European society of clinical microbiology and infectious diseases guidelines for antimicrobial stewardship in emergency departments (endorsed by European association of hospital pharmacists)

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Guidelines

European society of clinical microbiology and infectious diseases guidelines for antimicrobial stewardship in emergency departments (endorsed by European association of hospital pharmacists)

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ABSTRACT

Scope: This European Society of Clinical Microbiology and Infectious Diseases guideline provides evidence-based recommendations to support a selection of appropriate antibiotic use practices for patients seen in the emergency department (ED) and guidance for their implementation. The topics addressed in this guideline are (a) Do biomarkers or rapid pathogen tests improve antibiotic prescribing and/or clinical outcomes? (b) Does taking blood cultures in common infectious syndromes improve antibiotic prescribing and/or clinical outcomes? (c) Does watchful waiting without antibacterial therapy or with delayed antibiotic prescribing reduce antibiotic prescribing without worsening clinical outcomes in patients with specific infectious syndromes? (d) Do structured culture follow-up programs in patients discharged from the ED with cultures pending improve antibiotic prescribing?
Methods: An expert panel was convened by European Society of Clinical Microbiology and Infectious Diseases and the guideline chair. The panel selected in consensus the four most relevant antimicrobial stewardship topics according to pre-defined relevance criteria. For each main question for the four topics,

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Diagnostic tests
Emergency department
Guideline
Implementation
Rapid tests
Recommendations
Watchful waiting

a systematic review was performed, including randomized controlled trials and observational studies. Both clinical outcomes and stewardship process outcomes related to antibiotic use were deemed relevant. The literature searches were conducted between May 2021 and March 2022. In April 2022, the panel members were formally asked to suggest additional studies that were not identified in the initial searches. Data were summarized in a meta-analysis if possible or otherwise summarized narratively. The certainty of the evidence was classified according to the Grading of Recommendations Assessment, Development and Evaluation criteria. The guideline panel reviewed the evidence per topic critically appraising the evidence and formulated recommendations through a consensus-based process. The strength of the recommendations was classified as strong or weak. To substantiate the implementation process, implementation trials or observational studies describing facilitators/barriers for implementation were identified from the same searches and were summarized narratively.

Recommendations: The recommendations on the use of biomarkers and rapid pathogen diagnostic tests focus on the initiation of antibiotics in patients admitted through the ED. Their effect on the discontinuation or de-escalation of antibiotics during hospital stay was not reported, neither was their effect on hospital infection prevention and control practices. The recommendations on watchful waiting (i.e. withholding antibiotics with some form of follow-up) focus on specific infectious syndromes for which the primary care literature was also included. The recommendations on blood cultures focus on the indication in three common infectious syndromes in the ED explicitly excluding patients with sepsis or septic shock. Most recommendations are based on very low and low certainty of evidence, leading to weak recommendations or, when no evidence was available, to best practice statements. Implementation of these recommendations needs to be adapted to the specific settings and circumstances of the ED. The scarcity of high-quality studies in the area of antimicrobial stewardship in the ED highlights the need for future research in this field. **Teske Schoffelen, Clin Microbiol Infect 2024;30:1384**

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Scope

Antimicrobial use, including their overuse and misuse, is an important driver of antimicrobial resistance (AMR) [1,2]. Antimicrobial stewardship (AMS) is a key component of a multifaceted approach to mitigate the emergence of AMR and can be defined as a persistent effort by healthcare institutions to measure and improve the appropriate use of antimicrobials [3]. Appropriate antimicrobial prescribing requires the right diagnosis, drug, dose, duration and de-escalation (5Ds of stewardship). The primary goal of AMS is to optimize clinical outcomes (i.e. patient outcomes) while minimizing the unintended consequences of antimicrobial use, including adverse events, the selection of pathogenic organisms and the emergence of resistance [4].

The emergency department (ED) is an underrepresented setting in the literature on AMS interventions [5,6], and specific guidance on AMS in the ED is lacking. ED clinicians usually are not involved in hospitals' AMS committees [7,8]. However, a significant proportion of antibiotics prescribing for admitted patients with infection are initiated in the ED, making this setting a crucial focus of AMS programs. Furthermore, antibiotics started in the ED are often continued in the inpatient setting. Some initiatives such as the surviving sepsis guidelines address only a narrow subset of antibiotic prescribing in the ED (patients with sepsis) [9]. The setting and scope of the ED as a whole warrants a specified, more focused approach on AMS that is not sufficiently dealt with by existing guidelines on AMS [4,10].

This guideline targets healthcare professionals treating adult patients (>18 years of age) who present to the ED with a suspected infection, including ED physicians and advanced practice providers working in the ED but also infectious diseases physicians or other internists, pulmonologists and other consulting specialists such as clinical microbiologists and pharmacists.

The purpose of this guideline is to provide recommendations on a selection of high impact AMS objectives to optimize appropriate antibiotic use in ED patients. After an initial selection process among experts in the panel, we focused on four AMS objectives that are important for the ED and for which guidance is lacking or controversial.

Context

The ED increasingly serves as a rapid diagnostic centre for the healthcare system and is the primary source for hospital admissions. It can also be a setting for acute ambulatory care encounters [11]. As such, actions taken by emergency care providers have significant implications for AMS for both inpatients and outpatients. The following characteristics differentiate AMS in the ED from a general AMS approach [12]. First, AMS in the ED is concentrated around reaching a diagnosis quickly and accurately. This is facilitated by appropriate clinical examination and (if applicable) imaging. In addition, biomarkers can help to differentiate infections from other diagnoses and to differentiate between bacterial and viral infections. Rapid diagnostics, which include molecular techniques to diagnose bacterial/viral infections, are increasingly used in this context. Incorporating diagnostic test results in the process of making a clinical diagnosis in the ED may have the potential to significantly reduce unnecessary antibiotic use. Among the biomarkers frequently used in the ED, C-reactive protein (CRP) and procalcitonin (PCT) have been the most widely used [13]. With advancing technology, newer applications of rapid nucleic acid amplification tests (NAATs) have become available, with a higher sensitivity than antigen detection tests resembling that of laboratory-based PCR, coupled with much shorter turnaround times (TATs) [14,15]. Another major advance of diagnostic testing are multiplex PCR (mPCR) panels [16], mainly because of the wider range of pathogens covered within those tests. Key to the clinical utility of any rapid test, either biomarker or pathogen detection, is a short TAT, thereby providing the clinicians with information at the point-of-care that has the potential to meaningfully impact antimicrobial prescribing and other clinically relevant endpoints.

Second, AMS in the ED should focus on the collection of cultures and other microbiological tests when appropriate before starting antimicrobial therapy. Although traditional blood cultures generally take >24 hours to provide results with antibiogram and therefore cannot influence ED decision making, the ED does play a key role in ensuring collection before initiating antimicrobial therapy. Failure to do so represents a missed opportunity to tailor antimicrobial therapy to the pathogen and to de-escalate broad-

spectrum antibiotics. With the exception of patients admitted with sepsis, controversy remains over the selection of optimal patient populations for which blood cultures should be obtained in the ED [17–21].

Third, AMS in the ED is focused on empirical therapy selection. The choice of initial antibiotics is arguably the most important one for patients with life-threatening infections. Empirical therapy choices that take place in the ED have been extensively discussed in other guidelines. On the other hand, withholding empirical therapy when appropriate is a stewardship objective with great potential, e.g. for patients with infections that are potentially self-resolving, chronic or require further diagnostic testing before antibiotic initiation. Watchful waiting can be defined as no prescription, delayed prescription or prescription of non-antibiotic treatment (i.e. nonsteroidal anti-inflammatory drugs [NSAIDs]). Watchful waiting requires monitoring the patients for potential worsening symptoms (e.g. through a scheduled follow-up phone call or an in-person visit or by giving patients instructions on self-monitoring of signs and symptoms that should prompt them to seek medical attention again), while waiting for culture results. There is more published evidence on the concept of 'watchful waiting' for the primary care than for the ED setting [22–24].

Fourth, AMS in the ED needs to address follow-up for outpatients who are discharged from the ED either with or without antimicrobial therapy prescribed and pending microbiological cultures [25]. However, the optimal approach to ED culture follow-up and the impact of structured programs on clinical outcomes is unclear.

The patient population that is served by the ED varies by region. Patients who would present to primary care in one region may present to an ED in other regions depending on the variability in access to healthcare. Therefore, evidence from primary care studies may be indirectly considered. On the other hand, the ED offers more opportunities for testing than primary care; therefore, we do classify it as a different setting.

The ED as an episodic care setting offers challenges for AMS implementation, related to a relatively high rate of staff turnover compared with other clinical settings, rapid patient turnover, the need for quick decisions and overcrowding [7]. Selecting the most appropriate implementation strategies based on the specific facilitators/barriers encountered in the ED is therefore of utmost importance. Overall, few studies applying rigorous designs have assessed the impact of implementation strategies to improve antibiotic prescribing practices at the ED [5–7,26–29]. However, several studies have explored factors that influence antibiotic prescribing practices in the ED. Recurrent identified themes include diagnostic uncertainty, incomplete data (e.g. lack of clear records during transition of care, patients with altered consciousness), crowding associated cognitive load, perceived patient expectations, working environment of non-guideline compliant prescribing practices, poor access to follow-up care and concern about deterioration of the patient. These factors might therefore very well play a role when implementing the recommendations presented in this guideline [6,26,30–34]. Finally, in acute care, as in other settings, these influences were not given due consideration in the design of implementation strategies [30,35]. Box 1 describes some

Box 1

Implementation — general principles

Importance of a diagnostic analysis when implementing guideline recommendations

Implementation strategies aim to change practice. Because evidence-based practice depends on professionals actually enacting the recommended behaviour in daily practice, evidence-based change efforts should draw on behavioural science. Numerous change models and theories describe successful change as the result of a systematic, step-by-step approach in which an understanding of the facilitators/barriers for change is crucial to the selection of effective implementation strategies [36–41]. Thus, successful implementation requires a problem analysis, i.e. a diagnostic analysis to find out the factors that influence the success or failure to act on the recommended practice. These helping and hindering factors that influence a specific practice in a specific hospital or ward can be assessed by using semi-structured interviews with individual professionals involved in the practice, or by group interviews, questionnaires and/or observation. When exploring influencing factors, it is crucial to perform a diagnostic analysis for each specific prescribing practice separately: as each practice will elicit its own pattern of facilitators/barriers [39,40,42].

Generic determinants of professional practice: a checklist

Literature shows that changing a professional practice is a complex process determined by many factors. Combining published frameworks and taxonomies of factors that help or hinder improvements in healthcare, Flottorp et al. [43] developed a comprehensive, integrated overview of 57 potential determinants (facilitators/barriers) categorized into seven domains. The following categories of determinants are distinguished:

1. Guideline factors (e.g. the clarity of the recommendation, the evidence supporting the recommendation);
2. Individual health professional factors (e.g. familiarity with the recommendation, or the skills needed to adhere);
3. Patient factors (patient preferences, or real or perceived needs and demands of the patient);
4. Professional interactions (e.g. communication among professionals or referral processes);
5. Incentives and resources (e.g. availability of necessary resources);
6. Capacity for organizational change (e.g. capable leadership, or the relative priority given to making necessary changes);
7. Social, political and legal factors (e.g. payer or funder policies).

For a more complete overview of determinants, see 'Additional file 4 TICD Checklist—definitions, questions and examples' accompanying the Flottorp paper [43].

Tools to facilitate the selection of implementation strategies

These facilitators/barriers should inform the choice of implementation strategies, e.g. education to address a lack of knowledge, reminders if 'forgetting to apply the recommended practice' is the problem or an organizational process redesign if organizational constraints hinder the performance of the recommended practice. To ensure guideline recommended practice, many implementation strategies can be selected (Table S10) [44], often in combination. To guide the selection of a strategy that matches the prevailing determinants, several methods and tools can be used [39,40,45,46], including the additional worksheets 1–5 and 'Additional file 4 TICD Checklist—definitions, questions and examples' accompanying the Flottorp paper [43].

Implementation strategies at the ED: examples of common barriers and matching solutions

An implementation strategy must not only be aligned with prevailing helping and hindering factors. To be effective, the implementation strategies chosen must also take into account the unique ED workflow and healthcare system context [7]. To facilitate this 'translation' of AMS activities to ED-adapted activities, it is crucial to have an ED clinician be part of stewardship committees.

The fast-paced nature of the ED with a high turnover of staff who vary in affiliation and training, and with the need for quick decision making, presents specific challenges for the implementation strategies chosen. On the one hand, it may be important to adapt the implementation strategy to this specific environment. For example, if an educational gap (e.g. new best practice guideline) is identified as a driver of suboptimal antibiotic prescribing, the educational implementation strategy should be delivered asynchronously (E-learning) to account for shift work and be included as part of onboarding for new hires or rotating staff. If facilitating expert consultation is identified as a target strategy to improve suboptimal antibiotic selection in the ED, those specialty providers (e.g. infectious diseases, dermatology) must be available real time to provide guidance at the appropriate moment in the encounter to avoid unnecessary delays. Similarly, if audit and feedback is chosen as an implementation strategy—to address a lack of insight into one's own practices and to stimulate a sense of urgency—it should include ED-specific peer benchmarking data and involve review of specific recent cases from each individual provider. Beyond individual feedback, an ED dashboard displaying the number of ED patients treated in line with various recommendations, comparing it with explicit targets might be an efficient feedback option.

On the other hand, in an environment where individual clinicians rotate frequently and decisions need to be made quickly, it may be important to implement recommended practices by using or adapting this specific environment. So, it may be wise to ensure easily available protocols on recommended practices, to provide checklists, order forms and order sets and to introduce electronic clinical decision support to educate and remind professionals about recommended care [7,26,29]. These interventions are best when integrated into the electronic health record and designed with human factors principles and end-user input. In addition, one might introduce cues: environmental prompts that can be used to remind professionals of the recommended behaviour. These can be posters, stickers or other specific contexts or elements of contexts that professionals select to be their own cues.

implementation principles to, generically, provide advice on how to promote the uptake of recommended practices at the ED.

Questions addressed by the guideline

A formal selection procedure was followed to select AMS topics from a set of predefined quality indicators that was complemented by suggestions from the panel, according to the following relevance criteria: (a) Does this topic refer to an important clinical problem/question? (b) Is there important variation in practice performance on this topic? (c) Does establishing evidence about this topic likely lead to better patient outcomes and/or quality of care? (see Supplementary 1 and Table S1 for more details regarding the selection procedure). This procedure has led to the selection of the four AMS topics as foreground questions for the guideline panel.

The key questions are:

(a) Do biomarkers or rapid pathogen tests in patients presenting to the ED with various infectious syndromes improve antibiotic prescription upon admission and/or clinical outcomes?
(b) Does taking blood cultures in patients presenting to the ED with either community-acquired pneumonia (CAP), urinary tract infection (UTI) or skin and soft tissue infection (SSTI), without signs of sepsis, improve antibiotic prescription and/or clinical outcomes?
(c) Does watchful waiting without antibacterial therapy or with delayed antibiotic prescribing reduce antibiotic consumption without worsening clinical outcomes in patients presenting to the ED with a provisional diagnosis of lower respiratory tract infection (LRTI), acute exacerbation of chronic obstructive pulmonary disease (AECOPD), cystitis or diverticulitis?
(d) Do structured culture follow-up programs in adults discharged from the ED with cultures pending improve appropriateness of antibiotic prescription?

Because the literature often shows that evidence is not routinely translated into healthcare practice [37], this guideline also aims to provide advice, where possible, on how to promote the systematic uptake of the recommendations included in this guideline. To bridge this evidence-to-practice gap, implementation strategies are needed. Implementation strategies, or implementation interventions, aim to 'promote the systematic uptake of research findings and other evidence-based practices into routine practice, and, hence, to improve the quality and effectiveness of health services and care' [47]. For this particular guideline, the literature was reviewed (see Methods below) to provide advice on 'the way'—i.e. how—to ensure that antibiotics are actually used in ED practice in line with the recommendations presented in this guideline.

Additional key questions are:

(a) What implementation interventions to improve the uptake of the practices recommended in this guideline have been described in the literature?
(b) What factors that influence (help or hinder) the uptake of the recommended practices have been described in the literature? The latter studies form the basis for effective implementation strategies: an understanding of the key drivers of

current practice is crucial to generate ideas for the planning of meaningful interventions.

Methods

A systematic review of the literature was performed to support the recommendations. The certainty of the evidence was classified using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. Second, an expert panel translated the evidence to recommendations. Finally, the recommendations were discussed and revised until consensus was achieved, using the GRADE grid to reach decisions [48], adjudicating the strength of recommendations. The final list of recommendations was approved by the whole panel (see Supplementary 2 for more details on the task distribution of the guideline panel).

To substantiate the implementation advice, a pragmatic approach was chosen. For each of the key questions described above, implementation studies or observational studies describing facilitators/barriers for implementation were selected from the searches and were summarized narratively.

Literature search

Relevant clinical studies were identified through computerized literature searches using PubMed, Embase and the Cochrane Database of Systematic Reviews. Four separate search strategies for each topic were developed through the combination of title/abstract terms and Medical Subject Headings and adapted for the different databases without limits for dates (Supplementary 3). The systematic searches were conducted between May 2021 and March 2022. In April (ECCMID) 2022, the panel experts were formally asked to suggest any relevant clinical studies that were not found in the initial systematic search (these could also concern newer studies that were published after the search was performed) and if eligible these were added through May 2022. Reference check of included articles (snowballing) and of relevant reviews and guidelines was performed. For each topic, relevant implementation studies or observational studies describing facilitators/barriers for implementation were selected from these search results.

Inclusion criteria

We included comparative randomized controlled trials (RCTs) or observational studies (both retrospective and prospective studies, including cohort, cross-sectional, case-control and before-after studies). Only studies reporting on the defined relevant outcomes in adults were included. Relevant outcomes in this AMS guideline were considered to be both outcomes on antibiotic use and clinical outcomes. We considered appropriate antibiotic prescription in the ED as the most relevant antibiotic use outcome. We did not include conference proceedings and excluded case reports, case series (trial) protocols, opinion/editorials or summaries of other studies. Only studies written in English were included. The guideline addresses four main questions on ED-specific AMS topics. The questions were posed in the Population/participant, Intervention, Comparator/control, Outcome (PICO) framework. The full PICO questions are detailed in the Supplementary material (Supplementary 4). In brief, the PICOs were formulated as follow:

1. Biomarkers and rapid pathogen tests:

Population: Adult patients presenting to the ED with various infectious syndromes
Intervention: Biomarker testing (i.e. PCT, CRP) or rapid pathogen testing (i.e. antigen test, PCR/NAATs or mPCR).
Comparator: Standard of care and/or no dedicated testing
Outcomes: Antibiotic prescription upon admission, mortality, hospitalization/length of hospital stay, adverse effects, AMR rates, costs, supplemental investigations.

2. Blood cultures:
Population: Adult patients presenting to the ED with either (a) CAP, (b) UTI or (c) SSTI, with no signs of sepsis, who were either admitted or discharged from the ED. (See Supplementary 7.2. For definitions of infectious syndromes.)
Intervention: Obtaining blood cultures.
Comparator: Not obtaining blood cultures.
Outcomes: Any relevant clinical outcome, including mortality, length of hospital stay, length of antibiotic therapy, de-escalation of antibiotic therapy, failure of antibiotic therapy, adverse effects of antibiotics.

3. Watchful waiting/withholding antibiotics:*
Population: Adult patients presenting to the ED with a provisional diagnosis of either (a) LRTI, (b) AECOPD, (c) cystitis or (d) uncomplicated diverticulitis.
Intervention: Not (yet) prescribing antibiotics, with a defined strategy of follow-up of patients ('watchful waiting')
Comparator: Immediate start of antibiotics at diagnosis.
Outcomes: Antibiotic prescriptions, symptoms severity and duration, complications of not treating the infection including mortality (e.g. pneumonia, pyelonephritis, intra-abdominal abscess).

*Because scattered evidence from the ED setting was expected for this PICO specifically, it was decided in consensus to extend the search to studies on patients presenting to primary care because patients with some of the clinical syndromes could present themselves in both settings, and watchful waiting might be a more studied practice in primary care. While summarizing the evidence, the definition of watchful waiting and the patient population were precisely analysed to ensure that the conclusions from those studies could be valuable for the ED as well, being aware that patients presenting in the ED might be more severely ill and there might be more barriers to adequate follow-up.

4. Structured culture follow-up programs:
Population: Adult patients discharged from the ED with cultures pending.
Intervention: Structured culture follow-up process/program after discharge (defined as culture follow-up activities put together in an organized, deliberate way according to a documented protocol).
Comparator: Standard ED culture follow-up after discharge.
Outcomes: Appropriateness of antibiotic therapy choice (antimicrobial-microbe matching), rehospitalization and time to culture review.

Review procedure and data extraction

All articles identified by the search were screened on the basis of abstract for eligibility by two reviewers independently using Rayyan software [49] and non-relevant documents or duplicates were excluded. Full texts of potentially eligible articles were assessed in duplicate and discrepancies were resolved through discussion and, if necessary, by a third person. All panel members participated in the eligibility assessment. Relevant data were extracted into a predefined database. Data extraction and risk of bias assessment were performed by the evidence review group.

All steps described above, except for the risk of bias assessment, were also performed for studies describing implementation interventions and studies describing factors that influence (help or hinder) the uptake of the recommended practices.

Risk of bias assessment

Risk of bias assessment was performed for each study using the Effective Practice and Organization of Care criteria for controlled studies (including RCTs) and interrupted time-series and the Newcastle-Ottawa Scale for cohort studies, case-control studies and uncontrolled before-after studies [50,51]. Individual studies were classified overall as providing low, medium or high risk of bias evidence based on predefined criteria (Supplementary 5 for more details).

Data synthesis and development of recommendations

When deemed appropriate, quantitative synthesis of the data using meta-analysis was performed. Because of the large heterogeneity in design or patient population between studies, most of the data were summarized qualitatively. For PICO 1 and 4, we conducted random effects meta-analysis using R (version 4.2.2) for the dichotomous outcomes antibiotic use and appropriate antibiotic use. Available evidence for each foreground question was classified by the panel following the GRADE system [52]. Certainty of evidence was classified as high, moderate, low or very low. An expert panel translated the evidence to recommendations. The recommendations were formulated from an AMS perspective, with the focus on appropriateness of antibiotic use. The recommendations were discussed and revised until consensus was achieved, using the GRADE grid to reach decisions [48], adjudicating the strength of recommendations. Recommendations were classified as strong or weak [53]. When no evidence was available, good practice statements were designated based on expert opinion. The final list of recommendations was approved by the whole panel.

Recommendations

The recommendations are summarized in Table 1. The extensive summaries of evidence for each PICO including tables with included studies, conclusions and other considerations are available in the Supplementary material (Supplementary 7).

Biomarkers and rapid pathogen tests

Question 1.1

Do biomarkers (i.e. PCT, CRP) in patients presenting to the ED with various infectious syndromes improve antibiotic prescription upon admission and/or clinical outcomes?

Recommendations

- We suggest the use of PCT in the ED to guide the initiation of antibiotics for patients with suspected LRTI who are likely to be admitted to the hospital (weak recommendation for use, moderate certainty of evidence)
- We suggest the use of PCT in the ED to guide the initiation of antibiotics for patients with acute exacerbation of asthma who are likely to be admitted to the hospital (weak recommendation for use, low certainty of evidence)
- We suggest the use of PCT in the ED to guide the initiation of antibiotics for patients with AECOPD who are likely to be admitted to the hospital (weak recommendation for use, moderate certainty of evidence)
- We suggest against the use of PCT in the ED to guide the initiation of antibiotics for patients with dyspnea and suspected or known heart disease who are likely to be admitted to the hospital (weak recommendation against use, low certainty of evidence)
- We suggest against the use of PCT based on the criterion of fever alone in patients in the ED to guide the initiation of antibiotics (weak recommendation against use, very low certainty of evidence)
- We suggest against the use of CRP in the ED to guide the initiation of antibiotics for patients with respiratory tract infections (weak recommendation against use, very low certainty of evidence)

Review of evidence

Procalcitonin and lower respiratory tract infections. The evidence to support the use of PCT in the ED derives largely from RCTs (Table S2). Six studies reported crude numbers on the antibiotic prescription rate upon admission in the PCT arm compared with the standard-of-care control arm [54–59], half of which included a routine repeat measurement of PCT 6–24 hours after the initial evaluation, whereas in the other half, repeat measurements were recommended. In most studies, the number of overruled cases was not specified. Not all studies reported on the percentages of cases in which physicians adhered to the PCT guidance recommendation, but in those studies reporting, adherence varied between 41% and 90.8%.

Meta-analysis yielded a risk ratio (RR) of antibiotic use in the intervention arm of 0.84 (95% CI: 0.71–0.99), albeit with high study heterogeneity (Fig. 1). Four studies on patients with LRTI [55,58–60] reported hospitalization rates (with most patients being admitted to the hospital across the studies), showing no difference between the PCT and control arms. Two studies reported side effects, with one study showing a significantly lower rate of side effects including nausea, diarrhoea and rash in the PCT arm [59], whereas another study yielded no difference in serious adverse events between the study arms [55]. One study reported lower costs related to antibiotics in the PCT arm [54], whereas in another study, these savings were offset by the high cost associated with the high frequency of PCT measurements [60], leading to overall higher cost in the intervention arm. None of the studies reported AMR endpoints. Despite the moderate certainty of evidence for PCT (graded down because of suspicion of publication bias), largely based on low risk-of-bias RCTs with high study heterogeneity, the panel weighed in other factors as well, such as costs, equity and access. Therefore, the strength of the recommendation for PCT was adjudicated as weak.

Procalcitonin and patients with comorbidities. There were seven RCTs evaluating the use of PCT in patients with dyspnea (with or without heart failure), asthma or AECOPD [61–67] (Table S2). Of these, five studies reported on the effect of PCT in the ED on the initiation of antibiotics [61–63,65,66]. For patients with acute exacerbation of asthma, the pooled effect size for the RR of antibiotic use was 0.59 (95% CI: 0.50–0.69). For patients with AECOPD, the calculated effect size was 0.66 (95% CI: 0.48–0.92] (Fig. 1). We found no effect on antibiotic use in one study reporting crude numbers on patients with dyspnea with suspected or known heart disease [63]. None of the studies reported side effects, costs and AMR rates. Mortality rates reported in three studies showed no difference between study arms [61,63,67].

Table 1
Summary of recommendations

Recommendation	Strength of recommendation	Certainty of evidence
Rapid pathogen tests and biomarkers		
Biomarkers		
We suggest the use of procalcitonin in the ED to guide the initiation of antibiotics for patients with suspected LRTI who are likely to be admitted to the hospital	Weak	Moderate
We suggest the use of procalcitonin in the ED to guide the initiation of antibiotics for patients with acute exacerbation of asthma who are likely to be admitted to the hospital	Weak	Low
We suggest the use of procalcitonin in the ED to guide the initiation of antibiotics for patients with acute exacerbation of COPD who are likely to be admitted to the hospital	Weak	Moderate
We suggest against the use of procalcitonin in the ED to guide the initiation of antibiotics for patients with dyspnea and suspected or known heart disease who are likely to be admitted to the hospital	Weak	Low
We suggest against the use of procalcitonin based on the criterion of fever alone in patients in the ED to guide the initiation of antibiotics	Weak	Very low
We suggest against the use of CRP in the ED to guide the initiation of antibiotics for patients with respiratory tract infections	Weak	Very low
Rapid pathogen tests		
We suggest against the use of rapid NAAT or rapid antigen tests for influenza to reduce the initiation of antibiotics in the ED	Weak	Low
We suggest against the use of multiplex PCR for respiratory pathogens to reduce the initiation of antibiotics in the ED	Weak	Low
We suggest against the routine use of urinary antigen testing for *Streptococcus pneumoniae* in patients with LRTI in the ED	Weak	Very low
We suggest against the routine use of urinary antigen testing for *Legionella pneumophila* in patients with LRTI in the ED	Weak	Very low
We suggest the use of urinary antigen testing for *Legionella pneumophila* in patients with LRTI in the ED with suspected legionellosis or in outbreak settings to guide the use of narrow-spectrum antibiotic therapy	Good practice statement	Expert opinion
We suggest MRSA PCR for purulent skin and soft tissue infections in the ED to guide antibiotic therapy in setting with high prevalence of community-acquired MRSA	Weak	Very low
Blood cultures		
Community acquired pneumonia		
We suggest against obtaining blood cultures routinely in patients presenting to the ED with a diagnosis of non-severe CAP	Weak	Low
We suggest obtaining blood cultures in patients admitted with severe CAP, e.g. patients with PSI score IV or V or with indications for ICU admission	Good practice statement	Expert opinion
We suggest obtaining blood cultures in patients admitted with CAP and risk factors for or initiated on therapy for unusual or resistant pathogens[a]	Good practice statement	Expert opinion
We suggest obtaining blood cultures in patients admitted with CAP and immunocompromised state[b]	Good practice statement	Expert opinion
Urinary tract infection with systemic symptoms		
We suggest against obtaining blood cultures routinely in patients presenting to the ED with UTI with systemic symptoms without anatomical abnormalities of the urinary tract in whom a good-quality urine sample for culture is available	Weak	Very low
We suggest obtaining blood cultures in patients presenting to the ED with UTI with systemic symptoms and antibiotic pretreatment	Good practice statement	Expert opinion
We suggest obtaining blood cultures in patients presenting to the ED with a chronic indwelling catheter and UTI with systemic symptoms	Good practice statement	Expert opinion
We suggest obtaining blood cultures in immunocompromised[b] patients presenting to the ED with UTI with systemic symptoms	Good practice statement	Expert opinion
Skin and soft tissue infections		
We suggest against routinely obtaining blood cultures in patients presenting to the ED with cellulitis/erysipelas	Weak	Very low
We suggest obtaining blood cultures in immunocompromised[b] patients presenting to the ED with cellulitis/erysipelas	Good practice statement	Expert opinion
We suggest obtaining blood cultures in patients presenting to the ED with cellulitis/erysipelas in clinical situations associated with high risk of non-standard pathogens[c]	Good practice statement	Expert opinion
We suggest obtaining blood cultures in patients presenting to the ED with cellulitis/erysipelas who have an intravascular prosthesis, a pacemaker or a valvular prosthesis	Good practice statement	Expert opinion
Watchful waiting/withholding antibiotic treatment		
We recommend withholding antibiotics in patients presenting to the ED with LRTI and no clinical suspicion of pneumonia	Strong	Moderate
We suggest withholding antibiotics in patients presenting to the ED with non-severe acute exacerbation of COPD and low suspicion of bacterial pneumonia	Weak	Very low
We suggest against withholding antibiotics in patients presenting to the ED with a provisional diagnosis of cystitis	Weak	Moderate
We recommend withholding antibiotics in immunocompetent patients presenting to the ED with an uncomplicated diverticulitis	Strong	Moderate
Clear instructions on self-monitoring of signs and symptoms and when to re-seek medical attention should be given to all patients with LRTI, acute exacerbation of COPD or uncomplicated diverticulitis, who are discharged from the ED without antibiotics	Good practice statement	Expert opinion
Structured culture follow-up		
We recommend a structured culture follow-up process/program after discharge from the ED	Strong	Low

CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; ED, emergency department; ICU, intensive care unit; LRTI, lower respiratory tract infection; mPCR, multiplex polymerase chain reaction; MRSA, methicillin-resistant *Staphylococcus aureus*; NAAT, nucleic acid amplification test; PSI, Pneumonia Severity Index; UTI, urinary tract infection.

[a] Such as previous infection or colonization with unusual or resistant pathogens, advanced structural lung disease or recent travel to areas with unusual or resistant pathogens or recent hospitalization and systemic antibiotics.

[b] For example, inherited or acquired immune deficiency or drug-induced immunosuppression, including patients receiving cancer chemotherapy, patients infected with HIV with suppressed CD4 counts, and solid organ or bone marrow transplant recipients.

[c] For example, immersion injuries and animal bites.

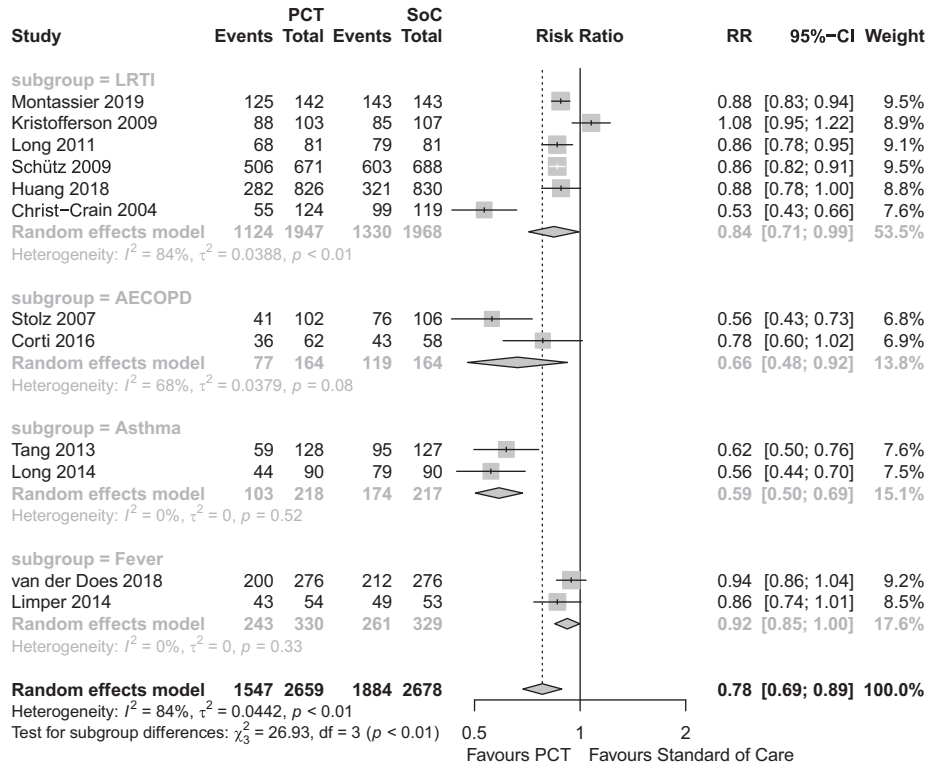

Fig. 1. Forest plot of the outcome 'antibiotic prescription' in randomized controlled trials comparing PCT vs. standard of care (SoC) in adult patients presenting to the ED with either lower respiratory infection (LRTI), acute exacerbation of COPD (AECOPD), asthma or fever. COPD, chronic obstructive pulmonary disease; ED, emergency department; PCT, procalcitonin.

Procalcitonin and patients with unspecified fever. One before-after study [68] and two RCTs [69,70] on PCT for patients with unspecified fever were included, with medium to high risk of bias (Table S2).

The before-after study reported cost savings after the introduction of PCT for patients diagnosed with sepsis (fulfilling systemic inflammatory response syndrome criteria), albeit lengths of stay remained unchanged [68].

The two RCTs used the inclusion criterion of fever alone to recruit patients. Both studies reported on the effect of a single PCT measurement on antibiotic initiation in the ED, and no significant difference was found between the intervention and the comparator (pooled RR: 0.92, 95% CI: 0.85–1.00) (Fig. 1). Both of these studies used a PCT threshold of 0.5 μg/L (in contrast to the threshold of 0.25 μg/L employed in the studies on LRTI patients mentioned above). Of note, in one of these studies, the majority of patients was diagnosed with a respiratory focus (39%), followed by a urinary focus in 20% [69]. With regard to hospitalization and mortality, no difference was found in the single study reporting on safety endpoints [69]. Costs were non-significantly lower in the PCT arm in one RCT [69]. Overall, the panel considered the patient cohorts studied in these two RCTs to be too heterogeneous, and the evidence to be of very low certainty. Hence, the panel decided not to recommend performing PCT in the ED based on the criterion of fever alone to guide initiation of antibiotic treatment.

CRP in respiratory tract infections

One RCT (medium risk of bias) reported no difference in antibiotic use between the intervention and control arms in patients with respiratory tract infection, including upper respiratory tract infection and LRTI [71] (Table S2). In addition, no difference in number of chest radiographs orders, length of hospital stay, rate of return visits or rate of hospitalizations during the follow-up period was reported. We found a scarcity of evidence for the ED setting. Indirect evidence can be inferred from the primary care literature including a Cochrane systematic review with meta-analysis on the use of CRP in primary care, which has shown a benefit with regard to antibiotic prescription at the index visit and up until day 28 during follow-up [72]. So in settings where the ED population reflects the primary care, CRP may be of benefit. However, as a general recommendation for the ED setting, the panel suggests against the use of CRP to guide the initiation of antibiotics for patients with respiratory tract infections in the ED.

Question 1.2

Do rapid pathogen tests in patients presenting to the ED with various infectious syndromes improve antibiotic prescription upon admission and/or clinical outcomes?

Recommendations

- We suggest against the use of rapid NAATs or rapid antigen tests for influenza to reduce the initiation of antibiotics in the ED (weak recommendation against use, low certainty of evidence)
- We suggest against the use of mPCR for respiratory pathogens to reduce the initiation of antibiotics in the ED (weak recommendation against use, low certainty of evidence)
- We suggest against the routine use of urinary antigen testing for *Streptococcus pneumoniae* in patients with LRTI in the ED (weak recommendation against use, very low certainty of evidence)
- We suggest against the routine use of urinary antigen testing for *Legionella pneumophila* in patients with LRTI in the ED (weak recommendation against use, very low certainty of evidence)

- We suggest the use of urinary antigen testing for *Legionella pneumophila* in patients with LRTI in the ED with suspected legionellosis or in outbreak settings to guide the use of narrow-spectrum antibiotic therapy (good practice statement for use, expert opinion)
- We suggest methicillin-resistant *Staphylococcus aureus* (MRSA) PCR for purulent SSTIs in the ED to guide antibiotic therapy in setting with high prevalence of community acquired-MRSA (weak recommendation for use, very low certainty of evidence)

Review of evidence

Rapid NAATs and rapid antigen detection tests for influenza

Most of the available evidence has stemmed from testing in patients with influenza-like illness. There were three observational studies on rapid antigen detection tests (RADTs), two of which reported crude numbers for meta-analysis, on the use of rapid antigen tests for influenza in the ED, all with high risk of bias and high heterogeneity [73–75] (Table S3). We calculated a pooled effect size (OR) for antibiotic use in patients undergoing RADT for influenza of 0.84 (95% CI: 0.50–1.42) (Fig. 2). There were conflicting results on the effect of RADT for influenza on additional diagnostic tests. One study reported a longer stay in the ED in the intervention arm (median 257 vs. 213 minutes) [73]. No study reported on mortality, AMR rates or costs.

Two randomized [76,77] and ten observational studies [78–87] on the use of Influenza rapid NAAT in the ED setting were identified (Table S3). Risk of bias was medium to high for the RCTs, and mostly high for the observational studies. The pooled effect size for the OR associated with antibiotic use in the intervention arm of five observational studies (that reported crude numbers) was 0.59 (95% CI: 0.36–0.99) (Fig. 2), albeit with heterogeneity. This favourable effect of NAAT on antibiotic use is contradicted and outweighed by the pooled effect size of the two RCTs (with low heterogeneity), which yielded an OR of 1.36 (95% CI: 0.99–1.86) (Fig. 2). Four studies evaluated the use of combined influenza and respiratory syncytial virus (RSV) testing in the ED setting with NAAT technologies [88–91], all but one with low-to-moderate risk of bias.

One study reported a lower rate of antibiotic prescription in the intervention arm [88]. Two studies reported shorter ED or hospital lengths of stay [88,90], whereas one study yielded a lower hospitalization rate [89]. Additional diagnostic tests were less frequently reported in the intervention arm in two studies [89,90]. In view of the high risk of bias of the observational studies, and the lack of an effect on antibiotic use in the RCTs on NAAT, which are deemed of higher diagnostic accuracy than antigen tests, the panel concluded that there is limited effect on antibiotic use.

Multiplex PCR

Overall, 14 studies on the use of mPCR panels in patients with respiratory tract infections in the ED were found, of which 9 were observational studies [92–100], and 5 were RCTs [101–105] (Table S3).

Overall, study reporting and findings were highly heterogeneous. Of the five RCTs, three had negative results for the outcome antibiotic use, all with low or medium risk of bias [101,102,105]. Two other (quasi-)randomized trials had serious methodological drawbacks [103,104]. One RCT reported a higher rate of single dose or short treatment courses, alongside a shorter duration of hospital stay in the intervention arm [102], and two other studies reported shorter treatment durations, partly stratified per test result [94,104].

There were similarly contradicting findings regarding hospital admission rates, length of stay, additional diagnostic testing and costs. Three studies found no mortality difference [100,102,105]. No studies reported on side effects or AMR rates. Of note, one major limitation of most studies is the long TAT in the intervention arms, which ranged from 2.3 hours in one study [102] to more than 19 hours in other studies [101,105], which may partly explain the overall weak impact on antibiotic use.

In light of the limitations named above, the panel decided to suggest against the use of mPCR for respiratory pathogens to reduce the initiation of antibiotics in the ED.

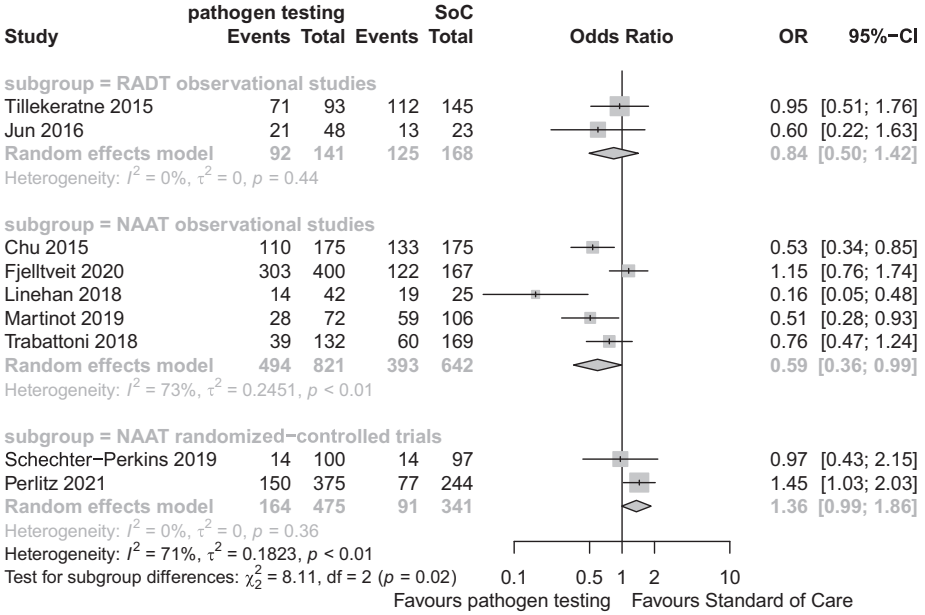

Fig. 2. Forest plot of the outcome 'antibiotic prescription' in adult patients with influenza-like illness in the ED in (a) observational studies, unadjusted results ($n = 2$), comparing the use of influenza virus rapid antigen detection test (RADT) vs. standard of care (SoC); (b) observational studies, unadjusted results ($n = 5$), comparing the use of influenza virus nucleic acid amplification test (NAAT) vs. SoC; (c) randomized controlled trials ($n = 2$), comparing the use of influenza virus NAAT vs. SoC. Note that Schechter-Perkins 2019 included paediatric and adult patients. ED, emergency department.

Antigen tests for Streptococcus pneumoniae and/or Legionella pneumophila

Three studies assessed the impact of rapid antigen tests from urine for *Streptococcus pneumoniae*, *Legionella pneumophila*, or both [106–108], two of which were observational studies with high risk of bias, including ill-defined patient cohorts (Table S4). One RCT reported no effect of urinary antigen testing for *S. pneumoniae* and *L. pneumophila* on several clinical outcomes, such as mortality, length of hospital stay and length of antibiotic treatment. Of note, patients in the intervention arm more often received a narrow-spectrum antibiotic treatment than those in the control arm; however, this potential benefit was off-set by a higher rate of clinical relapse in the subgroup of patients who were treated according to the antigen test result [108]. Two studies indicated higher costs related to urinary antigen testing [107,108]. In light of the existing evidence, the panel appraised the general usefulness of *S. pneumoniae* and *L. pneumophila* antigen tests as questionable, while acknowledging that in outbreak situations and in patients with an otherwise high pretest probability, *L. pneumophila* antigen testing in particular may be regarded as good practice.

Rapid NAAT for skin and soft tissue infections

There were two RCTs on the use of rapid NAAT for MRSA and methicillin-susceptible *Staphylococcus aureus* in the ED [109,110], both with medium risk of bias (Table S4).

In one study, patients receiving a rapid NAAT were prescribed beta-lactams more often than controls whereas MRSA-positive patients receiving rapid test results were more often prescribed antibiotics with MRSA coverage, indicating an increase in appropriate antibiotic treatment [109]. The authors found no differences in other clinical outcomes after 1 week or 3 months. In another study, the authors found that the introduction of an MRSA NAAT had no influence on the proportion treated with discordant antibiotics or the duration of discordant antibiotic use [110]. Because of the potential to increase appropriateness in antibiotic treatment in patients and settings with a high pre-test probability (i.e. with a MRSA carriage prevalence of >15%), the panel decided to recommend the use of rapid NAAT for MRSA.

Combined testing strategies and other considerations

Although it was not *a priori* a defined PICO or type of intervention, our search retrieved a few studies on different combinations of tests, e.g. biomarker + pathogen tests, pathogen test + pathogen test, or biomarker + biomarker [111–118]. Because of the heterogeneity in terms of interventions and clinical syndromes, and in view of the *a priori* lack of defined PICO with regard to combined testing approaches, the panel refrained from issuing any recommendation on this matter.

Biomarkers and rapid pathogen tests in the ED—How to implement the recommendations

We found five papers in which the performance of biomarkers or rapid pathogen tests by ED professionals was described in patients presenting to the ED with various infectious syndromes [112,119–122] (Table S11).

One before-after educational implementation study in one participating ED effectively increased ordering of biomarkers in the ED, specifically CRP and PCT [122]. The lack of additional studies on implementation strategies makes it impossible to draw conclusions on effective implementation strategies.

Four observational studies looked at determinants, i.e. factors that influenced the request of a rapid diagnostic test/biomarker in the ED [112,120,121] and/or the compliance of prescribing with test results [119,120] from which it is impossible to generate ideas for planning of meaningful interventions. Although these studies showed that there were differences related to disease factors (e.g. type of infection) [112,119,120], patient factors (e.g. age) [112,120], professional factors (e.g. experience, clinical background) [112,119,120] and settings (e.g. hospital department setting or country) [112,119,121], these studies did not explore the determinants that were responsible for these differences (see Box 1 for an overview of categories of determinants that might play a role in these differences). In other words, it was unclear, for example, whether a difference in respiratory panel PCR use between physicians and nurse practitioners/physician assistants was caused by differences in, for example, knowledge, availability of necessary resources and/or patient demand [112]. This makes it impossible to provide advice on how to address these reported types of determinants with a potentially effective implementation strategy as all three examples would ask for a different solution, professional education, the provision of resources or patient education, respectively.

Overall, the five studies showed two implementation challenges. First, the request of biomarkers or rapid pathogen tests was low in these observational studies, ranging between 19.2% and 36% [112,120,122] and 7.5 vs. 32.7 PCTs requested per 1000 ED admissions in laboratories with free or with restricted PCT availability, respectively [121]. Second, in these subgroups of patients, compliance with the test result recommendation was suboptimal, varying between 68.2% and 75% [119,120].

Overall, there is limited information on the appropriate use of rapid diagnostic tests or biomarkers in the ED, both on effective implementation strategies and on factors that influence recommended use.

Suggestions:

- Improvement strategies should focus on both the request of recommended tests and on compliance with test results
- No specific suggestions could be provided from the literature. See Box 1 for general guidance on implementation

Blood cultures

Question 2.1

Does taking blood cultures in patients presenting to the ED with CAP without signs of sepsis improve antibiotic prescription and/or clinical outcomes?

Recommendations

- We suggest against obtaining blood cultures routinely in patients presenting to the ED with diagnosis of non-severe CAP (weak recommendation against use, low certainty of evidence)
- We suggest obtaining blood cultures in patients admitted with severe CAP, e.g. patients with Pneumonia Severity Index score IV or V or with indications for intensive care unit admission (good practice statement for use, expert opinion)

- We suggest obtaining blood cultures in patients admitted with CAP and risk factors for unusual or resistant pathogens[1] (good practice statement for use, expert opinion)
- We suggest obtaining blood cultures in patients admitted with CAP and immunocompromised state[2] (good practice statement for use, expert opinion)

Review of evidence

Six observational studies were included that described patient outcomes in patients admitted with CAP in whom blood cultures were performed at admission (or in the first 24 hours) compared with patients with no blood cultures taken [123–128] (Table S4). Three observational studies of admitted patients with CAP did not find an association between blood culture performance and 30-day mortality (all adjusted for risk factors, e.g. disease severity) [124,126,127]. Four observational studies of admitted patients with CAP studied in-hospital mortality, of which three showed no evidence of benefit of blood culture performance [123–125]. The largest study [128] showed significant lower in-hospital mortality for those with moderate severity or greater CAP, but not for those with mild CAP. One observational study of admitted patients in Italy with CAP found that performance of blood cultures was associated with a longer mean duration of antibiotic therapy [124]. Because these were all observational studies with heterogeneous patient populations and a high risk of indication bias, no meta-analysis was performed. These observational studies cannot distinguish whether the clinical outcomes in the blood culture group were a direct consequence of the blood culture results or a marker of other improved processes of care.

Blood cultures in patients with CAP generally have a low yield of 7–11% [129,130], with a limited difference from the false-positive blood culture rate of ~5% [130,131]. The yield of blood cultures varies between populations and settings, but is also related to the regional epidemiology of the pathogens. Blood cultures are more often positive in CAP caused by *S. pneumoniae*, *S. aureus* or gram-negative bacteria. An association between the severity of CAP and a higher yield of blood cultures has been found in some studies [132–135], but not in others [130,136]. In patients with severe CAP, the threshold for ordering blood cultures is, however, lower because of the severity of the disease. In the CAP literature on blood cultures, immunocompromised patients are underrepresented, but it is reasonable to lower the threshold to collect blood cultures in this patient population.

Blood culture results have potential clinical consequences when the cultured microorganism is not covered or proves resistant to the empirical therapy, or when broad empirical coverage can be narrowed based on the blood culture result. A review of observational studies confirms that blood cultures seldom lead to adjustment of antibiotic treatment for CAP [129]. In a patient who is not improving, the empirical treatment is often escalated based on the clinical course, before the blood culture result and antibiogram are known. The reluctance of clinicians to de-escalate broad empirical therapy when blood cultures show, for example, *S. pneumoniae* or *H. influenzae*, is a factor that may play a role in this.

Of note, blood cultures can be valuable when the working diagnosis of CAP in the ED is uncertain and when there is an important differential diagnosis for which blood cultures are of added value.

[1] Such as previous infection or colonization with unusual or resistant pathogens, advanced structural lung disease, recent travel to areas with unusual or resistant pathogens or recent hospitalization and systemic antibiotics.

[2] For example, inherited or acquired immune deficiency or drug-induced immunosuppression, including patients receiving cancer chemotherapy, patients infected with HIV with suppressed CD4 counts and solid organ or bone marrow transplant recipients.

Question 2.2

Does taking blood cultures in patients presenting to the ED with UTI with systemic symptoms without signs of sepsis improve antibiotic prescription and/or clinical outcomes?

Recommendations

- We suggest against obtaining blood cultures routinely in patients presenting to the ED with UTI with systemic symptoms without anatomical abnormalities of the urinary tract in whom a good-quality urine sample for culture is available (weak recommendation against use, very low certainty of evidence)
- We suggest obtaining blood cultures in patients presenting to the ED with UTI with systemic symptoms and antibiotic pretreatment (good practice statement for use, expert opinion)
- We suggest obtaining blood cultures in patients presenting to the ED with a chronic indwelling catheter and UTI with systemic symptoms (good practice statement for use, expert opinion)
- We suggest obtaining blood cultures in immunocompromised[2] patients presenting to the ED with UTI with systemic symptoms (good practice statement for use, expert opinion)

Review of evidence

Four retrospective observational studies (low-quality evidence) were included [113,137–139] that showed no association between blood cultures taken from patients admitted with UTI and better clinical outcomes (Table S4). These studies were prone to bias, studying diverse patient populations and antibiotic treatment adjustments were not described, all of which requires a cautious interpretation of these results.

The yield of blood cultures in patients with UTI with systemic symptoms is relatively high; 15–51% depending on patient characteristics [140,141]. A relevant difference compared with CAP is that when a UTI is suspected, urine is generally easier to obtain for culture than sputum, and urine culture often already identifies the causative microorganism and its antimicrobial susceptibility. The finding of bacteraemia has little consequences for the duration of treatment of UTI with systemic symptoms [142,143]. The question is therefore in which patient blood cultures could be of added value if a properly collected urine culture is already available. In theory, this is when the urine culture is negative but the blood culture shows the causative agent (discordant result) or when a blood culture shows the most relevant microorganism in a polymicrobial urine culture [144,145].

In a review by Mills and Barros [146] of studies of patients with pyelonephritis, a relevant pathogen was found in only 0–2.4% of blood cultures that was not found in the urine culture. This did not lead to changes in antibiotic treatment in any of the patients. Subsequent studies also show very limited impact of blood cultures on the treatment of pyelonephritis [147–149]. Two Dutch observational studies on patients with UTI with systemic symptoms showed a slightly higher percentage of discordant culture results (5% [29/583] and 7% [57/800]) [150,151]. In both studies, a significant proportion of patients (29% and 36%) were already being treated with antibiotics at the time of culture collection. Active antibiotic treatment at the time of culture collection therefore appeared to be an independent risk factor for discordant culture results (OR: 3.30 [95% CI: 1.53–7.13] and OR: 2.06 [95% CI: 1.18–3.61]). These studies do not contain data on adjustment of antibiotic therapy based on blood culture results.

Specific studies on blood cultures in UTI with systemic symptoms in immunocompromised patients or diabetic patients are lacking, although in some of the observational studies described above, these conditions were not exclusion criteria. Whether the limited value of blood cultures in addition to urine cultures also

accounts for these patient groups is therefore unclear, while consequences of inadequate antibiotic treatment may be more severe.

Question 2.3

Do taking blood cultures in patients presenting to the ED with cellulitis/erysipelas without signs of sepsis improve antibiotic prescription and/or clinical outcomes?

Recommendations

- We suggest against routinely obtaining blood cultures in patients presenting to the ED with cellulitis/erysipelas (weak recommendation against use, very low certainty of evidence)
- We suggest obtaining blood cultures in immunocompromised[3] patients presenting to the ED with cellulitis/erysipelas (good practice statement for use, expert opinion)
- We suggest obtaining blood cultures in patients presenting to the ED with cellulitis/erysipelas in clinical situations associated with high risk of non-standard pathogens[4] (good practice statement for use, expert opinion)
- We suggest obtaining blood cultures in patients presenting to the ED with cellulitis/erysipelas who have an intravascular prosthesis, a pacemaker or a valvular prosthesis (good practice statement for use, expert opinion)

Review of evidence

Four studies were included [152–155], all observational studies with low-quality evidence, showing no difference in clinical outcomes in patients admitted with cellulitis/erysipelas from whom blood cultures were or were not taken (Table S4). In two prospective observational studies of patients with cellulitis who were admitted to hospital, the proportion of patients with poor clinical response/poor outcome was not different between those in whom blood cultures were performed compared with those in whom no blood cultures were performed [153,154]. In two retrospective observational studies of admitted patients with community-acquired cellulitis, performing blood cultures was associated with longer length of stay in hospital [152,155]. These observational studies, in which there are no systematic protocols for blood culture collection (e.g. blood cultures were drawn at the discretion of the treating physician), are prone to bias. No RCTs have been conducted to investigate the value of blood cultures for cellulitis/erysipelas. No study evaluating blood cultures in necrotizing fasciitis was identified, but because this condition generally is associated with concurrent sepsis, these infections are not to be viewed as uncomplicated SSTIs.

The pre-test probability of positive blood cultures in immunocompetent patients with uncomplicated cellulitis is low (<10%) based on observational studies. The pre-test probability is considerably higher in patients with comorbidity [156,157]. Reviews regarding the impact of blood cultures on treatment show that this is very limited [21,158]. An important consideration for performing blood cultures in patients with cellulitis in the ED is if there is a higher risk of a complicated course in the event of *S. aureus* bacteraemia (i.e. endovascular infection in patients with a vascular prosthesis, heart valve prosthesis or pacemaker/ implantable cardioverter-defibrillator [ICD]).

[3] For example, inherited or acquired immune deficiency or drug-induced immunosuppression, including patients receiving cancer chemotherapy, patients infected with HIV with suppressed CD4 counts and solid organ or bone marrow transplant recipients.

[4] For example, immersion injuries and animal bites.

Blood cultures in the ED—How to implement the recommendations

We found eight papers in which the performance of blood cultures by ED professionals was described in patients presenting to the ED with various infectious syndromes [152,156,159–164] (Table S12).

Four implementation studies aimed, among others, to optimize blood culture practices in patients with CAP presenting to the ED: one cluster randomized controlled multicentre trial [164] and three uncontrolled single-centre before-and-after studies [159,160,163]. It is impossible to draw conclusions about effective implementation strategies for selective culturing from these studies.

Only one uncontrolled single-centre before-and-after study [160] aimed at blood culturing in a subgroup of patients—as also suggested in this guideline's recommendations—as compared with extensive testing in the whole patient group. The authors showed a small decrease in the proportion of cultured patients after education on the prediction rule and regular feedback on its use (three times a week); low actual use of the prediction rule (in 36.5% of eligible patients) was shown.

The three remaining studies (one cluster randomized controlled multicentre trial [164] and two uncontrolled single-centre before-and-after studies [159,163]) tested five different implementation strategies to improve extensive blood culture practices that are not recommended in this guideline.

Four observational studies looked at determinants, i.e. factors that influenced blood culture performance in the ED [152,156,161,162], from which it is impossible to generate ideas for planning of meaningful interventions. Although these studies showed that there were differences between disease factors (e.g. severe condition) [152,156,161,162], patient factors (e.g. age, comorbidities) [152,156,161,162], professional factors (e.g. administration of antibiotics at the ED) [161], setting (e.g. region in the United States) [161], these studies did not explore the determinants that were responsible for these differences (see Box 1 for an overview of categories of determinants that might play a role in these differences). In other words, it was unclear, for example, whether a difference in blood culture performance in severe patients compared with non-severe conditions was caused by differences in, for example, self-perceived competence, habits or perceived risk of malpractice liability [156]. This makes it impossible to provide advice on how to address these reported types of determinants with a potentially effective implementation strategy.

Overall, the studies showed that there is limited information on selective culturing, both on effective implementation strategies and on factors that influence recommended culturing in selected patient groups.

Suggestions:

- No specific suggestions could be provided from the literature. See Box 1 for general guidance on implementation

Watchful waiting/withholding antibiotics

Question 3.1

Does watchful waiting without antibacterial therapy or with delayed antibiotic prescribing reduce antibiotic consumption without worsening clinical outcomes in patients presenting to the ED with a provisional diagnosis of LRTI?

Recommendations

- We recommend withholding antibiotics in patients presenting to the ED with LRTI and no clinical suspicion of pneumonia (strong recommendation for use, moderate certainty of evidence)

- Clear instructions on self-monitoring of signs and symptoms and when to re-seek medical attention should be given to all patients with LRTI who are discharged from the ED without antibiotics (good practice statement for use, expert opinion)

Review of evidence

Fifteen studies were included in the systematic review [165–179] (Table S5), all conducted in the primary care setting. The primary diagnosis for inclusion was acute bronchitis or LRTI, defined as cough and at least one symptom or sign localizing the infection to the lower tract (sputum, chest pain, dyspnea, wheeze). Most of the studies excluded patients with chronic lung disease or for whom there was a clinical suspicion of pneumonia. Twelve RCTs assessed clinical outcomes in patients with LRTIs treated with antibiotics (mostly macrolides or tetracyclines) vs. placebo. No difference was found in any of the included studies regarding symptoms worsening, complications (pneumonia), or hospital admission in patients treated with placebo compared with the ones receiving immediate antibiotics. The effect on symptoms' duration was inconsistent among the studies, and only 4studies out of 12 reported a slight improvement in symptom duration.

Three studies (two RCTs and one prospective cohort) compared the clinical benefit of delayed antimicrobial prescribing with an immediate and no-prescription policy in patients with LRTIs.

Clinical outcomes were similar for the three strategies in all the studies, with a consistent reduction in antimicrobial consumption in the delayed prescription arm compared with the immediate prescription (from 20% to 45% of patients taking their prescriptions in the delayed strategy compared with more than 90% in the immediate strategy). 'Delayed prescription' was not a standardized recommendation, and patients were advised to take their prescription if symptoms persisted for more than 3, 7, and 14 days. Reconsultations were significantly lower in patients receiving a delayed prescription. As for less common outcomes (i.e. death or hospitalization), only the prospective observational study had an adequate sample to allow such an evaluation, and no difference was found in the three arms.

On the one hand, the transferability of these results (from studies conducted in the outpatient setting) to the ED setting might be questioned, especially as the patient population (mostly young patients with few comorbidities) was very selected. On the other hand, it must be acknowledged that, especially in countries where the primary care setting is not strongly organized, patients with mild to moderate LRTIs could also present to the ED and receive unnecessary antibiotics. Additionally, the ED is generally more resourced than the ambulatory setting, and a more comprehensive evaluation (biochemistry, radiology) could help rule out LRTI complications (such as pneumonia) and identify patients with comorbidities and more severe presentations vs. patients with uncomplicated infections who do not benefit from immediate antibiotics.

Question 3.2

Does watchful waiting without antibacterial therapy or with delayed antibiotic prescribing reduce antibiotic consumption without worsening clinical outcomes in patients presenting to the ED with a provisional diagnosis of AECOPD?

Recommendations

- We suggest withholding antibiotics in patients presenting to the ED with non-severe AECOPD and low suspicion of bacterial pneumonia (weak recommendation for use, very low certainty of evidence)
- Clear instructions on self-monitoring of signs and symptoms and when to re-seek medical attention should be given to all patients with AECOPD who are discharged from the ED without antibiotics (good practice statement for use, expert opinion)

Review of evidence

Sixteen studies were included assessing the efficacy of antibiotics vs. placebo in AECOPD [180–195] (Table S6). Fourteen studies were RCTs, and two were retrospective cohorts. Five studies were conducted in the hospital setting, three in a mixed setting and eight in the outpatient setting. Nine studies had a high risk of bias, five medium and one low.

Patients were diagnosed with COPD mostly following the GOLD criteria [196]. Only one study specifically excluded patients with advanced disease at baseline (stage IV). Patients' mean age in the studies was, on average, between 65 and 70 years, and in all studies, more than 50% of patients were smokers or ex-smokers.

In all the studies evaluated, AECOPD was defined as an acute worsening of symptoms in patients with a previous diagnosis of COPD. A clear reference to the three cardinal symptoms described by Anthonisen et al. [180] (i.e. an increase in sputum volume, sputum purulence and an increase in dyspnea) was made in half of the studies. The remaining studies included patients based on different symptom combinations or specific treatment modifications (need for oral steroids). It is important to note that four studies were conducted before adopting the Anthonisen criteria for diagnosing AECOPD.

Among the studies conducted in the outpatient setting, the most common exclusion criteria were chronic asthma and concomitant comorbidities. Only 2 of the 11 studies enrolling outside of the hospitals excluded patients with pneumonia (based on the presence of fever in one study and positive x-ray in the other). One study mentioned that severely ill patients were excluded, but no definition was provided. In general, being all the patients managed as outpatients, it is fair to presume that severe exacerbations were excluded in all the studies.

Three out of five studies conducted in the hospital setting excluded patients with fever or suspected pneumonia. In one study, PCT >0.1 ng/mL was also an exclusion criterion.

Regarding clinical outcomes (symptom resolution, symptom duration, clinical deterioration), seven studies suggested a significant improvement in at least one outcome [180,185–187,190–192], and nine studies did not find any benefit of antibiotics over placebo [181–184,188,189,193–195]. Among the five studies conducted in the hospital, only one study (medium risk of bias) conducted in 1972 showed clinical improvement at day 12 in the two antibiotic-treated groups compared with the placebo. The other four studies did not show any benefit of antibiotics compared with placebo (two medium and two high risk of bias). The choice of different outcome measures and the heterogeneity among relevant variables (i.e. study year, included population, setting, antibiotic selection and concomitant administration of supportive therapy) made the results difficult to compare, and a synthesis through a meta-analysis was not applicable.

None of the studies evaluated delayed prescription in patients with AECOPD because all studies compared the use of antibiotics with placebo (in RCTs) or supportive therapy only (in prospective cohorts). In all the included RCTs, follow-up visits and/or self-monitoring of symptoms were required to adequately monitor the patient's clinical status as part of the study routine. During the follow-up period, additional antibiotics (on top of the ones foreseen by the trial) were prescribed by the treating physicians in a similar number of patients in the placebo and the antibiotic arm.

The definition of severity of AECOPD is still a matter of debate. For several years the setting where the patient is managed or the need for additional treatment (steroids or antibiotics) was used to define the episode's severity [196]. However, this classification is not informative regarding the patient's condition and has likely impacted the low generalizability of clinical trials focused on antibiotic treatment [197].

The ED is likely to admit patients with AECOPD presenting with a wide range of clinical severity and aetiologies. Although none of the included studies was conducted in the ED, the panel believes that a recommendation limiting the overuse of antibiotics for treating this condition is relevant from a stewardship perspective, especially considering that only a limited proportion of AECOPD have a bacterial ethology. Additionally, as outlined for LRTIs, the ED is generally more resourceful than the outpatient setting, and additional diagnostic tests (biomarkers, rapid diagnostics, radiology) might support clinicians in discriminating whether an acute exacerbation (despite the severity of its presentation) could benefit from early antibiotics.

Question 3.3

Does watchful waiting without antibacterial therapy or with delayed antibiotic prescribing reduce antibiotic consumption without worsening clinical outcomes in patients presenting to the ED with a provisional diagnosis of cystitis?

Recommendations

- We suggest against withholding antibiotics in patients presenting to the ED with a provisional diagnosis of cystitis (weak recommendation against use, moderate certainty of evidence)

Review of evidence

Thirteen studies (described in 15 publications) [198–212] were included in the systematic review, all but one were performed in the primary care setting (one was performed in the urology department) [205]. Ten were RCTs, two were prospective cohort studies and one was retrospective cohort study with data from a large national database (Table S7).

Cystitis was used interchangeable with 'uncomplicated lower UTI' and defined in all studies as a symptomatic diagnosis of acute symptoms of dysuria, frequency or urgency. Leukocyturia was part of the inclusion criteria of some studies [198,201,207]. Most excluded explicitly pregnant patients or diabetic patients. All studies were in adults (although some in patients >15 years), and all but one in women only (one with mixed population) [211].

The patients who did not receive immediate antibiotics were either treated with placebo (in three studies), no antibiotics (in one study), with NSAID (in five studies), self-help medication at patients' discretion (in one study) or delayed prescription (in three studies). In the retrospective database study [211], non-immediate antibiotic was defined by no antibiotic prescription on the same day as the UTI episode start date.

Overall, either NSAID as symptomatic treatment and delayed prescriptions or a combination of both reduced antibiotic consumption for cystitis in healthy women in primary care setting [199,202,204,207,208,210,212]. NSAIDs seem to have a larger effect (antibiotic use in 33–41%) than delayed prescription (antibiotic use in 57–77%).

Burden of symptoms (either severity or duration) seemed to be increased with either NSAID or delayed antibiotic prescriptions compared with immediate antibiotic prescriptions. Of the five studies that included symptom resolution as primary outcome, three studies (1130 patients) [204,207,212] favoured antibiotic therapy in terms of symptom resolution, whereas two studies (179 patients) [199,205] found no difference between NSAIDs and immediate antibiotics in terms of symptom resolution (reviewed by Carey et al. [213]). In the studies with either placebo or no antibiotic treatment as a comparator [198,201,203,206,209], the effect on symptom resolution was overall negatively affected by not prescribing antibiotics immediately at diagnosis.

Among studies that described pyelonephritis as an outcome, all showed higher risk of pyelonephritis in the patients not treated with immediate antibiotics [201,203,204,207,212], although the overall risk of pyelonephritis was low (0–5%). A recent meta-analysis analysing patient-level data from eight RCTs (>3500 patients) showed a significant difference between the proportion of patients with pyelonephritis or febrile UTI (3.6% in the non-antibiotic group vs. 0.4% in the immediate antibiotics) with an OR: 5.6 (95% CrI: 2.3–13.9) [214].

The rationale for delayed prescription is that 30–50% of patients with suspected UTI do not have infection and, even in those with culture positive infections, the illness is likely to be self-limiting. In the included studies, a substantial proportion (39–58%) achieved symptom resolution on day 3 or 4 with either NSAIDs or placebo [201,204,207,212]. However, this is a selected population of healthy non-pregnant women with uncomplicated cystitis. A certain proportion might be misdiagnosed as having cystitis, because inclusion in the studies was based on symptoms alone.

All studies were performed in ambulatory primary care, and it should be questioned whether the data in this setting can be translated to patients presenting to ED with symptoms of cystitis. Patients presenting with cystitis to the ED may have more often a complicated UTI with urinary tract anomaly, or UTI in men or in immunocompromised patients. The evidence that was found on not (yet) prescribing antibiotics for cystitis in primary care cannot be extended to those patients.

Delayed antibiotic prescription in UTI is not as common practice in primary care as it is in respiratory tract infection. The combination of symptomatic treatment and a delayed prescription might, however, be a safe option for a subgroup of healthy non-pregnant women with uncomplicated cystitis, because the overall risk of pyelonephritis was overall low in the studies (0–5%). In those women who prefer to withhold antibiotics even though this is associated with an increased burden of symptoms, this may be an acceptable alternative to immediate antibiotic prescription.

Question 3.4

Does watchful waiting without antibacterial therapy or with delayed antibiotic prescribing reduce antibiotic consumption without worsening clinical outcomes in immunocompetent patients presenting to the ED with uncomplicated diverticulitis without signs of sepsis?

Recommendations

- We recommend withholding antibiotics in immunocompetent patients presenting to the ED with an uncomplicated diverticulitis (strong recommendation for use, moderate certainty of evidence)
- Clear instructions on self-monitoring of signs and symptom and when to re-seek medical attention should be given to all patients with uncomplicated diverticulitis who are discharged from the ED without antibiotics (good practice statement for use, expert opinion)

Review of evidence

Ten studies (described in 12 articles) [215–226] were included in the systematic review (Table S8), of which seven were performed in the ED followed by inpatient (surgical) department [215,216,218,222–224,226], two were performed in inpatient department only (ED is not mentioned as the route of entry) [220,221] and one was performed at the outpatient clinic of gastroenterology [225]. Six were RCTs and four were retrospective observational studies. In all studies only patients with computed tomography (CT)- or ultrasound-proven uncomplicated diverticulitis were included (most studies included only patients with stage 1a according to Hinchey classification or stage 0 according to Neff classification). Signs of complicated diverticulitis and immunocompromised state were the most frequent exclusion criteria. As watchful waiting approach, eight studies performed clinical observation of patients in whom antibiotics were withheld, whereas in two studies patients were closely followed-up as outpatients [225,226]. No study evaluated delayed prescriptions in patients with diverticulitis because all studies compared the use of antibiotics with placebo or with no antibiotics with supportive therapy only (fluid therapy, diet restrictions).

Antibiotic use was described as an outcome in eight studies [215,216,220–222,224–226]. In patients in whom antibiotics were withhold initially, antibiotics were prescribed nevertheless because of aggravating symptoms and/or clinical signs in 1–4%. Three studies included symptom resolution as either primary [218] or secondary outcome [223,226]. Daniels et al. [218] found that time to clinical recovery was not significantly associated with an antibiotic prescription. Antibiotics were not found to have a significant positive effect on pain control in the first 48 hours [223,226]. The complication rate (abscess, perforation, obstruction or fistula) was compared between antibiotic and no antibiotic treatment in seven studies, all of which found no significant difference between the groups [215,216,218,220–222,224]. Readmission rate was not significantly different between the antibiotic-treated patients and the patients in whom antibiotics were withhold during the inpatient treatment of uncomplicated diverticulitis [215,218,221–223], nor was the rate of deferred admission in outpatients who were treated with either antibiotics or no antibiotics [225,226]. There was no universal definition for recurrence among the studies. However, most studies defined recurrence as readmission with acute diverticulitis after 1 month. The recurrence rate was not different in patients treated with antibiotics compared with patients not treated with antibiotics [215,216,218,220,222,224,225].

All studies describe a patient population in which CT scan was performed at inclusion, thereby ruling out complicated diverticulitis at the start of watchful waiting. In most of the included studies, patients off antibiotics were admitted for observation. This can be considered as very close watchful waiting. In the two outpatient trials [225,226], the clinical outcomes were also not different between the antibiotic group and non-antibiotic group. Other single-arm prospective cohort studies (not included in this literature review because they lacked a control group) describe a low complication rate (0–1.9%) in patients presenting to the ED with CT-verified uncomplicated diverticulitis that were treated as outpatients without antibiotics [227–229]. These patients were followed-up closely, either by daily telephone contact by a nurse [229], or clinical reassessment 24–48 hours after discharge from the ED [227,228].

On the basis of the included studies, it seems that routine administration of antibiotics to patients presenting to the ED with uncomplicated diverticulitis does not lead to better outcomes than withholding antibiotics. Recent meta-analyses of (partly the same) studies reached similar conclusions [230,231]. However, there should be a high index of suspicion for clinical conditions that might predispose to complications such as sepsis. High-risk patients such as immunocompromised patients, elderly patients and those with extensive comorbidities were not included in the studies. With the lack of any data for these patients, withholding antibiotics for uncomplicated diverticulitis for such patients is not advisable.

Watchful waiting/withholding antibiotics in the ED—How to implement the recommendations

We found 11 papers in which withholding of antibiotics by ED professionals was described in patients presenting to the ED with various infectious syndromes [71,215,221,222,232–238] (Table S13).

A first implementation study, an individually (patient) randomized controlled single-centre trial, aimed to stimulate ‘no antibiotic’ use in adults with LRTI. In this study all ED attendings and house staff were given an educational seminar on evidence-based evaluation and treatment recommendations including evidence on CRP levels. In all patients' charts a clinical algorithm with recommendations for chest X-ray study and antibiotic treatment was included. The study showed no additional value of placing the result of a CRP test (half of the patient study population) in the patient chart before being seen by a clinician [71]. It is difficult to draw conclusions from this study as contamination cannot be ruled out. Four additional implementation studies, of which two with a no-intervention control group, aimed to stimulate ‘no antibiotic’ use in patients presenting to the ED: one cluster randomized controlled multicentre trial on diverticulitis [235] and three studies on RTI: one multicentre controlled before-after study [234], one multicentre before-after study [236] and one single-centre before-after study [232]. Both studies with a no-intervention control group [234,235] evaluated multifaceted strategies that included some similar components: champions/leaders, education for professionals (including one-on-one—small group education/academic detailing), audit and feedback and patient educational materials. Both studies were performed in the United States and effectively increased withholding of antibiotics, showing a statistically significant improvement.

Four observational studies [215,221,222,237] and two implementation studies [232,236] looked at determinants, i.e. factors that influenced withholding antibiotics in the ED from which it is impossible to generate ideas for planning of meaningful interventions. Although these studies showed that there were differences related to disease factors (e.g. fever, CRP, white blood cell count [WBC]) [215,221,222,232,237], patient factors (e.g. age or gender) [232,236,237] and professional factors (e.g. clinical background) [232,236], these studies did not explore the determinants that were responsible for these differences (see Box 1 for an overview of categories of determinants that might play a role in these differences). This makes it impossible to provide advice on how to address these reported types of determinants with a potentially effective implementation strategy.

A fifth study, a survey, provided some first insights into determinants that might be important for EDs to address in an implementation study [233]. A minority of 22.4% of respondents stated that they would consider a non-antibiotic treatment approach. When asked about reasons for choosing this policy, they mentioned various disease and patient characteristics: low CRP/white blood count, short duration of symptoms, first presentation, age (<50 years) and female gender. In developing the necessary implementation activities to support withholding antibiotics in the ED, it is important to better understand, for example through interviews with ED professionals, how they define ‘uncomplicated’ and what their underlying reasons are for, for example, assuming the importance of age or gender. However, the information from the study seems to indicate the need to clearly, unambiguously specify what disease and patient characteristics define ‘uncomplicated’, to

prevent professionals developing and applying their own criteria for this, which will result in variations in care and potentially adverse outcomes of care (e.g. side effects of antibiotics). This is crucial information to be included in local protocols. Moreover, education for professionals should address and show evidence for such characteristics. Next, the majority of 77.6% respondents provided reasons for continued use of a conservative antibiotic approach. Although only brief information is provided and a more thorough exploration is needed, the study seems to indicate factors that have to do with professionals' perceptions and knowledge of the disease ('an infective process') and with outcome expectations regarding the working of antibiotics (prevent deterioration, provide quicker resolution, prevent recurrence, result in a shorter length of hospital stay). These should be addressed by education that presents compelling evidence In addition, respondents point at 'traditional teaching' for which both education and prompts or reminders to break habits might be important. Finally, respondents mentioned that they continued antibiotics when the patient already commenced antibiotics by the admitting doctor. These points at the importance of not focusing implementation activities mentioned above on individual professionals but on teams, engaging the team in consensus processes when developing protocols and identifying champions or opinion leaders to promote the withholding antibiotics approach.

A sixth, qualitative study comprehensively explored barriers to optimal antibiotic prescribing using a framework including various factors that affect care processes and outcomes [238]. Moreover, in multiple rounds of refinement using input from a multidisciplinary group of stakeholders, the authors matched the identified modifiable barriers/facilitators with proposed implementation activities to mitigate the barrier or enhance the facilitator. The authors suggested (a) a telehealth or community paramedicine program for reliable outpatient follow-up to address the lack of access to ED follow-up care; (b) exclusion of encounters involving inappropriate antibiotic requests from satisfaction metrics to address patient expectations; (c) diagnostic aides to address diagnostic uncertainty; (d) a shared decision-making tool to address fear of adverse outcome; and (e) a clinical decision support/best-practice alert to address perceived clinical equipoise and provider knowledge gaps.

Overall, there is limited information on how to promote a watchful waiting/withholding antibiotic in the ED approach, both on effective implementation strategies and on factors that influence recommended use.

Suggestions:

- The limited information points at the importance of combining education of professionals, audit and feedback and reminders. These interventions should not address individual professionals but teams, engaging the team in consensus processes when developing clear, unambiguous protocols and identifying champions or opinion leaders. Moreover, patient education/educational materials are needed.
- See Box 1 for general guidance on implementation

Structured culture follow-up

Question

Do structured culture follow-up programs in adults discharged from the ED with cultures pending improve appropriateness of antibiotic prescription?

Recommendations

• We recommend a structured culture follow-up process/program after discharge from the ED (strong recommendation for use, low certainty of evidence).

Review of evidence

All 12 studies identified were observational [239–250] assessing adults discharged from the ED with follow-up cultures pending and comparing between a structured culture follow-up process/program after discharge and standard ED culture follow-up after discharge (Table S9).

The structured culture follow-up programs included involving dedicated pharmacists in the majority of studies (n = 11). The comparators were somewhat diverse among different studies. The most common culture source was urine. All studies were single-centre and conducted in the United States.

Data on appropriateness of therapy choice were presented in six studies. Meta-analysis of these results showed higher appropriateness of therapy in the structured culture follow-up program (OR: 2.67, 95% CI: 1.79–3.98; p 0.14; I^2 = 40%) (Fig. 3). Six observational studies studied rehospitalizations. Three studies found no differences [243,248,249] whereas three studies found lower rehospitalization [242,246,247] in the structured culture follow-up process/program than in the standard ED culture follow-up after discharge. Three out of four observational studies found a significantly shorter time to culture review in the structured culture follow-up process/program than in the standard ED culture follow-up after discharge [240,243,249,250].

All studies were observational and mostly before-after studies. None of the studies adjusted for confounding but one [242]. The overall risk of bias in these studies was high. All published studies were from the United States, which limits the generalizability to other countries. Most of the structured culture follow-up programs were driven by or involved a pharmacist, which leaves the question whether this could also be a dedicated and trained nurse or physician. In general, it can be challenging and time-consuming to have dedicated staff for this task, particularly on weekend days.

Structured culture follow-up in the ED—How to implement the recommendations

We found 21 studies in which the implementation of a structured culture follow-up in the ED was studied (Table S14). These included all 12 studies mentioned above. Some studies evaluated the effect of the introduction of such a culture follow-up program on the time to culture review and/or time to patient notification; others also evaluated guideline compliant treatment based on culture follow-up or 'working time' saved by the ED physician during a shift. Finally, frequency of ED revisits within 72 hours and hospital admissions within 30 days were evaluated as patient outcomes.

Interestingly, in all studies the implementation strategy consisted of the introduction of organizational change in the ED, notably the employment of a healthcare professional or service to carry out the process of culture follow-up and provide advice on therapy (where appropriate). ED pharmacists were the most commonly utilized, sometimes comparing them with usual care (where no dedicated person was involved) or to alternative healthcare professionals (e.g. an ED nurse, nurse practitioner or ED physician). There seems to be an abundance of successful pharmacist-driven programs, but there is no consistent evidence that programs led by other healthcare professionals would perform differently. Data on cost efficiency of this organizational intervention were lacking, and more efficient solutions may be needed. An organizational intervention was the only studied implementation strategy, leaving the effect of other strategies such as (patient) education, reminders and feedback strategies unclear.

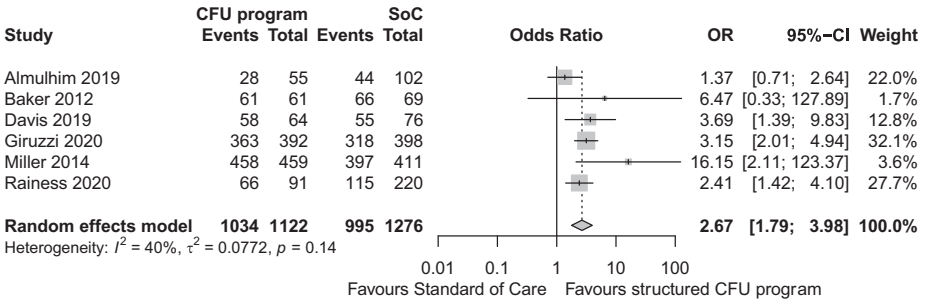

Fig. 3. Forest plot of the outcome 'appropriateness of antibiotic therapy' of structured culture follow-up (CFU) program vs. standard of care (SoC) after discharge of adult patients from the ED with cultures pending from observational studies (unadjusted results). ED, emergency department.

Essential elements of the organizatory intervention: patient selection

To facilitate the work of the healthcare professional, various system approaches are described to select the patients who need follow-up advice. In most studies, these systems collect (positive) culture results, but they may also select patients with certain ICD codes [239] or have an automated system to prompt the healthcare professional for an outpatient advice, once oral antibiotics for outpatient use are ordered [251]. For this, a clinical decision support software may be used [250] whereas others rely on more conventional methods such as daily e-mail alerts based on screened culture orders [246] or even paper printouts from the microbiology lab delivered at the ED pharmacist office [252].

Essential elements of the organizatory intervention: data analysis and interpretation

In a next step, the ED AMS outreach systems provide some kind of data analysis and/or interpretation: patient charts are reviewed and held against prevailing protocols. Miller et al. [245] used a structured data collection form. Some protocols are rule based and lead to a decision 'not to change, discontinue, modify, or discontinue and modify treatment' [253]. In most settings consultation takes place with a physician (either an ED physician or advanced care practice provider or primary care physician) for a final decision. A collaborative practice agreement may provide guidance for responsibilities of physician and pharmacist in this setting [252].

Essential elements of the organizatory intervention: reaching out

Finally, an activity needs to take place to execute the advice. This is sometimes done by contacting the local care provider [240,250,251] or the retail pharmacist to fill the (altered) prescription [241]. However, most often the patient is also directly contacted to receive feedback on the culture results and advice on antibiotic therapy. Communication is performed by phone but also by instant message, (electronic) mail and notes in the electronic medical record notes.

Determinants of practice

In one study [254] process evaluation showed that follow-up by an (urgent care) pharmacist was most effective to improve the adherence to the preferred choice of therapy (p 0.01), but not to guideline adherent dosing (p 0.28) or recommended duration of therapy (p 0.283]. In addition, most of the effect was seen in patients with UTI (p 0.037) and not in patients with wound infections (NS). The advice to change therapy was most successful in cases where cultures were positive and/or bug drug mismatch occurred [243,245,251,254].

Suggestions:

- Appropriate and timely culture follow-up for patients discharged from the ED can be effectively implemented using an organizational intervention i.e. the employment of an ED pharmacist or other healthcare professional. Within this intervention different steps (patient selection, data analysis and interpretation and outreach) are essential and should be organized.
- See Box 1 for general guidance on implementation

Description of the developing group

This guideline was developed after a call for guidelines projects of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) GL subcommittee end of 2019. One third of the expert panel was selected by the Executive Committee, one third was nominated by the guideline group leaders and one third was selected through an open call among ESCMID members. A multinational, multidisciplinary group of experts on AMS was selected from the field of emergency medicine, critical care, infectious diseases, clinical microbiology, clinical pharmacy and implementation science. An expert (MP) on guideline methodology and development was added to the group during the process. Conflict of interest statements were collected from all panel members before starting and after completion of the guideline development. The guideline development process is further detailed in the Supplementary material.

Discussion and research needs

This guideline does not cover all relevant topics of AMS in the ED. A list of other relevant AMS objectives (i.e. quality indicators) in the ED can be found in the Supplementary data (Supplementary 1). No recommendations on the paediatric population are provided by this guideline, because only studies addressing adults separately were included in the evidence review.

Another possible limitation of this guideline may be that only studies written in English were included in the systematic literature search. This may have biased the search favouring the inclusion of studies from higher-resource settings, affecting the generalizability to lower resource settings. In future updates of the guideline no language restriction will be applied.

Another limitation of this guideline is that it contains mainly weak recommendations and recommendations based on expert opinion, because of the absence of high-quality evidence in the area of AMS in the ED. The scarcity of high-quality AMS studies in the ED highlights the need for future research in this field. Moreover, many studies are on-going and the evidence might shift one way or another in the following years.

Evidence is currently lacking on the role of CRP measurement in AMS in the ED. Although data on CRP in primary care settings are available, the ED setting specifically still warrants additional

evidence on the use of CRP as an instrument to prevent unnecessary antibiotic prescribing. CRP remains a diagnostic test with little studies available, whereas an abundance of data is available on PCT, driven by a larger industry-based support that surrounded the introduction of PCT.

There is also a need for high-quality studies including a combined testing approach, i.e. in which biomarker(s) and rapid pathogen testing complement each other, ideally while being embedded in a stewardship framework, and ensuring a short TAT and the measurement of meaningful outcome parameters. Short(er) TATs should be a priority, alongside diagnostic accuracy, for companies to increase the potential for a clinically meaningful impact.

Another aspect that future studies should scrutinize are cross-sectoral approaches that include interventions taking place both in the ED and during the hospital stay, e.g. algorithms that make use of well-defined and meaningful repeat measurements to help discontinue inappropriate and unnecessary antibiotic treatment.

Similarly, future studies on the impact of pathogen tests, for which we did not find compelling evidence, could focus also on their potential to contribute to narrowing antibiotic treatment, an outcome which we did not specifically investigate within this guideline. Furthermore, high-quality studies are needed to establish the role of blood cultures in the ED for discontinuation or de-escalation of antibiotic therapy. In addition, there is a need for randomized studies on culture follow-up programs in the ED, especially in the European setting.

Author contributions

Conceptualization: all authors; methodology: TS, MPau, MH, JS; validation: all authors; formal analysis: TS, CPap, EC, KE, MPau, FR, MH, JS; investigation: all authors; writing—original draft: TS, CPap, MH, JS; review and editing: all authors; project administration: TS, JS.

Transparency declaration

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Updating

The guideline will be updated according to ESCMID recommendations.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2024.05.014.

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