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Audit of empirical antibiotic therapy for sepsis and the impact of early multidisciplinary consultation on patient outcomes.

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ABSTRACT

Objectives: To perform an audit of empirical antibiotic therapy (EAT) of sepsis at the emergency department and to analyse the impact of an antimicrobial stewardship (AMS) programme on process and patient outcomes.

Patients and Methods: A prospective, single-centre cohort study including patients with sequential organ failure assessment (SOFA) score ≥2 from whom blood cultures were taken was conducted between February 2019 and April 2020. EAT was assessed using eight applicable inpatient quality indicators (IQIs) for responsible antibiotic use. Patient outcomes were hospital length-of-stay (LOS), ICU admission, ICU LOS, and in-hospital mortality.

Results: The audit included 900 sepsis episodes in 803 patients. Full guideline adherence regarding choice and dosing was 45.9%; adherence regarding choice alone was 68.1%. EAT was active against all likely pathogens in 665/787 (84.5%) episodes. In the guideline non-adherent group, choice of EAT was inappropriate in 122/251 (48.6%) episodes. Changes within 3 days occurred in 335/900 (37.2%) episodes. Treating physicians changed administration route more often, whereas microbiological/infectious disease (ID)/AMS consultant advice resulted in de-escalation and discontinuation ($P = 0.000$). Guideline-adherent choice was associated with significantly shorter LOS (6 (4-11) vs. 8 (5-15) days). Full adherence was associated with significantly lower mortality (23 (6.4%) vs. 48 (11.3%)) and shorter LOS (6 (4-10) vs. 8 (5-14) days).

Conclusion: Five global quality indicators of EAT were measurable in routine clinical practice. Full adherence to guidelines was only moderate. Adherence to guidelines was associated with better patient outcomes.

Introduction

Mortality rates are high (15-23%) among patients presenting with sepsis at the emergency department (ED) [1,2]. Prompt initiation of appropriate antibiotic therapy is lifesaving for patients with septic shock. Intravenous (IV) antimicrobials are recommended as soon as possible (within 1 h) after recognition for both sepsis and septic shock [3]. Inappropriate use of antibiotics is a major driver of increasing antibiotic resistance [4-6], including against 'last-resort' antibiotics [7]. A microbiologically-confirmed diagnosis is necessary for targeted antibiotic therapy with proven in vitro activity against the causative pathogen [8]. However, because culture-based diagnostics require several days to complete, empirical antibiotic therapy (EAT) is necessary. Hospital EAT guidelines have been developed on (inter)national as well as local levels [9]. Appropriate antibacterial activity of EAT for sepsis consists of broad-spectrum antibiotics that cover likely causative pathogens and is chosen based on the site of infection and local epidemiology [9,10]. This is considered a global quality indicator (QI) for

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antibiotic therapy assessment among 51 inpatient QIs (IQIs) developed by Delphi consensus [11].

Studies have shown the impact of the initiation of appropriate EAT on patient outcomes, including a significant decrease in mortality in patients with bloodstream infection (BSI) [12,13]. In addition to guideline development, antimicrobial stewardship (AMS) interventions, such as antibiotic prescription review by infectious disease (ID) physicians or pharmacists, are feasible and can help reduce antibiotic misuse [14]. AMS is crucial in the ED, where acute infections are common and antibiotics are often prescribed [15]. Therefore, adherence to EAT guidelines and the change from empirical to targeted, narrow-spectrum antibiotics, benefits patients.

The aim of this study was to perform an audit of EAT for sepsis, including adherence to local guidelines, in the ED and to analyse the effect of microbiological and ID/AMS consultation on process and patient outcomes.

Patients and methods

Ethics

Written informed consent was obtained from all participants. Documented approval for the study was obtained from the Ethics Committee of Hasselt University and Jessa Hospital (18.106/infect18.03 and 19.51/infect.19.02).

Study design and patients

A prospective observational cohort study was performed between February 2019 and April 2020 at Jessa Hospital, Hasselt, a 981-bed teaching hospital (clinicaltrial.gov identifier NCT03841162). Jessa Hospital has implemented AMS in daily care and this consists of a microbiology laboratory and ID consultation service. Face-to-face AMS team rounds with the treating physician are performed weekly in specific departments, including the ICU. The AMS rounds are led by an ID physician and performed together with one microbiologist.

Adult patients presenting at the ED with suspected sepsis and from whom blood cultures were drawn were asked to participate. Patients were included after collection of the first set of blood cultures. Patients who presented multiple times at the ED during the study period could be included multiple times if they developed a new suspected sepsis episode. An episode was defined as new if it was $\geq$7 days after a positive culture with the same pathogen or $\geq$24 h after a positive culture with a different organism from the same site.

This study was a subanalysis of AMS aspects of the subpopulation of patients with sepsis based on a sequential organ failure assessment (SOFA) score $\geq$2. An analysis of risk factors for patient outcomes of the complete study cohort (1690 episodes of 1545 patients with suspected sepsis) has been reported [16]. The methods of microbiological diagnostics and definitions of infection diagnoses were identical in both analyses. Age, sex, comorbidities, clinical and laboratory parameters and relevant times were extracted from patient electronic medical records.

Microbiological diagnostics

Blood cultures were drawn for all patient episodes and analysed using the BACTEC FX (Becton Dickinson) system. Bacterial identification was by MALDI-TOF Biotyper (Bruker) and susceptibility testing by Phoenix TM 100 (Becton Dickinson). Blood cultures were processed 24h/day, 7d/week. Other microbiological diagnostics were performed when deemed relevant by the treating physician. This included cultures of urine, lower respiratory tract and samples of specific foci, urinary antigen tests for *Streptococcus pneumoniae* and *Legionella pneumophila* and polymerase chain reaction (PCR) for respiratory pathogens on nasopharyngeal swabs.

Infection diagnoses

The final diagnosis of infection was extracted from the treating physician's discharge letter and structured and validated according to ID definitions [17-21] by an experienced ID physician (I.C.G.) not involved in the care or consultation of study patients. Healthcare-associated infections (HCAI) were distinguished from community-acquired infections (CAI) based on ECDC guidelines [21]. Sepsis-3 definitions were used to define sepsis, i.e., all patients with a SOFA score $\geq$2, and septic shock [17].

Positive blood cultures were classified as true bacteraemia or as contamination according to CDC guidelines [18]. Patients with blood cultures positive for contaminants were considered negative for bacteraemia. Primary BSI was defined as true bacteraemia without a focus of infection. Patients with a central-line associated BSI (CLABSI) or with confirmed endocarditis were included in this group. Pneumonia was defined as an acute symptomatic infection of the lower respiratory tract with a new infiltrate [19]. Patients without infiltrate but treated for possible pneumonia were defined as having lower respiratory tract infection (lRTI). Influenza was defined by a positive influenza PCR test. Urosepsis was defined as a urinary tract infection (UTI) with confirmed true bacteraemia. Other UTIs were defined as upper UTI (pyelonephritis) or lower UTI (cystitis, prostatitis, etc) [20]. Other diagnostic categories are listed in supplementary Table 1.

Empirical antibiotic therapy assessment

Local antibiotic guidelines were made available on the hospital's intranet and regularly updated by the antibiotic committee. Antibiotic therapy was recorded for all patient episodes, including start and stop date and time of administration of each compound. Any change in antibiotic therapy, the type of change, and the reason for change were noted. No other antimicrobial therapy (antifungal, antiviral) was assessed. EAT was assessed using eight applicable IQIs for responsible antibiotic use (Table 1) [11].

Time of initiation and route of administration of EAT were recorded. The time intervals between antibiotic administration and ED triage or blood culture draw were calculated.

EAT initiated in the ED was assessed as adherent regarding choice of antibiotic and dose according to local hospital guidelines. All guidelines are shown in supplementary Table 1.

Information on likely causative pathogens, based on local epidemiology, was provided for all infections in the guidelines. EAT was defined as appropriate if it was active against all likely causative bacterial pathogens. Antimicrobial activity of EAT was assessed according to the susceptibility of pathogens isolated from relevant cultures. EAT was considered active if the bacteria identified were susceptible in vitro to at least one of the antibiotics administered.

Medical records were searched for reassessments of EAT within 3 days. In addition, the first change and the time of first change were assessed.

Changes within the first 3 days after initiation of EAT were recorded and categorised as follows: de-escalation, escalation, class switch, dosage change, change in administration route, or discontinuation. De-escalation was defined as the narrowing of antibiotic spectrum, or removal of unnecessary antibiotics in combination therapy (e.g., piperacillin-tazobactam to flucloxacillin). Escalation was the broadening of antibiotic spectrum, or the addition of antibiotics in combination therapy (e.g., penicillin to amoxicillin-clavulanic acid). Class switch was the switch from one class of

Table 1
List of the applicable DRIVE-AB global quality indicators for responsible empirical antibiotic use

	Quality indicator	Numerator description	Denominator description	Results
IQI-3	The prescribed antibiotic should be active against all the likely causative pathogens	Number of episodes where started EAT was active against likely pathogens	Total number of EAT episodes	665/787 (84.5%)
IQI-5	Broad-spectrum empirical antibiotic therapy should be changed to pathogen-directed therapy as soon as culture results become available	Number of episodes where cultures were positive and change to pathogen-directed therapy was performed correctly	Total number of EAT episodes and positive cultures	149/298 (50.0%)
IQI-7	Antibiotics for empirical therapy should be reviewed after the third day of treatment or when microbiological results become available	Number of episodes where EAT was reassessed or changed after three days of EAT	Total number of EAT episodes	Not measurable
IQI-11	Dosing and dosing interval of antibiotics should be prescribed according to guidelines	Number of episodes where doses of EAT were according to guidelines	Total number of EAT episodes	361/787 (45.9%)
IQI-15	Antibiotic therapy should be discontinued based on the lack of clinical evidence of infection	Number of episodes where EAT was discontinued	Total number of EAT episodes	Not measurable
IQI-18	Antibiotics should be prescribed according to local guidelines	Number of episodes where EAT was started according to the local guideline	Total number of EAT episodes	536/787 (68.1%)
IQI-45	Timeliness of administration of antibiotic therapy and prophylaxis should be compliant with guidelines	Number of episodes where the time of EAT start was according to guidelines	Total number of EAT episodes	Not measurable
IQI-51	Antibiotic therapy in adult patients with sepsis should be started intravenously	Number of episodes where EAT was started intravenously	Total number of episodes with EAT	734/787 (93.3%)

EAT: empirical antibiotic therapy; IQIs: Inpatient Quality Indicators [11]

antibiotics to another. Discontinuation of antibiotic therapy was the complete cessation of treatment before the planned end date. Other reasons for change were clinical deterioration or improvement based on the judgement of the treating physician or following ID/AMS team consultation.

Advice during ID/AMS team consultations was provided via telephone or in person. Medical records were searched for ID/AMS team consultations. Microbiological support/consultation was sought in the laboratory information system (GLIMS). Date and time, together with all advice provided, was recorded. Reasons for change by microbiological consultation were (partial) results from the blood culture system: bottle positivity, Gram-staining, pathogen identification, the antibiogram, or results from other cultures performed. These results were made available to the treating physician via telephone or the medical record.

Statistical analyses

Descriptive statistics were used to analyse patient characteristics, EAT, changes in therapy, and reason for change. Continuous data are shown as median (interquartile range [IQR]). Categorical data are reported as number and proportion. Univariate analyses were performed using Mann Whitney U or Kruskal Wallis test for continuous data and Chi-square for categorical data. A *P*-value of <0.05 was considered statistically significant. All analyses were done on episode level, except for age, sex and comorbidities, which were done on patient level. Analyses were performed using SPSS version 25 (IBM, Chicago, Illinois, USA).

Results

Patient and episode characteristics

Characteristics of the cohort are shown in Table 2. In total, 803 patients were included in the study. The median age was 75 (66-83) years, and 60.8% patients were male. Median Charlson Comorbidity Index (CCI) was 2 (1-3) with chronic kidney disease (25.3%), cardiac comorbidities (24.7%) and hypertension (29.6%) the most common.

In total, these patients experienced 900 sepsis episodes (SOFA score $\geq$2) during the study period. Sixty-five patients had 2 episodes, 12 patients had 3 episodes, one patient had 4 episodes and one patient had 5 episodes. Most referrals were from the home setting (712 [79.4%]). Only 6.3% were from long-term care facilities.

Median SOFA score was 3 (2-4). Septic shock was present in 8 (0.9%) episodes. In total, 125 (13.9%) episodes were HCAI. Median hospital length-of-stay (LOS) was 7 days, and 11.4% of patients were admitted to the intensive care unit (ICU), with a median ICU LOS of 4 days. In-hospital mortality was 8.9%.

Infection diagnoses

Supplementary Table 1 shows an overview of all infection diagnoses of the 900 sepsis episodes. Bacteraemia was present in 19.9% of episodes. The most common infections were pneumonia (21.8%), and upper UTI (10%). BSI, including CLABSI and endocarditis, were present in 5.2% of episodes. Cholangitis and cholecystitis were the most prevalent intra-abdominal infections (34 episodes [3.8%]), and erysipelas the most common acute bacterial skin and skin structure infection (ABSSSI) (26 episodes [2.9%]).

The total number of episodes with antibiotic therapy, together with all recorded changes, are shown in Table 3. All empirical antibiotics are listed in supplementary Table 2. Antibiotics were prescribed in 88.2% of sepsis episodes of which 787 (87.4%) were EAT. In seven episodes, antibiotic therapy was not started until a microbiological result was available. The most frequently prescribed empirical antibiotic was amoxicillin-clavulanic acid, which was used in 42.3% of episodes. Amikacin was the most frequently added antibiotic for combination therapy (10.3% of episodes).

Microbiological data

All relevant positive bacterial cultures, pathogens, and susceptibilities are shown in Supplementary Table 3.

In total, microbiological diagnostics yielded relevant bacterial pathogens in 33% of episodes. In 179 episodes with bacteraemia,

Table 2
Demographics, comorbidities and outcomes of patients admitted with sepsis at the emergency department on patient and episode level.

Variable	Total patientsn = 803
Age in years (median, IQR)	75 (66-83)
Sex (male)	448 (60.8)
CCI (median, IQR)	2 (1-3)
Cardiac comorbidities	190 (23.7)
Hypertension	237 (29.5)
Cerebrovascular disease	96 (11.8)
Chronic pulmonary disease	155 (19.3)
Chronic kidney disease	200 (24.9)
Liver disease	28 (3.5)
Diabetes	164 (20.4)
Solid malignancy	176 (21.9)
Haematological malignancy	27 (3.4)
	Total episodesn = 900
Referral*	712 (79.4)
Home	3 (0.3)
Other hospital	57 (6.3)
Long-term care facility	93 (10.4)
Referred by GP	26 (2.9)
Transport by EMS	6 (0.7)
Other	80 (8.9)
SOFA score (median, IQR)	3 (2-4)
Septic shockBacteraemiaCommunity-acquired infection	8 (0.9)179 (19.9)776 (86.2)
Healthcare-associated infection	124 (13.8)
LOS, in days (median, IQR)	7 (4-11)
ICU admission	103 (11.4)
ICU LOS, days (median, IQR)	4 (2-8)
In-hospital mortality	80 (8.9)

* Information not recorded in three patients. ED: emergency department; CCI: Charlson comorbidity index; GP: general practitioner; EMS: emergency medical service; SOFA: sequential organ failure assessment; LOS: length-of-stay; IQR: interquartile range. All numbers are presented as number (proportion) unless otherwise specified.

the median turnaround time (TAT) from blood culture collection until positivity was 14h6min (11:18-22:36) and Gram-stain results were reported after 4h18min (1:48–10:36). Pathogen identification and susceptibility results were available and reported 23h48min (19:00–37:48) and 47h48min (40:18–66:24) after blood culture collection, respectively.

Resistance rates in this study population were low. There were 16.3% multidrug-resistant Enterobacterales, of which there were seven extended spectrum beta-lactamase (ESBL)-producing *E. coli*, one methicillin-resistant *Staphylococcus aureus* (MRSA) and no vancomycin-resistant Enterococci. Supplementary Table 4 shows the antimicrobial resistance (AMR) prevalence of the most important invasive isolates of this cohort, the overall AMR prevalence of invasive isolates in our hospital, and the national AMR rates in EARS-net 2019 for comparison.

Empirical antibiotic therapy assessment

Overall, 787 EAT episodes were analysed. The results of the IQI assessment are presented in Table 1.

Timeliness of EAT (IQI-45) and start of intravenous EAT (IQI-51)

Although IQI-45 was applicable to the patient population, it was not assessable as such in our hospital. The guidelines did not provide a recommendation on the time to start empirical antibiotics.

The time of start of EAT was available for 95.8% of episodes. Table 3 shows the time interval between the first assessment by a nurse (triage) and the start of EAT, and the time interval between blood culture collection and EAT for 729 episodes, including seven with septic shock. In 4.5% of episodes, EAT was started before the collection of blood cultures. In one patient with septic shock, no EAT was prescribed but targeted therapy was started after microbiological results were available.

In almost all (93.3%) episodes, EAT was started intravenously (IQI-51).

Adherence to local guidelines, choice and dosing (IQI-18 & IQI-11)

In 68.1% of episodes with EAT, the choice of the antibiotic(s) was according to the guideline. In 67.4% of episodes the dose was also concordant. The dose was lower than recommended in 92.0% of non-dose-adherent episodes. Therefore, full adherence (choice and dosing) to EAT guidelines was 45.9%.

In 31.9% of episodes, the choice of antibiotic was not according to guidelines. In 27.1% of these episodes there was no definite final diagnosis of infection. In episodes with a diagnosis of infection, non-adherence was most frequent in RTIs (66 [26.3%]), and in UTIs (36 [14.3%]). Most commonly (in 58.2% of episodes) the choice of antibiotics was either too broad or too narrow. In 49.3% of these episodes, EAT was too broad for a CAI, or too narrow because an HCAI was treated as a CAI.

In 7/113 episodes without EAT, targeted antibiotic therapy was started after microbiological results were available. No antibiotic therapy was given in 106 (11.8%) episodes, which seemed justified in 92 (86.8%) episodes. Also of note, in one third of these episodes viral infections without bacterial coinfection were diagnosed, and in 50% no diagnosis could be made.

Appropriate antibiotic therapy (IQI-3)

The guidelines regarding choice of antibiotics were followed in 68.1% of episodes, i.e., EAT was active against all likely pathogens (appropriate). Of 251 non-choice-adherent episodes, 51.4% consisted of alternative antibiotics that were also active against all likely causative pathogens but were not recommended in the guidelines. Ninety percent of CAI were treated with antibiotics that were too broad according to the guidelines. In 122/251 (48.6%) episodes, the antibiotics were not active against all likely causative pathogens. Of those, the spec-

Table 3
Empirical antibiotic therapy for sepsis and changes

Variable	Totaln = 900 episodes
Antibiotic therapy	794 (88.2)
Empirical antibiotic therapy	787 (87.4)
Time to start (from triage)[a]	2h59min (2:06-4:24)
Patients with septic shock[b]	1h12min (1:06-3:06)
Time to start (from blood culture collection)[c]	2h12min (1:18-3:30)
Patients with septic shock[b]	36min (0:30-2:18)
First change within 3 days	335 (37.2)*
De-escalation	115 (34.3)
Escalation	64 (19.1)
Class switch	17 (5.1)
Stop	69 (20.6)
Dose	1 (0.3)
IV to PO	69 (20.6)
First change later than 3 days	201 (22.3)*
No change	225 (25.0)*
Decision to change within 3 days	
Treating physician	170 (50.8)
Microbiological result/consult	131 (39.1)
Positive blood culture	4 (3.0)
Gram stain result	5 (3.8)
MALDI-TOF result	22 (16.8)
Susceptibility result	47 (35.9)
Other culture/PCR	50 (38.2)
Negative blood culture	3 (2.3)
ID/AMS team consultation	34 (10.1)

*Duration of empirical therapy missing for 26 episodes. [a] n = 754/787. [b] n = 7/8 patients with septic shock because 1 patient with septic shock did not receive EAT

[c] n=729/754. IV: intravenous; PO: per os; ID: infectious disease; PCR, polymerase chain reaction; AMS, antimicrobial stewardship. All data are presented as number (proportion).

trum was considered too narrow for 42 (34.4%) HCAI episodes and for 77 (63.1%) CAI episodes. Antibiotic therapy was guideline-adherent in 287/336 (85.4%), 57/96 (59.4%), 38/95 (40.0%), and 11/17 (64.7%) episodes where amoxicillin-clavulanic acid, ceftriaxone, piperacillin-tazobactam, or meropenem were prescribed, respectively. In the non-guideline-adherent episodes, amoxicillin-clavulanic acid (33/49 [67.3%] episodes) and ceftriaxone (15/39 [38.5%] episodes) were considered too narrow, while piperacillin-tazobactam (48/57 [84.2%] episodes) and meropenem (6/6 [100.0%] episodes) were considered too broad. Other therapy was inappropriate because not all antibiotics in the recommended combination regimen were started (17 [13.9%] episodes), or because antibiotics were not active against pathogens more likely to be present in patients with specific risk factors, such as neutropenic patients or patients with complicated UTIs (at risk for *Pseudomonas aeruginosa* infection) in 10 (8.2%) episodes.

Post hoc assessment of antimicrobial activity

A flowchart is shown in Figure 1. Relevant pathogens were identified in 298 episodes. EAT showed in vitro activity against the isolated pathogens in 79.9% of episodes. Of those, 68.5% of episodes were guideline-adherent and 31.5% were not. Most importantly, of the 60 (20.1%) episodes with EAT that was not active against the identified pathogen in vitro, the choice of antibiotic was according to the guidelines in 30 (50.0%) episodes. However, pathogens in these episodes were more resistant than anticipated in the guidelines, and the antibiotic spectrum was not broad enough. This was the case for 12 UTI episodes, 10 intra-abdominal infections, 3 pneumonias, 3 ABSSSIs and 2 BSIs. In 19/60 (31.7%) episodes the choice of antibiotic did not adhere to the guidelines, and in 11 episodes no antibiotics were started (18.3%). In seven of these, targeted antibiotic therapy was started after a pathogen was isolated.

In vitro activity was more common in choice-adherent episodes (84.5%) compared with choice non-adherent EAT (71.4%; $P = 0.007$).

Review of empirical antibiotic therapy (IQI-7)

Reassessment within 3 days was not systematically mentioned in medical records; therefore, IQI-7 was not measurable for the episodes in which EAT was unchanged. However, in 16.0% of episodes an ID/AMS team consultation took place within 3 days. In 24.6% of episodes the ID/AMS team recommended to continue EAT unchanged.

All changes within the first 3 days of 335 EAT episodes, and the reason for change, are shown in Table 3. In 37.2% of episodes, the first change of antibiotic therapy occurred within 3 days. Median time to change was 1.68 (0.99-2.26) days. This change was most frequently de-escalation (34.3%) followed by discontinuation (20.6%) and escalation (19.1%). Table 4 shows types of EAT changes. The treating physician initiated the change in more than half of episodes. This was most frequently a change in administration route (IV to oral) when patients were discharged (39.4%). Microbiologists proposed changes to antibiotic therapy in 39.1% of episodes, most often in the form of de-escalation (58%). Microbiological advice was not followed in 20 episodes, resulting in an acceptance rate of 86.8%. Antibiotic therapy was changed based on ID/AMS team advice in 10.1% of episodes within the first 3 days. This was most frequently de-escalation (35.3%) or discontinuation (29.4%). In another 18 episodes, ID/AMS team advice was not followed, leading to a different change than proposed in 12/18 episodes, and no change in 6/18 episodes. This resulted in an acceptance rate for ID/AMS team advice of 34/52 (65.4%). The type of changes between groups was significantly different ($P = 0.000$). However, when analysed pairwise, there was no difference in type of change between microbiology and ID/AMS team consultation ($P = 0.142$). Significant differences were observed between treating physician and microbiologist ($P = 0.000$) and between treating physician and ID/AMS team consultant ($P = 0.001$).

Of the 426 episodes without change within the first 3 days, there was no change in half the episodes throughout the whole course of antibiotic therapy; a change was made by the treating physician later than 3 days in a quarter of episodes, and a final change following microbiology or ID/AMS team consultation was made after 3 days in 41 (9.6%) and 35 (8.2%) episodes, respectively.

Discontinuation based on the lack of clinical evidence of infection (IQI-15)

IQI-15 was not assessable because the reason for discontinuation was not always mentioned in the medical records. In total, the first change in EAT was discontinuation of antibiotic therapy in 312/787 (39.6%) episodes after a median time of 6 days (3-7 days). Microbiology and ID/AMS consultation recommended discontinuation of EAT in 29 (9.3%) and 42 (13.5%) episodes, respectively. EAT was discontinued in 25.7% of episodes because of a lack of a definitive diagnosis, in 14.1% of episodes with a (suspected) viral infection, and in 1.3% of episodes of inflammatory disease.

Patient outcomes

Differences in patient outcomes between the guideline-adherent groups and the guideline non-adherent groups, and between patients with or without in vitro active therapy are shown in Table 5. Mortality was significantly lower in patients who were started on fully adherent EAT (therapy-adherent regarding choice and dose) (6.4% vs. 11.3%). In addition, hospital LOS was significantly shorter in the fully adherent group (6 vs. 8 days). Regarding choice of EAT, ICU admission and hospital LOS were significantly

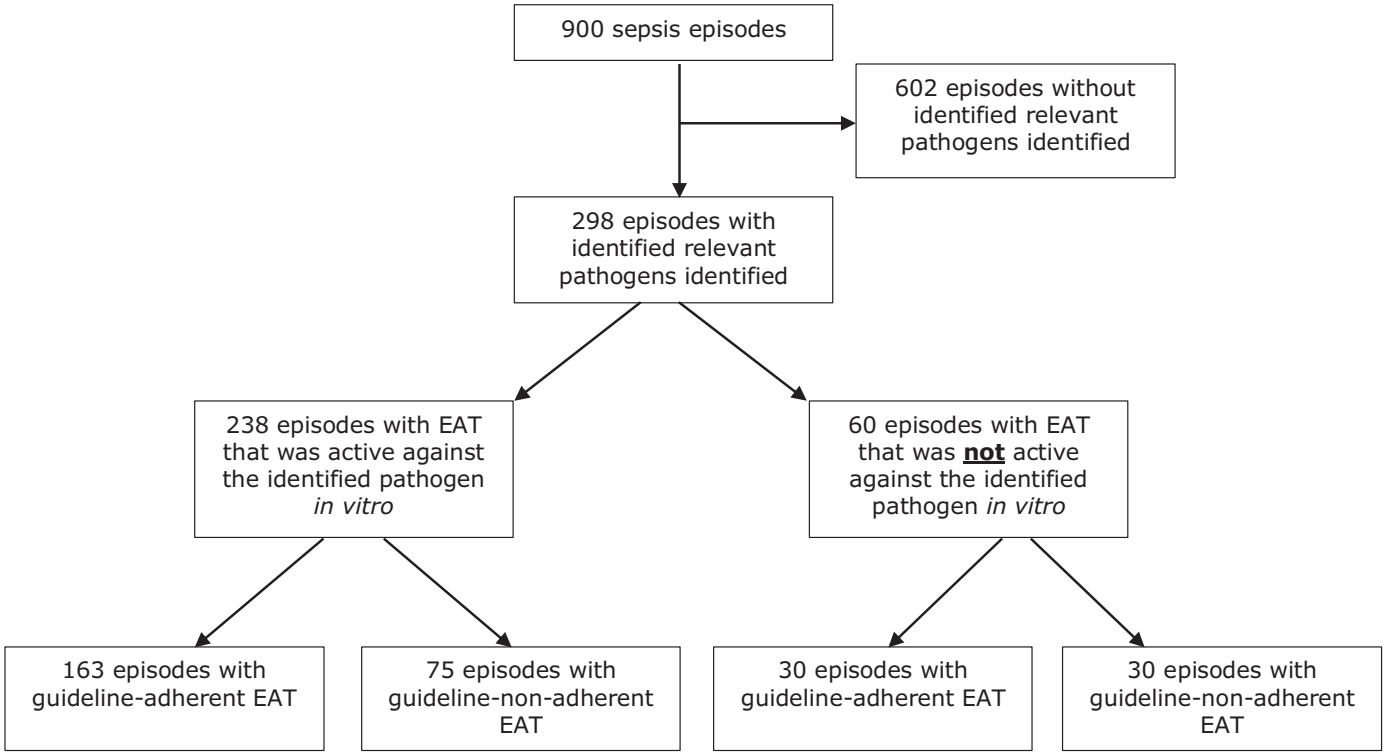

Figure 1. Assessment of antimicrobial activity of empirical antibiotic therapy (EAT) against isolated bacterial pathogens

Table 4
Type of change in empirical antibiotic therapy within 3 days initiated by treating physician, microbiology result, or ID/AMS team.

Change within 3 days	Treating physician n=170	Microbiology result n=131	ID/AMS team n=34
De-escalation	27 (15.9)	76 (58.0)	12 (35.3)
Escalation	28 (16.5)	27 (20.6)	9 (26.5)
Class switch	7 (4.1)	8 (6.1)	2 (5.9)
Discontinuation	41 (24.1)	18 (13.7)	10 (29.4)
Dose	0 (0.0)	1 (0.8)	0 (0.0)
IV to PO	67 (39.4)	1 (0.8)	1 (2.9)

ID: infectious disease; AMS: antimicrobial stewardship; IV: intravenous; PO: per os. All numbers are presented as number (proportion).

Table 5
Associations of patient outcomes with guideline-non-adherent and guideline-adherent empirical antibiotic therapy regimens, and with antimicrobial activity against isolated bacterial pathogens

	Non-adherencen = 426	**Full adherence (choice and dose)n = 361**	***P*-value**
In-hospital mortality	48 (11.3)	23 (6.4)	**0.017**
ICU admission	61 (14.3)	38 (10.5)	0.110
LOS, in days (median, IQR)	8 (5-14)	6 (4-10)	**0.000**
LOS ICU, in days (median, IQR)	4 (2-8)	3.5 (2-9)	0.596
	Non-adherenceregarding choiceof antibioticn = 251	**Adherenceregarding choiceof antibioticn = 536**	***P*-value**
In-hospital mortality	29 (11.6)	42 (7.8)	0.090
ICU admission	45 (17.9)	54 (10.1)	**0.002**
LOS, in days (median, IQR)	8 (5-15)	6 (4-11)	**0.000**
LOS ICU, in days (median, IQR)	3 (2-7)	5 (2-10)	0.079
	Dose lower than in guidelinen = 161	**Dose according to guidelinen = 361**	***P*-value**
In-hospital mortality	19 (11.2)	23 (6.4)	0.059
ICU admission	14 (8.7)	38 (10.5)	0.564
LOS, in days (median, IQR)	7 (4-12)	6 (4-10)	0.129
LOS ICU, in days (median, IQR)	5 (3-11)	3.5 (2-9)	0.539
	No antibiotic activity in vitron = 60	**Antibiotic activity in vitron = 238**	***P*-value**
In-hospital mortality	11 (18.0)	24 (10.0)	0.081
ICU admission	9 (14.8)	50 (20.8)	0.286
LOS, in days (median, IQR)	7 (5-15.5)	8 (5-13)	0.392
LOS ICU, in days (median, IQR)	3 (2.5-9.5)	3 (2-9)	0.782

ICU: intensive care unit; LOS: length-of-stay; IQR, interquartile range. All data are presented as number (proportion).

lower in the adherent group (10.1% vs. 17.9% and 6 vs. 8 days, respectively). No differences in mortality were found.

Discussion

This study was an audit of EAT in adult patients admitted to hospital with sepsis. Full prescriber adherence to the guidelines was less than 50%. The choice of antibiotics was more frequently guideline-adherent. Non-adherence regarding choice resulted in either too broad or too narrow antibiotics because differentiation into CAI or HCAI by the prescribing physician was suboptimal. Overall, empirical antibiotics were appropriate considering coverage of likely causative pathogens in most episodes, but inappropriate in almost half the episodes in the group that was guideline non-adherent regarding choice. EAT was active in vitro against relevant isolates in almost 80% of episodes. In vitro activity was significantly more frequent in patients receiving guideline-adherent EAT. Change of EAT within 3 days occurred in more than one third of episodes, with a significant difference in the type of change between treating physicians (mostly change in route of administration) and microbiology or ID/AMS team consultants (mostly de-escalation or discontinuation).

Full adherence to guidelines (choice and dose) was associated with lower mortality and shorter LOS. Adherence to guidelines (choice) was associated with significantly shorter LOS and fewer ICU admissions. Surprisingly, a dose lower than advised in the guidelines and lack of in vitro activity was not associated with worse outcome. Others have reported a beneficial effect of guideline adherence on outcomes of patients with community-acquired pneumonia (CAP) [22].

This is the first attempt to test the global DRIVE-AB IQIs [11] for measuring antibiotic use in daily practice. Three of eight potentially applicable IQIs of EAT were not measurable; two of these were because of missing information in the patient notes. Five of eight IQIs were evaluable. The guidelines did not provide specific recommendations on the time to start antibiotics; therefore, IQI-45 was not measurable. However, in this study, EAT was started within approximately 3 h after triage. This timeframe seems acceptable because in a large study that was limited almost exclusively to patients without shock, the risk for hospital death only increased after intervals of $\geq$5 h from presentation [23]. Indeed, the Infectious Diseases Society of America (IDSA) recently warned of a risk of antibiotic overuse because of overdiagnosis of sepsis when guidelines provide a time limit within which antibiotics should be administered and they argued that the association between antibiotic initiation and patient outcomes is only strong for patients with septic shock [24].

Adherence to local guidelines (IQI-18 and IQI-11) regarding choice and dosing, including reasons for non-adherence, has been reported by others, with disease severity the most influential extrinsic factor, particularly for EAT that was considered too broad [25,26]. The treating physician's fear was found to be the most influential intrinsic factor in one study [25]. Although the current study did not evaluate these factors, these previous findings are in accordance with the results of the current study. Changes by the treating physician were more often a change in administration route, which poses fewer risks than changes in spectrum or dose. Most changes after 3 days were made when the patients were clinically stable without a microbiology or ID/AMS team consultation.

Reassessment of EAT within the first 3 days (IQI-7) is recommended [27] and its effect on antibiotic use and beneficial patient outcomes has been reported [28,29]. If no change occurred, reassessment was not measurable in the current study because no information was recorded in the medical record; however, changes within 3 days could be assessed. The finding that the type of change differs among physicians is also reported in the literature. In one study, physician characteristics were an independent risk factor for guideline adherence [30].

Strengths of the current study are the prospective inclusion of many patients with confirmed sepsis and the assessment of both process and patient outcomes. The presence of a fast-operating microbiology laboratory and ID consultation service and a strong AMS programme with high acceptance rates among clinicians is beneficial. This study has some limitations. Firstly, the single centre design limits external validity. The AMR rate of invasive pathogens in the current cohort is within the range for Northern European countries. In countries with higher resistance rates, there may be fewer options for de-escalation. Mortality in the current sepsis cohort is somewhat lower than in other reports [1,2,31]; however, the data are not fully comparable because of differences in the definition of sepsis. Secondly, differences in outcomes and changes could be prone to selection bias as ID/AMS team consultations were mainly performed for the most severely ill patients. Finally, this study did not assess risk factors with an attributable effect on LOS, ICU admission, and mortality.

In conclusion, this study measured five of eight global IQIs of EAT in routine clinical practice. Feedback based on the results will enable improvement of the AMS programme. Full adherence to guidelines was only moderate, adherence to the recommended choice of antibiotics was higher. Most importantly, adherence to guidelines showed several benefits regarding patient outcomes.

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Declarations

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Competing Interests

All authors: no conflict of interest.

Ethical Approval

Documented approval for the study was obtained from the Ethics Committee of Hasselt University and Jessa Hospital (18.106/infect18.03 and 19.51/infect.19.02).

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