Adherence to local antimicrobial guidelines for initial treatment of community-acquired infections

Trine Langfeldt Hagen[1], Mathias Amdi Hertz[1], Gábor Balázs Uhrin[2], Michael Dalager-Pedersen[1], Henrik Carl Schønheyder[2, 3] & Henrik Nielsen[1, 3]

ABSTRACT

INTRODUCTION: Adherence to antimicrobial guidelines is key to ensuring a correct treatment of severe infections and to lessening misuse of broad-spectrum antimicrobials.

We conducted a retrospective cross-sectional study at the Emergency Department of Aalborg University Hospital, North Denmark Region. Our aim was to examine adherence to local antimicrobial guidelines in the empirical treatment of community-acquired infections and to identity any predictors of guideline non-adherence.

METHODS: We identified 1,555 patients who had blood cultures performed and were admitted to the medical emergency department in 2016. We reviewed the medical charts of 755 patients and included those who received at least one antibiotic prescription within the first 24 hours of admission. We excluded patients with known immunodeficiency, severe renal failure or hospitalisation within the previous month.

RESULTS: Of the 383 included patients, 203 (53%) received guideline-concordant antibiotic treatment. The treatment was guideline-concordant in 41% of patients with suspected sepsis of unknown origin, in 44% with pneumonia and in 37% with urinary tract infections. Patients with underlying chronic obstructive pulmonary disease (25%) received guideline-concordant treatment significantly more often (83%, $p < 0.01$) than other groups.

CONCLUSIONS: Adherence to local antimicrobial guidelines was not high. Further studies are needed to identify barriers to guideline adherence.

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TRIAL REGISTRATION: The study was registered with the Danish Data Protection Agency (R. no. 2008-58-0028).

Adherence to antimicrobial prescription guidelines is of importance when treating patients with severe infections. The guidelines should take local antimicrobial resistance patterns into consideration to ensure that the empiric therapy covers the predominant pathogens responsible for the infection. For community-acquired pneumonia, guideline-concordant antimicrobial therapy has been associated with shortened time to clinical stability, reduced length of stay and decreased in-hospital mortality [1, 2]. The beneficial effects are less clear in patients who are treated for bacteraemia or severe sepsis and septic shock [3-6]. Broad-spectrum antibiotics are major drivers of antibiotic resistance and their use may lead to adverse effects such as *Clostridium difficile* enterocolitis and infection or colonisation with multi-resistant Gram-negative bacteria [7, 8]. While the burden of antibiotic resistance is relatively low in Danish hospitals compared with other European countries, there have been notable upsurges of *C. difficile* and extended-spectrum beta-lactamase, AmpC and carbapenemase-producing Gram-negative bacteria on several Danish hospitals [9, 10]. To combat these trends, antimicrobial stewardship programmes are recommended by international bodies including the WHO and the European Union. This may include valuable tools such as antibiotic awareness campaigns, surveillance of consumption of antibiotics and antimicrobial resistance and audits of antibiotic prescribing [11]. It is crucial that physicians adhere to such programmes in order to obtain the ultimate goal of reducing the consumption of broad-spectrum antibiotics [7, 11, 12]. Nevertheless, several studies have shown that guideline non-adherence occurs frequently [7, 13-15]. The stated reasons for guideline non-adherence have been manifold, often including lack of awareness of local guidelines or perceived superior efficacy of broad-spectrum antimicrobials [14-17].

The Danish Health and Medicines Authority has issued a national guideline for the restrictive use of carbapenems, cephalosporins and fluoroquinolones [18]. To our knowledge, no previous audits have been published of prescription of empirical antimicrobial therapy in Danish hospitals. Thus, the extent of antimicrobial guideline adherence is unclear in this setting. The aim of this study was to examine antibiotic guideline adherence for treatment of suspected community-acquired infection in patients admitted to an emergency department at a Danish hospital and to identify any predictors of guideline non-adherence.

METHODS

Study design and setting

This retrospective cross-sectional study was conducted at Aalborg University Hospital, which is both a tertiary referral centre for the North Denmark Region (popula-

ORIGINAL ARTICLE

1) Department of Infectious Diseases, Aalborg University Hospital
2) Department of Clinical Microbiology, Aalborg University Hospital
3) Department of Clinical Medicine, Aalborg University, Denmark

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tion approximately 580,000) and a district hospital with facilities for acute care for local citizens. At the time of the study (1 January through 31 December 2012), the staff of the medical emergency department consisted of physicians from six different internal medicine specialties (endocrinology, gastroenterology, haematology, infectious diseases, nephrology and pulmonology).

Collection of data

The Danish Civil Registration System provides all Danish citizens with a unique personal identification number (CPR number), which is used for all healthcare-related contacts. This provides a unique possibility for following up on patients in the healthcare system. Data were collected by three of the authors (TH, MH and GU) through review of the electronic medical chart.

Antimicrobial treatment guidelines

The Antibiotic Subcommittee of the hospital's Pharmaceutical Committee includes pharmacists and specialists in clinical microbiology, infectious diseases, pulmonology, paediatrics, orthopaedic surgery and intensive care. The subcommittee has developed treatment guidelines for the most common community-acquired infections in immunocompetent patients [19]. The guidelines are distributed in leaflet form to all newly employed physicians and are easily available in electronic form from the hospital intranet. The guideline is regularly updated as required based on local resistance data for the most frequent pathogens.

Selection of participants and methods

Patients eligible for inclusion in this study were older than 15 years of age, had one or more blood cultures performed and one or more antibiotics prescriptions within the first 24 hours of admission to the Emergency Department. We used the request of a blood culture examination as a proxy for clinical suspicion of severe community-acquired infection. For patients readmitted during the study period, only the first admission was included.

The following criteria were used for exclusion: no in-hospital antibiotic prescription within 24 hours of admission, hospital admissions during the previous month,

TABLE 1

Local empirical antimicrobial treatment guideline recommendations for the most common community-acquired infections in immunocompetent patients.

Tentative diagnosis	Guideline recommendations	Reported allergy towards penicillin or other contraindication
Sepsis of unknown origin	Benzylpenicillin 1,2 g IV every 6 h + gentamicin 5 mg/kg IV every 24 h + metronidazole 500 mg IV every 12 h[a]	Cefotaxim 1 g IV every 8 h + gentamicin 5 mg/kg SD[a] + metronidazole 500 mg IV every 12 h[a]
Severe sepsis/septic shock	Piperacillin/tazobactam 2 + 0.25 g IV every 6 h + gentamicin 5 mg/kg IV SD[a]	Meropenem 500 mg IV every 6 h
	Or cefuroxime 750 mg IV every 4 h + gentamicin 5 mg/kg IV SD	
COPD, acute exacerbation	Cefuroxime 750 mg IV every 6 h	Roxithromycin 150 mg OR every 12 h
	Or amoxicillin/clavulanate 500/125 mg OR every 8 h	
Pneumonia CURB65 1-2	Benzylpenicillin 1.2 g IV every 6 h	Cefuroxime 750 mg IV every 6 h
		Or clarithromycin 500 mg IV every 12 h
Severe pneumonia, CURB65 score > 2	Benzylpenicillin 1.2 g IV every 6 h + ciprofloxacin 400 mg IV every 12 h	Cefuroxime 750 mg IV every 6 h + ciprofloxacin 400 mg IV every 12 h
Severe pneumonia, CURB65 score > 2, due to aspiration	Cefuroxime 750 mg IV every 6 h + metronidazole 500 mg IV every 12 h	-
Atypical pneumonia	Clarithromycin 500 mg IV every 12 h	-
	Or roxithromycin 150 mg OR every 12 h	
Cystitis	Pivmecillinam 400 mg OR every 8 h	Trimethoprim 200 mg OR every 12 h
Pyelonephritis	Ampicillin 1 g IV every 6 h + gentamicin 5 mg/kg IV every 24 h	Cefotaxime 1 g IV every 8 h + gentamicin 5 mg/kg IV SD[a]
Urosepsis	Ampicillin 1 g IV every 6 h + gentamicin 5 mg/kg IV every 24 h	Cefotaxime 1 g IV every 8 h + gentamicin 5 mg/kg IV SD[a]
Bacterial meningitis	Benzylpenicillin 1.8 g IV every 4 h + cefotaxime 3 g IV every 6 h	Meropenem 2 g IV every 8 h
Endocarditis	Benzylpenicillin 3 g IV every 6 h + gentamicin 3 mg/kg IV every 24 h	According to national guidelines
Erysipelas	Benzylpenicillin 1.2 g IV every 6 h + dicloxacillin 1 g IV every 6 h[a]	Cefuroxime 750 mg IV every 6 h
Gastroenteritis	Only antimicrobial treatment when known risk factors[b]	Azithromycin 500 g OR every 24 h
	Ciprofloxacin 500 mg IV or 400 mg OR every 12 h	
Biliary tract/abdominal infection	Benzylpenicillin 1.2 g IV every 6 h + gentamicin 5 mg/kg IV every 24 h + metronidazole 500 mg IV every 12 h	Cefotaxime 1 g IV every 8 h + gentamicin 5 mg/kg IV SD[a] + metronidazole 500 mg IV every 12 h

COPD = chronic obstructive pulmonary disease; CURB65 = confusion, urea, respiratory rate, blood pressure, age ≥65 yrs; IV = intravenously administered; SD = single dose; OR = orally administered.

a) Optional.

b) High-grade fever, age > 50 yrs, chronic ischaemic heart disease, known implant, immunosuppression and/or dysenteric symptoms.

severe renal failure requiring dialysis treatment and known innate or acquired immunodeficiency due to the human immunodeficiency virus or active treatment with immunosuppressive agents, including chemotherapy for solid or haematological cancers within the previous two years.

We used a structured data collection form to record information on gender, age, comorbidity, intravenous drug abuse, β-lactam allergy, travel history, antibiotic prescriptions within the past four weeks prior to hospital admittance, and permanent residence in a nursing home or similar institution. We registered data on whether leucocyte counts and C-reactive protein (CRP) levels were available to the treating physician before prescription of antibiotics.

We further noted the tentative diagnoses of community-acquired infections and recorded an "infection of unknown origin" if the physical examination and the laboratory and radiology results failed to identify an infection focus. We also registered whether the prescribing physician was on the staff of the Department of Infectious Diseases (ID).

Antibiotic use was documented and categorised by dosage as appropriate or not, and the guideline adherence as "guideline-concordant" or "guideline-discordant". Guideline-concordant treatment was defined as empiric therapy in accordance with the clinical diagnosis based on signs and symptoms and the local antimicrobial guideline (**Table 1**). A complete medical chart review was undertaken in case of guideline-discordant therapy in order to appraise the reasons for the decision.

Statistical analysis

Categorical variables were analysed using Fisher's exact test and chi-squared test, and continuous variables using the Mann-Whitney U test, as applicable. A p-value of < 0.05 was considered statistically significant.

Trial registration: The study was registered with the Danish Data Protection Agency (R. no. 2008-58-0028).

RESULTS

During the study period, 1,555 patients admitted to the medical emergency department had blood cultures performed. A random sample of 755 patients was screened for study inclusion, 383 of whom met the eligibility criteria.

The patient demographics and adherence rates are summarised in **Table 2**, **Table 3** and **Table 4**. The antibiotic prescriptions were guideline-concordant in 203 patients (53%). The most commonly suspected infections were pneumonia (44%), urinary tract infection (25%) and exacerbation of chronic obstructive pulmonary disease (COPD) (20%).

TABLE 2

Patient demographics.

Age, yrs, mean (range)	65.7 (15-100)
Gender, n (%)	
Male	192 (50.1)
Female	191 (49.9)
Allergy towards β-lactam antibiotics, n (%)	
Yes	31 (8.1)
No	347 (90.6)
Not registered	5 (1.3)
Travel history, n (%)	
Yes	36 (9.4)
No	61 (15.9)
Not registered	286 (74.7)
Renal insufficiency, n (%)	21 (5.5)
COPD, n (%)	97 (25.3)
Recent antibiotics, n (%)	120 (31.3)
Intravenous drug use, n (%)	2 (0.5)
Resident at nursing home/institution, n (%)	29 (7.6)
Given at least 1 diagnosis, n (%)	
Sepsis of unknown origin	49 (12.8)
Severe sepsis/septic shock	4 (1.0)
COPD: acute exacerbation	76 (19.8)
Pneumonia, no CURB65 score or CURB65 score 1-2	145 (37.9)
Severe pneumonia: CURB65 score > 2	8 (2.1)
Severe pneumonia due to aspiration	4 (1.0)
Atypical pneumonia	12 (3.1)
Cystitis	39 (10.2)
Pyelonephritis	38 (9.9)
Urosepsis	19 (5.0)
Bacterial meningitis	6 (1.6)
Endocarditis	0
Erysipelas	21 (5.5)
Gastroenteritis	19 (5.0)
Biliary tract/abdominal infection	12 (3.1)
Subtotal	360 (94)

COPD = chronic obstructive pulmonary disease; CURB65 = confusion, urea, respiratory rate, blood pressure, age ≥ 65 yrs.

There was no difference in concordance according to the patients' demographics, except for patients with COPD who were more likely to receive guideline-concordant treatment (83%, $p < 0.01$). Treatment for suspected sepsis of unknown origin (49 patients) was guideline-concordant in 41% of cases. Approximately half of the prescriptions were guideline-concordant in 169 patients (44% of the patients included) who were treated for suspected community-acquired pneumonia with no significant difference by CURB65 score or suspicion of either atypical or aspiration pneumonia. In patients with suspected urinary tract infection (n = 96), antibiotic prescriptions were less often guideline-concordant (37%).

A total of 25% of patients had pre-existing COPD, 5.5% had renal insufficiency not requiring dialysis treatment and 32% had received antibiotics within the previ-

ous four weeks. Only 25% had been asked about travel history, of whom 37% had recently travelled abroad. The most commonly prescribed antibiotics were cefuroxime (37%), benzylpenicillin (32%), gentamicin (16%) and ciprofloxacin (12%). The CRP value and leukocyte count were available at the time of antibiotic prescription in 46% of the patients. In patients with unknown CRP and leucocyte counts, antibiotic prescriptions were more often guideline-concordant than when the results were already available (60% versus 47%).

ID physicians did not prescribe guideline-concordant treatment significantly more often than non-ID physicians. However, they more often stated in the medical chart why they deviated from the guidelines.

DISCUSSION

In this retrospective observational study, we found that only 53% of the antimicrobial prescriptions were guideline-concordant in the Emergency Department, which agrees with other findings [13]. Most often, the treatment was non-adherent in patients with respiratory or urinary tract infections or sepsis of unknown origin, whereas patients with COPD more often received guideline-concordant treatment. The most frequently prescribed drug was cefuroxime, which, according to our guideline, was recommended only for the treatment of exacerbation of COPD, severe pneumonia in patients with allergy towards penicillin, and pneumonia due to aspiration (Table 1). However, physicians quite commonly prescribed cefuroxime for urinary tract infections, which accounts for many of the discordant prescriptions in this subgroup.

Non-adherence to antimicrobial guidelines often leads to more broad-spectrum therapy, but not necessarily more appropriate therapy [3, 13]. Junior physicians make many of the antibiotic prescriptions in Danish medical emergency departments. This practice is common in emergency departments in other countries, since junior physicians constitute the primary workforce in acute care [15, 16]. Only patients with severe or complicated infections are referred to a team of ID physicians, leaving most of the patients with infections being treated by non-specialists. This may lead to more broad-spectrum treatment of longer duration than is, in fact, necessary [15, 16].

It is possible to make interventions to improve antimicrobial prescribing. The most effective approach is multi-facetted interventions focusing on education of the prescribers by providing detailed antibiotic guidelines with advice on de-escalating antibiotic treatment, intravenous-to-oral switch strategies and dosage optimisation [7]. Some hospitals have implemented successful interventions leading to a decrease in the prescriptions of certain broad-spectrum antimicrobials [9, 12].

When focusing on educating the prescribers, it is important to target senior as well as junior physicians to change the prescribing etiquette in the entire group of physicians [15, 16]. Feedback to the prescribing physicians can be equally effective when performed as a telephone call or written suggestions in the medical charts [14], though combined interventions with face-to-face feedback are especially successful [12, 17].

Travel activity is increasing among Danish citizens, which increases importation of antimicrobial-resistant microorganisms. It was therefore concerning to discover that few patients were asked about their travel history, especially considering that more than one third of the patients who were, in fact, asked had indeed travelled recently.

Our study has several limitations. First, we did not have access to all patients who had antibiotics prescribed in the Medical Emergency Department, thus lim-

TABLE 3

Adherence to guideline recommendations according to patient demographics.

	Guideline adherence		
	yes (N = 203)	no (N = 180)	p-value
Age, yrs, median (IQR)	72 (59-80)	70 (50-81)	0.32
Gender, n (%)			0.17
Female	108 (53.2)	83 (46.1)	
Male	95 (46.8)	97 (53.9)	
Recent antibiotics, n (%)			0.05
Yes	73 (36)	48 (26.7)	
No	130 (64)	132 (73.3)	
Allergy towards β-lactam antibiotics, n (%)			0.83
Yes	17 (8.37)	14 (7.8)	
No	186 (91.6)	166 (92.2)	
Intravenous drug use, n (%)			0.93
Yes	1 (0.49)	1 (0.6)	
No	202 (99.5)	179 (99.4)	
Known renal insufficiency, n (%)			0.61
Yes	10 (4.9)	11 (6.1)	
No	193 (95.1)	169 (93.9)	
COPD, n (%)			< 0.01
Yes	76 (37.4)	21 (11.7)	
No	127 (62.6)	159 (88.3)	
Nursing home/institution, n (%)			0.6
Yes	14 (6.9)	15 (8.3)	
No	189 (93.1)	165 (91.7)	
Antibiotic prescribed by physician from the department of infectious diseases, n (%)			0.14
Yes	50 (24.6)	33 (18.3)	
No	153 (75.4)	147 (81.7)	
Traveling history, n (%)			0.69
Yes	16 (7.9)	15 (7.4)	
No	35 (17.2)	19 (9.4)	
Unknown	152 (74.9)	107 (52.7)	

COPD = chronic obstructive pulmonary disease; IQR = interquartile range.

TABLE 4

Guideline concordant and discordant treatment according to suspected site of infection.

Suspected site of infection	Total, n (% of included) (N = 383)	Adherence to guidelines, n (%) concordance (N_1 = 203 (53))	discordance (N_2 = 180 (47))	p-value
Sepsis of unknown origin	49 (12.8)	20 (40.8)	29 (59.2)	0.07
Septic shock	4 (1)	1 (25)	3 (75)	0.26
Exacerbation of COPD	76 (19.8)	63 (82.9)	13 (7.2)	0.00
Pneumonia				
CURB65 score 1-2 or unknown	145 (37.9)	74 (51)	71 (49)	0.55
CURB65 score > 2: severe	8 (2.1)	4 (50)	4 (50)	0.86
Pneumonia due to aspiration	4 (1)	1 (25)	3 (75)	0.26
Atypical pneumonia	12 (3.1)	7 (58.3)	5 (41.7)	0.71
Subtotal	169 (44.1)			
Urinary tract infections				
Cystitis	39 (10.2)	13 (33.3)	26 (66.7)	0.01
Pyelonephritis	38 (10)	14 (36.8)	24 (63.6)	0.04
Urosepsis	19 (5)	9 (47.4)	10 (52.6)	0.61
Subtotal	96 (25.1)			
Meningitis	6 (1.6)	5 (83.3)	1 (16.7)	0.13
Endocarditis	0			
Erysipelas	21 (5.5)	15 (71.4)	6 (28.6)	0.82
Gastroenteritis	19 (4.2)	8 (42.1)	11 (57.9)	0.33

COPD = chronic obstructive pulmonary disease; CURB65 = confusion, urea, respiratory rate, blood pressure, age ≥ 65 yrs.

iting us to the patient charts based on the performed blood cultures. This might lead to selection bias since not all patients receiving antibiotics were included. However, we estimate that few patients at our hospital received antimicrobial treatment without having blood cultures performed. Second, the reasons for prescribing guideline-discordant therapy were not always mentioned in the charts. Three authors reviewed the patient charts and there may have been a small amount of inter-observer-variation when deciding whether a prescription was guideline-concordant or not. The number of included patients was agreed upon arbitrarily after estimation that more than 300 included patients would be necessary. Lastly, the study data reflect the epidemiology and adherence in a single centre and some subgroups had few patients, while respiratory infections dominated. The strength of the study is that the sample size of medical charts is relative large. Moreover, our study provided information on the guideline adherence among unselected patients in a large emergency department, thus revealing insights into daily clinical practice.

Further studies (preferably prospective) on adherence to antimicrobial guidelines are necessary to find ways to strengthen the proper prescription of antimicrobials in order to ensure the correct treatment for patients and to limit future upsurges of multi-resistant bacterial infections and *C. difficile* enterocolitis in Danish hospitals. Furthermore, we hope that the implementation of an antimicrobial stewardship programme can be a decisive step in this direction.

CONCLUSIONS

Adherence to guidelines when prescribing empirical antibiotic therapy in community-acquired infections was low. Frequently, a more broad-spectrum antibiotic than needed was chosen.

It is necessary to enhance guideline adherence with multifaceted interventions to reduce the use of broad-spectrum antibiotics.

CORRESPONDENCE: *Trine Langfeldt Hagen.* E-mail: trine@hagen.ac

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