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Narrative Review

Impact of time to antibiotic therapy on clinical outcome in patients with bacterial infections in the emergency department: implications for antimicrobial stewardship

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ABSTRACT

Background: Rapid initiation of antibiotic treatment is considered crucial in patients with severe infections such as septic shock and bacterial meningitis, but may not be as important for other infectious syndromes. A better understanding of which patients can tolerate a delay in start of therapy is important for antibiotic stewardship purposes.

Objectives: To explore the existing evidence on the impact of time to antibiotics on clinical outcomes in patients presenting to the emergency department (ED) with bacterial infections of different severity of illness and source of infection.

Sources: A literature search was performed in the PubMed/MEDLINE database using combined search terms for various infectious syndromes (sepsis/septic shock, bacterial meningitis, lower respiratory tract infections, urinary tract infections, intra-abdominal infections and skin and soft tissue infections), time to antibiotic treatment, and clinical outcome.

Content: The literature search generated 8828 hits. After screening titles and abstracts and assessing potentially relevant full-text papers, 60 original articles (four randomized controlled trials, 43 observational studies) were included. Most articles addressed sepsis/septic shock, while few studies evaluated early initiation of therapy in mild to moderate disease. The lack of randomized trials and the risk of confounding factors and biases in observational studies warrant caution in the interpretation of results. We conclude that the literature supports prompt administration of effective antibiotics for septic shock and bacterial meningitis, but there is no clear evidence showing that a delayed start of therapy is associated with worse outcome for less severe infectious syndromes.

Implications: For patients presenting with suspected bacterial infections, withholding antibiotic therapy until diagnostic results are available and a diagnosis has been established (e.g. by 4–8 h) seems acceptable in most cases unless septic shock or bacterial meningitis are suspected. This approach promotes the use of ecologically favourable antibiotics in the ED, reducing the risks of side effects and selection of resistance. **P. Nauclér, Clin Microbiol Infect 2020;▪:1**

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Introduction

Early antibiotic administration is considered critical for certain infectious clinical syndromes, particularly septic shock and bacterial meningitis [1,2]. However, unnecessary empirical broad-spectrum antibiotic therapy is associated with side effects and entails an ecological cost through the selection of resistant pathogens. Many patients are infected by bacteria sensitive to narrow-spectrum antibiotics, especially patients presenting to the emergency department (ED) with common community-acquired infections. In addition, presumed bacterial infections are often non-bacterial (e.g. viral) or non-infectious conditions [3,4]. If deemed safe, delayed initiation of antibiotics until the availability of diagnostic test results (e.g. biomarkers, radiological examinations, point-of-care tests) could be an important part of antibiotic stewardship, enabling targeted, narrow-spectrum therapy and a reduction in unnecessary antibiotic use. To support stewardship programmes, we performed a narrative review to explore evidence for the impact of timing of antibiotic therapy on clinical outcomes in patients presenting to EDs with infectious syndromes of varying site and severity.

Methods

Scope and search strategy

Existing evidence on early antibiotic therapy for bacterial infections in the ED as a determinant of clinical success was retrieved using the PubMed engine (www.pubmed.gov) to search the MEDLINE database. Articles on sepsis/septic shock (including bloodstream infections, BSIs), bacterial meningitis, lower respiratory tract infections (RTIs), urinary tract infections (UTIs), non-surgical intra-abdominal infections (IAIs), and skin and soft tissue infections (SSTIs) that provide information on timing of antibiotics and clinical outcome (mortality, clinical cure) were extracted (Supplementary Material Table S1). No restrictions were applied for publication year or language. Additional relevant articles were added if encountered during the evaluation.

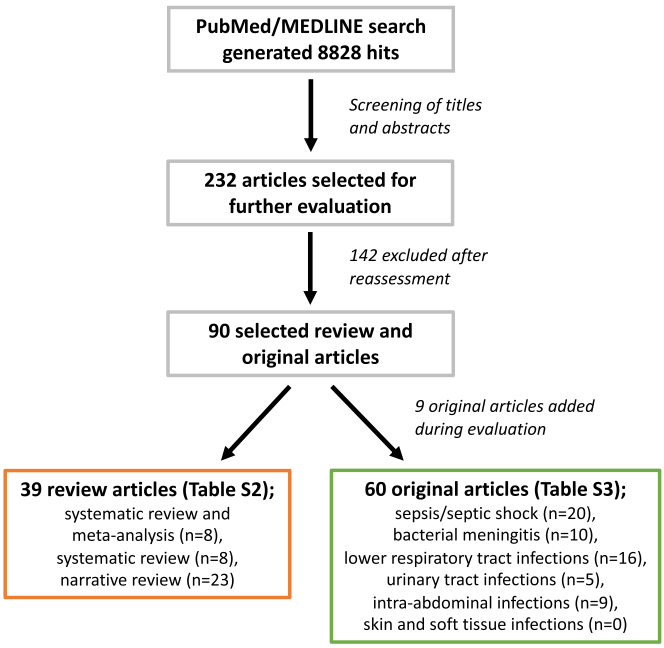

Fig. 1. Flow chart illustrating the search and screening process for relevant reviews and original articles providing information on early antibiotic therapy as a determinant of clinical outcome in community-onset bacterial infections.

Evaluation of articles

Screening of each article based on title and abstract was performed by one of the authors. If relevance was considered uncertain, the article was reviewed by a second author before a decision was made to reject or assess the full paper. Reviews were included to identify original articles of relevance. Articles were included in the final analysis only if they provided useful original data on time to antibiotics (determinant) AND clinical outcome (mortality, clinical cure, length of hospital stay). All comparative study designs (randomized controlled trials (RCTs), cohort or case–control, prospective or retrospective) were eligible. Articles that included paediatric patients were identified but not discussed given the limited data and different clinical presentations in this patient group. Both community-acquired and healthcare-associated infections were included provided that patients presented to the ED. If patients were included based on discharge diagnosis, articles were acceptable if disease onset occurred outside the hospital setting. Both time to any antibiotic and time to appropriate antibiotics were considered.

Results

Results of the literature search

The PubMed/MEDLINE search, performed on 26 June 2019, generated 8828 publications. Based on title and abstract screening, 232 articles were selected for full content assessment. Of these, 90 were included in the final analysis. Nine original articles were detected and added during the evaluation process. In total, 39 reviews (Supplementary Material Table S2) and 60 original articles (Supplementary Material Table S3) were identified (Fig. 1). Publication details of original research articles are listed in Supplementary Material Table S3 and the main results are summarized in Table 1. Of the original articles, four were RCTs and 56 were observational. Sepsis/septic shock was most frequently targeted (20 of 60), followed by RTIs ($n = 16$) and bacterial meningitis ($n = 10$). We found no studies investigating the impact of time to first antibiotic dose in patients with SSTIs. Half of the selected studies were published in 2014 or later, illustrating the growing interest in early antibiotic administration in the ED.

Evidence for early antibiotic therapy in sepsis

We found no RCTs but reviewed 20 observational studies that evaluated timely antibiotic administration for sepsis in the ED (Supplementary Material Table S3). Variable sepsis criteria were applied in the studies. For consistency within this review, we used 'sepsis' throughout to describe 'severe sepsis', and 'septic shock'. Most studies relied on retrospective analyses of hospital or intensive care unit (ICU) databases, or data collected prospectively for other purposes. As more severely ill patients are generally identified and treated sooner, yet carry a higher baseline risk of mortality, the studies usually adjusted for illness severity. However, the risk-adjustment methodologies differed between studies, and varied definitions of 'time zero' have been used, including ED arrival [5–10], triage [11–13], shock recognition [13,14], and commencement of a care bundle within 6 h after ED arrival [15].

Several retrospective studies have reported a temporal association between time to antibiotics and clinical outcome after adjustments for potential confounders [5–7,15–17]. Gaieski et al. found that the adjusted probability of death associated with a delay in appropriate antibiotic therapy increased gradually after 1 h [16]. Some studies did not assess antibiotic appropriateness but report an overall hour-by-hour impact [6,7,15]. Peltan et al. found that the

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Table 1
Summary of main findings and limitations of the reviewed original studies.

Infectious syndrome	No. of studies	Summary of results and comments
Sepsis	0 RCTs 20 observational studies	• Data from observational and register studies indicate an increase in mortality with delays in antibiotic administration, especially in the most critically ill patients with septic shock. • The studies used different definitions of "time zero", including ED arrival, triage, shock recognition and commencement of a care bundle within 6 hours after ED arrival. • A specific cut-off time for mortality benefit (e.g., initiation of therapy <1 or <3 hours after presentation) has not been defined. • The quality of evidence is low, and few studies have explored the interaction of timeliness and appropriateness of antibiotic administration in relation to mortality.
Bacterial meningitis	0 RCTs 10 observational studies	• One prospective and nine retrospective observational studies all reported an association between delayed initiation of antibiotic therapy and poor clinical outcome. • Limitations include confounding biases, small sample size and that patients who receive antibiotics early differ from other patients (e.g., in clinical presentation and pathogens). • Neurological symptoms by the time appropriate antibiotic therapy is initiated may be more relevant as a prognostic marker than time to initiation of antibiotics.
Lower respiratory tract infections	0 RCTs 16 observational studies	• 7/9 retrospective studies, including one subgroup analysis in septic patients, suggest that a delayed administration of antibiotics >4-8 hours is associated with worse outcomes. • 4/8 prospective studies showed no benefit from early antibiotics, while the other four did not preclude an effect. • Studies demonstrating an effect were retrospective and registry-based studies relied on diagnosis codes for case identification. • Studies show discrepant results on differential effects according to disease severity. • Many of the studies suffer from potential biases that impede the causal inference of delayed onset of therapy.
Urinary tract infections	0 RCTs 5 observational studies	• No studies were found that specifically evaluated early vs. delayed antibiotic therapy for UTIs in the ED. • One prospective and 3/4 retrospective observational studies showed no association between inappropriate empirical antibiotic therapy and mortality. • The studies may have been liable to confounding or bias. • The available data suggest severity of illness and co-morbidities are more important risk factors for mortality than time to administration of antibiotics in the ED.
Intra-abdominal infections	4 RCTs 5 observational studies	• Four RCTs on early vs. delayed initiation of carbapenem therapy for acute necrotizing pancreatitis showed variable results. • Retrospective observational studies on inappropriate empiric therapy suggest no association with clinical outcome in acute cholangitis or cholecystitis but a potential association in septic cirrhotic patients who develop spontaneous bacterial peritonitis and for BSIs of intra-abdominal origin.
Skin and soft tissue infections	0 RCTs 0 observational studies	• We found no studies that assessed the impact of time to first antibiotic dose in patients with SSTIs in the ED.

adjusted mortality risk increased with each hour of delay in door-to-antibiotic times and was significantly greater if antibiotics were administered >3 h after arrival in the ED compared to a within-1-h reference standard [7].

Other studies failed to find an hour-by-hour relationship between delay in antibiotic administration and mortality [8–14,18,19], including three prospective studies specifically designed to assess the impact of antibiotic timing [10,13,18]. A recent multicentre study using propensity scoring found that early treatment was associated with reduced in-hospital mortality in septic shock and that outcomes were significantly worse if treatment was delayed >3 h [11]. Joo et al. also found that antibiotic administration within 3 h in patients presenting to the ED with severe sepsis or septic shock was associated with lower in-hospital mortality (16.9% versus 22.9%; aOR 0.54; 95%CI 0.34–0.87) [8]. Whiles et al. reported an association of delayed therapy >5 h and risk of progression to septic shock in ED patients with severe sepsis [20].

Some studies indicated that early antibiotic treatment is associated with better survival rates only in patients who are critically ill [5], have high severity scores (APACHE score ≥21) [21] or require vasopressors [15]. Puskarich et al. noted that mortality was significantly higher among septic patients who received antibiotics only after shock had occurred (OR 2.4; 95%CI 1.1–4.5) [13]. Yet, once shock was present, the mortality rate remained steady throughout the first 6 h between triage and antibiotic administration. Wisdom et al. found no overall association between antibiotic delay and mortality; however, the authors did observe a trend towards increased mortality in the sickest patients when delays exceeded 6 h from triage [12].

In summary, the data are conflicting, but observational studies support the general view that early and effective antibiotic therapy is important for survival in sepsis, although a specific cut-off point has not been established. Patients with septic shock appear to benefit the most from early antibiotic administration. Frequent limitations of the available studies include a lack of data on confirmation of infection, microbiological results, appropriateness of antibiotic therapy, source control, co-morbidities, and treatment limitation decisions. Sepsis and septic shock were variably characterized across studies and the definition of time to antibiotic administration was also divergent.

Evidence for early antibiotic therapy in bacterial meningitis

We found ten studies on time to antibiotic therapy and outcome in adult patients with community-acquired bacterial meningitis

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(CABM) (Supplementary Material Table S3). All studies were observational [22–31] and only one was prospective [22]. Mortality was a primary outcome in all studies. Overall, the evidence is poor mainly because of the observational study design, confounding biases, and limited sample size.

In the only prospective study, comprising 156 patients with pneumococcal CABM, an interval >3 h between admission to an ICU and administration of an appropriate antibiotic was independently associated with 3-month mortality (OR 14.12; 95%CI 3.93–50.9) [22]. A retrospective study of 173 patients with CABM observed a linear relationship between door-to-appropriate-antibiotic time and mortality: 14% if 0–2 h, 17% if 2–4 h, 20% if 4–6 h, and 30% if > 6 h [23]. A retrospective investigation of 123 patients with CABM reported a sharp increase in mortality when door-to-appropriate-antibiotic time was >6 h (aOR 8.4; 95%CI 1.7–40.9) [25]. A retrospective study of 712 adults with CABM reported that mortality was increased by 12.6% (95%CI 3.1–23.1%) per hour of treatment delay after adjusting for confounding factors [28]. Finally, a retrospective study of 109 patients who received appropriate antibacterial treatment within 12 h of admission found an independent correlation between antibiotic delay and unfavourable outcome, defined as death or sequelae at discharge (OR = 1.30 per hour; 95%CI 1.08–1.57) [29].

These observational studies all showed an association between delayed antibiotic therapy and worse clinical outcome, but are biased by the following: patients who receive antibiotics early after admission differ from other patients in different aspects, including age, co-morbidities, clinical presentation, and causative pathogens. Neurological symptoms at the time appropriate antibiotic therapy is initiated may be more relevant as a prognostic marker than time to antibiotic. In this respect, a retrospective cohort study of 269 patients with CABM found a higher risk of unfavourable outcome in patients in whom the prognostic stage advanced from low risk ($p = 0.008$) or intermediate risk ($p = 0.003$) on arrival in the ED to high risk before administration of appropriate antibiotics [31].

Evidence for early antibiotic therapy in lower respiratory tract infections

We identified no RCTs, but 16 observational studies that investigated the effect of early initiation of any antibiotics, adjusting for potential confounders, in patients presenting to the ED with pneumonia (Supplementary Material Table S3) and one study on sepsis patients providing a subgroup analysis for pneumonia [15]. The studies often dichotomized time to first antibiotic dose to before versus after 4, 6 or 8 h. Patients receiving antibiotics with very long delays were also included in the group of delayed treatment, which complicates the interpretation of the results.

Seven of nine retrospective studies, including large registry-based investigations that might have difficulties in accurately defining time to therapy, suggested a beneficial effect on mortality of shorter time to initiation of antibiotic treatment [15,32–39]. In comparison, four of eight prospective studies showed no benefit of early antibiotics [40–42] while four presented estimates that did not preclude an effect [43–46]. Many of these studies suffer from potential biases hampering the causal inference. One prospective study, adjusting for variables covering most domains of potential confounding, observed a shorter length of hospital stay and a trend towards lower mortality (aOR 0.7; 95%CI 0.5–1.1) in patients receiving antibiotics within 4 h [44]. Although information bias and confounding seem limited in this study, there was a potential selection bias as only 2076 of 4506 patients eligible for the trial were included in the analysis. A meta-analysis from 2013 that included 14 studies showed no overall benefit in mortality when the time to antibiotics was <4 h (aOR 0.95; 95%CI 0.73–1.23) [47].

Most of the studies reviewed here did not report whether disease severity modified the effect. A small prospective study found no significant interaction between the CURB-65 score and time to initiation of antibiotics on time to clinical stability [40]. A large registry-based study reported similar protective effects of early antibiotics on 30-day mortality and 30-day readmission rate in patients admitted to ICU and non-ICU wards [34]. Another large registry-based study found that the aORs for mortality and length of stay were closer to 1 (smaller relative effect) in patients with a high pneumonia severity index (PSI) score than in those with a low PSI [32]. In contrast, one prospective study reported that antibiotic timing had an impact on mortality but only in patients with severe sepsis [45].

In summary, most retrospective studies suggest that a delay in antibiotic administration, in particular >4–8 h, is associated with worse outcomes, but prospective studies have failed to corroborate these findings. Studies show divergent results on differential effects relative to disease severity.

Impact of early antibiotic therapy for urinary tract infections

We found no studies comparing early to delayed antibiotic therapy for febrile UTIs (without sepsis). Five observational studies assessed effects of inappropriate empirical antibiotic therapy for infections where the cultured aetiological agent was resistant to the empirical regimen (Supplementary Material Table S3). In the only prospective study, Babich et al. reported that among 315 elderly patients with poor short- and long-term prognosis presenting with catheter-associated UTI and sepsis, inappropriate early therapy was not associated with increased mortality in a propensity-matched analysis. The mean time to appropriate therapy was not reported [48].

Two retrospective studies support these findings. Wiggers et al. reviewed outcomes of 469 adults with bacteraemic UTIs, 368 (79%) of whom received appropriate empirical therapy. There were no significant differences in mortality or time to cure between those receiving appropriate early (≤24 h) antibiotic therapy and those receiving appropriate therapy >24 h after culture collection [49]. In a multinational retrospective study of 981 patients with complicated UTIs, Eliakim-Raz et al. explored factors associated with 30-day mortality. While ICU admission, septic shock, and catheter-related UTI emerged as risk factors, neither inappropriate empirical antibiotic treatment nor the number of days until starting antibiotics was associated with clinical outcome [50].

In contrast, Lee et al. reported that among 164 patients with community-acquired, bacteraemic acute pyelonephritis, patients who received inappropriate empirical therapy (18%) had lower early clinical response rates (34.5% versus 82.2%; $p < 0.001$) and longer hospital stays (13.3 days versus 8.7 days; p 0.002) [51]. However, overall mortality and clinical cure rates were not affected. Esparcia et al. examined the outcomes of 270 elderly patients admitted to a non-ICU ward with a diagnosis of community-acquired UTI [52]. In univariate analyses inappropriate empirical antibiotic therapy was associated with mortality (OR 3.47; 95%CI 1.42–8.48). Confounding was likely, however, as a high APACHE score was also associated with mortality and no multivariate analyses were performed.

In summary, the available data suggest that the severity of illness at presentation and co-morbidities are more significant risk factors for mortality than time to initiation of antibiotics. Three studies evaluating inappropriate empirical therapy (often implicating a delay in effective treatment of >24 h) showed no

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association with clinical outcome. Two observational studies showed an association between delayed appropriate therapy and worse clinical outcome, but may have been subject to bias.

Impact of early antibiotic therapy for intra-abdominal infections

We identified five observational studies assessing the impact of early versus delayed antibiotic therapy for IAIs. Four RCTs assessed early carbapenem therapy for acute necrotizing pancreatitis, which is not an infectious disease at first presentation, and showed variable results (Supplementary Material Table S3).

Time to antibiotic therapy for other intra-abdominal conditions has been directly assessed only via small retrospective studies. In 2015, 2016, and 2019, Karvellas et al. reviewed the outcomes of patients receiving inappropriate (microbiologically ineffective) versus appropriate (microbiologically active) antibiotic therapy for septic shock due to cirrhotic spontaneous bacterial peritonitis (SBP), acute cholangitis, and acute cholecystitis [53–55]. For all reports, the time-to-antibiotics interval started only once patients were already in shock. After adjusting for confounders, a delay in appropriate antibiotic therapy was associated with increased mortality only among cirrhotic patients with SBP-related sepsis (OR 1.86; 95%CI 1.10–3.14) [53]. Tellor et al. retrospectively reviewed approximately 100 patients with BSI of intra-abdominal origin, 29 of whom received inappropriate antimicrobial therapy [56]. Patients who did not survive had a significantly longer time to appropriate antibiotic therapy (23 h versus 4 h). This delay, along with inadequate source control, was independently associated with mortality in multivariate analyses (aOR 3.86; 95%CI 1.28–11.64).

Thus, evidence for IAIs other than necrotizing pancreatitis is limited to a few observational studies on inappropriate empirical therapy, i.e., including also patients with very long delays (>24 h). These studies indicate no association with clinical outcome in acute cholangitis or cholecystitis but potentially in septic cirrhotic patients with SBP and BSIs with intra-abdominal sources of infection.

Discussion

The purpose of this review was to explore the evidence supporting early antibiotic therapy for community-onset bacterial infections in the ED. We addressed infectious syndromes where uncertainty exists about the importance of early antibiotic treatment (i.e. within hours) on patient outcome. Conditions that are determined by positive microbiological cultures were not included since the focus of the review was treatment in the ED, where such information is usually not available. Most data are derived from severely ill patients with sepsis and septic shock. Few studies included patients with infections of mild or moderate severity. These are, however, more commonly encountered in clinical practice and therefore of great importance for overall antibiotic use and selection of resistant pathogens.

The only RCTs identified in this review investigated antibiotic prophylaxis for acute pancreatitis, which is of limited relevance for the management of suspected bacterial infections in the ED. The observational studies are all vulnerable to potential confounding and bias. Information bias likely occurs in retrospective studies, particularly in registry-based studies, but also in prospective studies using data from clinical records. For example, registration of drug administration time may be inaccurate and the difference between recorded and actual time contingent on the severity of illness. Severely ill patients are likely to be identified earlier but still have a higher risk of dying. Reasons for delayed treatment are rarely explored; however, Filbin et al. identified vague, non-specific symptoms as an important confounder in an elderly, co-morbid population [19]. Selection bias is present in studies that include patients based on discharge diagnosis codes, and the necessity for informed consent can lead to differential inclusion in patients with an unfavourable or favourable clinical course.

Given these methodological concerns, the reviewed data should be interpreted with appropriate caution. Nevertheless, we believe some conclusions and recommendations can be formulated from these studies (Fig. 2). There is, for instance, enough evidence to support the early administration of appropriate antibiotic therapy in the most severe community-acquired infections, i.e. septic shock and bacterial meningitis. An ideal cut-off (e.g., <1 or <3 h after presenting to the ED) for mortality benefit has not been defined and remains controversial. In clinical practice, however, it should continue to be recommended that broad-spectrum antibiotic therapy be initiated as soon as possible. For these conditions, collection of samples for microbiological analyses and lumbar puncture (when bacterial meningitis is suspected) should be

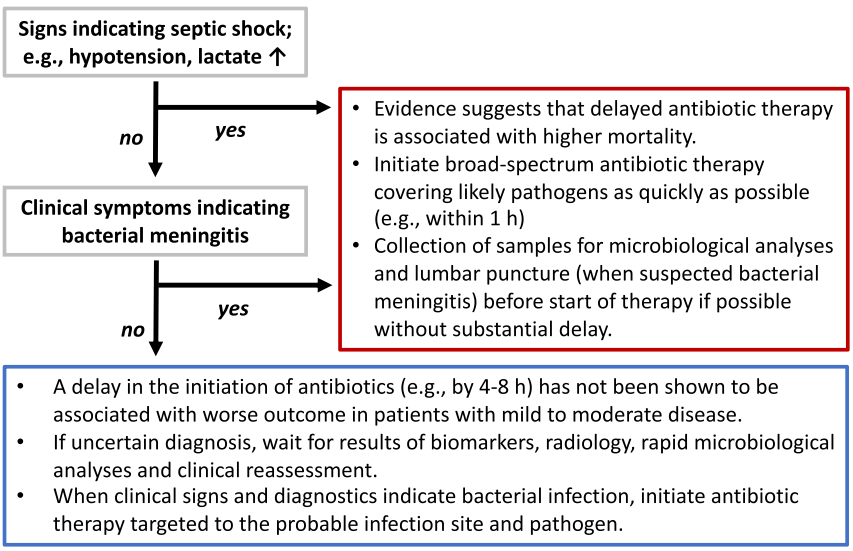

Fig. 2. Suggested approach to early or delayed antibiotic therapy for patients presenting to the emergency department with suspected bacterial infections.

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performed prior to antibiotic administration if feasible without causing a substantial delay in therapy initiation.

Importantly, this approach is probably not required in patients with other infectious syndromes of mild to moderate severity. For pneumonia, a longer interval of 4–8 h is normally regarded as early therapy, and for UTIs and IAIs, delays of appropriate therapy >24 h are often not associated with worse clinical outcome. However, it needs to be recognized that the review did not assess the importance of prompt antibiotic therapy in patients with immunosuppression. Allowing a few hours of delay in the initiation of antibiotics in non-severely ill patients with uncertain diagnosis could have important clinical implications (Fig. 2). Instead of immediate initiation of broad-spectrum therapy, antibiotics can be withheld until diagnostic results (biomarkers, radiological examination) are available and clinical reassessment has been performed, thereby promoting the use of narrow-spectrum and ecologically favourable antibiotics, as well as refraining from antibiotic therapy in patients with non-bacterial diseases. If rapid diagnostic tools for antibiotic susceptibility testing within 3–4 h become available, pathogen-directed therapy in the ED would be conceivable.

Knowledge gaps exist regarding which medical conditions require early antibiotics and the relevant cut-offs for time to therapy. Rapidly progressing bacterial infections, such as necrotizing fasciitis, may require prompt initiation of therapy in the ED for survival, also in the absence of septic shock, although no data to support this were found. The quality of evidence is hampered by practical and ethical difficulties in performing RCTs on this topic. Yet, one controlled trial randomizing 2672 patients to pre-hospital antibiotic administration or commencement in the ED (median 96-min difference) found no outcome difference, irrespective of illness severity [3]. Comparisons across study sites and RTCs of patients with less severe presentation, in whom the harm-to-benefit ratio of early antibiotics is unclear, should be considered. To provide clinically useful information study cohorts should represent patients with suspected infections in the ED and not only patients with a confirmed diagnosis in retrospect. Moreover, in future studies time to antibiotics should be clearly defined, documentation of the start of therapy should be accurate, and clinical outcomes in relation to appropriateness of therapy should be reported.

Conclusions

Early (e.g. <1–3 h) broad-spectrum therapy is justified in the most severely ill patients with septic shock or bacterial meningitis to reduce mortality. In patients with mild to moderate disease a delay of therapy (e.g. by 4–8 h) in the ED has not been shown to be associated with worse clinical outcome. Awaiting diagnostic results and performing clinical reassessment to establish a diagnosis could benefit patients and healthcare systems by guiding targeted empirical therapy and promoting appropriate antibiotic use. More robust evidence from prospective clinical trials is needed.

Author contributions

PN and TT coordinated the work. All authors contributed to the study design, search strategies, screening of articles, analysis and writing, and approved the final version of the manuscript.

Transparency declaration

All authors declare no conflict of interest.

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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.2020.02.032.

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