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. The Guideline committee recommends to prescribe empirical antibiotic therapy according to the guideline also for other infections.	Strong Strong	Low 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. The Guideline committee also recommends that the local antibiotic guide corresponds to the national antibiotic guidelines.	Strong Strong	Low *
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. The Guideline committee recommends to perform a bedside consultation in patients with bacterial endocarditis or (intra)vascular infections. 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 Weak Strong	Very low * *
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. The Guideline committee does not recommend the use of procalcitonin for guiding treatment duration of respiratory tract infections.	Weak Weak	High 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 Costs Resistance rates	Randomized controlled trials 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 Costs Resistance rates	Randomized controlled trials 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 Costs Resistance rates	Randomized controlled trials 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 Costs Resistance rates	Randomized controlled trials 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 Costs Resistance rates	Randomized controlled trials 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 Costs Resistance rates	Randomized controlled trials 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 Costs Resistance rates	Randomized controlled trials 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 Costs Resistance rates	Randomized controlled trials 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 Costs Resistance rates	Randomized controlled trials 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 Costs Resistance rates	Randomized controlled trials 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 Costs Resistance rates	Randomized controlled trials 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 Costs Resistance rates and use of antibiotics	Randomized controlled trials 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 Costs Resistance rates	Randomized controlled trials 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 Costs Resistance rates	Randomized controlled trials Observational studies	NA

4 Methodology of developing this guideline

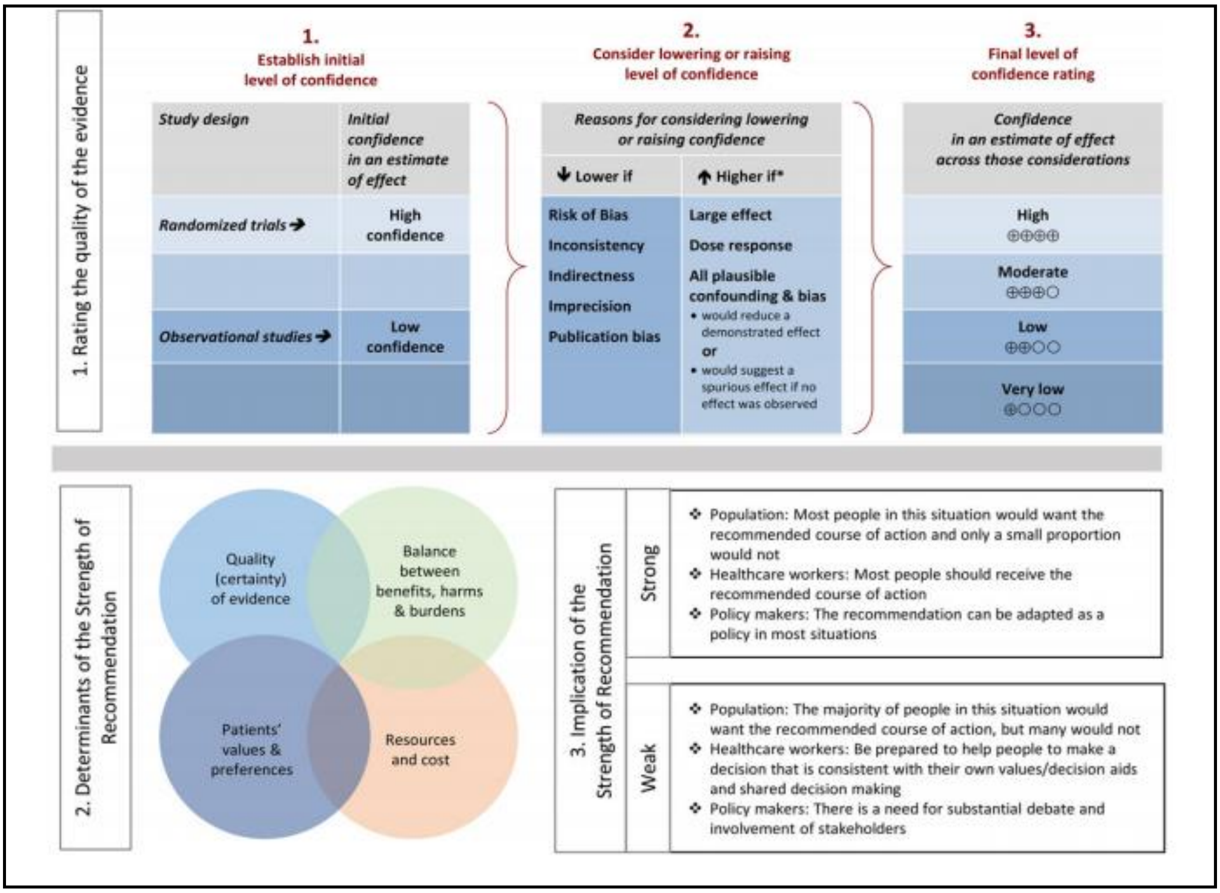
The guideline was written according to the Appraisal of Guidelines for Research & Evaluation (AGREE) instrument.[31] The recommendations in this guideline are based on the conclusions from the systematic reviews of the literature on the 14 Stewardship objectives and the Cochrane review on Stewardship 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).[ƚ]
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.

ƚ 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

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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.

10 Reference list

1. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ (Clinical research ed)* 2008; **336**(7650): 924-6.
2. Bell BG, Schellevis F, Stobberingh E, Goossens H, Pringle M. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. *BMC Infect Dis* 2014; **14**: 13.
3. WHO. Antimicrobial resistance: global report on surveillance 2014. 2014: 257.
4. Hulscher ME, Grol RP, van der Meer JW. Antibiotic prescribing in hospitals: a social and behavioural scientific approach. *Lancet Infect Dis* 2010; **10**(3): 167-75.
5. Spoorenberg V, Hulscher ME, Akkermans RP, Prins JM, Geerlings SE. Appropriate antibiotic use for patients with urinary tract infections reduces length of hospital stay. *Clin Infect Dis* 2014; **58**(2): 164-9.
6. Zarb P, Amadeo B, Muller A, et al. Identification of targets for quality improvement in antimicrobial prescribing: the web-based ESAC Point Prevalence Survey 2009. *J Antimicrob Chemother* 2011; **66**(2): 443-9.
7. Davey P, Peden C, Charani E, Marwick C, Michie S. Time for action-Improving the design and reporting of behaviour change interventions for antimicrobial stewardship in hospitals: Early findings from a systematic review. *Int J Antimicrob Agents* 2015; **45**(3): 203-12.
8. van Spreuwel PC, Blok H, Langelaar MF, Kullberg BJ, Mouton JW, Natsch S. Identifying targets for quality improvement in hospital antibiotic prescribing. *The Netherlands journal of medicine* 2015; **73**(4): 161-8.
9. Dellit TH, Owens RC, McGowan JE, Jr., et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis* 2007; **44**(2): 159-77.
10. Kaki R, Elligsen M, Walker S, Simor A, Palmay L, Daneman N. Impact of antimicrobial stewardship in critical care: a systematic review. *J Antimicrob Chemother* 2011; **66**(6): 1223-30.
11. Davey P, Brown E, Charani E, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev* 2013; (4): Cd003543.
12. Schuts EC, Hulscher ME, Mouton JW, et al. Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis. *Lancet Infect Dis* 2016.
13. Soni NJ, Samson DJ, Galaydick JL, et al. Procalcitonin-guided antibiotic therapy: a systematic review and meta-analysis. *Journal of hospital medicine* 2013; **8**(9): 530-40.
14. van den Bosch CM, Geerlings SE, Natsch S, Prins JM, Hulscher ME. Quality indicators to measure appropriate antibiotic use in hospitalized adults. *Clin Infect Dis* 2015; **60**(2): 281-91.
15. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ (Clinical research ed)* 2009; **339**: b2535.
16. Septimus EJ, Owens RC, Jr. Need and potential of antimicrobial stewardship in community hospitals. *Clin Infect Dis* 2011; **53 Suppl 1**: S8-S14.
17. Bosso JA, Drew RH. Application of antimicrobial stewardship to optimise management of community acquired pneumonia. *Int J Clin Pract* 2011; **65**(7): 775-83.
18. Charani E, Edwards R, Sevdalis N, et al. Behavior change strategies to influence antimicrobial prescribing in acute care: a systematic review. *Clin Infect Dis* 2011; **53**(7): 651-62.
19. Feazel LM, Malhotra A, Perencevich EN, Kaboli P, Diekema DJ, Schweizer ML. Effect of antibiotic stewardship programmes on Clostridium difficile incidence: a systematic review and meta-analysis. *J Antimicrob Chemother* 2014; **69**(7): 1748-54.
20. Filice G, Drekonja D, Greer N, et al. VA Evidence-based Synthesis Program Reports. Antimicrobial Stewardship Programs in Inpatient Settings: A Systematic Review. Washington (DC): Department of Veterans Affairs (US); 2013.
21. Patel D, Lawson W, Guglielmo BJ. Antimicrobial stewardship programs: interventions and associated outcomes. *Expert review of anti-infective therapy* 2008; **6**(2): 209-22.

22. Patel SJ, Larson EL, Kubin CJ, Saiman L. A review of antimicrobial control strategies in hospitalized and ambulatory pediatric populations. *The Pediatric infectious disease journal* 2007; **26**(6): 531-7.
23. Pulcini C, Botelho-Nevers E, Dyar OJ, Harbarth S. The impact of infectious disease specialists on antibiotic prescribing in hospitals. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases* 2014; **20**(10): 963-72.
24. Zhang YZ, Singh S. Antibiotic stewardship programmes in intensive care units: Why, how, and where are they leading us. *World journal of critical care medicine* 2015; **4**(1): 13-28.
25. Wagner B, Filice GA, Drekonja D, et al. Antimicrobial stewardship programs in inpatient hospital settings: a systematic review. *Infection control and hospital epidemiology* 2014; **35**(10): 1209-28.
26. Leone M, Bechis C, Baumstarck K, et al. De-escalation versus continuation of empirical antimicrobial treatment in severe sepsis: a multicenter non-blinded randomized noninferiority trial. *Intensive Care Med* 2014; **40**(10): 1399-408.
27. The Canadian Critical Care Trials Group. A randomized trial of diagnostic techniques for ventilator-associated pneumonia. *The New England journal of medicine* 2006; **355**(25): 2619-30.
28. Joffe AR, Muscedere J, Marshall JC, Su Y, Heyland DK. The safety of targeted antibiotic therapy for ventilator-associated pneumonia: a multicenter observational study. *J Crit Care* 2008; **23**(1): 82-90.
29. Buyle FM, Metz-Gercek S, Mechtler R, et al. Prospective multicentre feasibility study of a quality of care indicator for intravenous to oral switch therapy with highly bioavailable antibiotics. *J Antimicrob Chemother* 2012; **67**(8): 2043-6.
30. Sevinc F, Prins JM, Koopmans RP, et al. Early switch from intravenous to oral antibiotics: guidelines and implementation in a large teaching hospital. *J Antimicrob Chemother* 1999; **43**(4): 601-6.
31. Brouwers MC, Kho ME, Browman GP, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne* 2010; **182**(18): E839-42.
32. Pappas PG, Kauffman CA, Andes DR, et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis* 2016; **62**(4): e1-e50.
33. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *European journal of heart failure* 2012; **14**(8): 803-69.
34. Alexander PE, Gionfriddo MR, Li SA, et al. A number of factors explain why WHO guideline developers make strong recommendations inconsistent with GRADE guidance. *Journal of clinical epidemiology* 2016; **70**: 111-22.
35. Arnold FW, LaJoie AS, Brock GN, et al. Improving outcomes in elderly patients with community-acquired pneumonia by adhering to national guidelines: Community-Acquired Pneumonia Organization International cohort study results. *Archives of Internal Medicine* 2009; **169:**(16): 1515-24.
36. Asadi L, Eurich DT, Gamble JM, Minhas-Sandhu JK, Marrie TJ, Majumdar SR. Impact of guideline-concordant antibiotics and macrolide/beta-lactam combinations in 3203 patients hospitalized with pneumonia: prospective cohort study. *Clinical Microbiology & Infection* 2013; **19:**(3): 257-64.
37. Baudel JL, Tankovic J, Carrat F, et al. Does nonadherence to local recommendations for empirical antibiotic therapy on admission to the intensive care unit have an impact on in-hospital mortality? *Therapeutics & Clinical Risk Management* 2009; **5:**(3): 491-8.

38. Dambrava PG, Torres A, Valles X, et al. Adherence to guidelines' empirical antibiotic recommendations and community-acquired pneumonia outcome. *European Respiratory Journal* 2008; **32:**(4): 892-901.
39. Ewig S, Seifert K, Kleinfeld T, Goke N, Schafer H. Management of patients with community-acquired pneumonia in a primary care hospital: a critical evaluation. *Respiratory Medicine* 2000; **94:**(6): 556-63.
40. Ferrer M, Liapikou A, Valencia M, et al. Validation of the American Thoracic Society-Infectious Diseases Society of America guidelines for hospital-acquired pneumonia in the intensive care unit. *Clinical Infectious Diseases* 2010; **50:**(7): 945-52.
41. Frei CR, Attridge RT, Mortensen EM, et al. Guideline-concordant antibiotic use and survival among patients with community-acquired pneumonia admitted to the intensive care unit. *Clinical Therapeutics* 2010; **32:**(2): 293-9.
42. Frei CR, Restrepo MI, Mortensen EM, Burgess DS. Impact of guideline-concordant empiric antibiotic therapy in community-acquired pneumonia. *American Journal of Medicine* 2006; **119:**(10): 865-71.
43. Galayduyk N, Colodner R, Chazan B, Flatau E, Lavi I, Raz R. Adherence to guidelines on empiric use of antibiotics in the emergency room. *Infection* 2008; **36:**(5): 408-14.
44. Grenier C, Pepin J, Nault V, et al. Impact of guideline-consistent therapy on outcome of patients with healthcare-associated and community-acquired pneumonia. *Journal of Antimicrobial Chemotherapy* 2011; **66:**(7): 1617-24.
45. Huijts SM, van Werkhoven CH, Boersma WG, et al. Guideline adherence for empirical treatment of pneumonia and patient outcome. Treating pneumonia in the Netherlands. *Netherlands Journal of Medicine* 2013; **71:**(10): 502-7.
46. Kett DH, Cano E, Quartin AA, et al. Implementation of guidelines for management of possible multidrug-resistant pneumonia in intensive care: an observational, multicentre cohort study. *The Lancet Infectious Diseases* 2011; **11:**(3): 181-9.
47. Malone DC, Shaban HM. Adherence to ATS guidelines for hospitalized patients with community-acquired pneumonia. *Ann Pharmacother* 2001; **35**(10): 1180-5.
48. Marras TK, Jamieson L, Chan CK. Inpatient care of community-acquired pneumonia: the effect of antimicrobial guidelines on clinical outcomes and drug costs in Canadian teaching hospitals. *Canadian Respiratory Journal* 2004; **11:**(2): 131-7.
49. Maxwell DJ, McIntosh KA, Pulver LK, Easton KL. Empiric management of community-acquired pneumonia in Australian emergency departments. *Medical Journal of Australia* 2005; **183:**(10): 520-4.
50. Menendez R, Ferrando D, Valles JM, Vallterra J. Influence of deviation from guidelines on the outcome of community-acquired pneumonia. *Chest* 2002; **122:**(2): 612-7.
51. Menendez R, Reyes S, Martinez R, de la Cuadra P, Valles JM, Vallterra J. Economic evaluation of adherence to treatment guidelines in nonintensive care pneumonia. *European Respiratory Journal* 2007; **29**(4): 751-6.
52. Menendez R, Torres A, Zalacain R, et al. Guidelines for the treatment of community-acquired pneumonia: predictors of adherence and outcome. *American Journal of Respiratory & Critical Care Medicine* 2005; **172:**(6): 757-62.
53. Mortensen EM, Restrepo M, Anzueto A, Pugh J. Effects of guideline-concordant antimicrobial therapy on mortality among patients with community-acquired pneumonia. *American Journal of Medicine* 2004; **117:**(10): 726-31.
54. Newman J, Thompson C, Hussain Z, Bombassaro AM. Empiric antibiotic prescribing practice in febrile neutropenia: Compliance with IDSA guidelines. *Canadian Journal of Hospital Pharmacy* 2001; **54**: 255-63.
55. Pagano L, Caira M, Offidani M, et al. Adherence to international guidelines for the treatment of invasive aspergillosis in acute myeloid leukaemia: feasibility and utility (SEIFEM-2008B study). *Journal of Antimicrobial Chemotherapy* 2010; **65:**(9): 2013-8.

56. Pradelli J, Risso K, de Salvador FG, Cua E, Ruimy R, Roger PM. Community-acquired pneumonia: impact of empirical antibiotic therapy without respiratory fluoroquinolones nor third-generation cephalosporins. *European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology* 2014.
57. Reyes CS, Martinez TR, Cremades Romero MJ, Martinez ME, Soler Cataluna JJ, Menendez VR. Empiric treatment in hospitalized community-acquired pneumonia. Impact on mortality, length of stay and re-admission. *Respiratory Medicine* 2007; **101:**(9): 1909-15.
58. Silveira CD, Ferreira CS, Correa Rde A. Adherence to guidelines and its impact on outcomes in patients hospitalized with community-acquired pneumonia at a university hospital. *Jornal Brasileiro De Pneumologia: Publicacao Oficial Da Sociedade Brasileira De Pneumologia E Tisilogia* 2012; **38**(2): 148-57.
59. Triantafyllidis C, Kapordelis V, Papaetis GS, et al. Guidelines adherence for patients with community acquired pneumonia in a Greek hospital. *Eur Rev Med Pharmacol Sci* 2012; **16**(1): 1-9.
60. Wilke M, Grube RF, Bodmann KF. Guideline-adherent initial intravenous antibiotic therapy for hospital-acquired/ventilator-associated pneumonia is clinically superior, saves lives and is cheaper than non guideline adherent therapy. *European Journal of Medical Research* 2011; **16:**(7): 315-23.
61. Blasi F, Iori I, Bulfoni A, Corrao S, Costantino S, Legnani D. Can CAP guideline adherence improve patient outcome in internal medicine departments?.[Erratum appears in Eur Respir J. 2009 Jan;33(1):223]. *European Respiratory Journal* 2008; **32:**(4): 902-10.
62. Dean NC, Bateman KA, Donnelly SM, Silver MP, Snow GL, Hale D. Improved clinical outcomes with utilization of a community-acquired pneumonia guideline. *Chest* 2006; **130**(3): 794-9.
63. Garcia JC, Ferreira Filho OF, Grion CM, Carrilho CM. Impact of the implementation of a therapeutic guideline on the treatment of nosocomial pneumonia acquired in the intensive care unit of a university hospital. *Jornal Brasileiro De Pneumologia: Publicacao Oficial Da Sociedade Brasileira De Pneumologia E Tisilogia* 2007; **33:**(2): 175-84.
64. Marras TK, Chan CK. Use of guidelines in treating community-acquired pneumonia. *Chest* 1998; **113:**(6): 1689-94.
65. Sakaguchi M, Shime N, Iguchi N, Kobayashi A, Takada K, Morrow LE. Effects of adherence to ventilator-associated pneumonia treatment guidelines on clinical outcomes. *Journal of Infection & Chemotherapy* 2013; **19:**(4): 599-606.
66. Diaz A, Kuzmanic G, Platzer L, Sanfuentes F, Espinoza MA, Saldias F. [Medical outcomes and antimicrobial compliance according to the Chilean Society of Respiratory Diseases guidelines for hospitalized patients with community acquired pneumonia]. [Spanish]. *Revista Medica de Chile* 2003; **131:**(8): 847-56.
67. Horn D, Neofytos D, Fishman J, et al. Use of the PATH Alliance database to measure adherence to IDSA guidelines for the therapy of candidemia. *European Journal of Clinical Microbiology & Infectious Diseases* 2007; **26**(12): 907-14.
68. Miletin MS, Chan CK. The use of guidelines for the empirical treatment of hospital-acquired pneumonia. *Canadian Respiratory Journal* 2001; **8**: 255-60.
69. Huvent-Grelle D, Puisieux F, Tettart-Hevin K, et al. [Lung diseases in the elderly. Assessment of guidelines for the probabilistic prescription of antibiotics in a department of geriatric care]. [French]. *Presse Medicale* 2004; **33:**(8): 522-9.
70. Georges H, Chiche A, Alfandari S, Devos P, Boussekey N, Leroy O. Adult community-acquired bacterial meningitis requiring ICU admission: epidemiological data, prognosis factors and adherence to IDSA guidelines. *European Journal of Clinical Microbiology & Infectious Diseases* 2009; **28:**(11): 1317-25.
71. Mak CF, Choi DK, Wong RS, You JH. Clinical and economic analyses of antimicrobial therapy in fever wards of a Hong Kong teaching hospital. *International Journal of Clinical Pharmacology & Therapeutics* 2007; **45:**(12): 654-8.

72. Orrick JJ, Segal R, Johns TE, Russell W, Wang F, Yin DD. Resource use and cost of care for patients hospitalised with community acquired pneumonia: impact of adherence to infectious diseases society of america guidelines. *Pharmacoeconomics* 2004; **22**(11): 751-7.
73. Dik.J.H., Lo-Ten-Foe. J.R., Sinha. B., et al. Performing diagnostics, especially blood cultures, on-time for infectious patients reduces length of stay and costs. Abstract presented at the 25th ECCMID, April 25-28, 2015, Copenhagen.
74. Alvarez-Lerma F, Alvarez B, Luque P, et al. Empiric broad-spectrum antibiotic therapy of nosocomial pneumonia in the intensive care unit: a prospective observational study. *Crit Care* 2006; **10**(3): R78.
75. Bal AM, Shankland GS, Scott G, Imtiaz T, Macaulay R, McGill M. Antifungal step-down therapy based on hospital intravenous to oral switch policy and susceptibility testing in adult patients with candidaemia: a single centre experience. *Int J Clin Pract* 2014; **68**(1): 20-7.
76. Cremers AJ, Sprong T, Schouten JA, et al. Effect of antibiotic streamlining on patient outcome in pneumococcal bacteraemia. *J Antimicrob Chemother* 2014.
77. Eachempati SR, Hydo LJ, Shou J, Barie PS. Does de-escalation of antibiotic therapy for ventilator-associated pneumonia affect the likelihood of recurrent pneumonia or mortality in critically ill surgical patients? *J Trauma* 2009; **66**(5): 1343-8.
78. Elhanan G, Sarhat M, Raz R. Empiric antibiotic treatment and the misuse of culture results and antibiotic sensitivities in patients with community-acquired bacteraemia due to urinary tract infection. *Journal of Infection* 1997; **35**(3): 283-8.
79. Garnacho-Montero J, Gutierrez-Pizarraya A, Escoresca-Ortega A, et al. De-escalation of empirical therapy is associated with lower mortality in patients with severe sepsis and septic shock. *Intensive Care Medicine* 2014; **40**(1): 32-40.
80. Giantsou E, Liratzopoulos N, Efraimidou E, et al. De-escalation therapy rates are significantly higher by bronchoalveolar lavage than by tracheal aspirate. *Intensive Care Medicine* 2007; **33**(9): 1533-40.
81. Khasawneh FA, Karim A, Mahmood T, Ahmed S, Jaffri SF, Mehmood M. Safety and feasibility of antibiotic de-escalation in bacteremic pneumonia. *Infect* 2014; **7**: 177-82.
82. Khasawneh FA, Karim A, Mahmood T, et al. Antibiotic de-escalation in bacteremic urinary tract infections: potential opportunities and effect on outcome. *Infection* 2014; **42**(5): 829-34.
83. Knaak E, Cavalieri SJ, Elsasser GN, Preheim LC, Gonitzke A, Destache CJ. Does antibiotic de-escalation for nosocomial pneumonia impact intensive care unit length of stay? *Infectious Diseases in Clinical Practice* 2013; **21**(3): 172-6.
84. Kollef MH, Morrow LE, Niederman MS, et al. Clinical characteristics and treatment patterns among patients with ventilator-associated pneumonia. *Chest* 2006; **129**(5): 1210-8.
85. Koupetori M, Retsas T, Antonakos N, et al. Bloodstream infections and sepsis in Greece: over-time change of epidemiology and impact of de-escalation on final outcome. *BMC Infect Dis* 2014; **14**: 272.
86. Mokart D, Slehofer G, Lambert J, et al. De-escalation of antimicrobial treatment in neutropenic patients with severe sepsis: results from an observational study. *Intensive Care Medicine* 2014; **40:**(1): 41-9.
87. Schlueter M, James C, Dominguez A, Tsu L, Seymann G. Practice patterns for antibiotic de-escalation in culture-negative healthcare-associated pneumonia. *Infection* 2010; **38**(5): 357-62.
88. Schweizer ML, Furuno JP, Harris AD, et al. Comparative effectiveness of nafcillin or cefazolin versus vancomycin in methicillin-susceptible Staphylococcus aureus bacteremia. *BMC Infect Dis* 2011; **11**: 279.
89. Shime N, Kosaka T, Fujita N. De-escalation of antimicrobial therapy for bacteraemia due to difficult-to-treat Gram-negative bacilli. *Infection* 2013; **41**(1): 203-10.
90. Shime N, Satake S, Fujita N. De-escalation of antimicrobials in the treatment of bacteraemia due to antibiotic-sensitive pathogens in immunocompetent patients. *Infection* 2011; **39**(4): 319-25.

91. Berild D, Mohseni A, Diep LM, Jensenius M, Ringertz SH. Adjustment of antibiotic treatment according to the results of blood cultures leads to decreased antibiotic use and costs. *Journal of Antimicrobial Chemotherapy* 2006; **57:**(2): 326-30.
92. Cortoos PJ, Gilissen C, Laekeman G, et al. Length of stay after reaching clinical stability drives hospital costs associated with adult community-acquired pneumonia. *Scand J Infect Dis* 2013; **45**(3): 219-26.
93. Cunney RJ, McNamara EB, Alansari N, Loo B, Smyth EG. The impact of blood culture reporting and clinical liaison on the empiric treatment of bacteraemia. *Journal of Clinical Pathology* 1997; **50:**(12): 1010-2.
94. Engel MF, van Velzen M, Hoepelman AI, Thijsen S, Oosterheert JJ. Positive urinary antigen tests for Streptococcus pneumoniae in community-acquired pneumonia: a 7-year retrospective evaluation of health care cost and treatment consequences. *European Journal of Clinical Microbiology & Infectious Diseases* 2013; **32**(4): 485-92.
95. Schentag JJ, Ballow CH, Fritz AL, et al. Changes in antimicrobial agent usage resulting from interactions among clinical pharmacy, the infectious disease division, and the microbiology laboratory. *Diagn Microbiol Infect Dis* 1993; **16**(3): 255-64.
96. Oosterheert JJ, Bonten MJ, Buskens E, Schneider MM, Hoepelman IM. Algorithm to determine cost savings of targeting antimicrobial therapy based on results of rapid diagnostic testing. *J Clin Microbiol* 2003; **41**(10): 4708-13.
97. Jiang SP, Zhu ZY, Ma KF, Zheng X, Lu XY. Impact of pharmacist antimicrobial dosing adjustments in septic patients on continuous renal replacement therapy in an intensive care unit. *Scand J Infect Dis* 2013; **45**(12): 891-9.
98. Ritchie DJ, Reichley RM, Canaday KL, Bailey TC. Evaluation and financial impact of imipenem/cilastatin dosing in elderly patients based on renal function and body weight. *J Pharm Technol* 1993; **9**(4): 160-3.
99. Tachi T, Teramachi H, Asano S, et al. Impact of levofloxacin dose adjustments by dispensing pharmacists on adverse reactions and costs in the treatment of elderly patients. *Pharmazie* 2013; **68**(12): 977-82.
100. Helmons PJ, Grouls RJ, Roos AN, et al. Using a clinical decision support system to determine the quality of antimicrobial dosing in intensive care patients with renal insufficiency. *Qual Saf Health Care* 2010; **19**(1): 22-6.
101. Preston SL, Briceland LL, Lomaestro BM, Lesar TS, Bailie GR, Drusano GL. Dosing adjustment of 10 antimicrobials for patients with renal impairment. *Ann Pharmacother* 1995; **29**(12): 1202-7.
102. Hermanides HS, Hulscher ME, Schouten JA, Prins JM, Geerlings SE. Development of quality indicators for the antibiotic treatment of complicated urinary tract infections: a first step to measure and improve care. *Clin Infect Dis* 2008; **46**(5): 703-11.
103. van den Bosch CM, Hulscher ME, Natsch S, Wille J, Prins JM, Geerlings SE. Applicability of Generic Quality Indicators for Appropriate Antibiotic Use in Daily Hospital Practice: a Cross-sectional Point-prevalence multicenter Study. *Clin Microbiol Infect, 2016 Jul 15 [Epub ahead of print]* 2016.
104. Omidvari K, de Boisblanc BP, Karam G, Nelson S, Haponik E, Summer W. Early transition to oral antibiotic therapy for community-acquired pneumonia: duration of therapy, clinical outcomes, and cost analysis. *Respiratory Medicine* 1998; **92**(8): 1032-9.
105. Oosterheert JJ, Bonten MJM, Schneider MME, et al. Effectiveness of early switch from intravenous to oral antibiotics in severe community acquired pneumonia: Multicentre randomised trial. *British Medical Journal* 2006; **333**(7580): 1193-5.
106. Terg R, Cobas S, Fassio E, et al. Oral ciprofloxacin after a short course of intravenous ciprofloxacin in the treatment of spontaneous bacterial peritonitis: results of a multicenter, randomized study. *J Hepatol* 2000; **33**(4): 564-9.
107. Vogel F, Bodem G, Huth K, Kunze M, Rosch W, Koch HU. Treatment of lower respiratory tract infections, including pneumonia. A study comparing cefotaxime i.v. followed by cefixime oral with parenteral cefotaxime. [German]. *Fortschritte der Medizin* 1994; **112**(28): 41-4.

108. Castro-Guardiola A, Viejo-Rodriguez AL, Soler-Simon S, et al. Efficacy and safety of oral and early-switch therapy for community-acquired pneumonia: a randomized controlled trial. *The American journal of medicine* 2001; **111**(5): 367-74.
109. Ng FH, Wong WM, Wong BC, et al. Sequential intravenous/oral antibiotic vs. continuous intravenous antibiotic in the treatment of pyogenic liver abscess. *Aliment Pharmacol Ther* 2002; **16**(6): 1083-90.
110. Paladino JA, Sperry HE, Backes JM, et al. Clinical and economic evaluation of oral ciprofloxacin after an abbreviated course of intravenous antibiotics. *American Journal of Medicine* 1991; **91**(5): 462-70.
111. Monmaturapoj T, Montakantikul P, Mootsikapun P, Tragulpiankit P. A prospective, randomized, double dummy, placebo-controlled trial of oral cefditoren pivoxil 400mg once daily as switch therapy after intravenous ceftriaxone in the treatment of acute pyelonephritis. *Int J Infect Dis* 2012; **16**(12): e843-9.
112. Kohno S, Yanagihara K, Yamamoto Y, et al. Early switch therapy from intravenous sulbactam/ampicillin to oral garenoxacin in patients with community-acquired pneumonia: a multicenter, randomized study in Japan. *Journal of Infection & Chemotherapy* 2013; **19**(6): 1035-41.
113. Gangji D, Jacobs F, de Jonckheer J, et al. Randomized study of intravenous versus sequential intravenous/oral regimen of ciprofloxacin in the treatment of gram-negative septicemia. *American Journal of Medicine* 1989; **87**(5A): 206S-8S.
114. Amodio-Groton M, Madu A, Madu CN, et al. Sequential parenteral and oral ciprofloxacin regimen versus parenteral therapy for bacteremia: a pharmacoeconomic analysis. *Ann Pharmacother* 1996; **30**(6): 596-602.
115. Daver NG, Shelburne SA, Atmar RL, et al. Oral step-down therapy is comparable to intravenous therapy for Staphylococcus aureus osteomyelitis. *Journal of Infection* 2007; **54**(6): 539-44.
116. Regnier B. [Comparative study of intravenous ceftriaxone followed by oral cefixime versus ceftriaxone alone in the treatment of severe upper urinary tract infections]. *Presse Medicale* 1989; **18**(32): 1617-21.
117. Siegel RE, Halpern NA, Almenoff PL, Lee A, Cashin R, Greene JG. A prospective randomized study of inpatient iv. antibiotics for community-acquired pneumonia. The optimal duration of therapy. *Chest* 1996; **110**(4): 965-71.
118. Ribas Y, Bombardo J, Aguilar F, et al. Prospective randomized clinical trial assessing the efficacy of a short course of intravenously administered amoxicillin plus clavulanic acid followed by oral antibiotic in patients with uncomplicated acute diverticulitis. *Int J Colorectal Dis* 2010; **25**(11): 1363-70.
119. Burton ME, Ash CL, Hill DP, Jr., Handy T, Shepherd MD, Vasko MR. A controlled trial of the cost benefit of computerized bayesian aminoglycoside administration. *Clinical pharmacology and therapeutics* 1991; **49**(6): 685-94.
120. Dillon KR, Dougherty SH, Casner P, Polly S. Individualized pharmacokinetic versus standard dosing of amikacin: a comparison of therapeutic outcomes. *J Antimicrob Chemother* 1989; **24**(4): 581-9.
121. Fernandez de Gatta MD, Calvo MV, Hernandez JM, Caballero D, San Miguel JF, Dominguez-Gil A. Cost-effectiveness analysis of serum vancomycin concentration monitoring in patients with hematologic malignancies. *Clin Pharmacol Ther* 1996; **60**(3): 332-40.
122. Park WB, Kim NH, Kim KH, et al. The effect of therapeutic drug monitoring on safety and efficacy of voriconazole in invasive fungal infections: a randomized controlled trial. *Clinical Infectious Diseases* 2012; **55**(8): 1080-7.
123. Crist KD, Nahata MC, Ety J. Positive impact of a therapeutic drug-monitoring program on total aminoglycoside dose and cost of hospitalization. *Therapeutic Drug Monitoring* 1987; **9**(3): 306-10.

124. Destache CJ, Meyer SK, Bittner MJ, Hermann KG. Impact of a clinical pharmacokinetic service on patients treated with aminoglycosides: A cost-benefit analysis. *Therapeutic Drug Monitoring* 1990; **12**(5): 419-26.
125. Destache CJ, Meyer SK, Padomek MT, Ortmeier BG. Impact of a clinical pharmacokinetic service on patients treated with aminoglycosides for gram-negative infections. *DICP : the annals of pharmacotherapy* 1989; **23**(1): 33-8.
126. van Lent-Evers NA, Mathot RA, Geus WP, van Hout BA, Vinks AA. Impact of goal-oriented and model-based clinical pharmacokinetic dosing of aminoglycosides on clinical outcome: a cost-effectiveness analysis. *Therapeutic Drug Monitoring* 1999; **21**(1): 63-73.
127. Sveska KJ, Roffe BD, Solomon DK, Hoffmann RP. Outcome of patients treated by an aminoglycoside pharmacokinetic dosing service. *American Journal of Hospital Pharmacy* 1985; **42**(11): 2472-8.
128. Welty TE, Copa AK. Impact of vancomycin therapeutic drug monitoring on patient care. *Ann Pharmacother* 1994; **28**(12): 1335-9.
129. Bootman JL, Wertheimer AI, Zaske D, Rowland C. Individualizing gentamicin dosage regimens in burn patients with gram-negative septicemia: a cost--benefit analysis. *Journal of pharmaceutical sciences* 1979; **68**(3): 267-72.
130. Karam CM, McKinnon PS, Neuhauser MM, Rybak MJ. Outcome assessment of minimizing vancomycin monitoring and dosing adjustments. *Pharmacotherapy* 1999; **19**(3): 257-66.
131. Leon-Djian CB, Bourguignon L, Spath HM, Maire P. [Cost-effectiveness analysis of active TDM in elderly patients treated with aminoglycosides]. *Therapie* 2011; **66**(5): 445-52.
132. Raman K, Nailor MD, Nicolau DP, Aslanzadeh J, Nadeau M, Kuti JL. Early antibiotic discontinuation in patients with clinically suspected ventilator-associated pneumonia and negative quantitative bronchoscopy cultures. *Crit Care Med* 2013; **41**(7): 1656-63.
133. Singh N, Rogers P, Atwood CW, Wagener MM, Yu VL. Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. A proposed solution for indiscriminate antibiotic prescription. *American journal of respiratory and critical care medicine* 2000; **162**(2 Pt 1): 505-11.
134. Micek ST, Ward S, Fraser VJ, Kollef MH. A randomized controlled trial of an antibiotic discontinuation policy for clinically suspected ventilator-associated pneumonia. *Chest* 2004; **125**(5): 1791-9.
135. Montravers P, Dupont H, Gauzit R, et al. Strategies of initiation and streamlining of antibiotic therapy in 41 French intensive care units. *Crit Care* 2011; **15**(1): R17.
136. Schuts EC, van den Bosch CM, Gyssens IC, et al. Adoption of a national antimicrobial guide (SWAB-ID) in the Netherlands. *European journal of clinical pharmacology* 2016; **72**(2): 249-52.
137. Tsiata C, Tsekouras V, Karokis A, et al. Cost effectiveness of antibacterial restriction strategies in a tertiary care university teaching hospital. *Disease Management and Health Outcomes* 2001; **9**(1): 23-32.
138. Mansouri MD, Cadle RM, Agbahiwe SO, Musher DM. Impact of an antibiotic restriction program on antibiotic utilization in the treatment of community-acquired pneumonia in a Veterans Affairs Medical Center. *Infection* 2011; **39**(1): 53-8.
139. Mach R, Vlcek J, Prusova M, Batka P, Rysavy V, Kubena A. Impact of a multidisciplinary approach on antibiotic consumption, cost and microbial resistance in a Czech hospital. *Pharm World Sci* 2007; **29**(5): 565-72.
140. Anassi EO, Ericsson C, Lal L, McCants E. Using a pharmaceutical restriction program to control antibiotic use. *Formulary* 1995; **30**(11): 711-4.
141. Aubert G, Carricajo A, Vautrin AC, et al. Impact of restricting fluoroquinolone prescription on bacterial resistance in an intensive care unit. *J Hosp Infect* 2005; **59**(2): 83-9.
142. Du B, Chen D, Liu D, et al. Restriction of third-generation cephalosporin use decreases infection-related mortality. *Crit Care Med* 2003; **31**(4): 1088-93.

143. Lan CK, Hsueh PR, Wong WW, et al. Association of antibiotic utilization measures and reduced incidence of infections with extended-spectrum beta-lactamase-producing organisms. *J Microbiol Immunol Infect* 2003; **36**(3): 182-6.
144. Medina Presentado JC, Paciel Lopez D, Berro Castiglioni M, Gerez J. Ceftriaxone and ciprofloxacin restriction in an intensive care unit: less incidence of Acinetobacter spp. and improved susceptibility of Pseudomonas aeruginosa. *Rev Panam Salud Publica* 2011; **30**(6): 603-9.
145. Ntagiopoulos PG, Paramythiotou E, Antoniadou A, Giamarellou H, Karabinis A. Impact of an antibiotic restriction policy on the antibiotic resistance patterns of Gram-negative microorganisms in an Intensive Care Unit in Greece. *Int J Antimicrob Agents* 2007; **30**(4): 360-5.
146. White AC, Jr., Atmar RL, Wilson J, Cate TR, Stager CE, Greenberg SB. Effects of requiring prior authorization for selected antimicrobials: expenditures, susceptibilities, and clinical outcomes. *Clin Infect Dis* 1997; **25**(2): 230-9.
147. Arda B, Sipahi OR, Yamazhan T, et al. Short-term effect of antibiotic control policy on the usage patterns and cost of antimicrobials, mortality, nosocomial infection rates and antibacterial resistance. *Journal of Infection* 2007; **55**(1): 41-8.
148. Ozkurt Z, Erol S, Kadanali A, Ertek M, Ozden K, Tasyaran MA. Changes in antibiotic use, cost and consumption after an antibiotic restriction policy applied by infectious disease specialists. *Jpn J Infect Dis* 2005; **58**(6): 338-43.
149. Altunsoy A, Aypak C, Azap A, Ergonul O, Balik I. The impact of a nationwide antibiotic restriction program on antibiotic usage and resistance against nosocomial pathogens in Turkey. *Int J Med Sci* 2011; **8**(4): 339-44.
150. Martin C, Ofotokun I, Rapp R, et al. Results of an antimicrobial control program at a university hospital. *Am J Health-Syst Pharm* 2005; **62**(7): 732-8.
151. Morgan AS, Brennan PJ, Fishman NO. Impact of a vancomycin restriction policy on use and cost of vancomycin and incidence of vancomycin-resistant Enterococcus. *Ann Pharmacother* 1997; **31**(9): 970-3.
152. Woodward RS, Medoff G, Smith MD, Gray JL, 3rd. Antibiotic cost savings from formulary restrictions and physician monitoring in a medical-school-affiliated hospital. *American Journal of Medicine* 1987; **83**(5): 817-23.
153. Dancer SJ, Kirkpatrick P, Corcoran DS, Christison F, Farmer D, Robertson C. Approaching zero: temporal effects of a restrictive antibiotic policy on hospital-acquired Clostridium difficile, extended-spectrum beta-lactamase-producing coliforms and meticillin-resistant Staphylococcus aureus. *Int J Antimicrob Agents* 2013; **41**(2): 137-42.
154. Pakyz AL, Oinonen M, Polk RE. Relationship of carbapenem restriction in 22 university teaching hospitals to carbapenem use and carbapenem-resistant Pseudomonas aeruginosa. *Antimicrob Agents Chemother* 2009; **53**(5): 1983-6.
155. Bassetti M, Righi E, Ansaldi F, et al. Impact of limited cephalosporin use on prevalence of methicillin-resistant Staphylococcus aureus in the intensive care unit. *J Chemother* 2009; **21**(6): 633-8.
156. Brahmi N, Blel Y, Kouraichi N, et al. Impact of ceftazidime restriction on gram-negative bacterial resistance in an intensive care unit. *Journal of Infection & Chemotherapy* 2006; **12**(4): 190-4.
157. Falagas ME, Bliziotis IA, Michalopoulos A, et al. Effect of a policy for restriction of selected classes of antibiotics on antimicrobial drug cost and resistance. *J Chemother* 2007; **19**(2): 178-84.
158. Kim JY, Sohn JW, Park DW, Yoon YK, Kim YM, Kim MJ. Control of extended-spectrum {beta}-lactamase-producing Klebsiella pneumoniae using a computer-assisted management program to restrict third-generation cephalosporin use. *Journal of Antimicrobial Chemotherapy* 2008; **62**(2): 416-21.
159. de Jong E, van Oers JA, Beishuizen A, et al. Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial. *Lancet Infect Dis* 2016.

160. Petrikkos G, Markogiannakis A, Papaparaskevas J, et al. Differences in the changes in resistance patterns to third- and fourth-generation cephalosporins and piperacillin/tazobactam among Klebsiella pneumoniae and Escherichia coli clinical isolates following a restriction policy in a Greek tertiary care hospital.[Erratum appears in Int J Antimicrob Agents. 2007 Sep;30(3):287 Note: Papapareskevas Joseph [corrected to Papaparaskevas, Joseph]]. *Int J Antimicrob Agents* 2007; **29**(1): 34-8.
161. Regal RE, DePestel DD, VandenBussche HL. The effect of an antimicrobial restriction program on Pseudomonas aeruginosa resistance to beta-lactams in a large teaching hospital. *Pharmacotherapy* 2003; **23**(5): 618-24.
162. Sistanizad M, Kouchek M, Miri M, et al. Carbapenem Restriction and its Effect on Bacterial Resistance in an Intensive Care unit of a Teaching Hospital. *Iran* 2013; **12**(3): 503-9.
163. Raineri E, Pan A, Mondello P, Acquarolo A, Candiani A, Crema L. Role of the infectious diseases specialist consultant on the appropriateness of antimicrobial therapy prescription in an intensive care unit. *American Journal of Infection Control* 2008; **36:**(4): 283-90.
164. Lahey T, Shah R, Gittzus J, Schwartzman J, Kirkland K. Infectious diseases consultation lowers mortality from Staphylococcus aureus bacteremia. *Medicine* 2009; **88**(5): 263-7.
165. Forsblom E, Ruotsalainen E, Ollgren J, Jarvinen A. Telephone consultation cannot replace bedside infectious disease consultation in the management of Staphylococcus aureus Bacteremia. *Clinical Infectious Diseases* 2013; **56**(4): 527-35.
166. Rieg S, Peyerl-Hoffmann G, de With K, et al. Mortality of S. aureus bacteremia and infectious diseases specialist consultation--a study of 521 patients in Germany. *The Journal of infection* 2009; **59**(4): 232-9.
167. Honda H, Krauss MJ, Jones JC, Olsen MA, Warren DK. The value of infectious diseases consultation in Staphylococcus aureus bacteremia. *The American journal of medicine* 2010; **123**(7): 631-7.
168. Classen DC, Burke JP, Wenzel RP. Infectious diseases consultation: impact on outcomes for hospitalized patients and results of a preliminary study. *Clin Infect Dis* 1997; **24**(3): 468-70.
169. Lemmen SW, Hafner H, Kotterik S, Lutticken R, Topper R. Influence of an infectious disease service on antibiotic prescription behavior and selection of multiresistant pathogens. *Infection* 2000; **28**(6): 384-7.
170. van Buul LW, van der Steen JT, Veenhuizen RB, et al. Antibiotic use and resistance in long term care facilities. *J Am Med Dir Assoc* 2012; **13**(6): 568.e1-13.
171. Lim CJ, Kong DC, Stuart RL. Reducing inappropriate antibiotic prescribing in the residential care setting: current perspectives. *Clin Interv Aging* 2014; **9**: 165-77.
172. Lim CJ, Kwong M, Stuart RL, et al. Antimicrobial stewardship in residential aged care facilities: need and readiness assessment. *BMC Infect Dis* 2014; **14**: 410.
173. Assink-de Jong E, de Lange DW, van Oers JA, Nijsten MW, Twisk JW, Beishuizen A. Stop Antibiotics on guidance of Procalcitonin Study (SAPS): a randomised prospective multicenter investigator-initiated trial to analyse whether daily measurements of procalcitonin versus a standard-of-care approach can safely shorten antibiotic duration in intensive care unit patients--calculated sample size: 1816 patients. *BMC Infect Dis* 2013; **13**: 178.
174. Grimshaw JM, Thomas RE, MacLennan G, et al. Effectiveness and efficiency of guideline dissemination and implementation strategies. *Health technology assessment (Winchester, England)* 2004; **8**(6): iii-iv, 1-72.
175. Oxman AD, Thomson MA, Davis DA, Haynes RB. No magic bullets: a systematic review of 102 trials of interventions to improve professional practice. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne* 1995; **153**(10): 1423-31.
176. Teixeira Rodrigues A, Roque F, Falcao A, Figueiras A, Herdeiro MT. Understanding physician antibiotic prescribing behaviour: a systematic review of qualitative studies. *Int J Antimicrob Agents* 2013; **41**(3): 203-12.