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The effect of antibiotic treatment prior to hospital admission for community acquired infection and mortality and organ failure – a cohort study

Background

Globally, infectious disease is a leading cause of morbidity and mortality[1], with sepsis alone accounting for up to 20% of all deaths worldwide[2]. Over the past decades, management strategies and guidelines for early recognition and intervention have evolved significantly, and timely antimicrobial administration has been identified as a key predictor of reduced mortality[3]. Several studies have demonstrated an association between delayed antibiotic administration and increased mortality among patients with suspected sepsis[45]. Accordingly, the Surviving Sepsis Campaign has established guidelines recommending that a defined set of interventions be initiated within the first hour of recognizing sepsis or septic shock – including the aim to initiate antimicrobial treatment within 1 hour[6].

Nevertheless, considerable controversy persists regarding the relationship between early antibiotic administration and clinical outcomes in sepsis. Some studies have reported no significant difference in mortality between patients who received antibiotics within one hour of recognition, as per the guidelines, and those who received them later[7,8]. One study even found that patients who were treated with antibiotics within the first hour had longer in-hospital stays and higher mortality compared to those treated within the subsequent three hours[9].

These conflicting findings may be partly explained by the heterogeneity in the clinical presentation of sepsis, highlighting the limitations of “one-size-fits-all” treatment protocols, as well as by changing prescription practices to minimize drug resistance.

Another complicating factor is the influence of antibiotic exposure prior to admission. This has in one study been linked to an increased risk of subsequent sepsis, possibly due to antibiotic-induced microbiota disruption that facilitates bacterial translocation and dysregulated immune response[10]. Conversely, previous studies on community-acquired pneumonia (CAP) have shown that antibiotic treatment prior to hospitalization is associated with reduced incidence of septic shock[11,12], decreased

intensive care unit (ICU) admission rates[13] and a lower need for mechanical ventilation[11]. However, these studies were limited by relatively small sample sizes and by restrictive inclusion criteria, thereby lacking generalizability to an undifferentiated population with acute infections.

Collectively, these considerations underscore the need for further research on the complex relationship between antibiotic administration and sepsis outcomes, and particularly on the impact of antibiotic exposure prior to admission on the outcomes for patients with acute infections.

Main objective

With this study we aim to investigate the effect of antibiotic treatment initiated before hospitalization on mortality and risk of organ dysfunction in patients admitted with acute infection.

Hypothesis

Our hypothesis is that the course of an acute infection is modified by antibiotic treatment prior to hospital admission. Due to the exploratory nature of this study and the conflicting prior evidence this cannot be specified further.

Methods

Study population

This retrospective multicenter cohort study uses data from all admissions to emergency departments (ED) in Eastern Denmark from January 1, 2019, to January 31, 2023.
Inclusion criteria:

1. Age ≥ 18 years
2. Antibiotic treatment within the first 72 hours of hospital admission

Exclusion criteria:

1. Surgical intervention within the first 7 days of hospital admission
2. All non-infectious conditions, that resulted in antibiotic administration*
3. Hospital admission within 14 days prior to the current admission

*Defined as having an international classification of diseases 10th revision (ICD-10)-code corresponding to a severe, non-infectious condition recorded as the primary diagnosis during the first three days of admission and receiving antibiotic therapy during the same period.

Baseline characteristics

Data on the following baseline characteristics (prior to current hospital admission) will be extracted from the electronic health record (EHR):

- Patient demographics (age and gender)
- Comorbidities (diabetes, chronic obstructive pulmonary disease (COPD), rheumatic diseases, chronic kidney disease, cancer and hematological conditions)
- Hospital admission with administered antibiotics within the last year
- Outpatient visits during the last year

In addition, we will extract baseline data reflecting the severity of the patient's condition at admission. These characteristics must be recorded within the first 24 hours of hospitalization. We have identified the following as relevant indicators:

- Assessment tools
    - Early Warning Score (EWS)
    - Sequential orga failure assessment (SOFA)
    - Quick sequential organ failure assessment (qSOFA)
- Lab results
    - C-reactive protein (CRP), leucocytes, lactate, pH, creatinine, Alanine aminotransferase (ALAT), Aspartate transaminase (ASAT), bilirubin
- Admitting medical specialty
- Initial treatment
    - Need for vasopressor
    - Oxygen treatment
    - Mechanical ventilation
    - Type of antibiotic

Exposure of interest

Our exposure is antibiotic therapy given prior to hospital admission, defined as any prescription of antibiotics collected from a pharmacy within a minimum of 24 hours and up to a maximum of 4 weeks prior to hospital admission.

Outcome

Primary outcome:

- 30-day all-cause mortality.

Secondary outcomes:

- Incidence of ICU admission within 30 days after admission
- Days alive out of hospital 30 days after admission (DAOH-30)
- Incidence of sepsis and septic shock within 30 days after admission.

We follow the definition represented in Sepsis-3 stating that sepsis is defined by 1) the presence of both collection of a blood culture, 2) administration of any dose or duration of antibiotic within 24 hours of ED arrival and 3) SOFA-score ≥2 indicating organ failure. Septic shock is then defined as a subset of sepsis, clinically recognized by persisting hypotension requiring vasopressor to maintain MAP ≥ 65 mmHg and serum lactate level > 2 mmol/L in absence of hypovolemia[14].

Statistical analysis

Directed Acyclic Graph

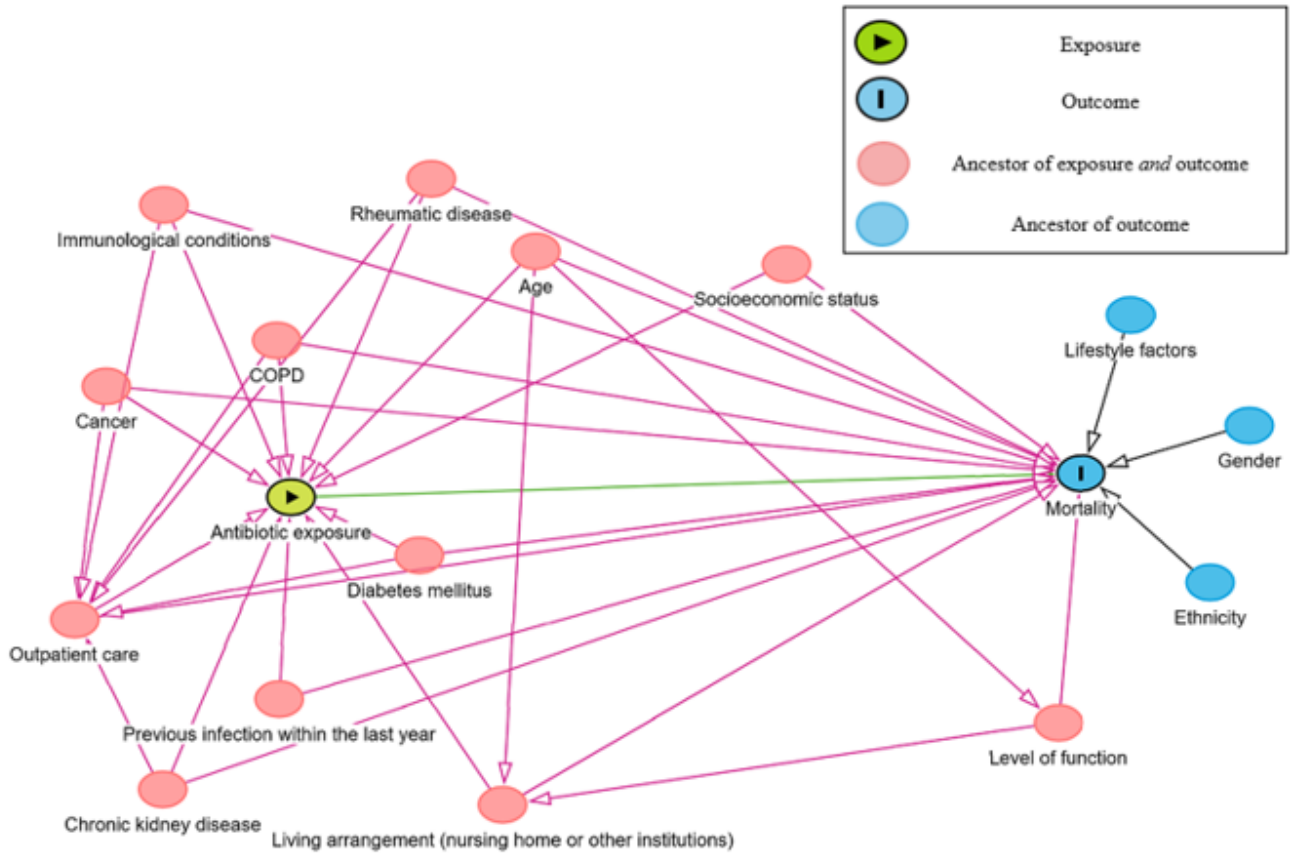

Figure 1 – directed acyclic graph

We have constructed a directed acyclic graph (DAG) to help identify potential confounders and to visualize the assumed causal relationships in this study.

Primary analysis

Variables

The primary exposure variable is antibiotic use prior to hospital admission, defined as any prescription of antibiotics collected from a pharmacy within a minimum of 24 hours and up to a maximum of 4 weeks prior to hospital admission, yes (1) or no (0) presented as number (n) and percentage (%).

The primary outcome is 30-day all-cause mortality presented as number (n) and percentage (%).

Secondary outcomes include:

- Incidence of ICU admission within 30 days after admission, presented as number (n) and percentage (%)
- Days alive out of hospital 30 days after admission (DAOH-30), presented as median and interquartile range (IQR)
- Incidence of sepsis and septic shock within 30 days after admission, presented as number (n) and percentage (%)

Analysis

The primary outcome will be analyzed using a Cox proportional hazards model to estimate hazard ratios (HR) with 95% confidence intervals (CI). P-values < 0,05 will be considered statistically significant. The model will be adjusted for age, previous hospital admission within the past year and the comorbidities identified in the DAG.

To evaluate the risk of sepsis, septic shock and ICU admission within 30 days after hospital admission, a multivariate logistic regression model will be constructed to estimate odds ratio (OR) with a 95% CI. The model will be adjusted for the same factors as mentioned above.

Sensitivity analyses

Several sensitivity analyses will be performed to test the robustness of the exposure. First, outcomes will be compared across antibiotic subtypes using three alternative classification approaches:

Initially, antibiotic subtypes will be divided according to presumed indication based on Danish prescribing patterns and clinical experience to assess whether associations differ according to indication [15,16].

Indication group	Common agents
Respiratory tract infections	Phenoxymethylpenicillin (J01CE02), amoxicillin (J01CA04), amoxicillin/clavulanic-acid (J01CR02), ampicillin (J01CA01), doxycycline (J01AA02), roxithromycin (J01FA06), clarithromycin (J01FA09), moxifloxacin (J01MA14), pivampicillin (J01CA02), erythromycin (J01FA01), cefuroxime (J01DC02), colistin (J01XB01), linezolid (J01XX08), levofloxacin (J01MA12), aztreonam (J01DF01)
Urinary tract infections	Pivmecillinam (J01CA08), nitrofurantoin (J01XE01), trimethoprim (J01EA01), ciprofloxacin (J01MA02), methenamine (J01XX05), sulfamethizol (J01EB02),
Skin and soft tissue infections	Dicloxacillin (J01CF01), flucloxacillin (J01CF05), clindamycin (J01FF01), cefalexin (J01DB01), lymecycline (J01AA04), tetracycline (J01AA07), linezolid (J01XX08), fusidic-acid (J01XC01)
Urogenital infections	Azithromycin (J01FA10), doxycycline (J01AA02), metronidazole (P01AB01), ceftriaxone (J01DD04)
Intra-abdominal or gastrointestinal infections	Amoxicillin–clavulanate (J01CR02),
Other	Meropenem (J01DH02), benzylpenicillin (J01CE01), gentamicin (J01GB03), piperacillin/tazobactam (J01CR05), vancomycin (J01XA01), tobramycin (J01GB01), fosfomycin (J01XX01)

Table 1 – classification by indication

Secondly, antibiotic subtypes will be categorized according to antimicrobial spectrum to assess whether associations differ by spectrum[17]. For pragmatic reasons, a simplified classification scheme

has been applied, distinguishing between broad-spectrum agents and narrow-spectrum agents targeting respectively gram-negative bacteria or gram-positive bacteria.

Antimicrobial spectrum	Antibiotic
Narrow gram-negative	Pivmecillinam (J01CA08), ciprofloxacin (J01MA02), sulfamethizol (J01EB02), nitrofurantoin (J01XE01), colistin (J01XB01), fosfomycin (J01XX01), tobramycin (J01GB01), aztreonam (J01DF01), gentamicin (J01GB03)
Narrow gram-positive	Phenoxymethylpenicillin (J01CE02), amoxicillin (J01CA04), ampicillin (J01CA01), trimethoprim (J01EA01), dicloxacillin (J01CF01), clindamycin (J01FF01), erythromycin (J01FA01), flucloxacillin (J01CF05), linezolid (J01XX08), fusidic-acid (J01XC01), vancomycin (J01XA01)
Broad	Amoxicillin/clavulanic-acid (J01CR02), azithromycin (J01FA10), roxithromycin (J01FA06), clarithromycin (J01FA09), cefalexin (J01DB01), lymecycline (J01AA04), doxycycline (J01AA02), , pivampicillin (J01CA02), moxifloxacin (J01MA14), tetracycline (J01AA07), ceftriaxone (J01DD04), cefuroxime (J01DC02), levofloxacin (J01MA12), meropenem (J01DH02), piperacillin/tazobactam (J01CR05)

Table 2 – classification by antimicrobial spectrum

Lastly, antibiotic subtypes will be divided according to the WHO AWaRe classification, which categorizes antibiotics into three groups respectively, access, watch or reserve – reflecting their relative potential to promote antimicrobial resistance[18].

WHO AWaRe category	Antibiotic
Access	Phenoxymethylpenicillin (J01CE02), amoxicillin (J01CA04), amoxicillin/clavulanic-acid (J01CR02), doxycycline (J01AA02), pivmecillinam (J01CA08), nitrofurantoin (J01XE01), trimethoprim (J01EA01), ciprofloxacin (J01MA02), dicloxacillin

	(J01CF01), flucloxacillin (J01CF05), clindamycin (J01FF01), cefalexin (J01DB01), azithromycin (J01FA10), doxycycline (J01AA02), metronidazole (P01AB01), sulfamethizol (J01EB02), lymecycline (J01AA04), ampicillin (J01CA01), pivampicillin (J01CA02), tetracycline (J01AA07), flucloxacillin (J01CF05), benzylpenicillin (J01CE01), gentamicin (J01GB03)
Watch	Roxithromycin (J01FA06), clarithromycin (J01FA09), moxifloxacin (J01MA14), erythromycin (J01FA01), ceftriaxone (J01DD04), cefuroxime (J01DC02), fosfomycin (J01XX01), fusidic-acid (J01XC01), tobramycin (J01GB01), levofloxacin (J01MA12), meropenem (J01DH02), piperacillin/tazobactam (J01CR05), vancomycin (J01XA01)
Reserve	Colistin (J01XB01), linezolid (J01XX08), aztreonam (J01DF01)

Table 3 – classification by AWaRe

Furthermore, outcomes will be compared according to the timing of antibiotic administration prior to hospital admission to evaluate whether associations differ by proximity of exposure. The timing will be categorized into the following time intervals according to initiation of treatment:

- 24 h - 1 week prior to admission
- 1 – 2 weeks prior to admission
- 2 – 3 weeks prior to admission
- 3 – 4 weeks prior to admission

Finally, patient who received in-hospital antibiotic treatment within the first 24 h of admission will be compared with the primary outcome of all cases.

Subgroup analyses

To explore whether the effect of the exposure differs among specific subsets of the population, the following subgroup analyses will be performed:

- Age (< 65 years or ≥ 65 years)
- Type of antibiotic treatment (in-hospital)
- Primary diagnosis
    - Pneumonia

- Urinary tract infection
- Abdominal infection
- Soft tissue infection

All subgroup analyses will be illustrated using a forest plot including 95% confidence intervals for each subgroup estimate.

Exploratory analyses

Two exploratory analyses will be conducted:

1. Potential interaction between pre-admission antibiotic treatment and antibiotic type administered at hospital admission
2. Association between pre-admission antibiotic treatment and subsequent development of organ dysfunction

Literature

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