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European Journal of Internal Medicine 78 (2020) 69–75

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original article

Non-adherence to antimicrobial guidelines in patients with bloodstream infection visiting the emergency department

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ARTICLE INFO

Keywords:
Guideline adherence
Antimicrobial stewardship

ABSTRACT

Objective: Non-adherence to antimicrobial guidelines in patients with bloodstream infection can result in undertreatment, overtreatment, or equivalent treatment, and could lead to suboptimal care. Our aim was to examine the association between non-adherence and appropriate coverage as well as to assess the impact of non-adherence on 30-day mortality.

Methods: We conducted a retrospective cohort study between 2012 and 2017 at a tertiary university hospital. Adult patients attending the emergency department with a bloodstream infection were included. Adherence was defined as guideline-recommended antibiotic therapy. Non-adherence was either undertreatment (too narrow-spectrum), overtreatment (too broad-spectrum), or equivalent treatment. Outcomes were appropriate coverage (i.e. antibiotic therapy that matches in vitro susceptibility of the isolated bacteria) and 30-day mortality.

Results: We included 909 patients of whom 395 (43.5%) were treated adherently, 355 (39.1%) were undertreated, 87 (9.6%) were overtreated, and 72 (7.9%) received an equivalent treatment. Overtreated patients were more severely ill, whilst undertreated patients had more favorable patient characteristics. Overtreatment did not result in higher appropriate coverage, whereas undertreatment was associated with lower coverage (OR[95%CI]: 0.18 [0.12; 0.26]). Overtreatment and undertreatment were not associated with 30-day mortality.

Conclusions: Guideline adherence likely depends on disease severity, because overtreatment was more often observed in patients with high disease severity and undertreatment in less severely ill patients. Undertreatment was associated lower appropriate coverage but not with higher mortality. However, this can be the result of residual confounding . Overtreatment did not result in higher appropriate antibiotic coverage nor a survival benefit . Therefore, overtreatment seems not justifiable.

1. Introduction

1.1. Background

Bacterial infections can result in considerable mortality and have a profound global burden [1–3]. Patients with a severe infection (e.g. sepsis) often present in an acute care setting, such as the emergency department (ED). To provide proper care in this setting, initiation of the antibiotic therapy that matches in vitro susceptibility of the causative bacteria (i.e. with appropriate coverage) is important [4]. However, the causative pathogen has yet to be identified by cultures and this process usually takes over 24 h. Therefore, antibiotic therapy in the ED is virtually always initiated empirically [4].

1.2. Importance

For patients with a suspected bacterial infection, guideline recommendations for empiric antibiotic therapy should depend on local prevalence of pathogens and antimicrobial resistance patterns [5]. Such antimicrobial guidelines usually provide recommendations for a specific working diagnosis (i.e. suspected source of infection). The aim of antimicrobial guidelines is to ensure that the antibiotic therapy with appropriate coverage is given before culture results become available, thereby preventing mortality. In addition, guidelines aim to reduce

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https://doi.org/10.1016/j.ejim.2020.04.013
Received 15 January 2020; Received in revised form 19 March 2020; Accepted 4 April 2020
Available online 25 April 2020

misuse of broad-spectrum antibiotic therapy, in order to prevent selection of antimicrobial resistance and adverse effects [6].

1.3. Goal of this investigation

Non-adherence to antimicrobial guidelines in patients with a proven bloodstream infection (BSI) is disadvantageous when it results in inappropriate coverage [7, 8]. Moreover, literature about non-adherence in the ED is scarce and discrepant. Rate of non-adherence ranged from 10 to 53% and these studies did not differentiate between different types of non-adherence (i.e. undertreatment, overtreatment, or equivalent treatment) [9–11]. Therefore, we intended to evaluate non-adherence to antimicrobial guidelines for adult patients with BSI attending the ED. Our aims were primarily to examine the association between the different types of non-adherence and appropriate coverage, and secondly to assess the impact of non-adherence on 30-day mortality.

2. Method

2.1. Study design and setting

We conducted a retrospective cohort study at the Erasmus University Medical Center Rotterdam (Erasmus MC), which is a tertiary university hospital in the Netherlands. We used data from all patients attending the ED with BSI from July 2012 through December 2017. The Medical Ethics Committee of the Erasmus MC reviewed this study and concluded that it did not fall under the scope of the Medical Research Involving Human Subjects Act and therefore no informed consent needed to be obtained. This study is thus approved and registered under MEC-2018-1744.

2.2. Selection of participants

Patients were eligible for inclusion if they were at least 18 years of age, had a guideline-specified working diagnosis, and had a laboratory proven bacterial BSI in the ED. BSI was defined as presence of a known pathogen (e.g. *E. coli*) in one blood culture or a common commensal (e.g. *S. epidermidis*) in at least two blood cultures collected on separate occasions within two days from ED admission [12, 13]. Only the first episode of BSI was included to prevent domination of results by individuals that frequently visited the ED.

2.3. Data collection and processing

Data were derived from an ED database and combined with a database from Medical Microbiology, containing all collected blood cultures [14]. The ED database included the working diagnosis, empiric antibiotic therapy administered during the ED visit, other patient characteristics, and mortality. General and demographic presenting patients characteristics collected were: sex, age, arrival (by ambulance or not), triage category (according to the Manchester Triage System) [15], disposition (direct intensive care unit admittance or other), chills [16], vomiting [16], need for vasopressors, and origin of infection (nosocomial or community-acquired) [17]. To further account for initial severity of disease we used the first recorded vital signs (i.e. body temperature, heart rate, respiratory rate, systolic blood pressure, oxygen saturation, and consciousness), whether there was need for any supplemental oxygen, and calculated the National Early Warning Score (NEWS) [18, 19] (Appendix A). Additionally, to account for comorbidity we collected all components of the age-adjusted Charlson Comorbidity Index (CCI) [20] (Appendix B). For mortality data we used municipal death registration records.

Patients with a positive blood culture in the ED were identified via the blood culture database of Medical Microbiology [14]. This database contained information about type of pathogen and its susceptibility (antibiogram). Blood cultures were performed using the BACTEC system (Becton Dickinson Diagnostic Instrument Systems, Sparks, Md) according to the manufactures protocol. Type of pathogen was identified by MALDI-TOF MS analysis (Microflex, Bruker Daltonics, Bremen, Germany). The in vitro susceptibility testing was performed using the VITEK 2 (bioMérieux, Marcy l'Etoile, France) system. Based on earlier applied antibiotic therapy in the ED and established in vitro susceptibility of the isolated pathogen, we determined whether coverage of the empiric therapy was appropriate or not. In accordance with previous studies the following situations were scored as inappropriate coverage of the isolated pathogen: no empiric antibiotic therapy, ineffective antibiotic therapy (based on antibiogram or if dosage was lower than guideline-recommended) or not intravenously administered antibiotic therapy (except for antibiotics with high bioavailability such as ciprofloxacin and metronidazole) [21].

Adherence to guidelines was defined as initial antibiotic therapy administered in the ED in accordance with local hospital guideline recommendations for empiric antibiotic therapy [22]. This definition corresponds to previous definitions of adherence in comparable study settings [9–11]. Our empiric guideline recommendations depend on national antimicrobial guidelines and are updated based on local prevalence and resistance patterns [23]. Guidelines provide recommendations for a specific working diagnosis, and are easily available online for all physicians in our hospital [22]. Guideline deviation was considered adherent if a proper motivation was described in the medical chart, i.e. if altered based on previous relevant cultures (only to broaden therapy), and comorbidity (e.g. sickle cell disease, functional asplenia). Additionally, empiric antibiotic therapy was considered adherent if altered after direct consultation with a clinical microbiologist or infectious diseases specialist, for example in case of renal disease (i.e. applying an alternative to gentamicin while preserving the antimicrobial spectrum if pre-existent glomerular filtration rate was <30 mL/min). In case of multiple working diagnoses, all highly suspected diagnoses needed to be covered. Absence of antibiotic prescription was considered adherent in case of a suspected cholecystitis (if not severely ill and if not immunocompromised) and gastro-enteritis (if not recently returned from traveling, without (persisting) high fever, no dysentery, and if not immunocompromised). Over the study period there were minor changes in hospital guidelines, which we took into account (see table 1: primary meningitis).

Conversely, non-adherence was defined as failure to treat in accordance with the hospital guidelines. Previous studies did not divide non-adherence into an undertreatment, overtreatment, and equivalent group [9–11]. We scored non-adherence as undertreatment if therapy was more narrow-spectrum than guideline-recommended therapy (e.g. not administering antibiotics, omitting recommended gentamicin). Overtreatment was scored if antibiotic therapy was more broad-spectrum than guideline-recommended therapy (e.g. administering additional antibiotic agents while not recommended). If antibiotic therapy was non-adherent, but equivalent with regard to spectrum, a separate equivalent group was introduced (e.g. amoxicillin/clavulanic acid with gentamicin is equivalent to cefuroxime with gentamicin for cholangitis, unknown sepsis, and urosepsis). Equivalent treatment was either in accordance with national antimicrobial guidelines, or not. For a detailed description of non-adherence scoring, see Appendix C.

The authors RS and AB independently reviewed all medical charts to score both working diagnosis and whether the given antibiotic therapy was adherent or not. In case of disagreement or doubt a meeting with acute internists (JA, SKN) and medical microbiologists (JDS and AV) was organized in which consensus was obtained.

2.4. Data analysis

We examined all presenting patient characteristics that reflect severity of disease among adherently versus (vs.) non-adherently (i.e. under-, over-, equivalently) treated patients. Based on distribution, data

Table 1
Working diagnoses and guideline-recommended antibiotic therapy in patients with bloodstream infection at the emergency department.

Suspected infection focus	Working diagnosis	N (%)	Subcategory	Guideline-recommend antibiotic therapy
Unknown	Sepsis	98 (10.8)	CA	Cefuroxime and gentamicin
			HA	Piperacillin/tazobactam and gentamicin
Febrile neutropenia	Sepsis	37 (4.1)		Meropenem
Urogenital	Sepsis or pyelonephritis	266 (29.3)	CA	Cefuroxime and gentamicin
			HA	Piperacillin/tazobactam and gentamicin
Respiratory	Mild pneumonia (CURB 0–1)	45 (5.0)	CA	Amoxicillin[a]
	Moderate pneumonia (CURB 2)	26 (2.9)	CA	Amoxicillin
	Severe pneumonia (CURB 3–5)	37 (4.1)	CA	Amoxicillin/clavulanic acid and ciprofloxacin[a]
	Pneumonia	25 (2.8)	HA	Piperacillin/tazobactam (and gentamicin if doubt about source or if septic)
	Aspiration	9 (1.0)	CA	- Amoxicillin/clavulanic acid[a] - Cefuroxime and metronidazole[a]
	Pulmonic abscess /pleura empyema	9 (1.0)		Amoxicillin/clavulanic acid
Abdominal	Sepsis	29 (3.2)	CA	Cefuroxime and metronidazole and gentamicin
			HA	Piperacillin/tazobactam and gentamicin
	Cholangitis	181 (19.9)		Cefuroxime and gentamicin
	Peritonitis, primary (SBP)	13 (1.4)		Ceftriaxone
	Peritonitis, secondary	11 (1.2)	CA	Cefuroxime and metronidazole[b] and gentamicin
	Gastro-enteritis	18 (2.0)	CA, returned from traveling; if (persisting) high fever, dysentery, immunocompromised	Initially without antibiotic therapy - Azithromycin[a] - Erythromycin and ciprofloxacin
Skin, soft tissue, bone	Cellulitis	22 (2.4)		Flucloxacillin[a]
	Erysipelas	14 (1.5)		Penicillin[a]
Central nervous system	Meningitis, primary	32 (3.5)	Before 2015: < 50 years, not immunocompromised	Ceftriaxone and amoxicillin
				Ceftriaxone
Intravascular, thorax	Intravascular catheter	19 (2.1)		- Vancomycin - Cefuroxime and gentamicin

Only working diagnoses with a prevalence ≥1.0% are shown in this table.
Abbreviations: CA, community-acquired; HA, hospital-acquired; CURB65, confusion, blood urea nitrogen, respiratory rate, systolic blood pressure, age ≥ 65; SBP, spontaneous bacterial peritonitis.
All antibiotic therapy had to be administered intravenously, except [a]for oral and [b]intraperitoneal administration was allowed.

were compared using unpaired t-tests, chi-squared tests, or Fisher's exact tests. Distribution of these patient characteristics should reveal whether there are differences in initial disease severity between adherently vs. non-adherently (i.e. under-, over-, equivalently) treated patients.

First, we investigated the association between non-adherence and appropriate antibiotic coverage with univariable logistic regression. We did not control for patient characteristics because we assume they affect appropriate antibiotic coverage only through (non)-adherence. However, secondly, for the association between non-adherence and 30-day mortality we did expect confounding by patient characteristics and therefore we used multivariable logistic regression to limit bias. We considered patient characteristics as confounders during further analyses if, based on expert knowledge, the characteristics were associated with (non)-adherence and 30-day mortality [24]. Additionally, we repeated the analyses for two subgroups of undertreatment: (1) after excluding patients that received no antibiotic therapy and (2) for patients in which gentamicin was omitted.

Results were presented as odds ratios (OR) with 95% confidence intervals (CI). All hypothesis tests were 2-sided, with a significance level of $p < 0.05$. We handled missing data using multiple imputations. For efficiency purposes we imputed 20 datasets using the chained equations method. Statistical analyses were performed using R version 3.6.3.

3. Results

3.1. Patient characteristics

We identified 1286 adult patients with a positive laboratory proven blood culture taken in the ED. We excluded 247 patients with a recurrent BSI during our study period, resulting in 1039 unique patients with BSI (Fig 1). 909 patients had a guideline-specified working diagnosis, which are shown in table 1. Most prevalent working diagnoses among patients with BSI were urosepsis/pyelonephritis (n = 266, 29.3%) and cholangitis (n = 181, 19.9%). In 893 (98.2%) patients we found a known pathogen (e.g. 311 *Escherichia coli*) and in 16 (1.8%) we found a common commensal on multiple blood cultures collected on separate occasions within two days from ED admission (e.g. 11 *Staphylococcus epidermidis*). See appendix D for more detailed information about the isolated bacteria. 30-day mortality was 11.4%.

Treatment was adherent for 395 (43.5%) patients, 355 (39.1%) were undertreated, 87 (9.6%) were overtreated, and 72 (7.9%) received equivalent treatment. Equivalently treated patients had therapy according to national guidelines in 49 patients (68.1%). Overtreated patients received on average more than two antibiotics. Main reasons for undertreatment were omitting recommended gentamicin (n = 217, 61.1%) and not administering antibiotics at all (n = 79, 22.3%). For a detailed description, see Appendix C.

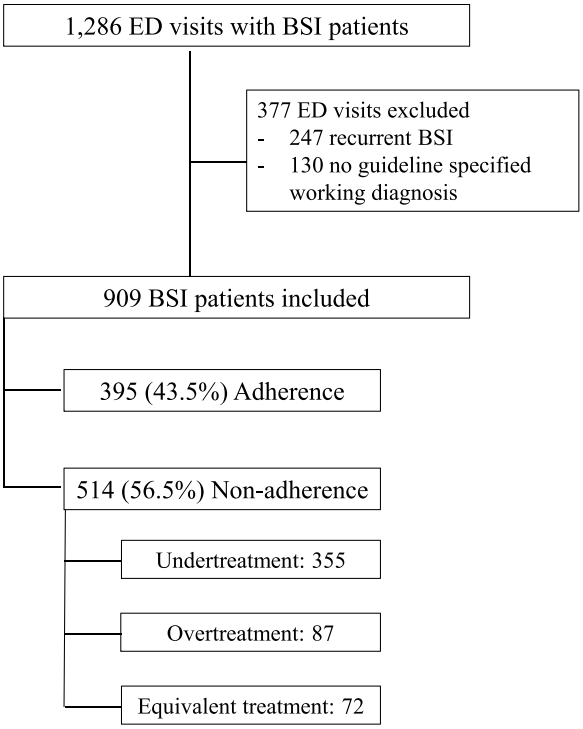

Fig. 1. Flowchart of study selection.
Abbreviations: ED, emergency department, BSI, bloodstream infection.

Undertreated patients had presenting characteristics that implied lower disease severity compared to adherently treated patients: they less frequently arrived by ambulance (16.6% vs. 30.1%), were less likely in high triage categories (14.7% vs. 33.3%), and were less often directly admitted to the intensive care unit (2.0% vs. 11.6%). In addition, undertreated patients had more normal vital signs and on average a lower NEWS of 4 (± 3.1) vs. 6 (± 3.8). Especially, patients with underlying mild liver disease and chronic kidney disease were more often undertreated. Undertreated patients more often had a working diagnosis of cholangitis, pyelonephritis, and urosepsis (Table 2). We found that omitting recommended gentamicin was more prevalent in patients with kidney disease (i.e. underlying chronic kidney disease and/or a suspected pyelonephritis/urosepsis). See Appendix C.

Overtreated patients had presenting characteristics that implied more critical illness than adherently treated patients. They were appointed to higher triage categories (52.4% vs. 33.3%) and had worse vital signs. On average, overtreated patients had a higher NEWS of 8 (± 4.3) vs. 6 (± 3.8). Overtreatment more frequently occurred in patients with underlying chronic pulmonary disease (25.3% vs. 12.2%). Overtreated patients were more often diagnosed with mild- and moderate community-acquired pneumonia (Table 2).

Equivalently treated patients had comparable presenting patient characteristics to adherently treated patients and thus an equal initial disease severity (NEWS of 6 (± 3.5) vs. 6 (± 3.8)). Only the number of patients in high triage categories was lower for equivalently treated patients (18.3% vs. 33.3%). Additionally, patients with underlying mild liver disease and malignancies were more frequently present in the equivalently treated group (Table 2).

3.2. Non-adherence and appropriate antibiotic coverage

Appropriate antibiotic coverage for the adherently treated was 89.1% (n = 352), for the undertreated 58.0% (n = 206), for the overtreated 94.3% (n = 82), and for the equivalently treated 86.1% (n = 62).

Undertreatment was associated with lower appropriate coverage compared to adherent treatment (OR[95%CI]: 0.18 [0.12; 0.26]). After excluding patients that received no antibiotic therapy, appropriate coverage increased from 58.0% to 74.6%. However, undertreatment remained associated with lower appropriate coverage (OR[95%CI]: 0.27 [0.16; 0.42]). Main reason for undertreatment was omitting gentamicin. If in these patients gentamicin was not omitted appropriate coverage would have increased from 72.8% to 91.7%. Which would be comparable to coverage of adherent treatment (OR[95%CI]: 1.35 [0.76; 2.41], Table 3).

Overtreatment did not result in higher appropriate coverage compared to adherent treatment (OR[95%CI]: 1.66 [0.77; 4.16]).

Equivalent treatment yielded equal appropriate coverage compared to adherent treatment (OR[95%CI]: 0.86 [0.44; 1.82], Table 3).

3.3. Non-adherence and 30-day mortality

Crude 30-day mortality for the adherently treated was 11.9% (n = 47), for the undertreated 9.9% (n = 35), for the overtreated 13.8% (n = 12), and for the equivalently treated 13.9% (n = 10). There was no association between the three types of non-adherence and 30-day mortality after both crude estimation and multivariable adjustment (OR[95%CI] ranging from: 0.65 [0.28; 1.53] to 1.87 [0.79; 4.41], Table 4).

After excluding patients that received no antibiotic therapy, mortality rate for undertreatment decreased from 9.9% to 9.1% and remained not associated with mortality (OR[95%CI]: 0.93 [0.52; 1.89]). Mortality rate was lower in undertreated patients in which gentamicin was omitted (6.0%), however, not significantly different from adherent treatment after adjustment for confounders (OR[95%CI]: 0.65 [0.29; 1.49]). Most patients that died in the gentamicin-omitted group received antibiotic treatment with inappropriate coverage (n = 7), which in 5 out of 7 patients would have been appropriate coverage if gentamicin was not omitted (see Table 4).

4. Limitations

Our study has several limitations. First, we used retrospectively collected data making our study prone to bias. However, the quality of available data was assumed to be high as all data used was essential for daily clinical practice. For only 13 patients (1.3%) documentation was unclear on whether antibiotic therapy was administered in the ED or after discharge, therefore we scored them as no (and thus inappropriate) antibiotic coverage.

Also, we want to emphasize that we only considered empiric treatment in the ED, as this was our main study objective. Depending on disease course and culture results, antibiotic therapy could have been modified later on resulting in a different definitive antibiotic treatment. Aside from empiric antibiotic treatment in the ED, this may have altered survival as well.

5. Discussion

Our study aimed to evaluate non-adherence to antimicrobial guidelines for adult patients with BSI attending the ED. Non-adherence was high, and mainly the result of undertreatment. Non-adherence can result in undertreatment, overtreatment, or equivalent treatment. As these are potentially distinctive groups with respect to severity of disease and outcome, we analyzed them separately. Previous studies did not differentiate between these different types of non-adherence [9–11]. We found that, compared to adherently treated patients, overtreated patients were more severely ill, whilst undertreated patients were less severely ill. As a result, guideline adherence likely depends on clinical disease severity.

In the most severely ill patients, overtreatment may be a consequence of a physicians' intention to ensure appropriate antibiotic

Table 2
Patient characteristics in adherently versus non-adherently (i.e. under-, over-, equivalently) treated patients .

Characteristic	Adherence n = 395 (43.5)	Undertreatment n = 355 (39.1)	P value	Overtreatment n = 87 (9.6)	P value	Equivalent treatment n = 72 (7.9)	P value
Sex, male	235 (59.5)	204 (57.5)	.57	57 (65.5)	.30	46 (63.9)	.48
Age, mean (SD)	61.0 (16.3)	61.6 (14.8)	.62	61.1 (14.4)	.99	58.9 (15.9)	.30
Arrival, by ambulance	119 (30.1)	59 (16.6)	<0.001	30 (34.5)	.43	19 (26.4)	.49
Triage category, immediate/very urgent[a]	122 (33.3)	50 (14.7)	<0.001	44 (52.4)	.001	13 (18.3)	.01
Direct intensive care unit admittance	46 (11.6)	7 (2.0)	<0.001	12 (13.8)	.58	5 (6.9)	.24
Chills	156 (39.5)	169 (47.6)	.03	32 (36.8)	.64	38 (52.8)	.04
Vomiting	88 (22.3)	99 (27.9)	.08	23 (26.4)	.40	18 (25.0)	.61
Need for vasopressors	24 (6.1)	5 (1.4)	.001	10 (11.5)	.07	1 (1.4)	.10
Vital signs, mean (SD)							
Body temperature, °C[b]	38.4 (1.3)	38.2 (1.1)	.08	38.4 (1.0)	.59	38.4 (1.1)	.99
Heart rate, /min[c]	109 (24.4)	102 (20.6)	<0.001	117 (24.0)	.007	109 (23.3)	.98
Respiratory rate, /min[d]	24 (8.6)	22 (7.1)	.003	27 (10.0)	.01	22 (7.2)	.11
Systolic blood pressure, mm Hg[e]	124 (28.5)	127 (24.6)	.08	120 (28.6)	.23	125 (35.2)	.77
Oxygen saturation,%[f]	95 (5.7)	96 (3.0)	.02	93 (9.9)	.07	96 (3.0)	.58
Any supplemental oxygen	195 (49.4)	99 (27.9)	<0.001	56 (64.4)	.01	35 (48.6)	.91
Consciousness, not alert[g]	64 (18.8)	19 (6.8)	<0.001	19 (24.4)	.26	8 (12.1)	.20
NEWS, mean (SD)[h]	6 (3.8)	4 (3.1)	<0.001	8 (4.3)	.001	6 (3.5)	.69
Comorbidities of the CCI							
Diabetes mellitus, uncomplicated	72 (18.2)	74 (20.8)	.37	14 (16.1)	.64	18 (25.0)	.18
Diabetes mellitus, end-organ damage	3 (0.8)	2 (0.6)	.74	3 (3.4)	.04	1 (1.4)	.59
Liver disease, mild	32 (8.1)	69 (19.4)	<0.001	7 (8.0)	.99	18 (25.0)	<0.001
Liver disease, moderate to severe	5 (1.3)	2 (0.6)	.32	0 (0.0)	.29	1 (1.4)	.93
Malignancy, leukemia, lymphoma, localized solid tumor	59 (14.9)	66 (18.6)	.18	6 (6.9)	.05	21 (29.2)	.003
Malignancy, metastatic solid tumor	48 (12.2)	50 (14.1)	.43	9 (10.3)	.64	15 (20.8)	.05
Chronic kidney disease	56 (14.2)	83 (23.4)	.001	13 (14.9)	.85	5 (6.9)	.09
Chronic pulmonary disease	48 (12.2)	45 (12.7)	.83	22 (25.3)	.002	6 (8.3)	.35
CCI, mean (SD)	4 (2.9)	5 (2.8)	.02	4 (2.9)	.84	5 (3.0)	.11
Origin, hospital acquired	205 (51.9)	199 (56.1)	.25	38 (43.7)	.17	46 (63.9)	.06
Ten most common working diagnoses							
Cholangitis	25 (6.3)	115 (32.4)	<0.001	5 (5.7)	.84	36 (50.0)	<0.001
Sepsis, urogenital	78 (19.7)	50 (14.1)	.04	7 (8.0)	.01	3 (4.2)	.001
Pyelonephritis	33 (8.4)	94 (26.5)	<0.001	1 (1.1)	.02	0 (0.0)	.01
Sepsis, unknown	59 (14.9)	25 (7.0)	.001	10 (11.5)	.41	4 (5.6)	.03
Mild CA pneumonia (CURB 0–1)	12 (3.0)	7 (2.0)	.35	20 (23.0)	<0.001	6 (8.3)	.03
Severe CA pneumonia (CURB 3–5)	18 (4.6)	14 (3.9)	.68	4 (4.6)	.99	1 (1.4)	.21
Febrile neutropenia	32 (8.1)	2 (0.6)	<0.001	1 (1.1)	.02	2 (2.8)	.11
Meningitis, primary	24 (6.1)	2 (0.6)	<0.001	6 (6.9)	.77	0 (0.0)	.03
Sepsis, abdominal	15 (3.8)	12 (3.4)	.76	0 (0.0)	.07	2 (2.8)	.67
Moderate CA pneumonia (CURB 2)	8 (2.0)	2 (0.6)	.08	16 (18.4)	<0.001	0 (0.0)	.22

Data are presented as number (percentage) of patients unless otherwise indicated.
Missing data are not yet imputed.
Abbreviations: SD, standard deviation; NEWS, national early warning score; CCI, charlson comorbidity index [20]; CURB65, confusion, blood urea nitrogen, respiratory rate, systolic blood pressure, age ≥ 65; CA, community-acquired..

[a] Data on triage category were missing for 44 (4.8%) patients.
[b] Data on body temperature were missing for 7 (0.8%) patients.
[c] Data on heart rate were missing for 18 (2.0%) patients.
[d] Data on respiratory rate were missing for 311 (34.2%) patients.
[e] Data on systolic blood pressure were missing for 14 (1.5%) patients.
[f] Data on oxygen saturation were missing for 39 (4.3%) patients.
[g] Data on consciousness were missing for 145 (16.0%) patients.
[h] NEWS imputed as normal.

Table 3
(Non-)adherence and appropriate antibiotic coverage.

Type of (non-)adherence	Appropriate antibiotic coverage (%)	Odds ratio	95% CI
Adherence (n = 395)	352 (89.1)	1.0	(reference)
Non-adherence:			
Undertreatment (n = 355)	206 (58.0)	0.18	[0.12; 0.26]
• No antibiotic therapy excluded (n = 276)	206 (74.6)	0.27	[0.16; 0.42]
• Gentamicin was omitted (n = 217)	158 (72.8)	0.33	[0.21; 0.51]
• If gentamicin would not have been omitted, i.e. adherence (n = 217)[a]	199 (91.7)	1.35	[0.76; 2.41]
Overtreatment (n = 87)	82 (94.3)	1.66	[0.77; 4.16]
Equivalent (n = 72)	62 (86.1)	0.86	[0.44; 1.82]

[a] This is a counterfactual group: these patients were not treated with recommended gentamicin, but we examined if coverage would have been appropriate if they did receive gentamicin (i.e. if treatment would been adherent).

Table 4
(Non-)adherence and 30-day mortality.

Type of (non-)adherence	30-day mortality (%)	Crude odds ratio [95% CI]	Adjusted odds ratio[a] [95% CI]
Adherence (n = 395)	47 (11.9)	1.0 (reference)	1.0 (reference)
Non-adherence:			
Undertreatment (n = 355)	35 (9.9)	0.82 [0.52; 1.30]	1.16 [0.65; 2.09]
• No antibiotic therapy excluded (n = 276)	25 (9.1)	0.73 [0.44; 1.20]	0.93 [0.52; 1.89]
• Gentamicin was omitted (n = 217)	13 (6.0)[b]	0.47 [0.25; 0.89]	0.65 [0.29; 1.49]
Overtreatment (n = 87)	12 (13.8)	1.17 [0.59; 2.17]	0.65 [0.28; 1.53]
Equivalent (n = 72)	10 (13.9)	1.19 [0.58; 2.30]	1.87 [0.79; 4.41]

[a] Adjusted for: sex, age, arrival, triage category, direct intensive care unit admittance, chills, vomiting, vasopressors, body temperature, heart rate, respiratory rate, systolic blood pressure, oxygen saturation, any supplemental oxygen, origin, consciousness, diabetes mellitus (uncomplicated), liver disease (mild), malignancy, chronic kidney disease, congestive heart failure, myocardial infarction, chronic pulmonary disease, perivascular disease, cerebrovascular accident, dementia, and connective tissue disease.

[b] Most of these patients that died received antibiotic treatment with inappropriate coverage, which in 5 out of 7 patients would have been appropriate coverage if gentamicin was not omitted.

coverage. However, our study shows that providing too broad-spectrum antibiotic therapy is not justifiable, because overtreatment was not associated with higher appropriate antibiotic coverage nor a survival benefit. Furthermore, overtreatment in general leads to risk of selection of antimicrobial resistance and adverse effects [6]. Therefore, adherence to the guidelines should be preferred to provide proper care, even when physicians encounter more severely ill patients. In accordance with previous studies, we found overtreatment was more frequent in patients with underlying chronic pulmonary disease and a suspected mild to moderate community-acquired pneumonia [25, 26]. Thus, for these patients with pulmonary disease, physicians should be extra alert to potential overtreatment.

In less severely ill patients, physicians might decide to give no or more narrow-spectrum antibiotic therapy than antimicrobial guidelines would recommend. Undertreatment was the leading type of non-adherence, thus, guidelines often advise more extensive treatment than physicians in practice provide in less severely ill patients. For these patients, clinical judgment of low disease severity potentially overruled guideline recommendations. However, undertreatment resulted in lower appropriate antibiotic coverage, also after excluding patients that received no antibiotic therapy. Main reason for undertreatment was omitting gentamicin. We found that if in these patients gentamicin was not omitted, appropriate coverage would have been comparable to coverage of adherent treatment. Undertreatment was not associated with higher 30-day mortality. Although from our data there seems no survival disadvantage for these less severely ill undertreated patients, we have to emphasize that confounding by (low) severity of disease could mask a survival disadvantage for undertreated patients. Thus, finding no survival disadvantage in this case can be the result of residual confounding, which was also demonstrated in previous studies [19]. Moreover, survival would have likely been better if these undertreated patients with proven BSI did receive the antibiotic treatment with appropriate coverage. Therefore, physicians should always be cautious when they decide to undertreat and realize that appropriate antibiotic coverage is significantly lower compared to guideline-adherent therapy. We found undertreatment was more frequent in patients with underlying chronic kidney disease and a suspected pyelonephritis/urosepsis. From literature and clinical practice this can be explained by the intention to spare these patients from treatment with nephrotoxic antibiotics such as gentamicin [27, 28]. In our data, we found that omitting recommended gentamicin was more prevalent in patients with kidney disease as well. However, as stated before, omitting gentamicin affects appropriate coverage and therefore we would argue that in these patients physicians should consult a medical microbiologist to find an alternative to gentamicin with comparable coverage.

Non-adherence in our study (56.5%) was high compared to previously reported non-adherence rates (10 to 53%). However, previous studies are likely underestimating the true non-adherence rate as they excluded patients that received no antibiotic therapy [9–11]. Also, we chose to score adherence very strictly to give an unbiased interpretation of absolute guideline adherence. Strict scoring resulted in a few patients that were non-adherent, but equivalently treated with regard to antibiotic spectrum. Equivalent treatment was frequently in accordance with national antimicrobial guidelines. Equivalently treated patients had comparable patient characteristics to adherently treated patients, indicating comparable illness. As expected, equivalent treatment yielded an equal rate of appropriate antibiotic coverage. Also, we found no difference in 30-day mortality.

6. Conclusion

In patients with BSI attending the ED, the majority of antibiotic therapy was non–adherent. Guideline adherence likely depends on clinical disease severity. Undertreatment was the leading type of non-adherence, mainly the result of omitting gentamicin, and most common in less severely ill patients. Undertreatment was associated with lower appropriate antibiotic coverage, but not with higher mortality. Although we found no survival disadvantage, previous studies have shown that this can be the result of residual confounding and survival would have likely been better if these patients with proven BSI received antibiotic therapy with appropriate coverage (i.e. guideline-adherent treatment). Therefore, physicians should always be cautious when they undertreat and realize that antibiotic coverage is significantly lower compared to guideline-adherent therapy. Overtreatment was given to the most severely ill patients and did not result in higher appropriate antibiotic coverage nor a survival benefit. Together with the risk of selection of antimicrobial resistance, overtreatment is not justifiable even in case of high disease severity.

Grant

None of the authors received any funding for carrying out this study.

CRediT authorship contribution statement

Romy Schuttevaer: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft, Writing - review & editing. **Anniek Brink:** Conceptualization, Formal analysis, Investigation, Writing - original draft, Writing - review & editing. **Jelmer Alsma:** Conceptualization, Writing - review & editing. **Willian van Dijk:** Formal analysis, Investigation, Writing - review & editing. **Damian C. Melles:** Conceptualization. **Jurriaan E.M. de Steenwinkel:** Conceptualization, Writing - review & editing. **Hester F. Lingsma:** Conceptualization, Methodology, Supervision. **Annelies Verbon:** Writing - review & editing, Supervision. **Stephanie C.E. Schuit:** .

Declaration of Competing Interest

The authors declare to have no conflict of interests.

Acknowledgements

Conceptualization: RS, AB, JA, JDS, DM, HL; Methodology: RS, HL; Formal analysis and investigation: RS, AB, WVD; Writing - original draft preparation: RS, AB; Writing - review and editing: RS, AB, JA, WVD, JDS, AV, SKN; Supervision: HL, AV, SKN.

The Medical Ethics Committee of the Erasmus MC reviewed this study and concluded that it did not fall under the scope of the Medical Research Involving Human Subjects Act and therefore no informed consent needed to be obtained. This study is thus approved and registered under MEC-2018-1744.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2020.04.013.

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