intended to decrease excessive prescribing were not associated with significant increase in mortality (RR 0,92, 95% CI 0,81 – 1,06).

**Conclusions**

Conclusions reported as published by Davey et al (2013).[11]

| Outcome | Quality | Conclusion |
|---|---|---|
| **Mortality** | Moderate | Pooled data show a non-significant decrease of mortality (intervention vs. control).ǂ |
| **Mortality - pneumonia** | Low | Pooled data show a significant decrease of mortality (intervention vs. control). |
| **Length of hospital stay** | Very low | Pooled data show a non-significant decrease of length of hospital stay (intervention vs. control). |
| **Readmission** | Very low | Pooled data show a significant increase of readmission rate (intervention vs. control). |
| **Microbiological outcomes** | Low | Pooled data shows a significant improvement of microbial outcomes (restrictive-persuasive) at 6 months. No significant difference between restrictive and persuasive interventions at 12 or 24 months. |

ǂ Intervention: any intervention intended to improve antibiotic prescribing. Comparison: usual care.

**Other considerations**

The distinction between restrictive and persuasive measures mainly applies to the restricted versus free availability of antibiotics to start empirical therapy. For other objectives, e.g., de-escalation or IV-oral switch, this distinction is not applicable. In our own systematic review, using a list of restrictive antibiotics generally resulted in a decrease of resistance rates, depending on the antibiotic class.

Overall, the conclusion that can be drawn from the Cochrane review is that any -single or combination- behavioural stewardship intervention might work to improve professionals' antibiotic use. The effects cannot, however, be predicted with great certainty as large differences in improvement were observed between the various studies that tested similar stewardship interventions. This Cochrane review is currently being updated with a special focus to identify which intervention components contribute to effectiveness. Such insight is necessary to better understand what works under what circumstances.

Several large systematic reviews that assessed the effectiveness of various interventions to improve professional practice came to the same conclusion: "There are no magic bullets for improving the quality of health care, but there are a wide range of interventions available that, if used appropriately, could lead to important improvement in professional practice and patient outcomes."[174,175]

'If used appropriately' in the last sentence refers to the necessity to select carefully the interventions most likely to be effective in light of the identified reasons for suboptimal quality. Looking at behaviour change theories and models, this crucial principle for successful change recurs through most publications: the choice of interventions should be linked as closely as possible to the results of a problem analysis. So, successful improvement of the quality of antibiotic use requires an understanding of the key drivers of current prescribing practices. The literature describes how, for example, clinical experience, knowledge, attitudes, routines, hospital antibiotic policies, professionals' collaboration and communication, care coordination and teamwork, care logistics, and differences in sociocultural and socioeconomic factors influence the appropriateness of antibiotic use in hospitals.[4,18,176] These determinants must be taken into account when choosing interventions to address these determinants. For example, lack of knowledge can be addressed by providing small group educational meetings, problems in care logistics can be addressed by redesigning processes in collaboration with all professionals involved, and reminders (prompts to perform an action during a consultation with a patient, for example provided by computer decision support systems) can be introduced if 'forgetting to apply the recommended prescribing practice' is the problem. Unfortunately behavioural determinants are currently not considered while developing interventions to optimize antibiotic

prescribing.[18] This is not an exception: in daily practice the chosen interventions to improve care are mostly based on implicit personal beliefs about human behaviour and change.

**Recommendation**

| Recommendation | Class | Quality |
|---|---|---|
| The Guideline committee does not make recommendations which Stewardship strategy should be used in general to achieve the Stewardship objectives. It is recommend to first do an inventory of barriers to guide which improvement strategy is most appropriate. | NA | Low |

## 7 Abbreviations

| | |
|---|---|
| A-team | Antibiotic Team |
| AGREE | Appraisal of Guidelines for Research & Evaluation |
| ASP | Antimicrobial Stewardship programs |
| CAP | Community-Acquired Pneumonia |
| CBA | Controlled Before After |
| CCT | Controlled Clinical Trial |
| CDI | Clostridium difficile infection |
| CI | Confidence Interval |
| DDD | Defined Daily Dose |
| GRADE | Grading of Recommendations Assessment, Development and Evaluation |
| HAP | Hospital-Acquired Pneumonia |
| HCAP | Health Care Associated Pneumonia |
| ICU | Intensive Care Unit |
| IDS | Infectious Diseases Specialist |
| IDSA | Infectious Diseases Society of America |
| ITS | Interrupted Time Series |
| IV | Intravenous |
| LOS | Length of stay |
| LTCF | Long Term Care Facility |
| MRSA | Methicillin-resistant Staphylococcus *aureus* |
| NRCT | Non-Randomized Controlled Trial |
| PCT | Procalcitonin |
| PET-scan | Positron Emission Tomography scan |
| PICO | Population, Intervention, Comparator, Outcome |
| QI | Quality Indicator |
| RCT | Randomized Controlled Trial |
| RIVM-CIb | National Institute for Public Health and the Environment (Rijksinstituut voor |

| | |
|---|---|
| | Volksgezondheid en Milieu) |
| RR | Risk Reduction |
| RRR | Relative Risk Reduction |
| SWAB | Dutch Working Party on Antibiotic Policy (Stichting Werkgroep Antibiotica Beleid) |
| TDM | Therapeutic Drug Monitoring |
| VAP | Ventilator-Associated Pneumonia |
| vs. | versus |

## 8 Funding and Conflict of Interest

For the development of this guideline, the SWAB was funded by the National Institute for Public Health and the Environment (RIVM-CIb), the Netherlands.

The SWAB employs strict guidelines with regard to potential conflicts of interests, as described in the SWAB Format for Guideline Development (www.swab.nl). Members of the Guideline committee have declared that they have no conflicts of interest.

## 9 Applicability

The guideline was developed and approved by a multidisciplinary committee consisting of experts delegated from the professional societies for Infectious Diseases (VIZ), Internal Medicine (NIV), Medical Microbiology (NVMM), Intensive Care (NVIC), Hospital Pharmacy (NVZA), Pediatrics (NVK),Elderly Care Medicine (Verenso), and a methodologists and quality of care expert. The guideline articulates the prevailing professional standard in March 2016 and contains general recommendations for the antibiotic treatment of hospitalized adults. It is likely that most of these recommendations are also applicable to children, but this has not been formally evaluated.

It is possible that these recommendations are not applicable in an individual patient case. The applicability of the guideline in clinical practice is the responsibility of the treating physician. There may be facts or circumstances which, in the interest of proper patient care, non-adherence to the guideline is desirable.

The validity of this guideline is five years; in 2021 or earlier if necessary, the guideline will be reevaluated.

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