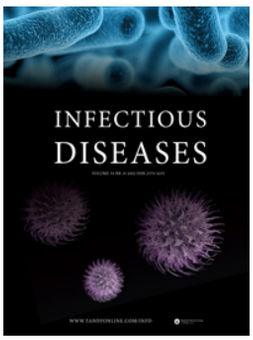

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ORIGINAL ARTICLE

High levels of discordant antimicrobial therapy in hospital-acquired bloodstream infections is associated with increased mortality in an intensive care, low antimicrobial resistance setting

Bjørn Waagsbø[a], Nora Stuve[b], Jan Egil Afset[c,d], Pål Klepstad[e,f], Skule Mo[f], Lars Heggelund[g,h] and Jan Kristian Damås[i,j]

[a]Regional Centre for Disease Control in Central Norway Regional Health Authority, Trondheim University Hospital, Trondheim, Norway; [b]Faculty of Medicine and Health Science, Norwegian University of Science and Technology, Trondheim, Norway; [c]Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway; [d]Department of Medical Microbiology, St. Olavs Hospital, Trondheim, Norway; [e]Department of Circulation and Medical Imaging, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology NTNU, Trondheim, Norway; [f]Department of Anaesthesiology and Intensive Care Medicine, St. Olavs hospital, Trondheim University Hospital, Trondheim, Norway; [g]Department of Clinical Science, Faculty of Medicine, University of Bergen, Bergen, Norway; [h]Department of Internal Medicine, Drammen Hospital, Vestre Viken Hospital Trust, Drammen, Norway; [i]Department of Infectious Diseases, St. Olav's Hospital, Trondheim University Hospital, Trondheim, Norway; [j]Centre of Molecular Inflammation Research, department of Clinical and Molecular Medicine, NTNU, Trondheim, Norway

ABSTRACT

Background: Bloodstream infections (BSI) occur frequently and are associated with severe outcomes. In this study we aimed to investigate proportions of patients that received discordant empirical antimicrobial therapy and its association to mortality.

Methods: A retrospective cohort study model was undertaken to outline BSI in an intensive care, single centre, and low antimicrobial resistance prevalence setting. We used descriptive statistics to delineate proportions of patients that received discordant empirical antimicrobial therapy, and a correlation model and a logistic regression model to calculate the association with mortality and predictors of receiving discordant therapy, respectively.

Results: From 2014 to 2018 we included 270 BSI episodes, of which one third were hospital-acquired. Gram negative, Gram positive, and anaerobic pathogens were detected in 49.0%, 45.3% and 5.7% respectively. The proportion of isolates that conferred extended-spectrum beta-lactamase (ESBL) properties were 5.9% among enterobactereales, and no methicillin-resistant Staphylococcus aureus isolates were detected. Empirical antimicrobial therapy for community-acquired (CA) and hospital-acquired (HA) BSI were discordant at day 0 in 6.5% and 24.4%, respectively ($p<.001$). Discordant therapy was significantly associated with mortality at day 28 ($p=.041$). HA-onset BSI, enterococcal BSI and BSI of intraabdominal origin were statistically significant predictors of receiving discordant therapy.

Conclusion: A significant proportion of HA-BSI did not receive effective antimicrobial therapy and this was significantly associated with mortality. The results underscore the need for more accurate diagnostic tools, improved communication between the microbiological laboratory and the clinicians, and antimicrobial stewardship measures.

KEYWORDS
Bloodstream infection
empirical antimicrobial therapy
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antimicrobial stewardship

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CONTACT
Bjørn Waagsbø
bjorn.waagsbo@stolav.no
Regional centre for disease control in Central Norway Regional Health Authority, Trondheim University Hospital, 7006 Trondheim, Norway

Introduction

Bloodstream infections (BSI) in patients hospitalised in intensive care units (ICU) are frequent and poses considerable risks for adverse events and death [1]. The mainstay of clinical approach has traditionally relied on early recognition of clinical symptoms and warning signs, blood culture sampling, antimicrobial susceptibility testing, and early initiation of antimicrobial and adjunctive therapy. The coverage of empirical antimicrobial therapy has traditionally been considered essential within the apprehensive timespan until pathogen-directed antimicrobial therapy.

However, in staphylococcal BSI, mortality rates at nearly 30% have not changed considerably over the past decades [2,3]. In addition, Gram-negative bacilli (GNB) has re-emerged as a predominant pathogen in BSI [4], and attributable mortality rates reach 15%–30% [5]. Sustained efforts to improve outcomes, mirrored in international sepsis guidelines, have had marginal effects on mortality rates [6]. Factors that influence on mortality include, but are not limited to, antimicrobial resistance (AMR), older age, burden of comorbidities, severity of illness at presentation, and inflammatory response [7].

The timely initiation of appropriate empirical antimicrobial therapy for patients in intensive care settings has been subjected to clinical studies, in particular patients with sepsis and septic shock [8,9]. Of note, only 50% of patients included in sepsis studies are bacteremic, indicating that sepsis studies may inaccurately predict risk of death in bacteremic patients [10]. In addition, diagnostic criteria for sepsis and septic shock were revised in 2016 [11].

The epidemiological situation on AMR reflects developments in therapy recommendations in clinical practice guidelines. In countries with low AMR-prevalence, several national guidelines still offer traditional, generic-based recommendations, particularly in Nordic countries. This is contrary to international clinical practice guidelines that largely encourage one or two likely effective broad-spectrum antimicrobials, with no specific generic substances given [6].

Discordant empirical antimicrobial therapy is referred to situations where the instituted regimen does not comply with antimicrobial susceptibility profile to cover for isolated pathogens. It has traditionally been linked to increased risk of death [12]. However, recent studies have failed to support this finding, relying more on patient and disease factors to explain increased risk of death [5].

In this study, we aimed to detect and describe the proportion of patients that received discordant empirical antimicrobial therapy in a tertiary care teaching university hospital, intensive care, and low AMR-prevalence setting. We also wanted to outline the proportion of patients that underwent antimicrobial therapy de-escalation in accordance with the reported antimicrobial susceptibility profile, and the association between empirical therapy and risk of death.

Methods

Patients evaluated for inclusion were hospitalised with clinical signs of infection and concomitant bacteraemia at presentation to the ICU at a 1.000-bed university teaching hospital in Norway. The hospital offer tertiary care health services to about 320.000 local and 725.000 regional inhabitants. We used in-hospital patient registries to identify eligible ICU-stays for a period of 60 months from 1 January 2014, and combined these stays with microbiological registries to identify episodes of concomitant bacteraemia at presentation.

A bloodstream infection (BSI) episode was defined by growth of one or more pathogenic microbes in blood cultures combined with clinical evidence of systemic infection. Subsequent BSI-episodes with similar aetiology were included if new clinical deterioration occurred after minimum 30 days. A retrospective data collection was undertaken to include patient characteristics, clinical status at presentation, laboratory results, and antimicrobial therapy. Patients aged below 16 years were excluded. Positive blood cultures drawn <48 h following hospital admittance were considered community-acquired infections. The remaining cases, that had blood cultures drawn >48 h following hospital admittance, were subjected to comprehensive evaluation in accordance with the ICU case definitions for hospital-acquired ICU-infections from the European Centre for Disease Prevention and Control [13].

Blood cultures were drawn at clinical indications as judged by the on-call medical staff at presentation. We used aerobic and anaerobic Bactec FX vacutainer culture bottles, incubated in a BD BACTECTMFX Instrument (Becton Dickinson, Sparks, MD, USA). Aetiology of bacterial isolates were identified using MALDI-TOF mass spectrometry, on occasions supplemented with standard biochemical methods [14]. Antimicrobial susceptibility testing was performed using the EUCAST disc diffusion method [15]. Minimal inhibitory concentration (MIC) was determined by agar gradient method using Liofilchem®

MIC test strips (Liofilchem, Italy). The results were interpreted according to breakpoints from NordicAST [16] and EUCAST [17]. Blood cultures containing possible skin contaminants were excluded if they had been classified as such by the microbiology laboratory in agreement with the attending medical doctor.

Empiric antimicrobial therapy was defined by the time from initiation of antibiotics until results of antimicrobial susceptibility testing was available to the attending medical doctor, and classified as appropriate, discordant or uncertain based on a comprehensive evaluation of type of infection, bacterial species, and susceptibility of the isolated pathogen to the administered drug or drug combination. Further, therapy was deemed appropriate or discordant if the isolated bacteria were *in vitro* susceptible to at least one of the administered antimicrobials, or non-susceptible to all of the administered antimicrobials, respectively. In circumstances of aetiology with no established clinical breakpoints for microbial susceptibility, therapy was considered to have uncertain efficacy.

We used descriptive statistics to delineate included cases with BSI and the corresponding antimicrobial therapy. The proportions of discordant empiric therapy was calculated each ensuing day. We used a Pearson Chi square association model to calculate statistical differences between community- and hospital-acquired BSI episodes. A univariate and multivariate logistic regression model predicted factors associated with receiving discordant antimicrobial therapy. Both analyses were computed by the use of IBM SPSS Statistics 27. Instituted antimicrobial therapy was also subjected to evaluation against therapy recommendations as presented in national therapy guidelines [18]. Antimicrobial de-escalation was assessed and described with the use of descriptive statistics.

All identified patients with BSI that were alive at study initiation were retrospectively asked for consent, whereas deceased patients were included without consent. The study was approved by the Regional Committee for Medical and Health Research Ethics (REK-mid 2019/528), hospital administration representatives, and data protection officials.

Results

Characteristics of patients

Over the studied time period 3369 and 4230 patients met criteria for ICU hospitalisation and bacteraemia, respectively. Merging these data provided 357 unique patients with 361 episodes of BSI, of which 92 were excluded as contamination of the blood culture, fungemia, lack of data, patient still hospitalised at end of study or age below 16 years. Hence, a total of 270 episodes of bacterial BSI were included in the analysis, of which 180 (66.6%), and 90 (33.3%) were classified as community-acquired (CA) or hospital-acquired (HA) infections, respectively. Patient characteristics are presented in Table 1.

The primary site of infection was assumed to be the urinary tract in 23.7% of the BSI episodes, abdomen in 20.4%, lower respiratory tract in 19.3%, skin and soft tissues in 9.6%, intracerebral structures in 3.3%, bone and joints in 1.9%, and other origins in 7.4% of infections. In 14.4% of the BSI episodes, the source of infection was not established. Infection sources are presented in Table 2.

Bacterial isolates

A total of 296 bacterial isolates were identified from the 270 BSI episodes. The mean time to identification and corresponding susceptibility results was 2.8 days (95% CI 2.7–3.0). Monomicrobial BSI constituted 249 of the 270 (92.2%) episodes, whereas polymicrobial BSI with two or three bacterial species were detected in 16 (5.9%), and 5 (1.9%) episodes, respectively. Gram-negative pathogens were detected in 145 (49.0%), Gram-positive pathogens in 134 (45.3%), and anaerobic pathogens in 17 (5.7%). The most frequently isolated pathogens were *Enterobacterales* (41.6%) and *Staphylococcus aureus* (15.2%). Only six (5.9%) *Enterobacterales* isolates proved to be cefotaxime resistant, indicating an extended-spectrum beta-lactamase (ESBL) positive isolate, and none of the 45 *S. aureus* BSI isolates were meticillin-resistant. Aetiological results are presented in Table 3.

Empirical antimicrobial therapy

Complete information on empirical antimicrobial therapy was available for all inclusions. Prior to blood culture sampling at presentation, 45 of 270 (16.7%) BSI episodes already received antimicrobial therapy, to which 15 of 45 (33.3%) recovered BSI pathogens were *in vitro* susceptible. Initially, combination regimens of narrow-spectrum beta-lactams and an aminoglycoside were administered to 86 of 270 (31.9%) BSI-episodes, whereas a broad-spectrum beta-lactam administered in monotherapy or in combination with metronidazole were administered to 162 (60.0%) episodes. These regimens consisted largely of cefotaxime or ceftriaxone in combination with metronidazol, piperacillin-tazobactam in

Table 1. Patient characteristics of included BSI episodes.

Patient characteristics	Total ($n = 270$)	CA ($n = 180$)	HA ($n = 90$)	p Value[a]
Male, *n* (%)	158 (58.5)	101 (63.9)	57 (36.1)	–
Age, median (q1-q3)	67 (57–75)	70 (62–79)	64 (49–73)	<.001
Age, *n* (%)				
<35	17 (6.3)	7 (3.9)	10 (11.1)	<.001
35–49	35 (13.0)	23 (12.8)	12 (13.3)	
50–64	66 (24.4)	39 (21.7)	27 (30.0)	
65–80	115 (42.6)	77 (42.8)	38 (42.2)	
>80	37 (13.7)	34 (18.9)	3 (3.2)	
Charlson comorbidity index, *n* (%)				
0–1	128 (47.4)	101 (56.1)	27 (30.0)	.002
2–3	90 (33.3)	47 (26.1)	43 (47.8)	
≥4	52 (19.3)	32 (17.8)	20 (22.2)	
Comorbid conditions, *n* (%)				
Congestive heart failure	30 (11.1)	19 (10.3)	11 (12.8)	
Dementia	4 (1.5)	4 (2.2)	0 (0.0)	
Chronic pulmonary disease	50 (18.5)	34 (18.5)	16 (18.6)	
Rheumatologic disease	35 (13.0)	24 (13.0)	11 (12.8)	
Mild liver disease	11 (4.1)	7 (3.8)	4 (4.7)	
Moderate or severe liver disease	6 (2.2)	4 (2.2)	2 (2.3)	
Diabetes with chronic complication	12 (4.4)	8 (4.3)	4 (4.7)	
Hemiplegia or paraplegia	14 (5.2)	12 (6.5)	2 (2.3)	
Renal disease	37 (13.7)	20 (10.9)	17 (19.8)	
Any malignancy without metastasis	59 (21.9)	25 (13.6)	34 (39.5)	<.001
Metastatic solid tumour	22 (8.1)	14 (7.6)	8 (9.3)	
Intensive care treatment, *n* (%)				
Continuous veno-venous hemodiafiltration	33 (12.2)	19 (10.3)	14 (16.3)	
Dialysis	9 (3.3)	3 (1.6)	6 (7.0)	.032
Non-invasive respirator	60 (20.2)	40 (21.7)	20 (23.3)	
Invasive respirator	145 (53.7)	86 (46.7)	59 (68.6)	<.001
Severity of disease, median (q1-q3)				
SAPS-II[b]	43 (32–55)	42 (33–54)	45 (31–58)	
Mortality - all cause, *n* (%)				
≤ 7 days between BC taken and death	43 (18.5 %)	26 (19.3 %)	17 (17.3 %)	
≤ 28 days between BC take and death	82 (35.2 %)	45 (32.6 %)	37 (38.8 %)	.003
≤ 90 days between BC taken and death	108 (46.4 %)	65 (48.1 %)	43 (43.9 %)	
In hospital mortality	87 (32.2)	49 (27.2)	38 (42.2)	.013

[a]Only comparisons with statistically significant differences are shown. [b]Simplified Acute Physiology Score.

Table 2. Site of infection for included BSI episodes.

	Total		CA-BSI		HA-BSI		p Value
Site of infection	n	%	n	%	n	%	p-value
Urinary tract	64	23.7 %	58	32.2 %	6	6.7 %	<.001
Abdomen	55	20.4 %	30	16.7 %	25	27.8 %	.033
Lower respiratory tract	52	19.3 %	34	18.9 %	18	20.0 %	
Unknown	39	14.4 %	14	7.8 %	25	27.8 %	<.001
Skin and soft tissue	26	9.6 %	18	10.0 %	8	8.9 %	
Other	20	7.4 %	13	7.2 %	7	7.8 %	
Intracerebral structures	9	3.3 %	9	5.0 %	0	0.0 %	
Bone/joints	5	1.9 %	4	2.2 %	1	1.1 %	
Total	270	100 %	180	100 %	90	100 %	

monotherapy, or any carbapenem. The remaining BSI episodes received other combinations. Antimicrobial regimens were frequently changed both before and after the time point when microbial identification and susceptibility profile were reported, including frequent and interrupted single dose administrations. The mean number of regimen alterations was 2.1 (95%CI 1.9–2.3). At day 0, 1 and 2 after blood culture sampling, the narrow-spectrum betalactam-aminoglycoside combination regimen was administered to 32%, 21% and 11% of BSI episodes, respectively.

Empirical antimicrobial therapy was found to be appropriate for 218 (80.7%) of the 270 BSI episodes at day 0, discordant for 33 (12.2%), and of uncertain efficacy for 5 (1.9%). At day 0, 14 (5.2%) of the BSI episodes received no empirical antimicrobial therapy. The proportion of BSI episodes that received appropriate empiric antimicrobial therapy increased the ensuing days among patients that were still alive. Statistical analyses revealed significant differences between community- or hospital-acquired BSI episodes. At day 0, CA-BSI and HA-BSI episodes received discordant empirical antimicrobial therapy in 6.5% and 24.4% cases (p=.00003), respectively. This statistically significant difference remained unchanged throughout the therapy course. Towards the end of the observed therapy, discordant empirical antimicrobial therapy for CA-BSI and

HA-BSI episodes were 2.4% and 9.3% (p=.0388), respectively. Data on empirical antimicrobial therapy are presented in Table 4 and displayed in Figure 1.

Mortality

Fatal outcomes were frequent among included BSI-episodes. All-cause mortality at day 7, 28 and 90, and in hospital mortality were 18.5%, 35.2%, 46.4% and 32.2%, respectively. Receiving discordant therapy for HA-BSI was statistically significant associated with mortality at day 28 (X^2=3.884, p=.049). The calculated relative risk of mortality for HA-BSI that received discordant antimicrobial therapy was 1.64 (95% CI 1.01–2.64). For CA-BSI this association was not statistically significant at day 28 (X^2=0.415, p=.519), and the corresponding relative risk was 1.26 (95% CI 0.64–2.48). Fisher exact cross tabulation analyses for all BSI-episodes revealed that either receiving a narrow-spectrum betalactam (p=.008) or a broad-spectrum antimicrobial (p=.003) were statistically associated with mortality at day 28.

Table 3. Aetiology of included BSI-episodes.

Group	Episodes	Proportions	AMR
Gram negative bacteria	145	49.0 %	
Escherichia coli	86	29.1 %	4 ESBL (4.6 %)
Klebsiella spp.	23	7.8 %	2 ESBL (8.7 %)
Other Enterobacterales	14	4.7 %	
Enterobacter cloacae	8	2.7 %	
Pseudomonas aeruginosa	7	2.4 %	
Other Gram negative bacteria	7	2.4 %	
Gram positive bacteria	134	45.3 %	
Staphylococcus aureus	45	15.2 %	0 MRSA
Streptococcus pneumoniae	20	6.8 %	
Alpha-hemolytic streptococci	18	6.1 %	
Beta-hemolytic streptococci	18	6.1 %	
Enterococcus faecalis	13	4.4 %	0 VRE
Coagulase negative staphylococci	9	3.0 %	1 MRSE
Enterococcus faecium	7	2.4 %	0 VRE
Enterococcus spp.	2	0.7 %	0 VRE
Other Gram positive bacteria	2	0.7 %	
Anaerobic bacteria	17	5.7 %	
Bacteroides spp.	7	2.4 %	
Eggerthella lenta	4	1.4 %	
Clostridium spp.	3	1.0 %	
Other anaerobic bacteria	3	1.0 %	

Predictors of discordant antimicrobial therapy

Half of BSI episodes caused by ESBL producing Enterobacterales received discordant empirical antimicrobial therapy at admission to the ICU. A univariate and multivariate logistic regression model predicted that hospital-acquired BSI, enterococcal BSI, and intraabdominal focus, were significantly associated with receiving discordant antimicrobial therapy. All covariates included in the regression model are presented in Table 5. Neither receiving narrow-spectrum betalactam nor broad-spectrum antimicrobials as empirical therapy were associated with discordant empirical therapy.

Table 4. Coverage of empirical antimicrobial therapy according to *in vitro* susceptibility testing.

	Total		CA-BSI		HA-BSI		
	n (%)	95% CI	*n* (%)	95% CI	*n* (%)	95% CI	*p* Value
Day 0							
Appropriate	218 (80.7)	(0.76–0.85)	162 (88.0)	(0.83–0.93)	56 (65.1)	(0.55–0.75)	<.001
Discordant	33 (12.2)	(0.08–0.16)	12 (6.5)	(0.03–0.10)	21 (24.4)	(0.15–0.33)	<.002
Uncertain efficacy	5 (1.9)	(0.00–0.03)	3 (1.6)	(0.00–0.03)	2 (2.3)	(0.01–0.06)	
No treatment	14 (5.2)	(0.03–0.08)	7 (3.8)	(0.01–0.07)	7 (8.1)	(0.02–0.14)	
Alive	270		184		86		
Day 1							
Appropriate	226 (86.3)	(0.82–0.90)	164 (91.6)	(0.88–0.96)	62 (74.7)	(0.65–0.84)	<.001
Discordant	27 (10.3)	(0.07–0.14)	11 (6.1)	(0.03–0.10)	16 (19.3)	(0.11–0.28)	<.002
Uncertain efficacy	3 (1.1)	(0.00–0.02)	2 (1.1)	(0.00–0.03)	1 (1.2)	(0.01–0.04)	
No treatment	6 (2.3)	(0.00–0.04)	2 (1.1)	(0.00–0.03)	4 (4.8)	(0.00–0.09)	
Alive	262		179		83		
Day 2							
Appropriate	228 (91.2)	(0.88–0.95)	162 (94.7)	(0.91–0.98)	66 (83.5)	(0.75–0.92)	<.004
Discordant	18 (7.2)	(0.04–0.10)	7 (4.1)	(0.01–0.07)	11 (13.9)	(0.06–0.22)	<.006
Uncertain efficacy	2 (0.8)	(0.00–0.02)	2 (1.2)	(0.00–0.03)	0	0	
No treatment	2 (0.8)	(0.00–0.02)	0	0	2 (2.5)	(0.1–0.06)	
Alive	250		171		79		
Day 3							
Appropriate	225 (92.6)	(0.89–0.96)	158 (95.2)	(0.92–0.98)	67 (87.0)	(0.80–0.95)	<.024
Discordant	16 (6.6)	(0.03–0.10)	6 (3.6)	(0.01–0.06)	10 (13.0)	(0.05–0.20)	<.007
Uncertain efficacy	2 (0.8)	(0.00–0.02)	2 (1.2)	(0.00–0.03)	0	0	
No treatment	0	0	0	0	0	0	
Alive	243		166		77		
Day 4–9							
Appropriate	226 (94.2)	(0.91–0.97)	159 (96.4)	(0.94–0.99)	67 (89.3)	(0.82–0.96)	<.032
Discordant	11 (4.6)	(0.02–0.07)	4 (2.4)	(0.00–0.05)	7 (9.3)	(0.03–0.16)	<.039
Uncertain efficacy	2 (0.8)	(0.00–0.02)	2 (1.2)	(0.00–0.03)	0	0	
No treatment	1 (0.4)	(0.00–0.01)	0	0	1 (1.3)	(0.01–0.04)	
Alive	240		165		75		

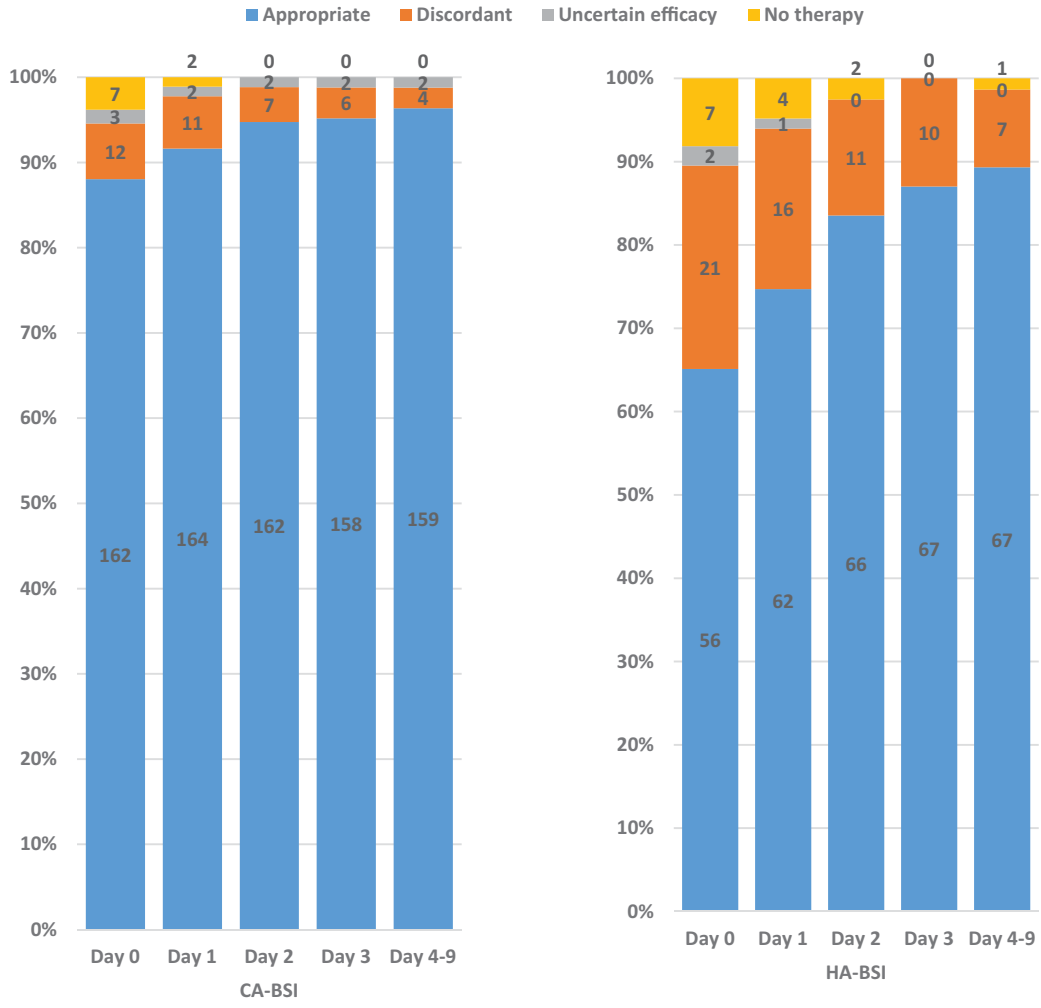

Figure 1. Coverage of empirical antimicrobial therapy according to *in vitro* susceptibility testing.

Table 5. Predictors of discordant empirical antimicrobial therapy.

	Univariate logistic regression			Multivariate logistic regression		
Predictor	OR	*p* Value	95% CI	OR	*p* Value	95% CI
Hospital-acquired BSI	3.952	<0.0001	2.142–7.292	4.164	<0.001	1.958–8.857
Charlson comorbidity index	0.849	0.745	0.745–0.968			
SAPS-II	0.999	0.872	0.982–1.016			
Age	0.998	0.866	0.980–1.017			
Concurrent gram positive and negative	12.72	0.002	2.493–64.902	3.098	0.053	0.074–129.337
Gram positive	1.114	0.654	0.635–2.063			
Gram negative BSI	0.61	0.103	0.337–1.105			
Enterobacterales	0.387	0.004	0.202–0.741	0.202	0.003	0.071–0.574
S aureus	0.325	0.04	0.111–0.949			
Enterococcus spp	22.885	<0.0001	7.308–71.666	10.297	0.002	2.344–45.224
Non-glucose fermenter	2.366	0.249	0.548–10.216			
Lower respiratory tract	1.031	0.935	0.491–2.166			
Urinary tract	0.197	0.003	0.068–0.570	0.427	0.236	0.105–1.743
Skin and soft tissue	1.466	0.416	0.583–3.684			
Central nervous system	0.468	0.479	0.057–3.823			
Intraabdominal	2.841	0.002	1.475–5.474	3.1	0.033	1.097–8.754
Other focus	0.942	0.866	0.470–1.886			
Narrow-spectrum betalactam	0.664	0.221	0.345–1.278			
Broad-spectrum antimicrobial	1.686	0.124	0.866–3.283			

Of episodes categorised as receiving uncertain antibiotic coverage, this was uniformly related to missing breakpoints for the administered drug-bug combination.

Antimicrobial therapy de-escalation

De-escalation of antimicrobial therapy was assessed for all 270 BSI episodes. Based solely on antimicrobial

susceptibility testing, de-escalation from a broad-spectrum to a narrow-spectrum antimicrobial agent would have been feasible in 194 (71.9%) BSI episodes. Of these, 27 (13.9%) actually underwent de-escalation. Mean time to de-escalation for survivors was 7.2 days (95% CI 6.1–8.2). Cases not eligible for de-escalation strategies were fatal BSI episodes, BSI-episodes already on narrow-spectrum therapy, and microbes not susceptible to narrow-spectrum therapy, reported in 12.2%, 11.1% and 4.8% of episodes, respectively.

Discussion

In this retrospective, observational cohort study in an intensive care, low antimicrobial resistance prevalence setting, we found that from day 0 until day 9 an increasing proportion of BSI-episodes received appropriate empirical antimicrobial therapy. However, discordant therapy was more frequent in HA-BSI than CA-BSI at all therapy days, and discordant antimicrobial therapy in HA-BSI was associated with increased mortality at day 28.

The proportion of BSI episodes receiving appropriate antimicrobial therapy was comparable to that reported in other studies from Norway [19,20]. In general, and as shown in this study, AMR prevalence is still low in Norway. A 2015 national action plan has nontheless put forward several comprehensive antimicrobial stewardship measures in order to preserve rational antimicrobial therapy usage and maintain the favoruable AMR prevalence [21]. However, therapy recommendations on BSI and other severe infections remained unchanged in Norway during the study period, promoting a narrow-spectrum betalactam-aminoglykoside combination regime for sepsis with uknown origin or aetiology. If severe renal failure is present, standard alternatives are benzylpenicillin in combination with ciprofloxacin, piperacillin-tazobactam, or cefotaxime. In clinical circumstances with a presumed or documented origin, specific therapy recommendations are established. In contrast, scince 2016, international clinical practice guidelines have addressed emerging resistance and advocated broad-spectrum antimicrobials to which all likely pathogens are susceptible [6].

Of note, BSI-studies from countries high in AMR prevalence tend to report higher rates of discordant empirical antimicrobial therapy [22–24]. In a large, retrospective, multicenter study from the United States comprising over 21.600 BSI-episodes, discordant empirical antimicrobial therapy was reported in 19%. Discordant empirical antimicrobial therapy was shown to be independently associated with about 50% increased risk of mortality (adjusted odds ratio 1.46 (95% CI 1.28–1.66; $p<.0001$). The study further reported that BSI with antibiotic-resistant phenotype strongly predicted reciving discordant empirical antimicrobial therapy (OR 9.09) [25]. In our study setting with low prevalence of AMR, Cefotaxime-resistant *Enterobacterales* were evident in only 5.9% of BSI episodes, and all *S. aureus* isolates were meticillin-sensitive.

Despite the low AMR-prevalence, we have provided other predictors associated with increased risk for receiving discordant antimicrobial therapy. We did observe a statistically significant association between HA-BSI leading to death by day 28, and discordant antimicrobial therapy. In the regression models, HA-BSI was identified as a predictor of receiving discordant antimicrobial therapy. This was also the case for enterococcal BSI, and for BSI of intraabdominal origin. However, several established risk factors for mortality have previously been reported, and discordant empirical antimicrobial therapy alone can hardly explain reasons for death in a setting with low prevalence of AMR [25].

Interestingly, empirical antimicrobial therapy with a narrow-spectrum betalactam, allthough often in combination with an aminoglycoside, did not predict discordant therapy, in support of national clinical practice guidelines. Nevertheless, discordant narrow-spectrum betalactam or broad-spectrum antimicrobial therapy were both associated with increased risk of mortality at day 28. Our data do not provide information regarding the timely initiation of appropriate, concordant empirical antimicrobial therapy. In several other studies, however, the timely initiation is reported to be a key determinant for survival [26,27]. It also indicates that national clinical practice guidelines might need to address specific BSI subpopulations, such as hospital-aqcuired infections. In line with others, our findings call for strengthened diagnostic and antimicrobial stewardship efforts for the early recognition, and to improve prescribing practices [25]. In addition, receiving discordant antimicrobial therapy beyond the time point of antimicrobial susceptibility reporting, was observed in several BSI cases. Stewardship measures need to be implemented in order to eliminate these proportions.

We observed several considerable differences between BSI-episodes aquired within community or hospital settings. First, the association between HA-BSI and mortality was not observed in CA-BSI. Second, a significantly larger proportion of HA-BSI episodes were of

abdominal or of unknown origin. Third, a significant larger proportion of HA-BSI episodes occurred in patients with malignant disease or chronic renal failure. Forth, while the simplified acute severity score (SAPS-II) did not differ among groups, a larger proportion of HA-BSI episodes received invasive mechanical ventilation. Finally, HA-BSI more often received discordant antimicrobial therapy. These observations should encourage clinical practice guidelines to view HA-BSI and CA-BSI as independent clinical incidents. This has not been delineated in norwegian guidelines.

Pathogen-directed antimicrobial therapy is hampered by the inherent time lag between culture sampling and results of in-vitro susceptibility analysis. The introduction of rapid detection systems are likely to provide early pathogen identification and susceptibility reports [28]. This, in line with proper antibiotic stewardship measures, have demonstrated favourable outcomes [29]. All BSI episodes included in our study were subjected to standard laboratory strategies for identification and susceptibility testing. Within the intensive care unit there were no specific antibiotic stewardship measures launched prior or during the study time period.

Time to antimicrobial therapy de-escalation was considerably delayed or deferred. On average, de-escalation was performed 4.4 days beyond the finalisation of the antimicrobial susceptibility testing, to only 14% out of nearly 72% of patients that were eligible based upon cultures with susceptibility testing. We did not undertake further studies to delineate circumstances leading to continued broad-spectrum antimicrobial therapy, as preferred over targeted therapy. Continued broad-spectrum antimicribial therapy seemed to be the preferred strategy in our study, allthough this is not as important as administering antimicrobial therapy active against the most likely pathogens [30]. Others have previously shown that antibiotic de-escalation strategies in the ICU is a well tolerated and safe management strategy even in critically ill patients [31,32].

Our study has several limitations. We did not systematically assess the role of source control in BSI episodes, nor proportions of BSI-episodes with or without sepsis syndrome or septic shock. Minimum inhibitory concentrations for detected pathogens were not assesed. To some extent, patient data relied on the attendings doctor's ability to document the clinical cource. This might have influenced on results. However, of most importance to the limitations is the time data, that were only avaliable as dates and not as hours, thus reducing accuracy of time measurements.

Conclusion

The prompt initiation of adequate empirical antimicrobial therapy is considered essential in BSI. Our study provides important information about coverage of such therapy in a low AMR-prevalence setting. Hospital-acquired BSI posed a significant risk of receiving discordant antimicrobial therapy, and was independently associated with mortality. Antibiotic policy-makers should be aware of this and depict strategies to mitigate the mortality burden of BSI.

Ethical approval

Ethics approval and consent to participate.

The study protocol was evaluated and approved by the Regional Committees for Medical and Health Research Ethics, Central (2017/1439), data protection officials, and hospital administration. The study was conducted in line with the conclusion from the Regional Committees for Medical and Health Research Ethics, Central, that informed consents were required to access, participate and publish the data, for all patients that were alive. The study was conducted in accordance with the principles of the Declaration of Helsinki, and the guidelines for medical and health research from The Norwegian National Research Ethics Committees.

Consent for publication

All contributing authors reviewed the manuscript before publication and gave their approval to publish the work.

Author contributions

BW and NS collected the data. BW, NS, JEA, PK, SM, LH and JKD analysed the data. All authors contributed to the writing of the manuscript. All authors approved the submitted manuscript.

Disclosure statement

Author Bjørn Waagsbø is a representative and holds a 20% position to the directory group in the Norwegian Directorate of Health that seek to revise recommendations in the national clinical practice guideline for antimicrobial therapy.

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ORCID

Lars Heggelund http://orcid.org/0000-0002-1669-1032

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