Bjørn Waagsbø

Antimicrobial therapy and adherence to guideline recommendations: Studies on pneumonia and bloodstream infections.

NTNU
Norwegian University of
Science and Technology

Bjørn Waagsbø

Antimicrobial therapy and adherence to guideline recommendations: Studies on pneumonia and bloodstream infections

Thesis for the Degree of Philosophiae Doctor

Trondheim, May 2023

Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
Department of Clinical and Molecular Medicine

Bruk av antibiotika etter retningslinjer: Studier på pneumoni og blodbane-infeksjoner

Sammendrag på norsk

Effektiv antibiotika er en forutsetning for moderne medisinsk behandling innen nær alle medisinske spesialiteter. Merforbruk av antibiotika er imidlertid ansett som en betydelig driver av antibiotikaresistens, som igjen øker risiko for terapisvikt og mortalitet. Årsaker til merforbruk kan skyldes antibiotikaforskrivninger som er unødige, feil eller suboptimale. I Norge er antibiotikaforbruk generelt lavt sammenlignet med europeiske land, og antibiotikaresistens i Norge er lavest i verden. Gode kvalitative studier som kan belyse korrekt bruk og eventuelt merforbruk av antibiotika i Norge mangler.

I denne doktoravhandlingen har jeg satt søkelys på gjennomføringen av kvalitative studier som kan belyse antibiotikabruk til hyppig forekommende infeksjoner i sykehus. Vi valgte samfunnservervet pneumoni (CAP) og blodbaneinfeksjoner (BSI) diagnostisert og behandlet i sykehus som modeller til disse studiene. Vårt formål var å etablere studier som kunne gi tilstrekkelig gode kunnskaper om kvalitative forhold ved antibiotisk terapi til disse infeksjonene. Vi gjennomførte derfor fire retrospektive observasjonsstudier, hvorav to om CAP og to om BSI.

I første studie gjorde vi en intervensjon i akuttmottaket ved St. Olavs hospital for å øke antall pasienter som gjennomgikk korrekt oppsamling av representativt luftveissekret ved ekspektorat eller indusert sputum ved CAP. Antall pasienter som gjennomførte test økte signifikant, og diagnostisk nytteverdi av ekspektorat eller indusert sputum økte også signifikant fra 41.2 % til 62.0 %. Studien viste at relativt moderate tiltak i akuttmottaket kan øke antallet pasienter som får gjennomført korrekt diagnostisk test etter prosedyre, og oppnå økt diagnostisk nytteverdi.

I andre studie undersøkte vi om andelen pasienter med CAP som ble forskrevet førstelinje-behandling kunne påvirkes over tid med en målrettet intervensjon ved å promotere retningslinje-anbefalinger. Over en seks-årsperiode økte andelen med smalspektrede β-laktamer signifikant fra 56.1 % til 74.4 %. Andelen som mottok bredspektrede regimer avtok signifikant i samme periode fra 34.1 % til 17.1 %. Studien viste at CAP er en egnet modell for antibiotikastyringstiltak.

I tredje studie samlet vi data retrospektivt fra 270 pasienter med dyrkningspositiv blodbaneinfeksjon behandlet i intensivavdeling. Ved samfunnservervet BSI, var empirisk antibiotisk terapi konkordant på dag 0, 1, 2, 3 og 3-9 hos henholdsvis 88.0 %, 91.6 %, 94.7 %, 95.2 % og 96.4 %. Imidlertid, ved sykehuservervet BBI var slik terapi konkordant hos

bare 65.1 %, 74.7 %, 83.5 %, 87.0 % og 89.3 %. For alle dager viste en assosiasjonsmodell statistisk signifikante forskjeller. Diskordant terapi ved sykehuservervet BSI var statistisk signifikant assosiert med mortalitet på dag 28. Studien viste at empirisk antibiotika til BSI var i langt større grad dekkende for samfunns- enn sykehuservervede infeksjoner.

I fjerde studie inkluderte vi alle dyrkningspositive BSI-episoder gjennom ett helt kalenderår (2019). Studiepopulasjonen utgjorde totalt 756 BSI-episoder, hvor behandling hovedsakelig ble ivaretatt ved ordinær sengeavdeling. Hos 536 av 756 (70.6 %) BSI-episoder ble empirisk antibiotika valgt i henhold til anbefalinger i nasjonal faglig antibiotikaretningslinje, hos 190 av 756 (25.1 %) ble andre regimer valgt. Til BSI-episoder som mottok behandling i henhold til retningslinjen, var andelen med konkordant antibiotika 85.5 % og diskordant 14.2 %. Til BSI-episoder som mottok andre regimer var tilsvarende andeler 73.7 % og 26.3 %. En assosiasjonsmodell viste en statistisk signifikant sammenheng mellom valg av antibiotika etter retningslinjen og konkordans. En mortalitetsanalyse viste at diskordant terapi var signifikant assosiert med både intra-hospital og langtids mortalitet. Studien viste at antibiotikavalg ut fra anbefalinger i nasjonal faglig retningslinje var sterkt assosiert med dekkende antibiotisk terapi.

Studiene har gitt verdifull kunnskap om antibiotikabruk til nøkkelinfeksjoner ved et universitetssykehus i Norge med presumptivt lavt antibiotikaforbruk og i omgivelser med lav antibiotikaresistens. Både diagnostikk ved infeksjoner, og empirisk og målrettet antibiotika er viktige faktorer for rasjonelt antibiotikabruk, og disse er lett påvirkbare med relativt beskjedne styringstiltak. Dette er viktig av flere grunner. For det første, mer rasjonelt antibiotikabruk kan oppnås uten å affisere mortalitet eller antall reinnleggelser. For det andre, selv relativt beskjedne styringstiltak og intervensjoner kan påvirke antibiotikabruk gunstig. For det tredje, gunstige resultater kan oppnås selv i et lavforbruksland som Norge. Og for det fjerde, redusert antibiotikabruk kan hindre økning i antibiotikaresistens.

Ovennevnte avhandling er funnet verdig til å forsvares offentlig for graden PhD i medisin

Disputas finner sted i auditorium MTA, Fred Kavli-bygget, 12. mai 2023.

Acknowledgements

I would like to take the opportunity to express my gratitude to all contributors to the submitted work and the PhD thesis.

I would especially like to thank the Norwegian University of Science and Technology for extending a helpful hand when needed. Due to unforeseen events from the birth of my youngest son, the finalization of my thesis took me a little longer than estimated. I am very grateful that my project could proceed as planned and be finalized within reasonable time. It took a great amount of admirable solutions by the collaborating parties for which I am very grateful.

Professor Jan Kristian Damås, my main supervisor, and Professor Lars Heggelund, my co-supervisor, have passionately guided me through the work, for which I am very grateful. Both professors have extensive experience in clinical medicine and academic work, of which the submitted work and thesis heavily rely on, and of which a have greatly benefitted from.

A great deal of the planning and initiation of antimicrobial therapy projects was carried out together with my close collaborators of the Antimicrobial stewardship team at St. Olavs Hospital in Trondheim. I wish to express my gratitude to both the Regional Competence Center for Infection Control and Hygiene in Mid-Norway and St. Olavs University Hospital.

Lastly, I would express my deepest gratitude to all my friends and family that have encouraged and supported me throughout the project. Especially I would give my thanks to my closest family. In addition, I would give a special thanks to my former tutor, Doctor Anders Sundøy, who always encouraged and inspired me to pursue my interest in academia.

The work here presented was mostly carried out at clinical wards at St. Olavs Hospital, Trondheim University Hospital, and in four hospitals in Møre og Romsdal Hospital Trust. The work was funded from the Liaison Committee for Education, Research and Innovation in Central Norway.

Trondheim, April 2023

Bjørn Waagsbø

Abstract

Effective antimicrobial therapy are a prerequisite for modern medical treatment in all medical specialties. However, overuse of antimicrobial therapy is considered a driver of antimicrobial resistance, which eventually increases the risk of therapy failure and mortality. In general, reasons for overuse are unnecessary, inappropriate or suboptimal antimicrobial prescriptions. In Norway, antimicrobial consumption is generally low compared to European countries, and antimicrobial resistance is among the lowest in the world. Good qualitative studies that emphasize the correct and rational use or possible overuse of antimicrobial therapy are lacking.

In this doctoral thesis, I have focused on qualitative studies that can highlight the prescribing of antimicrobial therapy to key infections frequently encountered in hospital settings. We chose community-acquired pneumonia (CAP) and bloodstream infections (BSI) diagnosed and managed in hospital settings as models. Our aim was to establish studies that could provide sufficiently knowledge about qualitative aspects for these infections. We therefore conducted four retrospective, observational studies, of which two on CAP and two on BSI.

In the first study, we launched an intervention in the emergency room setting to increase proportions of patients that underwent collection of representative respiratory secretions of expectorate or induced sputum in CAP. The number of patients who completed the test increased significantly. In addition, we observed an increase in diagnostic yield from 41.2 % to 62.0 %. The study showed that relatively modest measures in the emergency room setting could increase the proportions of microbiologically confirmed cases of CAP.

In the second study, we investigated whether the proportion of patients prescribed with first-line antimicrobial therapy for CAP could be influenced by a targeted intervention that promoted clinical guideline recommendations. Empiric first-line antimicrobial therapy with narrow-spectrum β-lactams increased significantly from 56.1 % to 74.4 % over the six-year period. The proportion that received broad-spectrum regimens decreased significantly from 34.1 % to 17.1 % in the corresponding period. The study showed that CAP is a suitable model for antimicrobial stewardship measures.

In the third study, we retrospectively collected data from 270 patients with culture-positive BSIs in the intensive care setting. In community-acquired BSIs, empirical antimicrobial therapy was concordant on day 0, 1, 2, 3, and 3-9 in 88.0 %, 91.6 %, 94.7 %, 95.2 % and 96.4 %, respectively. However, in hospital-acquired BSIs, such therapy was concordant in only 65.1 %, 74.7 %, 83.5 %, 87.0 %, and 89.3 %. For all days, an association model returned statistically significant differences. Discordant antimicrobial therapy for hospital-acquired BSIs was significantly associated with mortality on day 28. The study

showed that empirical antimicrobial therapy for community-acquired BSIs was far more sufficient to cover for the detected pathogen, as compared to hospital-acquired BSIs.

In the fourth study, we included all culture-positive BSI episodes throughout an entire calendar year, comprising a total study population of 756 cases. The BSI episodes were mainly managed in ordinary hospital ward settings outside of the ICU. In 70.6 % of episodes, empirical antimicrobial therapy were guideline-adherent, and in 25.1 %, other regimens were chosen. For BSI episodes that received guideline-adherent antimicrobial therapy, 85.5 % were concordant, and 14.2 % were discordant. For BSI episodes that received non-adherent regimens, the corresponding proportions were 73.7 % and 26.3 %, respectively. An association model returned a statistically significant relationship between guideline-adherent antimicrobial therapy and concordance. A mortality-analysis showed that discordant antimicrobial therapy was significantly associated with both intra-hospital and long-term mortality. The study thus provided validation to antimicrobial prescriptions compliant with clinical practice guideline recommendations.

The studies have provided valuable insights and knowledge about antimicrobial therapy to key infections at a university hospital in Norway with presumptive low antimicrobial consumption and in low resistance environments. Both diagnostic aspects and empirical and targeted antimicrobial therapies are important factors for the rational use of antimicrobial therapy. This is important for several reasons. Firstly, it can likely be achieved without affecting mortality and morbidity. Secondly, it can be achieved by even modest efforts, for instance by increasing adherence to clinical practice guideline recommendations. Thirdly, it can be achieved even in countries with low antimicrobial usage. And fourthly, it has the potential to reduce antimicrobial usage and thereby suppress drivers of antimicrobial resistance

List of papers

Paper I

Waagsbø B, Buset EM, Longva JÅ, Bjerke M, Bakken B, Ertesvåg AS, Holmen H, Nikodojevic M, Tran TT, Christensen A, Nilsen E, Damås JK, Heggelund L.
Diagnostic stewardship aiming at expectorated or induced sputum promotes microbial diagnosis in community-acquired pneumonia.
BMC Infect Dis 22, 203 (2022). https://doi.org/10.1186;s12879-022-07199-4

Paper II

Waagsbø B, Tranung M, Damås JK, Heggelund L.
Antimicrobial therapy for community-acquired pneumonia during stewardship efforts and a coronavirus pandemic: An observational study.
BMC Pulm Med 22, 379 (2022). https://doi.org/10.1186/s12890-022-02178-6

Paper III

Waagsbø B, Stuve N, Afset JE, Klepstad P, Mo S, Heggelund L, Damås JK.
High levels of discordant antimicrobial therapy in hospital-acquired bloodstream infections is associated with increased mortality in an intensive care, low antimicrobial resistance setting.
Infect Dis (Lond). 2022 Oct;54(10):738-747. doi: 10.1080/23744235.2022.2083672

Paper IV

Grøv K, Håland E, **Waagsbø B**, Salvesen Ø, Damås JK, Afset JE.
Empirical antimicrobial therapy for bloodstream infections not compliant with guideline was associated with discordant therapy, which predicted poorer outcome even in a low resistance environment.
Infect Dis (Lond). 2022 Dec;54(12):833-845. doi: 10.1080/23744235.2022.2109208

Abbreviations

AMR   Antimicrobial resistance

AMS   Antimicrobial stewardship

AST   Antimicrobial susceptibility test

BSI   Bloodstream infection

CA   Community-acquired

CAP   Community-acquired pneumonia

CDC   Center of Disease Control and Prevention

CoV   Coronavirus

ECDC   European Centre for Disease Prevention and Control

ESBL   Extended spectrum beta-lactamase

HA   Hospital-acquired

HICs   High-income countries

LMICs   Low- and middle-income countries

MRO   Multidrug-resistant organism

MRSA   Methicillin-resistant Staphylococcus aureus

MDR   Multidrug resistant

PNSP   Penicillin non-susceptible pneumococcus

SARS   Severe Acute Respiratory Syndrome

WHO   World Health Organization

Table of contents

Introduction

Global antimicrobial consumption

Studies on antimicrobial consumption to humans among countries and regions are scarce. However, a few rigorous studies have provided valuable information.

Trends and drivers of antimicrobial consumption in 76 countries were analyzed in a rigorous study from a trans-Atlantic collaboration in 2017 (1). Daily doses of consumed antimicrobial therapy increased from 2000 to 2015 by 65 %. The increase was driven largely by low- and middle-income countries (LMICs), as evident by a significant association between consumption and gross domestic product per capita growth. A particularly rapid increase was noted for glycylcyclines, oxazolidinones, carbapenems, and polymyxins. The study group also provided projections of global antimicrobial consumption reaching 200 % in 2030, as compared to 2015, assuming no policy changes.

In another study, partly from the same collaborators, rapid increase in overall antimicrobial consumption was reported between 2000 and 2015 (2). Antimicrobial agents from the WHO-specified Watch-group, and the Access-group, increased by 91 % and 26 %, respectively. Furthermore, proportions of countries in which Access-antimicrobials represented at least 60 % of their total antimicrobial consumption, which is the WHO national-level target, decreased from 76 % to 55 % during the 15-year period.

Using hospital pharmacy sales databases, another study showed that overall antimicrobial consumption increased by 35 % in the period from 2000 to 2010 for 71 countries combined (3). Brazil, Russia, India, China, and South Africa accounted for 76% of this increase. Importantly, there was a significant increase in the consumption of last-resort antimicrobial agents like carbapenems and polymyxins, which increased 45 % and 13 %, respectively.

A comprehensive spatial modelling study that sought to provide data on global antimicrobial consumption among children aged below five years for lower respiratory tract infections, demonstrated important and substantial disparities among geographical areas, and an overall increase in antimicrobial consumption over time (4). From 2000 to 2018, the authors concluded with an overall global increase of 46 % in antimicrobial consumption. Among antimicrobial agents that increased the most were fluoroquinolones and third-generation cephalosporins. High-income (HICs) and upper-middle-income countries in North America, Europe and the Middle East outperformed low-income countries by nearly a ten-fold margin.

The impact of the global coronavirus pandemic on antimicrobial consumption was recently investigated by worldwide cross-sectional time-series analyzes (5). In March 2020

overall antimicrobial sales in 66 developed and developing countries significantly increased as compared to March 2019. However, in the ensuing months between April to August 2020, antimicrobial consumption decreased by nearly 19 % compared with previous year. The authors concluded that the WHO global action plan on antimicrobial resistance might have influenced positively on overall antimicrobial consumption. Contrary to this, an expert commentary later replied that antimicrobial prescriptions to covid-19 cases were surprisingly large in LMICs, and that decreased antimicrobial sales rather reflected a pronounced decline in community transmission or serious under-testing of infections (6).

A recent report from the European Centre of Disease Prevention and Control pinpoints main trends for antimicrobial consumption throughout European countries (7). Overall, there is a 23 % reduction in human consumption for all antimicrobial generic substances combined, between 2011 and 2020. However, the reduction is most profound in the Coronavirus Disease 2019 (covid-19) pandemic, constituting 18 % reduction from 2019 and 2020. A true reduction of this magnitude is nevertheless unlikely, because several interventions to curb the covid-19 pandemic are believed to have influenced the numbers. Firstly, a change in infectious disease epidemiology, as evident by a profound reduction in the prescribing of antimicrobial therapy for respiratory infections and infections in younger individuals. Secondly, non-pharmaceutical interventions to reduce SARS-CoV-2 transmission have been extensive. Thirdly, lockdown, re-organization and re-prioritization of primary care services may have influenced antimicrobial prescribing for milder and self-limiting conditions.

Interestingly, there are overwhelmingly significant differences in antimicrobial consumption among European countries, both in the community and in hospital settings (7). In 2020, mean consumption of antimicrobials in humans was estimated to 16.4 DDD per 1.000 inhabitant per day, ranging from 8.5 in the Netherlands and 28.9 in Cyprus. This represents deviations of –48 % and +76 % from the mean, respectively. In community-acquired infections treated outside of hospital settings throughout European countries, broad-spectrum antimicrobial agents were consumed 3.5 times higher than were narrow-spectrum antimicrobial agents. This implies that adherence to clinical practice guideline recommendations is substandard. Of note, increasing ratios are reported from eastern European countries, and decreasing ratios from western and northern countries.

In hospital settings, the overall consumption of broad-spectrum generic substances has increased throughout European countries, with few exceptions (7). The ratio between broad-spectrum antimicrobial therapy to total hospital consumption is of particular interest when assessing differences between countries in Europe. In Norway in 2020, this

ratio was 19 %, the lowest in Europe, whilst in Bulgaria it was 63 %. Mean ratio was 39 % among 25 eligible countries, of which six countries had ratio below the 25 % quartile, and six countries had a ratio above the 75 % quartile. This underscores the fact that broad-spectrum antimicrobial therapy consumption varies significantly in Europe, and that there indeed exists a north-south, and west-east gradient. In this case, broad-spectrum antimicrobial therapy was defined as glycopeptides, third- and fourth-generation cephalosporins, monobactams, carbapenems, fluoroquinolones, polymyxins, piperacillin-tazobactam, linezolid, tedizolid and daptomycin.

Antimicrobial consumption in Norway

In Norway, total human antimicrobial consumption is reported annually as DDD per 1.000 inhabitants per day, using sales data from the Norwegian Drug Wholesales Statistics Database (8). For most antimicrobial classes, consumption rates in Norway are among the lowest in Europe, especially for broad-spectrum antimicrobial agents such as penicillin enzyme-inhibitor coformulations, cephalosporins, carbapenems, monobactams, fluoroquinolones, glycopeptides, and oxazolidinones.

A previous study from Norway, however, reported from 2002 until 2007 that a significant increase in overall and broad-spectrum antimicrobial consumption, reaching 17 % and 48 %, respectively (9). The authors concluded that the increase was unjustified considering low prevalence of AMR in Norway.

A decrease in total human antimicrobial consumption is also evident for Norway in the last decade, as it is for European countries combined. Since 2012, this decrease constitutes 32 %, of which 13 % were reported during the first SARS-CoV-2 pandemic year. Sales of phenoxymethylpenicillin, amoxicillin, macrolides and doxycycline declined significantly during March to May 2020, representing agents commonly prescribed for respiratory tract infections. Of note, penicillins constitute nearly 40 % of the total amount of antimicrobial sales in Norway in 2020, although among these, there is a gradual shift from beta-lactam sensitive penicillins toward the extended-spectrum penicillins like amoxicillin, ampicillin and pivmecillinam.

Norwegian hospitals account for approximately 8 % of total sales of antimicrobial agents. The SARS-CoV-2 pandemic also affected antimicrobial sales to hospitals in Norway, as extensive measures to prepare for high numbers of covid-19 patients were taken (8). Nonetheless, broad-spectrum antimicrobial consumption is reduced in Norway. Since 2012, the number of bed days, DDDs, and DDD per 100 bed days are -19 %, -31 % and -15 %, respectively (8). Consequently, narrow-spectrum penicillins are still highly utilized in Norwegian hospitals, even in severe infections.

Overuse and misuse

Since the introduction of antimicrobial therapy in clinical practice over 70 years ago, indiscriminate use has afflicted the medical communities. Public health officials and infectious diseases physicians have for decades advocated for preservation. Although, the understanding and interpretation of the term indiscriminate use has been debated. A 2016 review used a systematic approach to define and measure appropriate antimicrobial usage in hospital settings (10). Here, the authors proposed terminology and definitions for unnecessary, inappropriate, and suboptimal antimicrobial therapy. Definitions are outlined in the method section.

Studies indicate that increases in antimicrobial consumption are highly likely to be caused by inappropriate use (3). In LMICs widespread non-bacterial infections like dengue fever, malaria, chikungunya, and various encephalitis pathogens, account for a substantial part (11). Also contributing to the inappropriate use, is antimicrobial therapy for self-limiting acute diarrheal infections, especially in high-density populations in India, Bangladesh, China, Thailand, and the Philippines (12). However, such infectious diseases are not endemic in Europe, and do not explain misuse or overuse of antimicrobial therapy in European countries. A recent study from India that analyzed private-sector consumption, found especially high rates of broad-spectrum agents, high consumption of fixed-dose combinations discouraged by the WHO, large share of non-approved agents in fixed-dose combinations, and overwhelming consumption rates of unapproved formulations (5).

Earlier studies across the world have shown seasonal variations in antimicrobial consumption. Both in the northern and southern hemisphere, antimicrobial consumption peaked in wintery months (3), contrary to findings from India, which peaked in the summer (13). Another study from India found that nearly 70 % of hospitalized patients diagnosed with dengue hemorrhagic fever, were prescribed third-generation cephalosporins or fluoroquinolones (14). Transmission of dengue correlates with post-monsoon season, highest in September, lowest in January (15).

Economic growth, as evident by the per capita gross domestic product, has been shown to significantly correlate with increased antimicrobial consumption in low and middle-income countries (2). This is partly explained by the access to goods and services, including health care. In addition, increasing urbanization around the globe can facilitate the transmission of infectious diseases, and may contribute to the link between economic growth and increased antimicrobial consumption (16). Urbanization is also associated with declining air quality due to fossil fuel-based transportation and household cooking, ultimately increasing incidences of lower respiratory airway conditions resembling infections (17).

A major contribution to the overuse of global antimicrobial consumption is the overwhelming lack of clean water, improved sanitation, and immunization in a vast majority of LMICs (3). As compared to HICs, antimicrobial therapy was introduced while essential sanitary infrastructure remained abundant in LMICs. Antimicrobial therapy is therefore commonly used as a substitute for public health measures (18).

The emergence and spread of antimicrobial resistant bacteria have contributed to the increase in antimicrobial consumption (19). This applies for all countries worldwide, but especially for LMICs. In addition, inadequate sanitation is thought to explain widespread antimicrobial resistance in low-income countries (20).

Contrary to these findings, there is a lack of associations between economic growth and antimicrobial consumption for HICs. A longitudinal, observational study from 19 European countries from 1999 to 2007, reported interesting, yet complex, results for ambulatory antimicrobial prescriptions (21). Apart from the nature of the health care system, factors describing climate, burden of disease, demography, and socioeconomics each partially explained differences in antimicrobial prescribing rates. Especially humidity, healthcare expenditures, feelings of distrust, proportions of the population aged above 65 years, and the availability of clinical practice guideline recommendations were positively associated with increased prescribing rates. On the other hand, restrictions on marketing, population density, number of antimicrobial agents available, educational attainment, and the extent to which people described themselves as atheistic rather than religious were negatively associated with antimicrobial prescribing. The authors concluded that a myriad of factors influenced antimicrobial consumption, but importantly, a substantial proportion of factors were likely to be modifiable by policy measures.

The study by Blommaert underscores that antimicrobial consumption to a considerable extent is driven by social and cultural norms regarding attitudes toward prescribing practices in high-income countries (1). Embedding judicious and cautious practices as normative values should therefore be the mainstay of antimicrobial policy. This should presumably also be applied in LMICs to curb the increasing antimicrobial consumption here. People that previously did not have access to, or could afford, antimicrobial therapy, now face cephalosporins, fluoroquinolones and carbapenems sold over the counter without a documented clinical need (22).

In a large multicenter study from the United States, a study group that focused on antimicrobial prescribing to hospitalized patients, found that major improvements in the prescribing were possible to 37 % of included patients (23). Furthermore, a model that estimated effects on a 30 % reduction in the consumption of broad-spectrum antimicrobial therapy, returned a 26 % reduction in *Clostridioides difficile* incidents. From

earlier, multiple studies mostly performed in the United States, led the Infectious Diseases Society of America (IDSA) in late 1980s to disclose that antimicrobial agents were used inappropriately in over 50 % of cases (24).

An analysis from the Organization for Economic Co-operation and Development (OECD) suggests that up to 75 % of antimicrobial prescriptions to residents in long term care facilities are inappropriate when assessing the need for antimicrobial therapy, duration, and choice of antimicrobial agent (7). Moreover, up to 95 % of antimicrobial therapy prescribed in these settings are initiated without laboratory or diagnostic testing. The report also encompasses the challenges that overuse, and misuse of antimicrobial therapy pose to antimicrobial resistance (AMR) in long term care facilities.

In Norway, studies on overuse or misuse of antimicrobial therapy are scarce. However, a few studies have reported results on various interventions to promote judicious and rational antimicrobial therapy. In a multicenter, cluster-randomized controlled intervention study, audit with feedback and academic detailing were implemented to infectious diseases-, pulmonary- and gastroenterology specialists (25). Overall adherence to national guidelines increased from 60 % to 66 %, which did not reach statistical significance when compared with the control group. Within the pulmonary ward, a significant 30 % increase in use of Penicillin G to treat community-acquired pneumonia and infectious COPD exacerbations was reported. Overall broad-spectrum antimicrobial therapy was significantly reduced at 12- and 18-months post intervention, but within the gastroenterology ward, it increased again from 7 months.

At a local hospital in Norway with a general medical and surgical ward, we have previously reported in a prospective, observational study that the use of ciprofloxacin on 92 % of occasions was non-adherent to clinical practice guideline recommendations (26). We have also previously reported in a prospective, intervention study that unnecessary intravenous antimicrobial therapy days were significantly reduced from 83 % to 48 % after a campaign that focused on adherence to revised guideline recommendations in a general medical ward (27). In that study, the reduction of unnecessary intravenous antimicrobial therapy days also significantly affected length of hospital stay, which was reduced from 7.0 to 6.3 days.

In the ReAct group, an internationally independent global network group dedicated to combat AMR, it is stated that large variations in antimicrobial consumptions among countries are due to socioeconomic factors, cultural differences, financial incentives, fear of lawsuits, and the lack of treatment guidelines (28). A thorough review from Scandinavian authors in 2019, pointed out multiple reasons for what was termed irrational use of antimicrobial therapy in Europe (29). Patient-related drivers for irrational

antimicrobial usage were lack of public knowledge and awareness about AMR, access to antimicrobial therapy without prescription, and access to leftover packages. Physician-related drivers were inadequate knowledge, attitudes and perception of prescribing, pharmaceutical promotion, and various patient-doctor interactions. Laboratory-related drivers were lack of rapid and sufficient diagnostic testing.

Antimicrobial resistance

The World Health Organization reported in 2014 an alarming rate of AMR in commonly encountered bacteria in community- and hospital-acquired infections, to multiple classes of antimicrobial agents. The Antimicrobial Resistance Global Report on Surveillance concluded that AMR is an increasingly serious threat to global public health, a problem that is so serious that it threatens the achievements of modern medicine. The report also forecasts that a post-antibiotic era, in which common infections and minor injuries can kill, is a real possibility (30).

In Europe, prevalence of AMR in frequently encountered bacteria is reported annually by the European Centre of Disease Prevention and Control (ECDC) in cooperation with WHO Regional Office for Europe (31). Proportions of clinically relevant pathogens with AMR are also visually available from the online atlas surveillance tool. AMR trends in Europe are of great concern, as AMR is increasing and widespread. The 2020 report also concludes that effectively tackling AMR requires greater efforts and investments. Policymakers, health professionals, patients and governmental and non-governmental organizations have a role to play in addressing the public health threat of AMR.

Figure 1. Proportions of Escherichia coli (left) and Klebsiella pneumoniae (right) that are reported resistant to third-generation cephalosporins in European countries in 2021.
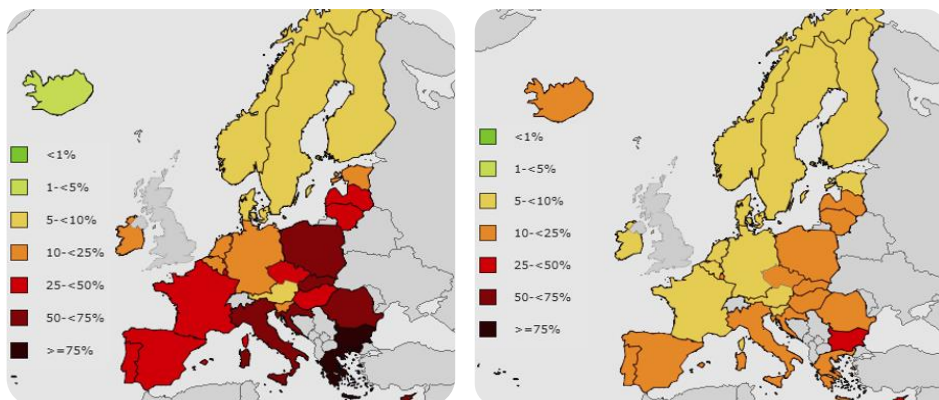
The burden of AMR demonstrates serious challenges in Europe. Estimations on morbidity and mortality showed that in 2015 over 670.000 infections occurred due to AMR pathogens, and that approximately 33.000 individuals died as a direct consequence of these infections. In addition, the estimated quality of life for patients that contracted AMR infections was demonstrated to be poor. Disability-adjusted life-years (DALYs) in these patients were comparable to that of patients suffering from malignant cancer (32). Healthcare costs because of AMR infections in European countries combined are believed to exceed 1.1 billion euro annually between 2015 and 2050, if no effective actions are implemented and if AMR development follow the projected trends (7, 33). Much of the estimated expenditures are due to longer hospital stays, slower recovery rates, and higher risk of complications, which all contribute to an estimated 570 million more hospital days within 2050.

The magnitude and the increasing rate of AMR-related infections across the world have recognized the need for coordinated actions. In a global action plan on antimicrobial resistance from the WHO in 2015, five objectives to combat AMR were outlined (34):

1. Improve awareness and understanding through effective communication, education, and training.
2. Strengthen the knowledge and evidence base through surveillance and research.
3. Reduce the incidence of infection through effective sanitation, hygiene, and infection prevention measures.
4. Optimize use of antimicrobial medicines in human and animal health.
5. Develop the economic case for sustainable investment in all countries to increase investments in new medicines, diagnostic tools, vaccines, and other interventions.

In Europe, the Organization for Economic Cooperation and Development (OCDC), the European Centre of Disease Prevention and Control (ECDC), the European Food and Safety Agency (EFSA), and the European Medicines Agency (EMA) have issued a One Health response action plan in 2022. This plan focusses on top priorities from national action plans on AMR from various European countries, that include the evaluation and monitoring of the implementation of national AMR action plans, the integrated and expanded AMR surveillance in bacteria from humans, animals and the environment, and the investment in effective cost-saving interventions, such as antimicrobial stewardship programs, and infection prevention and control measures (7).

Relationship between antimicrobial consumption and resistance
The impact of antimicrobial consumption on the emergence of antimicrobial resistance is particularly important, yet complex to delineate. Observational data suggest significant correlations (35).

In a European surveillance study from 1998 to 1999, a study group aimed to investigate the relationship between proportions of penicillin non-susceptible (PNSP) invasive *Streptococcus pneumoniae* isolates, and sales data for β-lactam and macrolide antimicrobial therapy directed against that microbe (36). A regression model that included data from eleven countries, demonstrated a linear relationship between β-lactam and macrolide consumption and the proportion of PNSP. The authors concluded that AMR was correlated with the use of β-lactams and macrolides, and that extended, prospective surveillance was warranted. In addition, several studies have previously demonstrated that proportions of PNSP could be halted (37) or even reversed (38), if antimicrobial therapy were prescribed judiciously and rationally.

In a British-Icelandic study, the investigators used population genetic methods and epidemiological observations to assess the influence of the selective pressure imposed by antimicrobial therapy volume on the temporal changes in AMR (39). The authors concluded that the time scale for emergence of AMR under a constant selective pressure was typically much shorter than the decay time after cessation of or decline in antimicrobial therapy volume. In addition, significant reduction in AMR required equally significant reductions in antimicrobial consumption. This was also demonstrated in a Finnish study, where nationwide macrolide-resistance in *Streptococcus pyogenes* declined from 20 % to less than 10 % in a campaign to withhold macrolides (40).

A joint study group from several European countries reported the relationship between in-hospital antimicrobial consumption volumes and AMR rates for four epidemiologically significant pathogens causing bloodstream infections (41). The pathogens investigated were *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. They concluded that the increased consumptions of multiple antimicrobial agents each were positively associated with AMR development.

Increased antimicrobial consumptions have also been associated with increased rates of MDR pathogens. In a recent retrospective, single-center study from Malaysia, antimicrobial therapy and broad-spectrum antimicrobial therapy increased from 2018 to 2020 by 39 % and 38 %, respectively (42). In that same period, relative MRSA and ESBL infection rates increased significantly. The use of extended-spectrum cephalosporins and fluoroquinolones was positively correlated with the emergence of MRSA, ESBL and MDR *Acinetobacter baumannii* resistance.

In a large surveillance study from Germany comprising over 170.000 bacterial isolates sampled within 64 intensive care units, consumption data were analyzed with data on AMR (43). From 2001 to 2011 total antimicrobial consumption increased by 15 %, and carbapenems, fluoroquinolones, glycopeptides and third generation cephalosporins

increased by 184 %, 20 %, 47 % and 11 %, respectively. In that same timespan, *Escherichia coli* ESBL increased from 1.3 % to 16.7%, and *Klebsiella pneumoniae* ESBL from 4.5 % to 20.3 %. Proportions of imipenem-resistant *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and Klebsiella pneumoniae, third-generation cephalosporin-resistant and fluoroquinolone-resistant *Escherichia coli* and *Klebsiella pneumoniae* also increased significantly.

In western China, a study group reported in a retrospective, descriptive analysis that from 2014 to 2016 there was a significant association between resistance density of *Klebsiella pneumoniae* ESBL and the use of β-lactam-β-lactamase inhibitor combinations, fluoroquinolones, and carbapenems (44). For *Escherichia coli* ESBL, a particularly strong correlation was evident for only the use of β-lactam-β-lactamase inhibitor combinations. Similar correlations were elucidated between carbapenem-resistant *Pseudomonas aeruginosa* and the use of carbapenems and quinolones.

Interestingly, the opposite effect was reported in an experimental simulation study from the United States (45). By using literature inputs, the study group simulated interactions between patients and healthcare workers at various levels of antimicrobial consumptions within an intensive care unit. If absolute antimicrobial consumptions were reduced by 10 % or 25 %, they estimated a significant reduction in prevalence of MDR pathogens by 11 % and 28 %, respectively.

Antimicrobial stewardship

In medical history, the term antimicrobial stewardship is novel and imaginative. The term is not easily translated to all languages. On the other hand, strategies to raise awareness and precautions on antimicrobial prescriptions have existed as long as antimicrobial therapy has been available.

Around 2005, workgroups from the United States published papers to address measures to combat the increasing threat of AMR. (46, 47). Later, position papers and detailed descriptions from major organizations appeared.

- The Association for Professionals in Infection Control and Epidemiology (APIC) and Society for Healthcare Epidemiology of America (SHEA): **Antimicrobial stewardship** is an inter-professional effort and involves optimal, prudent antimicrobial use for patients across the continuum of care: acute, inpatient, long-term care, and outpatient setting (48).
- Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): The primary goal of **antimicrobial stewardship** is to optimize clinical outcomes while minimizing unintended consequences of

antimicrobial use, including toxicity, the selection of pathogenic organisms, and the emergence of resistance (49).

- European Centre for Disease Prevention and Control (ECDC) and National Institute for Health and Care Excellence (NICE): **Antimicrobial stewardship** embodies an organizational or healthcare-wide approach to promoting and monitoring judicious use of antimicrobials to preserve their future effectiveness (50, 51).
- Centre for Disease Control and Prevention (CDC): **Antibiotic stewardship** is the effort to measure and improve how antibiotics are prescribed by clinicians and used by patients (52).

Successful antimicrobial stewardship relies heavily on hospital infrastructure facilities. Among these are hospital leadership commitment, department accountability, pharmacy expertise, prescription tracking systems, reporting systems, and educational programs (52).

Key interventions that are promoted in antimicrobial stewardship programs for hospitals are multifaceted (52). A prerequisite is that both hospital leaders, clinical physicians, microbiologists, pharmacists, and nurses should recognize that stewardship actions are intrinsically needed. Key interventions should incorporate prospective audit with feedback, restrictions, preauthorization, and facility-specific treatment recommendations. Many other actions may also improve antimicrobial consumption but should not be a substitute for the abovementioned core elements.

Clinical practice guidelines for antimicrobial therapy

Updated and easily available clinical practice guideline recommendations for empirical antimicrobial therapy in infections are endorsed by most professional organizations (49). Recommendations in hospital settings should especially target frequently encountered clinical syndromes such as infections in the upper and lower respiratory tract, urinary tract, bloodstream, intraabdominal organs, and skin- and soft tissues.

In clinical studies, interventions that seek to optimize empirical antimicrobial therapy to be compliant with clinical practice guideline recommendations, have turned out successful in terms of clinical outcomes, adverse events, costs, and AMR, according to a systematic review and meta-analysis (53).

Specific treatment guidelines can also greatly enhance the effectiveness of prospective audit and feedback, and preauthorization by offering clear-cut recommendations for optimal use in hospital settings. This applies to both clinical infections and as well to surgical prophylaxis. It also applies to circumstances where computer-based decision tools are available.

In Norway, clinical practice guideline recommendations for antimicrobial therapy have functioned at a national level since 2014 for hospital settings. Central health authorities have later provided funding for a comprehensive revision through 2020 to 2022. The guideline is highlighted as pivotal for the preservation of low AMR prevalence in the annual AMR-report (8). The recommendations are heavily utilized in everyday clinical practice among physicians according to user data, although rigorous studies on compliance are lacking.

Aims

The overall aim of this doctoral thesis was to collect qualitative data on antimicrobial therapy to key infections within hospital settings, and to build evidence for augmented antimicrobial stewardship in settings with low overall antimicrobial consumption and resistance. In such settings, the documented rationale for antimicrobial therapy should preferably compare to those in high-consumption and high-prevalence settings. However, there is a profound lack of high-quality studies that address qualitative aspects of both diagnostic assessments and antimicrobial therapy to commonly encountered infections in Norway.

Another aim was to provide support for the implementation of, and the judicious use of existing clinical practice guideline recommendations to safeguard the sound and rational use of antimicrobial therapy. Clinical practice guideline recommendations in Norway have traditionally relied on evidence-based international literature, decades of clinical practice, and national AMR prevalence among pathogenic bacteria. We hypothesized that guideline adherence generally was safe and at reasonable levels. We therefore wanted to explore patient outcomes when adherence and non-adherence were compared.

We conducted four observational studies of which two also contained interventional designs for the microbiological confirmation and the antimicrobial therapy for CAP. The latter two studies focused on adherence to clinical practice guideline recommendations in BSIs. All studies were conducted with the aim to bring forth bedside, clinically relevant diagnostic problems and therapeutic decisions to commonly encountered infections at hospitals.

I the first CAP-study, we aimed to increase proportions that were microbiologically confirmed by a multifaceted intervention in the emergency room setting at hospital admittance. In the second CAP-study, we aimed to increase proportions of patients that received first-line antimicrobial therapy over a six-year longitudinal intervention.

In the two BSI-studies, we aimed to investigate proportions that received optimal, concordant antimicrobial therapy, within the ICU and at general ward settings.

Qualitative data and strengthened knowledge about key infections in hospitals are essential for improvement of management. The work submitted may contribute to addressing unmet needs, in terms of strengthened antimicrobial stewardship efforts.

Materials and methods

Overview

All four studies were conducted over 6 years from 2017, and all were planned, initiated, managed, and completed by the study group at the Norwegian University of Science and Technology (NTNU) and St. Olavs University Hospital, Trondheim. A study group was organized and administered by the doctoral student.

All studies that were undertaken sought to explore diagnostic and antimicrobial aspects of key infections managed in the hospital setting. The figure below gives an overview of studies and papers, with corresponding titles and the number of scientific hypotheses that each study was designed to explore.

Study (paper)	Title	Number of scientific hypotheses investigated
I	Diagnostic stewardship aiming at expectorated or induced sputum promotes microbial diagnosis in community-acquired pneumonia	3
II	Antimicrobial therapy for community-acquired pneumonia during stewardship efforts and a coronavirus pandemic: An observational study	5
III	High levels of discordant antimicrobial therapy in hospital-acquired bloodstream infections is associated with increased mortality in an intensive care, low antimicrobial resistance setting	5
IV	Empirical antimicrobial therapy for bloodstream infections not compliant with guidelines was associated with discordant therapy, which predicted poorer outcome even in a low resistance environment	4

Methods applied

Data on antimicrobial consumption is largely available from national databases as whole sales from hospital pharmacies to hospital trusts (54). Antimicrobial storage of generic substances at hospital wards is marginal and the amount of discarded, expired or returned substances are also marginal. This means that data on antimicrobial consumption from these sources could reliably estimate consumption, quantitatively. However, they do not necessarily mirror actual administered doses. Most importantly, they do certainly not contain qualitative data.

Data on the prevalence of antimicrobial resistance is also available through national databases and annual reports at a country and county level (8). Specific prevalence data for individual hospitals are not routinely available in Norway.

To provide qualitative data on diagnostic performance and administered antimicrobial therapy, we therefore needed to conduct a series of observational studies. This allowed for the collection of multiple variables that could emphasize qualitative data. By these methods, we patiently and judiciously included thousands of eligible patients from key infection groups admitted to our own hospital wards. This granted us an opportunity to gain valuable information on diagnostic and therapeutic performance. The studies are therefore clinically relevant, conducted at a ward level, close to all included patients, and close to the point of bedside decision-making.

Of particular interest were diagnostic and therapeutic aspects of key infections that represent major patient groups normally managed in hospitals. Of these were community-acquired pneumonia (CAP) and bloodstream infections (BSIs). We hypothesized that both diagnostic and therapeutic aspects could be modified by modest diagnostic and antimicrobial stewardship measures.

We undertook four cohort observational studies throughout the study period. Study I and II also included the implementation of a diagnostic and an antimicrobial intervention, which allowed for a classical before-and-after comparison.

All studies were performed using a retrospective model for collecting and registration of data.

Study populations
We chose to investigate two quantitatively large patient groups normally managed as in-patients, namely CAP, and BSIs.

- **Study I (Expectorated or induced sputum in CAP)**
    - Included episodes (n = 1.280) were patients aged above 18 years that had received a diagnosis and in-hospital medical therapy for CAP, and for that stay had CAP ascribed as a primary diagnosis to the discharge letter. Months from March through May in 2016 until 2018 were included, and only to departments of medicine, pulmonology, and intensive care unit. The intervention was launched within the university hospital only, and five other local hospitals were used for comparison.
    - Exclusions constituted nosocomial pneumonias, CAP complicated with secondary nosocomial infections during the treatment course, readmissions within 30 days, and pneumonia as secondary diagnosis.

- **Study II (Antimicrobial therapy for CAP over six years)**
    - Included episodes (n = 1.112) were CAP-episodes that were hospitalized between months of March through May for six consecutive years from 2016 through 2021. Criteria for identification were ICD-10 J13 to J18.9 as a primary diagnosis on discharge letters. Only the departments of medicine, pulmonology or intensive care unit were eligible.
    - Excluded cases constituted all episodes of ventilator-associated pneumonias, pneumonia in nursing home residents, in the returned traveler, in the immunocompromised patient, in patients diagnosed with chronic obstructive pulmonary disease, and in lower respiratory tract infections other than pneumonia. We also excluded cases if length of stay exceeded 28 days.
- **Study III (Bloodstream infection in the ICU)**
    - Included BSI episodes (n = 270) were adult patients >16 years admitted to the ICU where blood cultures grew one or more pathogenic microbes combined with clinical evidence of systemic infection. We used an in-house administrative system to identify eligible BSI episodes between January 2014 until December 2018.
    - Exclusions were made for bacteria that were regarded as blood culture contaminants, fungal growth, and cases lost to follow-up.
- **Study IV (Bloodstream infections in general wards over one year)**
    - Included episodes were patients with a laboratory confirmed culture-positive BSI, retrieved from an in-house laboratory administrative system. All included BSI episodes (n = 756) were aged 18 or above and admitted to St Olavs hospital between January through December 2019.
    - Exclusions constituted episodes with false positive cultures, typically contaminants like coagulase-positive staphylococci, *Corynebacterium* sp, and *Bacillus cereus*, and episodes of fungal growth. Cases lost to follow-up were also excluded.

All studies included adult patients aged above 16 or 18 years of age that were admitted to a regular hospital stay for at least 24 hours. Eligible patients were identified using selected search criteria within an in-hospital administrative database. We chose ICD-10 diagnostic codes as prerequisites for identification of targeted patient groups.

Multiple exclusion criteria were applied to minimize patient bias.

For study I, we also included community-acquired pneumonia patients from five other local hospitals in the region, to establish comparison against the interventional site.

Data collection and handling

Once the study populations were identified, the study group undertook multiple steps to collect, verify and secure patient data. In the studies provided, we uniformly used retrospective methodology to collect data variables. All variables were collected and recorded in dedicated data software systems, mostly Microsoft Excel and Statistical Package for the Social Sciences. All files contained anonymized data, using a personalized password code for the correct identification of included patients.

In case of unverified registered content within the files, the study group jointly decided the next steps.

All files were stored at protected hospital servers located in the hospital area. The study group performed and produced all elements of study I-IV at location using authenticated hospital software and hardware.

Definitions

Terminology, definitions, and examples for appropriate antimicrobial prescribing was proposed in 2016 (10).

- **Unnecessary prescriptions** refer to situations where antimicrobial agents are used for non-infectious syndromes, non-bacterial infections, therapy beyond the indicated duration, redundant therapy, and the continuation of broad-spectrum antimicrobial therapy when cultures have grown pathogens that are sensitive to narrow-spectrum agents.
- **Inappropriate prescriptions** refer to situations where the causative infecting pathogen is resistant to the antimicrobial prescribed, or in situations where antimicrobial prescribing disobeys unequivocal clinical practice guideline recommendations.
- **Suboptimal prescriptions** refer to situations where antimicrobial agents in the setting of established infection can be improved either by drug dosing, drug route, or drug choice.

In the studies provided by our group, we implemented these terminology and definitions. We also used the following definitions for concordant and discordant antimicrobial therapy.

- **Concordant antimicrobial therapy** referred to circumstances where the recovered pathogen was susceptible to the antimicrobial regimen as demonstrated by in vitro susceptibility tests.

- **Discordant antimicrobial therapy** referred to circumstances where the recovered pathogen was non-susceptible to the antimicrobial regimen as demonstrated by in vitro susceptibility tests or intrinsic (natural occurring) resistance to that regimen.

Statistical analyses

In the studies provided, we uniformly used retrospective methodology to collect data variables. In the context of observational studies, descriptive statistics were used to analyze and display all inclusions, groups, and subgroups.

To further analyze and answer specific scientific questions we used different statistical approaches that are summarized below.

Study I

Diagnostic stewardship aiming at expectorated or induced sputum promotes microbial diagnosis in community-acquired pneumonia.

Investigations undertaken	Statistical analyzes applied
Do study populations differ between years?	Descriptive statistics.
Can increased numbers of patients undergoing expectorate/induced sputum be achieved?	Pearson Chi square association model.
Can increased diagnostic yield be achieved?	Pearson Chi square association model.

Study II

Antimicrobial therapy for community-acquired pneumonia during stewardship efforts and a coronavirus pandemic: An observational study.

Investigations undertaken	Statistical analyzes applied
Does the study population differ between years?	Descriptive statistics.
Does an increase in proportions that received preferred antimicrobial therapy exist?	Pearson Chi square association model.
Does a decrease in proportions that received broad-spectrum antimicrobial therapy exist?	Pearson Chi square association model.
Does an increase in microbiologically confirmed cases exist?	Pearson Chi square association model.
Does therapy duration differ between years?	One-way ANOVA comparison

Study III

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

Investigations undertaken	Statistical analyzes applied
Do study populations differ between groups?	Descriptive statistics.

Do differences in proportions that received discordant antimicrobial therapy exist between CA- or HA-BSI in the ICU?	Pearson Chi square association model.
Does mortality differ between CA- or HA-BSI in the ICU exist?	Pearson Chi square association model.
What are predictors of discordant antimicrobial therapy in the ICU?	Logistic regression model.

Study IV

Empirical antimicrobial therapy for bloodstream infections not compliant with guidelines was associated with discordant therapy, which predicted poorer outcome in a low resistance environment.

Investigations undertaken	Statistical analyzes applied
What are characteristics of the study population?	Descriptive statistics.
Is there an association between adherence to guideline recommendations and concordant antimicrobial therapy?	Fisher association model.
What are predictors for discordant antimicrobial therapy?	Logistic regression model.
Is there an association between discordant antimicrobial therapy and mortality?	Log-rank test for overall difference in survival.
What are predictors for mortality?	Logistic regression model.

Ethical considerations

All studies were conducted according to study protocols, which were approved by the Regional Committees for Medical and Health Research Ethics, Norwegian University of Science and Technology. The approval of study I and II is covered by the same decision, as study II is an elongation of study I. All studies were also approved by data protection officials and the hospital administration.

The studies were conducted in accordance with the principles of the Declaration of Helsinki, and the guidelines for medical and health research from The Norwegian National Ethics Committee.

Study III and IV were conducted with informed consent and the option to withdraw from the study to all patients. In accordance with the approval, we were not obliged to obtain consent for participation in study I and II, and consent for publication for any study.

We collected, handled, and stored all patient data on secure servers. To preserve patient confidentiality, all patient data were anonymized using a transfer key between files. All data was, and will be, kept for preservation according to data regulations.

Results: Summary of papers

Paper I

Diagnostic stewardship aiming at expectorated or induced sputum promotes microbial diagnosis in community-acquired pneumonia

In this study, we recognized the fact that community-acquired pneumonia (CAP) is a frequent infection leading to hospital admittance, and that antimicrobial therapy is linked to the frequently missing microbiological confirmations. Despite efforts to clarify that respiratory tract secretions are warranted for microbiological analyzes for all patients hospitalized for CAP, sampling numbers remain low. On the other hand, sampling from the upper respiratory tract is common in certain countries, but its diagnostic yield is hampered because of low sensitivity.

We therefore conducted an intervention at the emergency room level targeting microbiological approach for suspected CAP from 2016 through 2018. The intervention was aimed at upscaling numbers and quality of respiratory tract secretions sampled from the lower respiratory tract. We used the online material library and recommendations from the European Respiratory Society to tailor the intervention strategy. The intervention was launched at the emergency room level at a tertiary care, teaching university hospital, with multiple educational sessions to on-call physicians and emergency room nurses. Five other local hospitals were used for comparison. Data were collected retrospectively between each study year, the first prior to the intervention, the second and third year, after the intervention. We then used simple descriptive statistics to delineate patient characteristics, microbiological strategies, aetiology, and antimicrobial therapy.

We included 1.280 hospitalized CAP cases that altogether delivered 1.444 respiratory samples. Patient characteristics did not differ among study years and locations. At the intervention site, sampling numbers rose already early in the first intervention year and expectorated or induced sputum numbers increased significantly (Pearson Chi square statistic value 5; 9.807, n = 425, p = 0.007). The diagnostic yield from these samples also increased significantly (Pearson Chi square statistic value 3; 3.888, n = 114, p = 0.0486). By the end of the intervention, the diagnostic yield of expectorated or induced sputum had increased from 41.2 % to 62.0 %. For the whole cohort, microbiologically confirmed CAP-episodes constituted 29.1 %

We therefore concluded that the targeted diagnostic intervention turned out successful in terms of increased numbers of and diagnostic yield from expectorated or induced sputum

for the CAP population. Samples from the lower respiratory tract outperformed other sampling sites.

Figure 2. Diagnostic yield from expectorated or induced sputum in community-acquired pneumonia pre-intervention (2016) and post-intervention (2017 and 2018).
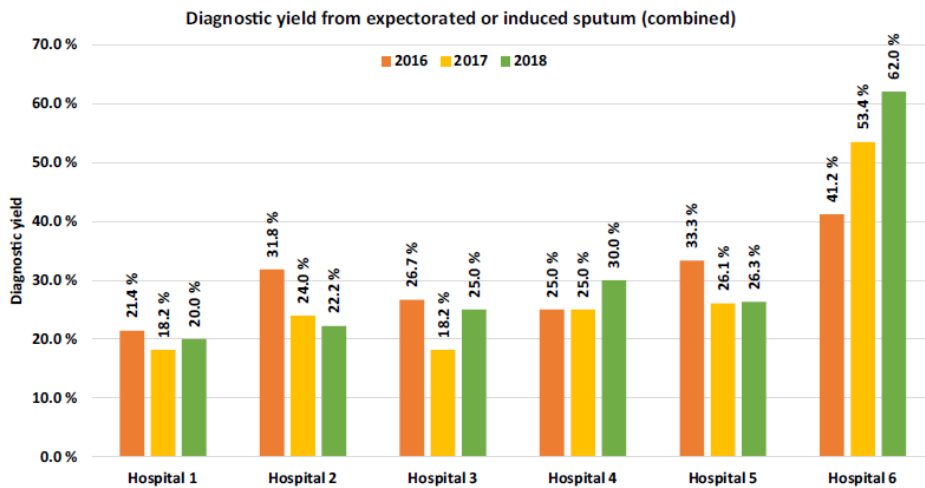
Paper II

Antimicrobial therapy for community-acquired pneumonia during stewardship efforts and a coronavirus pandemic: An observational study.

In this study, we undertook further investigations on the empirical therapy for community-acquired pneumonia (CAP) for six consecutive years, which incorporated considerable efforts to optimize administered therapy according to clinical practice guideline recommendations. It also included therapy for CAP during a coronavirus pandemic.

A dedicated antibiotic team pointed out hospitalized CAP among adults as a potential target for antimicrobial stewardship measures at a 1.000 bed, tertiary care, teaching university hospital. The aim was to increase adherence to national clinical practice guideline recommendations through multiple steps in the emergency room setting. This intervention included repeated tutoring sessions for assessments of disease severity, respiratory tract sampling, the timely administration of empirical antimicrobial therapy, selection of empirical regimens, de-escalation strategies, targeted antimicrobial therapy, oral regimen conversion, and the overall therapy duration. The primary endpoint was

proportions that received narrow-spectrum β-lactams, and broad-spectrum antimicrobial therapy. We collected all data retrospectively and used selected months from 2016 – 2021 in the analysis.

The investigation identified 1.112 eligible CAP episodes from six consecutive years. Annual proportions that received narrow-spectrum β-lactams increased significantly from 56.1 % to 74.4 % (Pearson Chi square 17.3, df 5, p = 0.004), and correspondingly proportions that received broad-spectrum antimicrobial therapy decreased from 34.1 % to 17.1 % (Pearson Chi square 19.4, df 5, p = 0.002), a relative reduction of 49.9 %. Mortality and 30-day readmission rates remained unchanged. Trends were heavily affected during the first coronavirus pandemic year, as cefotaxime was commonly administered. Furthermore, microbiologically confirmed cases increased significantly from 33.7 % to 56.2 % during the study period. De-escalation strategies were frequently unutilized as broad-spectrum antimicrobial therapy was continued to 66.4 % of included cases despite microbiologically confirmation and a susceptibility-test that proved that narrow-spectrum β-lactams were effective. Mean overall therapy duration was 11.0 days (95 % CI 10.9 - 11.1), which exceeded clinical practice guideline recommendations substantially.

We therefore concluded that empirical antimicrobial therapy for adult, hospitalized CAP is modifiable through continuous, yet modest efforts, and that CAP is a suitable model condition that is sensitive for stewardship measures.

Figure 3. Proportions of empirical antimicrobial regimens for community-acquired pneumonia pre-intervention (2016), and post-intervention 2017-2021).
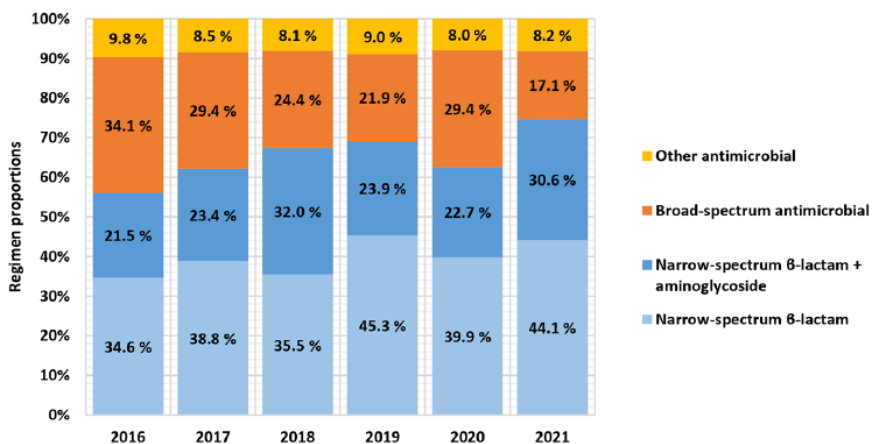
High levels of discordant antimicrobial therapy in hospital-acquired bloodstream infections is associated with increased mortality in an intensive care, low antimicrobial resistance setting

In this study, we focused on the initially administered antimicrobial therapy to culture-positive BSIs in the ICU setting at a tertiary care, teaching university hospital with low rates of AMR in the environment.

We used a retrospective, observational study design and collected data from admissions from 2014 through 2018. Data on BSI episodes were retrospectively collected and analyzed before inclusion. Descriptive statistics were used to delineate included BSI episodes, and an association model to calculate statistical differences between community- (CA) and hospital-acquired (HA) episodes, and a logistic regression model to predict factors associated with discordant antimicrobial therapy.

A total of 270 BSI episodes that conveyed 296 bacterial isolates were included from 2014 through 2018, of which 5.9 % conferred extended spectrum β-lactamase properties (ESBL). Of included BSI episodes 145 (49.0 %) were Gram-negative, and 134 (45.3 %) were Gram-positive isolates. Monomicrobial infections constituted 92.2 % of BSI episodes. Concordant empirical antimicrobial therapy on day 0, 1, 2, 3, and 3-9 for community-acquired BSIs increased steadily from 88.0 %, 91.6 %, 94.7 %, 95.2 %, and 96.4 %, respectively. For hospital-acquired BSIs the corresponding rates of concordant therapy were 65.1 %, 74.7 %, 83.5 %, 87.0 %, and 89.3 %, respectively. For all days in the therapy course, an association model provided statistically significant differences in concordant therapy among community- or hospital acquired BSIs (Pearson Chi square, p = 0.0003). Discordant therapy for hospital-acquired BSI was significantly associated with mortality on day 28 (Pearson Chi square 3.884, p = 0.049). The estimated relative risk of mortality on day 28 for hospital-acquired BSIs that received discordant antimicrobial therapy was 1.64 (95 % CI 1.01 - 2.64). The same associations could not be established for community-acquired BSIs. A multivariate logistic regression model predicted that hospital-acquired BSI, enterococcal BSI, and BSI from an intraabdominal origin were significantly associated with discordant antimicrobial therapy. Based on cultures and antimicrobial susceptibility tests, we concluded that antimicrobial de-escalation strategies were feasible in 71.9 % of included BSI episodes. However, actual performed de-escalation was noted only in 13.9 % of eligible cases.

The study led us to conclude that discordant empirical antimicrobial therapy was frequent among hospital-acquired BSI episodes, and that mortality may be affected by this. Efforts to minimize discordant therapy need attention in the ICU setting. Clinical practice

guideline recommendations that clearly differ between acquisition conditions are warranted.

Figure 4. Coverage of empirical antimicrobial regimens in bloodstream infections managed in the intensive care unit according to in vitro susceptibility testing.
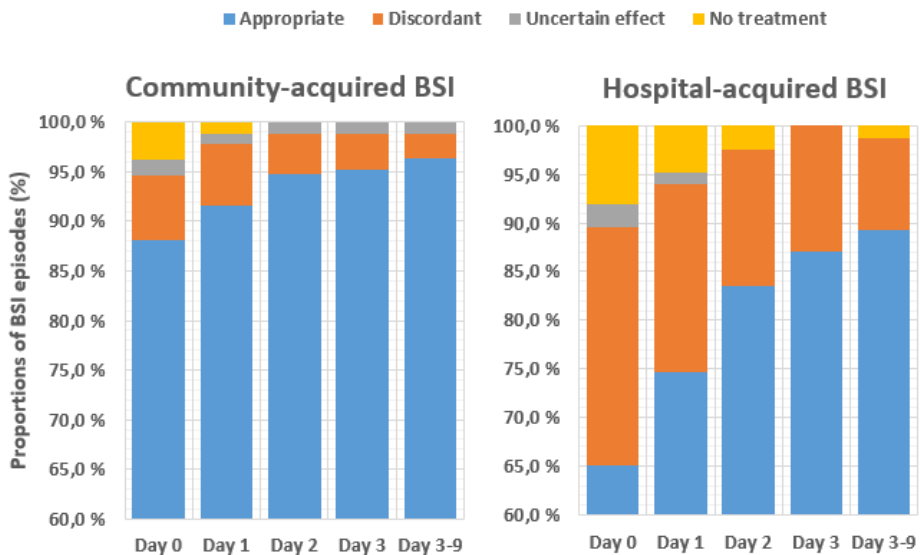
Paper IV

Empirical antimicrobial therapy for bloodstream infections not compliant with guidelines was associated with discordant therapy, which predicted poorer outcome even in a low resistance environment.

In this study, we focused on all unselected, consecutive bloodstream infections (BSI) throughout one calendar year in 2019 at a tertiary care, teaching university hospital. Included cases were mostly managed outside of intensive care settings. The aim was to characterize the appropriateness of empirical antimicrobial therapy, adherence to national clinical practice guideline recommendations, de-escalation practices, and mortality.

We applied a retrospective, observational model to assess all identified, culture-positive BSI episodes among hospitalized adults throughout 2019.

The study cohort constituted 694 unique patients with 756 identified BSI episodes, of which *Escherichia coli* and *Staphylococcus aureus* constituted 35.6 % and 17.1 % of episodes, respectively. Empirical antimicrobial therapy was guideline-adherent in 536 (70.9 %). In 190 (25.1 %) of cases, other non-adherent regimens were initiated. In BSI episodes that received guideline-adherent therapy, the proportions that evidently turned out concordant or discordant were 85.5 % and 14.2 %, respectively. Of BSI episodes that received non-adherent therapy, the corresponding proportions were 73.7 % and 26.3 %, respectively. An association model returned a statistically significant association between guideline-adherent and concordant empirical antimicrobial therapy (Fisher exact test, p = 0.001). De-escalation of antimicrobial therapy was feasible, but unutilized, in 31.1 % of BSI episodes. In a multivariate logistic regression model, independent predictors of discordant empirical antimicrobial therapy were surgical department, type of empirical regimen, bacterial species, and AMR phenotype. Of notice, a regime consisting of a third-generation cephalosporin returned a ten-fold increased risk of discordant therapy (Odds ratio 9.91, 95 % CI 3.8 - 26.2), as compared to narrow-spectrum β-lactam in combination with an aminoglycoside. Furthermore, independent predictors of intra-hospital mortality were coverage of the empirical regimen, co-morbidities, disease severity, site of infection, and type of empirical regimen. Both intra-hospital and long-term unadjusted all-cause mortality were increased for BSI episodes that received discordant empirical antimicrobial therapy (Log-rank test, p = 0.001).

The study led us to conclude that the initiation of empirical antimicrobial therapy for BSI should preferably rely on national clinical practice guideline recommendations, as this increased the likelihood of receiving concordant therapy.

Figure 5. Association between compliance with clinical practice guideline recommendations and concordant versus discordant antimicrobial therapy.
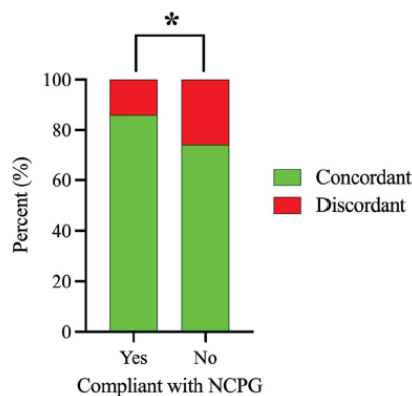
Discussion

Through the studies, we have reported several performance data on both diagnostic procedures (55) and antimicrobial prescribing (56) for CAP. In addition, we have reported antimicrobial prescribing for BSIs within the intensive care unit (57) and at a ward level (58).

All studies extend much needed qualitative data on the management of frequently encountered infections at a teaching university hospital in Norway. Importantly, all studies were conducted in close proximity to bedside decision-making physicians at a clinical ward level.

Through these studies, we aimed to contribute with data that could facilitate antimicrobial stewardship, and to bring extra validity to clinical practice guideline recommendations for antimicrobial therapy. The results that are here described offer knowledge on both inappropriate, unnecessary, and suboptimal use of antimicrobial therapy, in a low consumption and low AMR setting. The findings were expected, but data on the magnitude and range of such findings are not frequently reported.

We have also reported important circumstances that underscore that antimicrobial therapy prescribing in line with guideline recommendations provides favorable outcomes for key infections. Lastly, we have issued evidence to support continued antimicrobial stewardship efforts in hospital settings.

Methodological considerations

All studies conducted were observational studies, and all data were collected by retrospective methods. Several limitations apply to these circumstances, both in terms of internal and external validity (59). This is discussed in the following chapters. For all studies, we used the validated STROBE checklist to conduct and publish study results (60). Observational studies are valuable for establishing statistical associations between variables, and to a much lesser extent causality.

Selection bias

Observational cohort studies are prone to selection bias and thereby imperfect external validity. In our studies, we included cases based on primary diagnosis at discharge. However, a wide array of exclusion criteria were applied to diminish cohort heterogeneity and thereby selection bias. Results might have influenced if episodes of CAP or BSI as secondary diagnoses at discharge letters had been included. For especially complex cases, selection bias might also have influenced on results.

Observational studies are also susceptible to loss to follow-up of included cases, although to our experience, this was not evident to more than 1 % of included cases in our cohorts.

Confounding factors

Confounding factors refer to circumstances in which the effects of an exposure are mixed with the effects of an additional factor or a set of factors. The observed results may thereby be a distortion of the true relationship, and yield differences in outcomes that occur because of differences in the baseline risks of the comparison groups. Selection bias may lead to confounding, especially for observational and interventional studies (59).

In our CAP diagnostic-study, selection bias may have contributed to confounding, as individual patients likely were unevenly motivated and instructed to undergo expectorated or induced sputum.

In the CAP therapy-study, selection bias may also have contributed to confounding, as on-call physicians that initiated antimicrobial therapy unevenly were able to assess disease severity, allergies, risk of MDR pathogens, and other factors. In addition, our efforts to promote clinical practice guideline recommendations may have acted unevenly on key staffing in the emergency room.

In the BSI-studies, we investigated adherence to antimicrobial guideline recommendations. Here, the main entry criteria for inclusion were a positive blood culture, and this reduces selection criteria. However, antimicrobial therapy for severe infections implies judicious clinical evaluation by the attending physician and adhering to guideline recommendations requires confidence that the recommendations are trustworthy and sufficient. In our studies, we took steps to secure the documentation of disease severity, but this is always difficult to correctly interpret and replicate in study settings. Severely ill patients may have received non-adherent antimicrobial therapy, and this may have negatively influenced the association between adherence and low mortality.

Case-mix is also frequently challenging the results in observational studies on severe infections like BSI with or without sepsis syndrome. The origin of included infections varied, as did also the extent of other therapies like surgery, and organ-supportive measures. To increase internal validity, we adjusted the analyses for confounding factors, but not for all, and particularly not for the extent of surgery and other procedures performed.

Detection bias

The study group took several steps to diminish detection bias. We blinded the assessment of adherence to guideline recommendations, and the assessment of patients with special conditions like an AMR pathogen, kidney failure or antibiotic allergies. This may have

contributed to the reduction of the risk that knowledge of which intervention was received, rather than the intervention itself, affected the outcome.

Electronic medical records were used to collect data on mortality, readmissions, and length of stay. A limitation to all the studies is that readmission data were available through the in-house medical record system for the study site only.

Performance bias

The methodology in the studies performed may have introduced performance bias, especially in the two interventional studies on CAP diagnostics and CAP therapy. Firstly, expectorated, or induced sputum are a practical, time-consuming, and performance-dependent procedure, as compared to no procedure or sampling from the upper respiratory tract. Secondly, the ability to correctly perform the procedure depends heavily on motivational and educational factors among involved nurses and on-call physicians.

In the longitudinal CAP therapy study, we repeatedly presented updated and clear-cut recommendations on CAP management to clinicians in the emergency room setting, to evoke attention to therapy guideline recommendations. The fact that adherence increased throughout the study period may reflect that prescribing physicians regarded the guideline recommendations as credible.

Management of complicated or severe infectious diseases may require other therapies for optimal outcomes. These therapies are highly dependent on the extent of complications and severity, and are individualized according to patient-, disease-, and pathogen-related risk factors. In our BSI-studies, we recognize that other therapies than antimicrobial therapy may have introduced performance bias, especially the extent of surgery and organ-supportive measures performed.

In the reporting of the study results, we did not undertake classical interrupted time-series analyzes. In the intervention studies, we realized that the transition from standard management of CAP diagnosis and CAP therapy to the warranted goals of the intervention had to be launched gradually to emergency room staffing. Immediate changes were regarded unlikely. We therefore used association models for the comparisons of categorical variables before and after the intervention.

Attrition bias

Attrition bias refers to the circumstance when systematic differences in the way study participants are lost from the study exist (61). The observed effect in a study may be affiliated with differences in the number of remaining participants rather than the intervention itself.

The methodology applied in our observational studies reduced attrition bias. All exclusion criteria were established before we performed the analyzes.

Sample size

Statistically significant differences between groups in observational studies depend on the statistical level used, and sample sizes (62, 63). We sought to include sufficient samples sizes to achieve representative and reliable results but did not undertake specific sample size calculations. For the CAP diagnostic study, the CAP antimicrobial study, the BSI-ICU-study, and the BSI-ward-study, we included 1.280, 1.112, 270, and 756 episodes, respectively.

Study population

We investigated diagnostics and therapy-related aspects in commonly encountered infections in a university teaching hospital in mid-Norway. Both CAP and BSI constitute major patient groups in hospital settings throughout all countries. All inclusion- and exclusion processes, and patient characteristics are provided, making assessments of the study populations transparent.

A strength to our studies is that the populations investigated were not diagnosed based on clinical judgement only. In the CAP-studies the CAP diagnosis was radiographically confirmed in >90 % of included cases. In the BSI-studies, all included cases were microbiologically confirmed.

However, detailed data on specific areas like diagnostics and guideline-adherence are scarce. For that reason, in addition to the nature and the magnitude of our results, the studies conducted are likely to attract some attention. In Norway, not all local hospitals inhabit designated infectious diseases departments or even specialists. However, we believe that the study populations investigated do not differ among hospitals, regions, or countries, in particular countries with comparable AMR prevalence. We therefore also believe that results from our studies are readily generalizable and applicable to a broader population.

Clinical context

Microbiological confirmation of lower respiratory tract infections remains challenging, and even high-quality studies fail to provide advantageous results (64). There is an unmet need to improve diagnostic strategies to this highly frequent condition (65). We believe that our protocol that targeted the upscaling of numbers and the quality of performance of expectorated and induced sputum might prove beneficial, especially in terms of diagnostic and antimicrobial stewardship. By relatively modest interventional efforts, microbiologically confirmed cases reached 62.0 %. In broader terms, this means that a

considerable larger number of CAP cases can be offered pathogen-directed antimicrobial therapy according to the susceptibility test.

In the CAP therapy study, adherence to clinical practice guideline recommendations with first-line antimicrobial therapy increased significantly. We believe that our study results are applicable to a broader extent, and to other countries, especially in circumstances where guidelines are readily available, updated, and credible.

In the BSI-studies we primarily investigated proportions with concordant versus discordant antimicrobial therapy, adherence with clinical practice guideline recommendations, and the related outcomes. Our two studies provide valuable information about the BSI population. The studies also provide support to the clinical practice guideline recommendations.

Temporal factors

AMR in frequently encountered pathogens in CAP and BSI is still considered low in Norway. However, ESBL-rates have steadily increased over the last decade, reaching 5.8 % and 3.1 % for *Escherichia coli* in blood- and urine cultures in 2021, respectively. Corresponding rates for *Klebsiella pneumoniae* was 6.7 % and 4.5 % (8). This has elicited some concern and awareness. Of note, during the last three years ESBL in *Escherichia coli* recovered from blood culture samples has declined from 7.1 % in 2019 to 6.5 % in 2020, and finally 5.8 % in 2021.

All hospitals in Norway have since 2016 been obliged to implement AMS programs, especially focusing on the prescribing of broad-spectrum antimicrobial therapy. Key elements in the AMS programs are prospective audit with feedback, restrictions and preauthorization, and the implementation of syndrome-based clinical practice guideline recommendations (49). However, a nationwide study based on on-site interviews with professionals involved in the implementation of AMS programs, reported in 2021 that stewardship structures were widely established, but leadership commitment and implementation of interventions were often lacking (66).

The clinical practice guideline recommendations in Norway were established in 2013 on a national level. Throughout the study period, the contents of every chapter were revised and re-published from 2020 from the Directorate of Health. CAP diagnostics and therapy recommendations remained mostly unchanged, except for severe pneumonia managed in the ICU setting (67).

All these circumstances may have influenced antimicrobial therapy prescribing, especially empirical antimicrobial therapy in the emergency room setting.

We recognize the fact that observational studies both have advantages and disadvantages. However, collecting and extracting data to observational studies may turn out to be complicated. Although electronic records were readily available, the documented data were not primarily written for research purposes. Unstandardized data was common. We took multiple steps to standardize the collected data in order to be able to perform statistical analyzes more accurately. Clinical data that was ambiguous, were addressed individually by our joint study group.

Performance measurement in specific circumstances, such as community-acquired pneumonia, is debated (68). Over the last decade, multiple studies have focused on the quality-of-performance measures, as judged by adherence to guideline recommendations. Because CAP is one of the most frequent reasons for hospital admittance, and the fact that antimicrobial therapy very often is over-prescribed, a preferred approach is to target an evidence-based benchmark threshold for each specific indicator (68). In our studies, we have reported such indicators, and we believe that this might contribute to the understanding of how antimicrobial therapy is prescribed and how it could be modified.

Acquired knowledge

Antimicrobial usage

Differences in antimicrobial consumption among countries are astonishing. Numerous studies, of which several were reviewed in the introduction of this thesis, have addressed drivers for disparities. However, reasons for large variations are only poorly explained (2). In Norway, and at our university teaching hospital, antimicrobial consumption and prevalence of AMR remain low (8).

However, narrowing down the actual prescribed antimicrobial therapy courses to representative CAP and BSI cohorts within hospital settings, our studies show that usage raises some concerns. We have here documented that CAP and BSI-proportions that receive other empirical antimicrobial therapy courses than those recommended from clinical practice guidelines, are considerable. Broad-spectrum antimicrobial therapy was initiated to 34 % of CAP episodes before the intervention, 60 % of intensive care BSI cases, and 25 % of ward-level BSI-cases. However, maximizing the focus on CAP through measures implemented in the emergency room setting reduced the proportion that received broad-spectrum agents by nearly 50 %, without affecting mortality or re-admission rates. This proves that CAP is a suitable model condition for antimicrobial stewardship efforts. In a recent, cluster-randomized intervention study from 12 hospitals in the Netherlands, broad-spectrum antimicrobial therapy for non-severe CAP were

decreased from 6.5 to 4.8 days, a relative reduction of 27 % (69). Both Norway and the Netherlands are traditionally viewed as low antimicrobial consumption countries.

The studies conducted also have highlighted therapy durations, and the timely transition to targeted and oral antimicrobial therapy to key infections in hospital settings. In CAP, therapy courses exceeded recommendations on durations considerably, as mean duration was 11.0 days. Similar findings are reported by other investigators (70-72). However, a recent meta-analysis comprising 21 trials and over 4.000 patients with CAP regardless of disease severity, provided evidence that shorter duration (<6 days) was non-inferior to longer courses (>7 days)(73). And, in a recent double-blind, randomized, placebo-controlled, non-inferiority trial from France, 3 days of β-lactam therapy plus 5 more days of placebo, was non-inferior to 5 more days of amoxicillin-clavulanate, for CAP episodes that met clinical stability criteria (74). We did not address clinical stability criteria specifically in our studies but reported that approximately 70 % achieved 0-1 points of the CRB65-criteria at admission, and additional 24 % achieved 2 points. This indicates that CAP admissions were mainly non-severe.

Microbiologically confirmed CAP-episodes that were transitioned to targeted antimicrobial therapy constituted only 25 % of included cases. For most CAP episodes, an intravenous to oral conversion was feasible, but unutilized. In BSI-episodes managed in the intensive care setting, 14 % of nearly 72 % eligible cases were transitioned 4.4 days beyond the reported antimicrobial susceptibility tests. In BSIs in the general ward setting, 68.9 % of eligible cases were transitioned to targeted antimicrobial therapy.

Antimicrobial resistance
The studies conducted have revealed that AMR prevalence in frequently encountered CAP and BSI pathogens remain at low levels in the regional environment. This is in accordance with national reports (8). Methicillin-resistant *Staphylococcus aureus* were undetected among 25 staphylococcal CAP episodes, and 45 staphylococcal BSI episodes in the ICU-setting. We detected one MRSA among 129 staphylococcal BSI-episodes in the ward-level setting.

Extended-spectrum beta-lactamase cases constituted 0 % of CAP episodes, 5.9 % of BSI episodes in the intensive care setting, and 6.0 % of BSI episodes at a ward-level.

Microbiological aspects in antimicrobial stewardship
Microbiological confirmation in CAP is warranted for several reasons. Firstly, CAP represents the most prevalent infectious disease that leads to hospitalization (65). Secondly, aetiology of CAP is impacted by several factors like exposure, patient characteristics, and travel history, and over time by other factors, like vaccines and

epidemics (75). Thirdly, microbiologically misdiagnosed CAP triggers off unnecessary, inappropriate, or suboptimal antimicrobial therapy (76). And fourthly, mortality in CAP remains high in many circumstances (77). For these reasons, all professional authorities have by now recommended that steps to secure microbiological confirmations for in-patients should be taken.

Our efforts to scale up the numbers, and the quality of expectorated or induced sputum sampling, provided several results that need attention. We concluded that expectorated, or induced sputum outperformed other respiratory secretions, and that efforts to increase sampling frequencies and techniques, provided significantly more microbiological confirmations in CAP, reaching 62.0 %. Importantly, despite our efforts to scale up numbers of patients undergoing microbiological testing in CAP, any test was applied to only 31.2 % of eligible CAP cases, and particularly lower at non-interventional hospitals. Proportions that underwent procedures to collect samples from the respiratory tract were comparable to previous studies (76, 78, 79). Contrary to this, older studies state that approximately 75 % of patients with a lower respiratory tract infection can correctly produce a sputum sample of good quality (80). Our observational data indicate that expectorated or induced sputum sampling is frequently skipped.

We believe that microbiological strategies in lower respiratory tract infections are highly important to secure the rational use of antimicrobial therapy. Nucleic acid amplification tests have the capacity to detect a wide array of bacterial and viral pathogens in representative lower respiratory secretions (81). Microbiological confirmation in lower respiratory tract infections has yielded convincing results in terms of clinical outcomes and resource utilization. Both mortality (82), overall antimicrobial consumption (83), length of hospital stay (84), and the need for infection control measures (85), are reduced when CAP aetiology is confirmed. NAAT strategy, applied routinely and judiciously to CAP episodes, therefore seems justified.

Pathogens causing BSI are on the other hand much more likely to be microbiologically detected and confirmed. Using standard laboratory practice by whole blood culturing, and mass spectrometry for identification, the infecting pathogen accompanied by the susceptibility tests were reported on average at day 2.8 in our BSI studies.

Rapid detection, identification and reporting of susceptibility are regarded essential for the administration of optimal antimicrobial therapy in BSI. Time to initiation of effective antimicrobial therapy has been demonstrated to be the single strongest predictor of outcome in a large retrospective study comprising over 2.300 patients with septic shock (86). Delay of appropriate therapy beyond the time point of hypotension was associated with a 7.6 % decrease in survival each hour. In a prospective study from 15 hospitals in

Spain, inappropriate empirical antimicrobial therapy was independently associated with increased mortality at day 14 and 30, among 801 BSI episodes managed outside of intensive care settings (87). In a retrospective registry study from New York State, over 49.000 patients from 149 hospitals that had completed a 3-hour sepsis-bundle of care within 12 hours after arrival, longer time to the administration of antimicrobial therapy was associated with increased risk of mortality (OR 1.04 per hour) (88). And more recently, a multicenter study from the United States comprising over 21.000 BSI episodes, discordant empirical antimicrobial therapy was shown to be independently associated with about 50 % increased risk of mortality (adjusted OR 1.46), and an AMR phenotype strongly predicted receiving discordant therapy (OR 9.09) (89).

In our two BSI studies, we found some evidence to support the rapid detection and reporting of bacterial pathogens, although observational studies do not concisely point out causality. Mortality was significantly increased in BSI episodes that received discordant antimicrobial therapy, both in ICU settings and at ward-level.

Antimicrobial stewardship efforts

A frequently cited paper from the Cochrane library discusses interventions to improve antimicrobial therapy prescribing practices for hospital settings (90). The main findings of this systematic analysis were that interventions, with high certainty, were effective in increasing compliance with antimicrobial therapy policy, reducing duration of therapy, and reducing length of stay. Of particular interest, enablement of interventions consistently increased intervention effects, and interventions were successful in safely reducing unnecessary antimicrobial consumption without increasing mortality. The authors thereby concluded that interventions that provided advice or feedback to clinicians were most effective in reducing unnecessary antimicrobial consumption, and that additional trials comparing antimicrobial stewardship with no interventions, were unlikely to alter the conclusions stated.

In our studies, we did not undertake prospective audit interventions to safeguard optimal microbiological sampling or prescribing in CAP or BSI. However, by interventions that included training sessions and educational programs we achieved noteworthy and statistically significant increase in microbiologically confirmed CAP episodes. The findings warrant continued efforts to secure and uphold a rigorous diagnostic approach to the CAP population. We are not aware of similar results from interventions aiming at enhancing diagnostic yield from expectorated or induced sputum.

We concluded in the CAP therapy study that CAP is a suitable model condition that is sensitive to antimicrobial stewardship measures. Efforts to assure that CAP management was in accordance with clinical practice guideline recommendation turned out successful,

in term of increased proportions that received first-line therapy. Nonetheless, non-adherence to clinical practice guideline recommendations was frequent, especially for empirical regimens in non-severe CAP, timely de-escalation to targeted antimicrobial therapy, timely transition to oral regimens, and for overall therapy duration. We believe that CAP, as a major constituent of infections in hospital settings, warrants firmer stewardship.

For the discussions of antimicrobial stewardship measures in the two BSI studies conducted, we refer to the next chapter.

Clinical practice guideline adherence

Adherence to clinical practice guideline recommendations is particularly important for antimicrobial therapy. Misuse and overuse have the potential to propel the emergence of novel and more extended antimicrobial resistance, while inappropriate or suboptimal therapy may increase risk of therapy failure. The role of clinical practice guideline recommendations needs to sustain a high degree of credibility in order to function effectively. This is particularly important in settings where recommendations still promote narrow-spectrum antimicrobial agents to cure infections.

In Norway, the clinical practice guideline recommendations on antimicrobial therapy for hospital settings are similar to all hospitals from 2013, and easily accessed through an online digital platform at a national level (67). From 2020 until 2022, all recommendations were revisited and revised through a nationally coordinated program. However, scientifically approaches to evaluate and validate Norwegian recommendations are scarce, as are also studies on guideline adherence. A large retrospective, observational study from Western Norway demonstrated that 30-day mortality and in-hospital mortality for infections managed within the pulmonology, infectious diseases, and gastroenterology departments, were significantly lower in the guideline-adherent than non-adherent cohorts (91). The authors concluded that adherence was associated with favorable outcomes in terms of mortality and length of stay. In another single center study from Northern Norway, the combination of audit with feedback-interventions, and the distribution of a pocket version of guideline recommendations, yielded an increase from 61.7 % to 83.8 % of first-line therapy to patients admitted to the pulmonology department (92).

We have published four studies that address the adherence to guideline recommendations. Two of the studies included CAP cases managed within hospital settings, in which adherence to diagnostic approaches and the potential to modify adherence were investigated. We concluded that adherence was substandard regarding

microbiological approaches and empirical antimicrobial therapy for CAP. However, through interventional approaches both were unsurprisingly modifiable.

The BSI studies, on the other hand, demonstrated differences in mortality between groups. We reported that hospital-acquired BSIs in intensive care settings were identified as a predictor of receiving discordant antimicrobial therapy, and this was independently associated with mortality at day 28, as compared to concordant therapy. Interestingly, narrow-spectrum β-lactams in intensive care settings for BSI predicted concordant therapy. Adhering to clinical practice guideline recommendations provided significantly more concordant therapy on day 0, 1, 2, 3, and 3-9 for community-acquired BSIs as compared to hospital-acquired episodes. The estimated relative risk of mortality on day 28 for hospital-acquired BSIs that received discordant antimicrobial therapy was 1.64 (95 % CI 1.01 - 2.64). The same associations could not be established for community-acquired BSIs.

In the much larger BSI study, mostly managed outside of intensive care settings, we addressed adherence to clinical practice guidelines more comprehensively. Overall, prescribed antimicrobial therapy was guideline-adherent in 70.6 % and non-adherent in 25.1 %. Furthermore, receiving guideline-adherent empirical antimicrobial therapy was statistically significantly associated with receiving concordant therapy. Furthermore, overall all-case fatality rate was increased among patients that received discordant antimicrobial therapy, as compared to patients that received concordant therapy. This provides validity to and support for the national clinical practice guideline recommendations. It is also in line with a previous antimicrobial stewardship guideline that encourages the implementation of standardized therapy recommendations for specific clinical syndromes (93). A recent systematic review of nine stewardship objectives from nearly 150 clinical studies concluded that guideline-adherent empirical antimicrobial therapy was associated with a relative risk reduction for mortality of 35 % (53). The extent of this reduction is considerable.

Reasons for non-adherence to clinical practice guideline recommendations are difficult to elucidate. In everyday clinical practice, physicians are not obliged to document all assessment strategies, and this is a major limitation to observational studies. Furthermore, the clinical practice guideline recommendations are one-way communicative, and do not offer either interaction nor feedback facilities. Physicians are therefore not challenged or obliged to document reasons for non-adherence. In a multicenter observational study encompassing over 1.200 patient admissions from Western Norway, adherence to clinical practice guideline recommendations for the initiation of antimicrobial therapy was identified as a key target for antimicrobial stewardship interventions (94). As was also antimicrobial therapy initiated within the

emergency room setting. We agree with these statements and believe that our studies bring validation to them.

Efforts to reduce unnecessary, inappropriate, or suboptimal antimicrobial therapy have mostly relied on awareness campaigns. Such strategies may turn out successful in the short run, however, might prove difficult to uphold eventually. From our studies, we have identified multiple indicators, such as empirical and targeted antimicrobial therapy, microbiological confirmations, de-escalation strategies, and therapy duration for commonly encountered infection in hospital settings. We believe our studies bring evidence to support that firm adherence to clinical practice guideline recommendations is rational and judicious. This statement is supported by a recent Scandinavian review on drivers of irrational antimicrobial use in Europe (29), a much-cited 2016 review on AMR (95), and the European Union One-Health Action plan (7).

A recent review, with the support from the OECD, points to financial strategies to promote the prudent use of antimicrobial therapy (96). Among the strategies included that were associated with improved short term antimicrobial prescriptions were capitation and salary reimbursement, cost containment interventions, pay-for-performance initiatives, penalties, and one-off bonus payment. Interestingly, financial penalties as a strategic measure were associated with the greatest decrease in inappropriate antimicrobial prescriptions. The nature of the health care system varies between countries and continents. In a public, non-profitable hospital health care system, like the Norwegian, we believe that financial strategies placed on prescribers are unfitted and improper. The publication of quality-of-performance indicators applied to antimicrobial therapy prescribing settings are somehow revealingly meaningful and relevant and should be in the interest of patients, clinicians, and hospital administrators.

In a nationwide antimicrobial stewardship campaign in France targeting unnecessary antimicrobial therapy for flu-like symptoms among over 453 million data records, consumption decreased by nearly 27 % (97). The campaign addressed both the general public and health care providers, mainly in the winter season, seeking to raise awareness on appropriate use of antimicrobial therapy. All regions in France accomplished equivalent results, and all antimicrobial classes underwent a decline, except for fluoroquinolones. The study provides little support to hospital settings, but underscores that awareness is linked to human behavioral factors.

Human behavioral factors seem to play a substantial role in antimicrobial therapy prescription among physicians. To our knowledge, the decision to adhere or not to clinical practice guideline recommendations for the initiation of antimicrobial therapy are somehow linked to factors outside of the guidelines. There seems to exist a suspicion that

therapy recommendations do not sufficiently cover the actual medical case being managed, and that other antimicrobial agents than those proposed, are warranted. Also, there seems to exist a premise that therapy recommendations for severe cases are inevitably transferable to non-severe cases in the hospital setting. In the emergency room setting, decisions on appropriate antimicrobial therapy seem to be clouded by concurrent non-infectious conditions like asymptomatic bacteriuria, leading to non-adherence. In addition, there seems to exist some degree of apprehension with de-escalation strategies and shorter versus longer therapy durations. In a prospective study from a distinguished hospital in Maryland, physicians often reported shorter durations than those actually prescribed, revealing reluctance to adhere to recommended durations (98).

Our studies were conducted without the power to identify or detect behavioral factors among prescribers. Eventually, we have several reasons to suspect that behavioral factors have impacted substantially both in the CAP and the BSI studies. We also have reasons to believe that the interventions conducted have diminished some degree of distrust and insecurity to guideline recommendations. We need more studies to understand the impact of human behavioral factors in decisive moments when determining antimicrobial therapy, and why most effective behavioral change techniques are not more widely adopted within hospital settings (99).

Concluding remarks

Antimicrobial therapy for common infectious syndromes in hospital settings is typically viewed as empirical before, and targeted beyond, microbiological confirmation. If attempts to obtain a microbiological diagnosis turn out unsuccessful, empirical antimicrobial therapy is usually continued throughout the infection course.

In my thesis, I have pointed out important determinants for antimicrobial usage in frequently encountered infections in hospital settings. Both empirical and targeted antimicrobial therapy are somewhat receptive to considerable change through diagnostic and antimicrobial stewardship measures. This is notable for several reasons. Firstly, it can likely be achieved without affecting mortality and morbidity. Secondly, it can be achieved by even modest efforts, for instance by increasing adherence to clinical practice guideline recommendations. Thirdly, it can be achieved even in countries with low antimicrobial usage. And fourthly, it has the potential to reduce antimicrobial usage and thereby suppress drivers of antimicrobial resistance.

Efforts to secure guideline adherence is one measure that is likely to uphold sufficient bacterial coverage while demonstrating rational and judicious antimicrobial usage. Observational studies are valuable and highly needed to confirm guideline adherence. We need stronger evidence to understand antimicrobial prescribing at a ward-level, whether it is appropriate, inappropriate, unnecessary, or suboptimal. It seems that therapy guidelines that promote rational, and in the case for Norway, narrow-spectrum regimens, are not sufficient. In addition, we need effective measures to assure adherence.

Antimicrobial stewardship is highlighted as perhaps the only effective way to avoid the emergence of antimicrobial resistance, according to European health authorities (7). Especially because novel antibacterial molecules are unaccounted for. It is a rational measure to secure appropriate regimens. In my thesis, I have also shown that stewardship interventions are highly likely to turn out successful, although sustainable and lasting results are challenging.

References

1. Klein EY, Van Boeckel TP, Martinez EM, Pant S, Gandra S, Levin SA, et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. Proc Natl Acad Sci U S A. 2018;115(15):E3463-E70.

2. Klein EY, Milkowska-Shibata M, Tseng KK, Sharland M, Gandra S, Pulcini C, et al. Assessment of WHO antibiotic consumption and access targets in 76 countries, 2000-15: an analysis of pharmaceutical sales data. Lancet Infect Dis. 2021;21(1):107-15.

3. Van Boeckel TP, Gandra S, Ashok A, Caudron Q, Grenfell BT, Levin SA, et al. Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. Lancet Infect Dis. 2014;14(8):742-50.

4. Browne AJ, Chipeta MG, Haines-Woodhouse G, Kumaran EPA, Hamadani BHK, Zaraa S, et al. Global antibiotic consumption and usage in humans, 2000-18: a spatial modelling study. Lancet Planet Health. 2021;5(12):e893-e904.

5. Khouja T, Mitsantisuk K, Tadrous M, Suda KJ. Global consumption of antimicrobials: impact of the WHO Global Action Plan on Antimicrobial Resistance and 2019 coronavirus pandemic (COVID-19). J Antimicrob Chemother. 2022;77(5):1491-9.

6. Sulis G, Pai M, Gandra S. Comment on: Global consumption of antimicrobials: impact of the WHO Global Action Plan on Antimicrobial Resistance and 2019 coronavirus pandemic (COVID-19). J Antimicrob Chemother. 2022;77(10):2891-2.

7. ECDC O, EFSA and the EMA. Briefing note: Antimicrobial resistance in the EU/EEA. 2022.

8. 2020 NN-V. Usage of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Norway. 2020.

9. Haug JB, Berild D, Walberg M, Reikvam A. Increased antibiotic use in Norwegian hospitals despite a low antibiotic resistance rate. J Antimicrob Chemother. 2011;66(11):2643-6.

10. Spivak ES, Cosgrove SE, Srinivasan A. Measuring Appropriate Antimicrobial Use: Attempts at Opening the Black Box. Clin Infect Dis. 2016;63(12):1639-44.

11. Weaver SC. Urbanization and geographic expansion of zoonotic arboviral diseases: mechanisms and potential strategies for prevention. Trends Microbiol. 2013;21(8):360-3.

12. Neiderud CJ. How urbanization affects the epidemiology of emerging infectious diseases. Infect Ecol Epidemiol. 2015;5:27060.

13. Kotwani A, Holloway K. Trends in antibiotic use among outpatients in New Delhi, India. BMC Infect Dis. 2011;11:99.

14. Bhaskar ME, Moorthy S, Kumar NS, Arthur P. Dengue haemorrhagic fever among adults--an observational study in Chennai, south India. Indian J Med Res. 2010;132:738-40.

15. Hati AK. Dengue serosurveillance in Kolkata, facing an epidemic in West Bengal, India. J Vector Borne Dis. 2009;46(3):197-204.

16. Alirol E, Getaz L, Stoll B, Chappuis F, Loutan L. Urbanisation and infectious diseases in a globalised world. Lancet Infect Dis. 2011;11(2):131-41.

17. Brugha R, Grigg J. Urban air pollution and respiratory infections. Paediatr Respir Rev. 2014;15(2):194-9.

18. Armstrong GL, Conn LA, Pinner RW. Trends in infectious disease mortality in the United States during the 20th century. JAMA. 1999;281(1):61-6.

19. Nordmann P, Naas T, Poirel L. Global spread of Carbapenemase-producing Enterobacteriaceae. Emerg Infect Dis. 2011;17(10):1791-8.

20. Walsh TR, Weeks J, Livermore DM, Toleman MA. Dissemination of NDM-1 positive bacteria in the New Delhi environment and its implications for human health: an environmental point prevalence study. Lancet Infect Dis. 2011;11(5):355-62.

21. Blommaert A, Marais C, Hens N, Coenen S, Muller A, Goossens H, et al. Determinants of between-country differences in ambulatory antibiotic use and antibiotic resistance in Europe: a longitudinal observational study. J Antimicrob Chemother. 2014;69(2):535-47.

22. Morgan DJ, Okeke IN, Laxminarayan R, Perencevich EN, Weisenberg S. Non-prescription antimicrobial use worldwide: a systematic review. Lancet Infect Dis. 2011;11(9):692-701.

23. Fridkin S, Baggs J, Fagan R, Magill S, Pollack LA, Malpiedi P, et al. Vital signs: improving antibiotic use among hospitalized patients. MMWR Morb Mortal Wkly Rep. 2014;63(9):194-200.

24. Marr JJ, Moffet HL, Kunin CM. Guidelines for improving the use of antimicrobial agents in hospitals: a statement by the Infectious Diseases Society of America. J Infect Dis. 1988;157(5):869-76.

25. Wathne JS, Kleppe LKS, Harthug S, Blix HS, Nilsen RM, Charani E, et al. The effect of antibiotic stewardship interventions with stakeholder involvement in hospital settings: a multicentre, cluster randomized controlled intervention study. Antimicrob Resist Infect Control. 2018;7:109.

26. Andreassen V, Waagsbo B, Blix HS. Ciprofloxacin usage at a local hospital. Tidsskr Nor Laegeforen. 2020;140(14).

27. Waagsbo B, Sundoy A, Paulsen EQ. Reduction of unnecessary i.v. antibiotic days using general criteria for antibiotic switch. Scand J Infect Dis. 2008;40(6-7):468-73.

28. ReAct. A complex global challenge 2022 [Available from: https://www.reactgroup.org/antibiotic-resistance/a-complex-global-challenge/.

29. Machowska A, Stalsby Lundborg C. Drivers of Irrational Use of Antibiotics in Europe. Int J Environ Res Public Health. 2018;16(1).

30. Organization WH. Antimicrobial resistnace global report on surveillance: 2014 summary. 2014.

31. ECDC. Antimicrobial consumption in the EU/EEA. Annual epidemiological report for 2020. 2020.

32. Cassini A, Hogberg LD, Plachouras D, Quattrocchi A, Hoxha A, Simonsen GS, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria

in the EU and the European Economic Area in 2015: a population-level modelling analysis. Lancet Infect Dis. 2019;19(1):56-66.

33. ECDC EEatO. Briefing note: Antimicrobial Resistance, Tackling the Burden in the European Union. 2019.

34. Organization WH. Global Action Plan on Antimicrobial Resistance 2015 [Available from: https://www.who.int/publications/i/item/9789241509763.

35. Levy SB, Marshall B. Antibacterial resistance worldwide: causes, challenges and responses. Nat Med. 2004;10(12 Suppl):S122-9.

36. Bronzwaer SL, Cars O, Buchholz U, Molstad S, Goettsch W, Veldhuijzen IK, et al. A European study on the relationship between antimicrobial use and antimicrobial resistance. Emerg Infect Dis. 2002;8(3):278-82.

37. Molstad S, Cars O. Major change in the use of antibiotics following a national programme: Swedish Strategic Programme for the Rational Use of Antimicrobial Agents and Surveillance of Resistance (STRAMA). Scand J Infect Dis. 1999;31(2):191-5.

38. Kristinsson KG. Modification of prescribers' behavior: the Icelandic approach. Clin Microbiol Infect. 1999;5 Suppl 4:S43-S7.

39. Austin DJ, Kristinsson KG, Anderson RM. The relationship between the volume of antimicrobial consumption in human communities and the frequency of resistance. Proc Natl Acad Sci U S A. 1999;96(3):1152-6.

40. Seppala H, Klaukka T, Vuopio-Varkila J, Muotiala A, Helenius H, Lager K, et al. The effect of changes in the consumption of macrolide antibiotics on erythromycin resistance in group A streptococci in Finland. Finnish Study Group for Antimicrobial Resistance. N Engl J Med. 1997;337(7):441-6.

41. Frank U, Kleissle EM, Daschner FD, Leibovici L, Paul M, Andreassen S, et al. Multicentre study of antimicrobial resistance and antibiotic consumption among 6,780 patients with bloodstream infections. Eur J Clin Microbiol Infect Dis. 2006;25(12):815-7.

42. Tan SY, Khan RA, Khalid KE, Chong CW, Bakhtiar A. Correlation between antibiotic consumption and the occurrence of multidrug-resistant organisms in a Malaysian tertiary hospital: a 3-year observational study. Sci Rep. 2022;12(1):3106.

43. Meyer E, Gastmeier P, Deja M, Schwab F. Antibiotic consumption and resistance: data from Europe and Germany. Int J Med Microbiol. 2013;303(6-7):388-95.

44. Wushouer H, Zhang ZX, Wang JH, Ji P, Zhu QF, Aishan R, et al. Trends and relationship between antimicrobial resistance and antibiotic use in Xinjiang Uyghur Autonomous Region, China: Based on a 3 year surveillance data, 2014-2016. J Infect Public Health. 2018;11(3):339-46.

45. Barnes SL, Rock C, Harris AD, Cosgrove SE, Morgan DJ, Thom KA. The Impact of Reducing Antibiotics on the Transmission of Multidrug-Resistant Organisms. Infect Control Hosp Epidemiol. 2017;38(6):663-9.

46. Fishman N. Antimicrobial stewardship. Am J Infect Control. 2006;34(5 Suppl 1):S55-63; discussion S4-73.

47. Paskovaty A, Pflomm JM, Myke N, Seo SK. A multidisciplinary approach to antimicrobial stewardship: evolution into the 21st century. Int J Antimicrob Agents. 2005;25(1):1-10.

48. Moody J, Cosgrove SE, Olmsted R, Septimus E, Aureden K, Oriola S, et al. Antimicrobial stewardship: a collaborative partnership between infection preventionists and health care epidemiologists. Am J Infect Control. 2012;40(2):94-5.

49. Dellit TH, Owens RC, McGowan JE, Jr., Gerding DN, Weinstein RA, Burke JP, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis. 2007;44(2):159-77.

50. ECDC. Proposals for EU guidelines on the prudent use of antimicrobials in humans. 2017.

51. Excellence NIfHaC. Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use 2015 [Available from: https://www.nice.org.uk/guidance/ng15.

52. Prevention CfDCa. Core Elements of Antibiotic Stewardship 2021 [Available from: https://www.cdc.gov/antibiotic-use/core-elements/index.html.

53. Schuts EC, Hulscher M, Mouton JW, Verduin CM, Stuart J, Overdiek H, et al. Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis. Lancet Infect Dis. 2016;16(7):847-56.

54. KAS. Antibiotikaforbruksrapporter for norske sykehus 2022 [Available from: https://www.antibiotika.no/antibiotikaforbruksrapporter-for-norske-sykehus/.

55. Waagsbo B, Buset EM, Longva JA, Bjerke M, Bakkene B, Ertesvag AS, et al. Diagnostic stewardship aiming at expectorated or induced sputum promotes microbial diagnosis in community-acquired pneumonia. BMC Infect Dis. 2022;22(1):203.

56. Waagsbo B, Tranung M, Damas JK, Heggelund L. Antimicrobial therapy of community-acquired pneumonia during stewardship efforts and a coronavirus pandemic: an observational study. BMC Pulm Med. 2022;22(1):379.

57. Waagsbo B, Stuve N, Afset JE, Klepstad P, Mo S, Heggelund L, et al. High levels of discordant antimicrobial therapy in hospital-acquired bloodstream infections is associated with increased mortality in an intensive care, low antimicrobial resistance setting. Infect Dis (Lond). 2022;54(10):738-47.

58. Grov K, Haland E, Waagsbo B, Salvesen O, Damas JK, Afset JE. Empirical antimicrobial therapy for bloodstream infections not compliant with guideline was associated with discordant therapy, which predicted poorer outcome even in a low resistance environment. Infect Dis (Lond). 2022;54(12):833-45.

59. Grimes DA, Schulz KF. Bias and causal associations in observational research. Lancet. 2002;359(9302):248-52.

60. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008;61(4):344-9.

61. Nunan D, Aronson J, Bankhead C. Catalogue of bias: attrition bias. BMJ Evid Based Med. 2018;23(1):21-2.

62. Johnston KM, Lakzadeh P, Donato BMK, Szabo SM. Methods of sample size calculation in descriptive retrospective burden of illness studies. BMC Med Res Methodol. 2019;19(1):9.

63. Vassar M, Holzmann M. The retrospective chart review: important methodological considerations. J Educ Eval Health Prof. 2013;10:12.

64. Bartlett JG. Diagnostic tests for agents of community-acquired pneumonia. Clin Infect Dis. 2011;52 Suppl 4:S296-304.

65. Musher DM, Thorner AR. Community-acquired pneumonia. N Engl J Med. 2014;371(17):1619-28.

66. Skodvin B, Hogli JU, Gravningen K, Neteland MI, Harthug S, Akselsen PE. Nationwide audit and feedback on implementation of antibiotic stewardship programmes in Norwegian hospitals. JAC Antimicrob Resist. 2021;3(2):dlab063.

67. Helsedirektoratet. Antibiotika i sykehus 2022 [Available from: https://www.helsedirektoratet.no/retningslinjer/antibiotika-i-sykehus.

68. File TM, Jr., Gross PA. Performance measurement in community-acquired pneumonia: consequences intended and unintended. Clin Infect Dis. 2007;44(7):942-4.

69. Schweitzer VA, van Heijl I, Boersma WG, Rozemeijer W, Verduin K, Grootenboers MJ, et al. Narrow-spectrum antibiotics for community-acquired pneumonia in Dutch adults (CAP-PACT): a cross-sectional, stepped-wedge, cluster-randomised, non-inferiority, antimicrobial stewardship intervention trial. Lancet Infect Dis. 2022;22(2):274-83.

70. Egelund GB, Jensen AV, Andersen SB, Petersen PT, Lindhardt BO, von Plessen C, et al. Penicillin treatment for patients with Community-Acquired Pneumonia in Denmark: a retrospective cohort study. BMC Pulm Med. 2017;17(1):66.

71. Vaughn VM, Flanders SA, Snyder A, Conlon A, Rogers MAM, Malani AN, et al. Excess Antibiotic Treatment Duration and Adverse Events in Patients Hospitalized With Pneumonia: A Multihospital Cohort Study. Ann Intern Med. 2019;171(3):153-63.

72. Aliberti S, Blasi F, Zanaboni AM, Peyrani P, Tarsia P, Gaito S, et al. Duration of antibiotic therapy in hospitalised patients with community-acquired pneumonia. Eur Respir J. 2010;36(1):128-34.

73. Tansarli GS, Mylonakis E. Systematic Review and Meta-analysis of the Efficacy of Short-Course Antibiotic Treatments for Community-Acquired Pneumonia in Adults. Antimicrob Agents Chemother. 2018;62(9).

74. Dinh A, Ropers J, Duran C, Davido B, Deconinck L, Matt M, et al. Discontinuing beta-lactam treatment after 3 days for patients with community-acquired pneumonia in non-critical care wards (PTC): a double-blind, randomised, placebo-controlled, non-inferiority trial. Lancet. 2021;397(10280):1195-203.

75. Moberley S, Holden J, Tatham DP, Andrews RM. Vaccines for preventing pneumococcal infection in adults. Cochrane Database Syst Rev. 2013(1):CD000422.

76. Holter JC, Muller F, Bjorang O, Samdal HH, Marthinsen JB, Jenum PA, et al. Etiology of community-acquired pneumonia and diagnostic yields of microbiological methods: a 3-year prospective study in Norway. BMC Infect Dis. 2015;15:64.

77. Fine MJ, Smith MA, Carson CA, Mutha SS, Sankey SS, Weissfeld LA, et al. Prognosis and outcomes of patients with community-acquired pneumonia. A meta-analysis. JAMA. 1996;275(2):134-41.

78. Fally M, Israelsen S, Anhoj J, Benfield T, Tarp B, Kolte L, et al. The increasing importance of Haemophilus influenzae in community-acquired pneumonia: results from a Danish cohort study. Infect Dis (Lond). 2021;53(2):122-30.

79. Roysted W, Simonsen O, Jenkins A, Sarjomaa M, Svendsen MV, Ragnhildstveit E, et al. Aetiology and risk factors of community-acquired pneumonia in hospitalized patients in Norway. Clin Respir J. 2016;10(6):756-64.

80. Neill AM, Martin IR, Weir R, Anderson R, Chereshsky A, Epton MJ, et al. Community acquired pneumonia: aetiology and usefulness of severity criteria on admission. Thorax. 1996;51(10):1010-6.

81. Hanson KE, Azar MM, Banerjee R, Chou A, Colgrove RC, Ginocchio CC, et al. Molecular Testing for Acute Respiratory Tract Infections: Clinical and Diagnostic Recommendations From the IDSA's Diagnostics Committee. Clin Infect Dis. 2020;71(10):2744-51.

82. Quah J, Jiang B, Tan PC, Siau C, Tan TY. Impact of microbial Aetiology on mortality in severe community-acquired pneumonia. BMC Infect Dis. 2018;18(1):451.

83. Roger PM, Montera E, Lesselingue D, Troadec N, Charlot P, Simand A, et al. Risk Factors for Unnecessary Antibiotic Therapy: A Major Role for Clinical Management. Clin Infect Dis. 2019;69(3):466-72.

84. Wabe N, Li L, Lindeman R, Yimsung R, Dahm MR, Clezy K, et al. The impact of rapid molecular diagnostic testing for respiratory viruses on outcomes for emergency department patients. Med J Aust. 2019;210(7):316-20.

85. van Rijn AL, Nijhuis RHT, Bekker V, Groeneveld GH, Wessels E, Feltkamp MCW, et al. Clinical implications of rapid ePlex(R) Respiratory Pathogen Panel testing compared to laboratory-developed real-time PCR. Eur J Clin Microbiol Infect Dis. 2018;37(3):571-7.

86. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006;34(6):1589-96.

87. Retamar P, Portillo MM, Lopez-Prieto MD, Rodriguez-Lopez F, de Cueto M, Garcia MV, et al. Impact of inadequate empirical therapy on the mortality of patients with bloodstream infections: a propensity score-based analysis. Antimicrob Agents Chemother. 2012;56(1):472-8.

88. Seymour CW, Gesten F, Prescott HC, Friedrich ME, Iwashyna TJ, Phillips GS, et al. Time to Treatment and Mortality during Mandated Emergency Care for Sepsis. N Engl J Med. 2017;376(23):2235-44.

89. Kadri SS, Lai YL, Warner S, Strich JR, Babiker A, Ricotta EE, et al. Inappropriate empirical antibiotic therapy for bloodstream infections based on discordant in-vitro susceptibilities: a retrospective cohort analysis of prevalence, predictors, and mortality risk in US hospitals. Lancet Infect Dis. 2021;21(2):241-51.

90. Davey P, Marwick CA, Scott CL, Charani E, McNeil K, Brown E, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev. 2017;2:CD003543.

91. Wathne JS, Harthug S, Kleppe LKS, Blix HS, Nilsen RM, Charani E, et al. The association between adherence to national antibiotic guidelines and mortality, readmission and length of stay in hospital inpatients: results from a Norwegian multicentre, observational cohort study. Antimicrob Resist Infect Control. 2019;8:63.

92. Hogli JU, Garcia BH, Skjold F, Skogen V, Smabrekke L. An audit and feedback intervention study increased adherence to antibiotic prescribing guidelines at a Norwegian hospital. BMC Infect Dis. 2016;16:96.

93. Barlam TF, Cosgrove SE, Abbo LM, MacDougall C, Schuetz AN, Septimus EJ, et al. Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis. 2016;62(10):e51-77.

94. Wathne JS, Skodvin B, Charani E, Harthug S, Blix HS, Nilsen RM, et al. Identifying targets for antibiotic stewardship interventions through analysis of the antibiotic prescribing process in hospitals - a multicentre observational cohort study. Antimicrob Resist Infect Control. 2020;9(1):114.

95. Holmes AH, Moore LS, Sundsfjord A, Steinbakk M, Regmi S, Karkey A, et al. Understanding the mechanisms and drivers of antimicrobial resistance. Lancet. 2016;387(10014):176-87.

96. Yoshikawa Y, Feldhaus I, Ozcelik E, Hashiguchi TCO, Cecchini M. Financial strategies targeting healthcare providers to promote the prudent use of antibiotics: a systematic review of the evidence. Int J Antimicrob Agents. 2021;58(6):106446.

97. Sabuncu E, David J, Bernede-Bauduin C, Pepin S, Leroy M, Boelle PY, et al. Significant reduction of antibiotic use in the community after a nationwide campaign in France, 2002-2007. PLoS Med. 2009;6(6):e1000084.

98. Avdic E, Cushinotto LA, Hughes AH, Hansen AR, Efird LE, Bartlett JG, et al. Impact of an antimicrobial stewardship intervention on shortening the duration of therapy for community-acquired pneumonia. Clin Infect Dis. 2012;54(11):1581-7.

99. Mayor S. Feedback to doctors cuts unnecessary antibiotic use in hospitals, review finds. BMJ. 2017;356:j713.

Paper I

RESEARCH

Open Access

Diagnostic stewardship aiming at expectorated or induced sputum promotes microbial diagnosis in community-acquired pneumonia

Bjørn Waagsbø[1*], Eva Margrethe Buset[2], Jørn-Åge Longva[3], Merete Bjerke[2], Birgitte Bakkene[4], Anne-Stine Ertesvåg[2], Hanne Holmen[4], Marko Nikodojevic[2], To Thy Tran[4], Andreas Christensen[5,6], Einar Nilsen[7], Jan Kristian Damås[8,9†] and Lars Heggelund[10,11†]

Abstract

Purpose: Studies on aetiology of community-acquired pneumonia (CAP) vary in terms of microbial sampling methods, anatomical locations, and laboratory analyses, since no gold standard exists. In this large, multicentre, retrospective, regional study from Norway, our primary objective was to report the results of a strategic diagnostic stewardship intervention, targeting diagnostic yield from lower respiratory tract sampling. The secondary objective was to report hospitalized CAP aetiology and the diagnostic yield of various anatomical sampling locations.

Methods: Medical records from cases diagnosed with hospitalized CAP were collected retrospectively from March throughout May for three consecutive years at six hospitals. Between year one and two, we launched a diagnostic stewardship intervention at the emergency room level for the university teaching hospital only. The intervention was multifaceted aiming at upscaling specimen collection and enhancing collection techniques. Year one at the interventional hospital and every year at the five other emergency hospitals were used for comparison.

Results: Of the 1280 included cases of hospitalized CAP, a microbiological diagnosis was established for 29.1% among 1128 blood cultures and 1444 respiratory tract specimens. Blood cultures were positive for a pathogenic respiratory tract microbe in 4.9% of samples, whereas upper and lower respiratory tract samples overall provided a probable microbiological diagnosis in 21.3% and 47.5%, respectively. Expectorated or induced sputum overall provided aetiology in 51.7% of the samples. At the interventional hospital, the number of expectorated or induced sputum samples were significantly increased, and diagnostic yield from expectorated or induced sputum was significantly enhanced from 41.2 to 62.0% after the intervention (p = 0.049). There was an over-representation of samples from the interventional hospital during the study period. Non-typeable *Haemophilus influenza* and *Streptococcus pneumoniae* accounted for 25.3% and 24.7% of microbiologically confirmed cases, respectively.

*Correspondence: bjorn.waagsbo@stolav.no
†Jan Kristian Damås and Lars Heggelund contributed equally to this work
[1] Regional Centre for Disease Control in Central Norway Regional Health Authority, St. Olavs Hospital Trondheim University Hospital, Trondheim, Norway
Full list of author information is available at the end of the article

Conclusion: Expectorated or induced sputum outperformed other sampling methods in providing a reliable micro-biological diagnosis for hospitalized CAP. A diagnostic stewardship intervention significantly improved diagnostic yield of lower respiratory tract sampling.

Keywords: Pneumonia, Community-acquired pneumonia, Aetiology, Microbiology, Diagnostic yield, Expectorated sputum, Induced sputum, Antibiotic stewardship, Diagnostic stewardship

Introduction

Pneumonia is the most prevalent infectious disease that leads to hospitalization [1]. Pathogenesis encompasses the transmission of infectious microbes to the respiratory epithelium, and subsequently micro-aspirations to the alveoli [2]. Over decades *Streptococcus pneumoniae* has invariantly been reported as the most frequent pathogen in CAP, but in later years non-typeable *Haemophilus influenza* (NTHi) has emerged as most frequent in some studies [3, 4].

Microbiological diagnosis of lower respiratory tract infections remains challenging. High quality studies with targeted protocols have provided only poor or medium quality results, even with the incorporation of novel technologies or invasive techniques to detect the infecting agent [5]. Also, patient characteristics vary greatly in both age, acquisition, aetiology, severity, systemic involvement, immune response, and coexisting diseases. Ultimately, it is challenging to design and conduct rigorous studies on pneumonia that give meaningful and generalizable results.

In Scandinavian countries, empiric antimicrobial therapy have traditionally relied on narrow-spectrum beta-lactams, such as penicillin V and G, primarily aiming at the traditionally most important bacterial CAP microbe in a Nordic setting, *Streptococcus pneumoniae* [6, 7].

A specific pathogen-directed antimicrobial therapy is endorsed by most professional societies [1], although a majority of pneumonias will succumb to empirical therapy alone and without efforts to secure a microbiological diagnosis. Recommendations for empiric antimicrobial therapy therefore still have to rely on the composite of patient characteristics, travel history, exposure to known transmission settings, disease severity, and the knowledge of local prevalence of antimicrobial resistance.

Underscored by the ongoing covid-19 pandemic, there is accelerating recognition of viruses as causes of pneumonia. Furthermore, other layers of uncertainty and complexity in the microbiological diagnosis of pneumonia is connected to the role of colonizing or true infectious microbes, and the clinical implications of polymicrobial infections [8, 9].

In this study, we summarized the results on the microbiological diagnosis of hospitalized CAP, in a regional, low antimicrobial resistance prevalence setting. In addition, we wanted to explore the potential of diagnostic stewardship measures to achieve enhanced diagnostic yield of expectorated or induced sputum sampling for microbiological diagnosis.
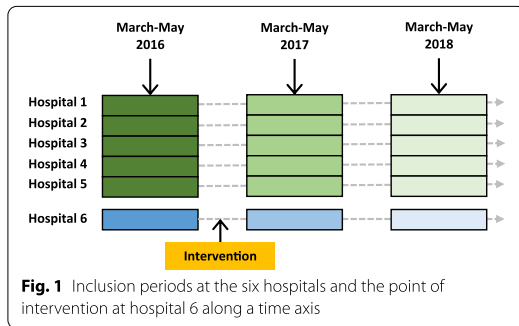
Materials and methods

Patients hospitalized with the diagnosis of pneumonia (ICD-10 J13-J18.9) in the county of Møre and Romsdal, and Sør-Trøndelag in the period March–May for three consecutive years from 2016 to 2018, were considered for inclusion. These months were chosen in order to minimalize the impact of influenza virus disease, and restructuring of hospital staffing during the summer holiday. Five local hospitals and a larger teaching university hospital cover nearly 580.000 inhabitants in the region.

Prerequisites for inclusion were a minimum of 24-h hospital stay in the medical, pulmonary or intensive care unit, initiation of antibiotics for pneumonia, and the pneumonia diagnosis reported as a primary diagnosis. Persons under 18 years of age, nosocomial pneumonias, CAP complicated with secondary nosocomial infections during the treatment course, readmissions within 30 days, as well as pneumonia as secondary diagnosis, were excluded.

Over the inclusion period, diagnostic stewardship measures targeting specimen sampling for microbiological confirmation were implemented. The intervention was launched subsequently to the first study year in 2016 at hospital 6 only. The two ensuing post-intervention years were compared with the pre-intervention year. The five other hospitals were used for comparison. Figure 1 describes the inclusion periods and timing of the intervention.

Included in the intervention was the publication of charts indicating diagnostic yield of the respiratory specimens from various anatomical locations, review lectures to emergency department staff, including on call doctors and nurses, and specific training sessions emphasizing correct timing, motivational factors and expectoration techniques, as depicted by the European Respiratory Society at their online resource centre [10]. All interventional measures aimed at upscaling specimen collection numbers, both expectorated and induced sputum, and enhancing health care provider and patient techniques. Microbiologists at the laboratories were unaware of

Waagsbø *et al. BMC Infectious Diseases*   (2022) 22:203

Page 3 of 9

Fig. 1 Inclusion periods at the six hospitals and the point of intervention at hospital 6 along a time axis

the intervention, seeking to maintain standard testing strategy during post-intervention study years. Detailed information about the intervention is available in the Additional file 1: Appendix.

A retrospective data collection was performed after each inclusion period. Discharge letters, medical records, radiological journal, and laboratory data from microbiological and biochemistry tests were recorded. In cases difficult to interpret, a joint study task force consisting of specialists in infectious diseases and clinical microbiology reviewed the patient information.

Bacteriological confirmation was established with the use of conventional laboratory culture techniques. Detection of pathogenic bacteria in blood cultures were consistently considered significant. Respiratory tract pathogens were considered significant if respiratory tract samples yielded mono- or duo-microbial growth in semi-quantitative cultures. Lower respiratory tract samples were cultured if microscopy by the microbiologist revealed significant leucocytosis, as outlined by the polymorphonuclear to squamous epithelial cell ratio [11]. Atypical pathogens and respiratory viruses were detected by the use of nuclear acid amplification techniques (NAAT). The decision to perform NAAT was based on both requests from the attending doctor as well as individual clinical evaluation by the microbiologist at the study sites. All three independent and collaborating, public microbiological laboratories in the region performed all analyses. Protocols to aid decisions were largely identical between laboratories.

Diagnostic yield from microbiological testing strategies were defined as the proportions of samples with a detectable, reliable pathological airway microbe that were targeted by antimicrobial therapy, as compared to all patients undergoing microbiological testing. The study group used all the collected data to determine the clinical role of the detected pathogen. Appointed variables were presented with simple descriptive statistics.

Microbiological data from the five local hospitals were compared to the corresponding data from the university hospital. We applied the chi-square test for binominal data to detect statistical differences in sampling numbers and diagnostic yield between hospitals and years in the study period.

The protocol for each study year was evaluated and approved by the Regional Ethics Committee (2017/1439), data protection officials, and hospital administrations for both health trusts.

Results

The study identified 1852 unique hospital stays for CAP, of which 1280 (69%) met all inclusion criteria. Of these 63% and 37% were admitted to the five local hospitals combined and the university hospital, respectively. Microbiological analyses were performed at three laboratories. Descriptive statistics for the whole patient population, the clinical, laboratory and imaging data are presented in Table 1.

Nasopharyngeal, pharyngeal, tracheal, and bronchoalveolar secretions, expectorated or induced sputum, and aspirated pleural effusion were not routinely or consistently collected among patients ascribed with pneumonia diagnosis. In addition, disease severity correlated inconsistently with microbiological sampling. For all years and hospitals combined, a total of 1.444 respiratory tract samples were subjected for microbiological analyses, of which non-pathogenic airway microbes were reported in 120 (8.3%) tests, and mixed oral cavity flora in 135 (9.3%) tests. For 793 of 1444 (54.9%) patient samples, laboratory testing reported a negative result. In 908 of 1280 cases (70.9%), the pneumonia diagnosis was established without respiratory tract specimen sampling. Samples collected from the various anatomical locations are presented in Table 1, and the distributions of polymicrobial infections are presented in Fig. 2.

The diagnostic yield of respiratory tract samples collected from different anatomical locations demonstrated considerable variations in performance. Expectorated or induced sputum from all years and hospitals combined, conferred microbiological confirmation in 148 of 286 (51.7%) cases, whereas the corresponding yield for nasopharyngeal, pharyngeal, and tracheal secretions, bronchoalveolar lavage and pleural effusion was 24.2%, 13.5%, 42.9%, 26.4% and 11.1% respectively.

Specific diagnostic stewardship measures were systematically implemented in the university hospital between the two first study years from 2016 to 2017 (Fig. 1). There was a statistically significant increase in the number of patients undergoing expectorated or induced sputum collection, X^2 (5, N = 425) = Chi-square statistic value 9.8705, p = 0.007, in this period. Also, a significantly

Waagsbø *et al. BMC Infectious Diseases* (2022) 22:203

Page 4 of 9

Table 1 Patient and selected diagnostic and infection characteristics in included CAP cases

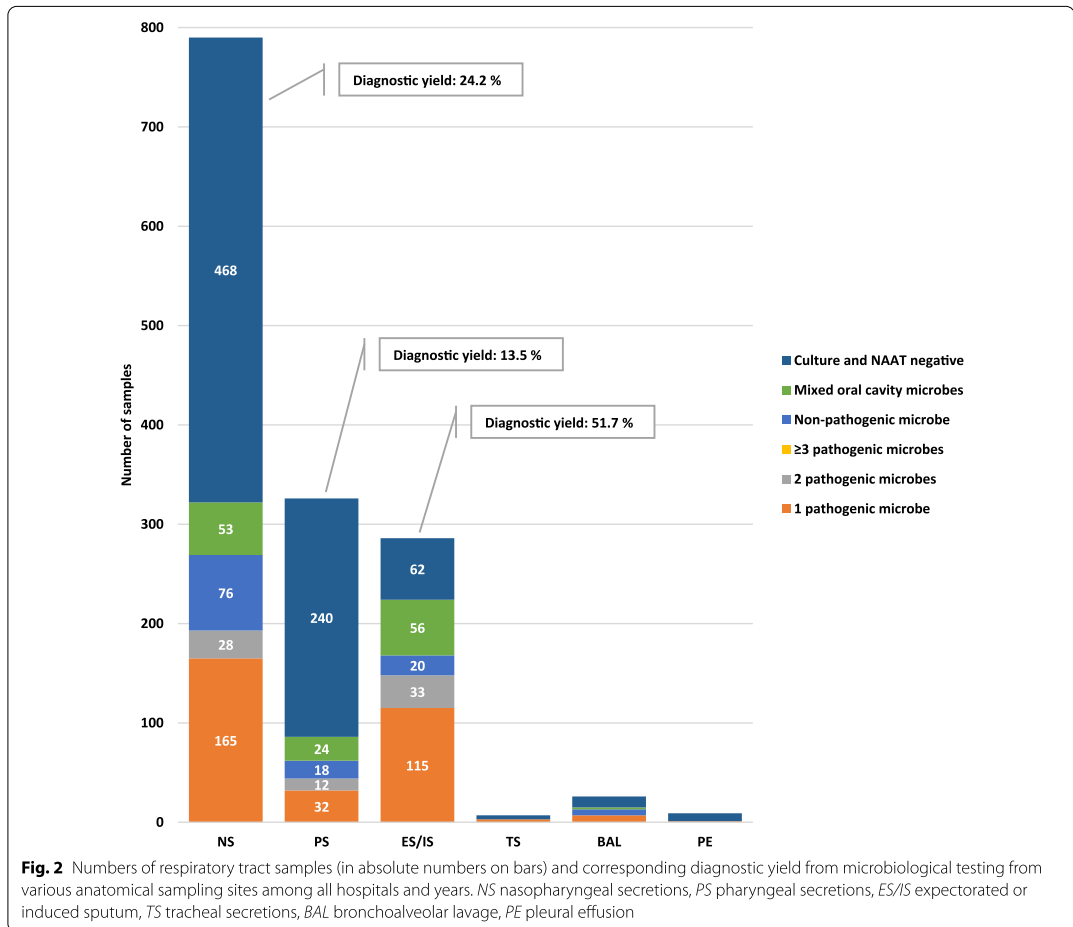| Variable	Hospital 1	Hospital 2	Hospital 3	Hospital 4	Hospital 5	Hospital 6	All
Intervention site	No	No	No	No	No	Yes	
n	123	283	132	117	158	467	1280
Age average(years)	71.5	75.1	71.8	71.7	73.6	69.8	72
Age > 65 years (%)	74.8%	81.2%	75.0%	69.2%	75.3%	69.8%	73.9%
Male gender (%)	58.1%	50.1%	58.6%	50.4%	49.4%	52.3%	52.1%
Nursing home resident (%)	4.1%	3.5%	8.3%	1.7%	5.1%	5.8%	4.9%
Comorbidity status							
Chronic obstructive pulmonary disease	13 (10.6)	32 (11.3)	16 (12.1)	23 (19.7)	31 (19.6)	61 (13.1)	176 (13.8)
Chronic congestive heart disease	10 (8.1)	38 (13.4)	18 (13.6)	20 (17.1)	36 (22.8)	58 (12.4)	180 (14.1)
CRB65 score (%)							
0	22.0%	12.0%	22.0%	19.7%	22.2%	25.1%	20.7%
1	46.3%	50.5%	41.7%	50.4%	55.7%	46.0%	48.2%
2	24.4%	29.0%	28.8%	23.1%	17.1%	23.1%	24.4%
3	7.3%	8.1%	7.6%	6.0%	5.1%	5.1%	6.3%
4	0.0%	0.4%	0.0%	0.9%	0.0%	0.6%	0.4%
Antimicrobial therapy before microbiological testing (average per year)	23.4%	19.4%	17.4%	23.4%	19.4%	20.6%	20.6%
ICU admittance, n (%)	19 (15.4)	42 (14.8)	26 (19.7)	23 (19.7)	10 (6.3)	37 (7.9)	157 (12.2)
Positive pressure ventilation							
Non-invasive, n (%)	9 (7.3)	34 (12.0)	12 (9.1)	14 (12.0)	13 (8.2)	87 (18.6)	169 (13.2)
Invasive, n (%)	1 (0.8)	4 (1.4)	5 (3.8)	4 (3.4)	2 (1.2)	5 (1.1)	21 (1.6)
Definite or probable new radiological infiltrate, n (%)	87 (70.7)	251 (88.7)	101 (76.5)	98 (83.4)	143 (90.5)	418 (89.5)	1098 (85.6)
Diagnostic tests performed							
Nasal secretions, n (%)	23 (18.7)	78 (27.6)	27 (20.5)	23 (19.7)	41 (25.9)	112 (24.0)	304 (23.8)
Pharyngeal secretions, n (%)	11 (8.9)	14 (4.9)	14 (10.6)	11 (9.4)	17 (10.8)	54 (11.6)	121 (9.5)
Expectorated or induced sputum, n (%)	35 (28.5)	65 (23.0)	34 (25.8)	34 (29.1)	60 (38.0)	171 (36.6)	399 (31.2)
Tracheal secretions, n (%)	1 (0.8)	4 (1.4)	5 (3.8)	4 (3.4)	2 (1.3)	5 (1.3)	21 (1.6)
Bronchoalveolar lavage, n (%)	2 (1.6)	6 (2.1)	2 (1.5)	2 (1.7)	3 (1.9)	11 (2.4)	26 (2.0)
Pleural effusion aspiration, n (%)	1 (0.8)	3 (1.1)	1 (0.8)	1 (0.9)	2 (1.3)	16 (3.4)	24 (1.9)
Blood culture, n (%)	118 (95.9)	272 (96.1)	121 (91.7)	112 (95.7)	139 (88.0)	452 (96.8)	1214 (94.8)
NAAT, n (%)	26 (21.1)	68 (24.0)	34 (25.8)	22 (18.8)	44 (27.8)	127 (27.2)	321 (25.1)

NAAT nuclear acid amplification test

higher diagnostic yield from expectorated or induced sputum samples was demonstrated between 2016 and 2018, X^2 (3, N = 114) = Chi-square statistic value 3.8888, p = 0.04861. By the end of the study, diagnostic yield from expectorated or induced sputum reached 62.0%. There were no statistically significant differences between hospitals in the pre-interventional year, but samples from the interventional hospital were over-represented during the study period. Results are presented in Fig. 3.

For the entire cohort, aetiological diagnosis was established in 372 of 1280 (29.1%) of the pneumonia cases. The infecting agent was evident by blood cultures in 55 of 1128 (4.9%) samples. In upper respiratory tract specimens, cultures and nucleic acid amplification test (NAAT), yielded 197 of 1116 (17.7%) aetiological confirmations in mono-microbial infections, and 40 of 1116 (3.6%) in duo-microbial infections. Corresponding results from lower respiratory tract specimens were 126 of 328 (38.4%) in mono-microbial infections and 30 of 328 (9.1%) in duo-microbial infections. Nucleic acid amplification test (NAAT) detected the infecting pathological agent in 46 of 286 (16.1%) of the lower airway samples.

NTHi and *Streptococcus pneumoniae* were the most frequently isolated microbes in blood cultures and respiratory tract specimens combined, accounting for 94 (25.3%) and 92 (24.7%) of 372 microbiologically confirmed pneumoniae cases respectively. Respiratory viruses were detected in 28 of 372 (7.5%) microbiologically confirmed pneumonia cases. No pathogenic microbes harbouring special drug-resistant phenotypic patterns were recovered, such as extended spectrum beta-lactamase (ESBL), methicillin-resistant *Staphylococcus aureus* (MRSA), or multidrug resistant *Pseudomonas*

Waagsbø *et al. BMC Infectious Diseases*   (2022) 22:203

Page 5 of 9

Fig. 2 Numbers of respiratory tract samples (in absolute numbers on bars) and corresponding diagnostic yield from microbiological testing from various anatomical sampling sites among all hospitals and years. *NS* nasopharyngeal secretions, *PS* pharyngeal secretions, *ES/IS* expectorated or induced sputum, *TS* tracheal secretions, *BAL* bronchoalveolar lavage, *PE* pleural effusion

aeruginosa. *Streptococcus pneumoniae* was uniformly penicillin-susceptible. NTHi in blood cultures and lower respiratory tract samples were ampicillin resistant in 20.0% and 19.1%, respectively. Aetiological findings from respiratory tract samples and blood cultures are presented in Fig. 4.

Discussion

This study provides further insight to the aetiological diagnosis and distributions of hospitalized CAP in a low antibiotic resistance prevalence setting. Aetiology was confirmed by routine microbiological testing in 29.1% of included cases. In addition, strategic diagnostic stewardship measures demonstrated that efforts to target microbiological sampling frequencies and techniques turned

out successful, in terms of enhanced microbiological diagnostic yield.

The proportions of patients that routinely underwent procedures to collect samples from the respiratory tract were comparable to previous studies [3, 9, 12–14]. A diagnostic yield of 4.9% in blood cultures and 39.5% in cultured respiratory tract samples is also within the range found in comparable studies. It is noteworthy that a particularly high overall diagnostic yield of 51.7% was observed in expectorated or induced sputum, and this outperformed other anatomical sampling sites.

Samples from the upper respiratory tract are not routinely used for determining CAP aetiology. However, such samples were frequently performed to included cases in our study. A previously published review on

Waagsbø *et al. BMC Infectious Diseases*   (2022) 22:203

Page 6 of 9

Fig. 3 Change in diagnostic yield from expectorated or induced sputum between hospitals and pre- and post-interventional years

	Hospital 1	Hospital 2	Hospital 3	Hospital 4	Hospital 5	Hospital 6
2016	3/14	7/22	4/15	3/12	6/18	14/34
2017	2/11	6/25	2/11	3/12	6/23	31/58
2018	2/10	4/18	2/8	3/10	5/19	49/79

Fig. 4 Frequencies of microbiological aetiology in blood cultures and upper and lower respiratory tract samples

the usefulness of aetiological tests for CAP concluded that samples from the upper respiratory tract should be performed to patients that are unable to produce an adequate, purulent sputum at admission [15]. This was

also reflected in Swedish clinical practice guidelines from 2016 [16].

Expectorated or induced sputum is the standardized procedure for tuberculosis management. However, it's role in common lower respiratory tract infections has

Waagsbø et al. BMC Infectious Diseases   (2022) 22:203

Page 7 of 9

faded over time, although approximately 75% of patients can produce an adequate sputum sample at admission [17], and that sensitivity of sputum examination is >75% for detecting bacterial pathogens [18]. In our study, expectorated or induced sputum provided considerable diagnostic yield of 51.7%, although this diagnostic strategy was only applied to 31.2% of patients diagnosed with CAP. Furthermore, by relatively modest interventional efforts, the diagnostic yield of expectorated or induced sputum increased to 62.0%. We are not aware of similar results from interventions aiming at enhancing diagnostic yield from expectorated or induced sputum at a ward-level in CAP. It seems that such samples nonetheless provide valuable microbiological confirmations in CAP and should be the preferred method for respiratory tract sampling. However, sampling from the respiratory tract is inevitable hampered by infection control measures in viral pandemic situations. Our study was underpowered to detect whether diagnostic yield from lower respiratory tract samples were benefitted from increased numbers or quality of expectorated or induced sputum. Also of note, bronchoalveolar lavage sampling was infrequent, most likely due to low numbers of severe disease, low AMR prevalence, and few complications. For this reason, we concluded that the calculated diagnostic yield did not reflect expected yield.

NTHi as the most prevalent CAP pathogen in our study, is in line with recent studies from Denmark [3] and Germany [19]. Traditionally, community-acquired lower respiratory tract infections in patients with structural pulmonary diseases, especially chronic obstructive pulmonary disease (COPD), are more likely to be caused by NTHi [4, 20]. Of notice, we found COPD in only 27% of patients with NTHi infection. This may indicate that clinical practice guidelines in Nordic countries underestimate the prevalence of NTHi infections in CAP, and thereby offer inadequate therapy recommendations. The potential emerging relative prevalence of NTHi in CAP, may be related to pneumococcal vaccination, although an absolute increase is also possible [21]. In Norway, people aged >65 years, or diagnosed with conditions known to increase risk of pneumococcal disease, are recommended to receive a pneumococcal vaccine, but data on adherence are lacking. In addition, routine pneumococcal vaccination to children was introduced in 2006.

No clinical signs or symptoms in acute respiratory tracts infections are pathogen specific. International guidelines on diagnostic strategies and antimicrobial therapy in hospitalized CAP often favour thorough microbiological evaluation and testing, in particular in severe infections [22]. Even so, exposure to special transmission settings, underlying comorbid conditions, and disease severity all represent considerable

pitfalls to microbiological testing and empiric antimicrobial therapy outcomes. In our study, the lack of a consistent diagnostic testing strategy was evident at the study sites.

A recent review claims that representative respiratory tract secretions applied to highly sensitive nucleic acid amplification tests (NAAT) today have the capacity to detect common viral and bacterial pathogens as well as selected drug-resistant determinants [23]. Turnaround time for NAAT tests targeting multiple viral and bacterial pathogens are increasingly rapid and may decline to minutes. In terms of antimicrobial stewardship, a negative test may withhold empirical coverage, and a positive test may permit individualized pathogen-directed therapy. Further, efforts to establish a reliable microbiological diagnosis in pneumonia have proved beneficial in terms of clinical outcomes and resource utilization. Both mortality [24], overall antimicrobial therapy consumption [25], broad spectrum antibiotic consumption [26], infection-control practices [27], and length of stay [28], are significantly reduced by such strategy. Our study was conducted with the use of traditional cultures of respiratory tract secretions. NAAT provided aetiological confirmation in only 16% of tests in our study.

The diagnostic yield of any strategy to detect the infecting bacteria in CAP is likely to be influenced by the timing of specimen collection in view of antimicrobial therapy. In our study, 20.6% of included cases received antimicrobial therapy before microbiological sampling. A rigorous study of CAP among immune-competent adults, demonstrated that the infecting agent was significantly more frequently detected in blood cultures prior to empirical antimicrobial therapy [12]. The same finding did not apply for respiratory tract specimens. International guidelines have previously stated that pre-treatment Gram stain and culture of expectorated sputum should be performed only if good-quality specimens can be obtained and quality performances measures for collection, transport, and processing of samples can be met [29]. In a recent published systematic review, Gram staining of sputum samples still seem to provide valuable diagnostic information, in particular for *S. pneumonia* and *H. Influenzae* detections, in an antibiotic stewardship perspective [30].

Severity assessment in pneumonia is not routinely conducted and documented in clinical practice, especially outside of intensive care settings. The CRB65-score is uniformly recommended to aid empirical antimicrobial therapy in all settings, and to assess microbiological diagnostic strategies [7]. With few exceptions, the study group calculated the CRB65-score retrospectively in our study. This may indicate that other undocumented approaches, if any, to assess disease severity, exist. In our cohort, the

Waagsbø *et al. BMC Infectious Diseases*   (2022) 22:203

Page 8 of 9

distributions of CRB65-score of 1 or 2 was 69–77%, and CRB65-score of 3–4 was 4–10% among all study sites. These findings indicate that included cases were largely non-severe CAP, and that disease severity did not differ significantly between study sites. It also indicates that the hospitalization for non-severe CAP is common, contrary to guideline recommendations, and that other circumstances for hospitalization are often emphasized.

Antimicrobial stewardship measures are considered crucial to prevent harmful outcomes from antimicrobial resistance [31]. In countries with low AMR prevalence, microbiological confirmed cases of CAP allow for pathogen-directed, narrow-spectrum therapy. Of importance, only 29% of included hospitalizations for CAP cases underwent microbiological diagnostic approach in our study. This should encourage clinicians to reinforce sampling techniques and to scale up sampling numbers, preferably lower respiratory tract secretions.

Testing for respiratory viruses in a broad panel scale is encouraged by antibiotic stewardship guidelines to reduce inappropriate antimicrobial usage [32]. This recommendation relies on studies that have classical pre- and post-intervention models, to calculate the reduction of antibiotic consumption. Other strategies, combining NAAT testing with serum biomarkers or host immune-response analyses, shows promising results [33]. We did not undertake antibiotic usage calculations in the present study. Moreover, we wanted to describe the aetiology of hospitalized CAP in a region with low prevalence of antimicrobial resistance, and to highlight that diagnostic yield from lower respiratory tract specimens may increase with the use of simple efforts to sustain adequate sampling.

The study has some limitations. Firstly, all data from included cases were extracted retrospectively. Secondly, inclusion criteria relied on the attending doctor's ability to correctly catalogue patient data. Thirdly, we may have missed designated respiratory tract specimens collected in primary health care settings prior to hospitalization. Fourthly, details on the individual patient's ability to comply with testing strategy recommendations were not available. Fifthly, respiratory tract samples were stored overnight, and for three hospitals transported to the laboratory before handled. Finally, microbiology results may be affiliated by the non-identical in-house laboratory protocols and procedures among the laboratories.

In conclusion, this study shows that modest efforts to scale up sampling frequencies and enhance sampling techniques, provided significantly more microbiological confirmations in hospitalized CAP. Also, expectorated or induced sputum outperformed other respiratory secretions. We advise others to conduct similar interventions in order to establish rigorous cost–benefit analyses for

the role of such interventions, and to calculate the potential reduction of antimicrobial consumption. We also emphasize the need for closer adherence to clinical practice guidelines in terms of diagnostic approaches.

Supplementary Information

Additional file 1. Appendix: Detailed information about the intervention.

Declarations

Ethics approval and consent to participate

Consent for publication
No.

Competing interests
The authors mentioned below have no relevant financial or non-financial interests to disclose. Eva Margrethe Buset, Jørn-Åge Longva, Merete Bjerke, Birgitte Bakkene, Anne-Stine Ertesvåg, Hanne Holmen, Marko Nikodojevic, To Thy Tran, Andreas Christensen, Einar Nilsen, Jan Kristian Damås, Lars Heggelund. Author Bjørn Waagsbø is a representative to the directory group in the Norwegian Directorate of Health, that seek to revise recommendations in the national clinical practice guideline for antimicrobial therapy, and holds a 20% position for this representation between 2018 and 2021.

Author details
[1] Regional Centre for Disease Control in Central Norway Regional Health Authority, St. Olavs Hospital Trondheim University Hospital, Trondheim, Norway. [2] Central Norway Hospital Pharmacy Trust, Ålesund, Norway. [3] Department of Medicine, Ålesund Hospital, Møre and Romsdal Hospital Trust, Ålesund, Norway. [4] Central Norway Hospital Pharmacy Trust, Trondheim, Norway.

Waagsbø *et al. BMC Infectious Diseases*   (2022) 22:203

Page 9 of 9

[5]Department of Microbiology, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway. [6]Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway. [7]Department of Microbiology, Møre and Romsdal Hospital Trust, Ålesund, Norway. [8]Department of Infectious Diseases, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway. [9]Department of Clinical and Molecular Medicine, Centre of Molecular Inflammation Research, NTNU, Trondheim, Norway. [10]Department of Clinical Science, Faculty of Medicine, University of Bergen, Bergen, Norway. [11]Department of Internal Medicine, Drammen Hospital, Vestre Viken Hospital Trust, Drammen, Norway.

References

1. Musher DM, Thorner AR. Community-acquired pneumonia. N Engl J Med. 2014;371(17):1619–28.
2. Faner R, et al. The microbiome in respiratory medicine: current challenges and future perspectives. Eur Respir J. 2017;49(4):1602086.
3. Fally M et al. The increasing importance of Haemophilus influenzae in community-acquired pneumonia: results from a Danish cohort study. Infect Dis (Lond), 2020: 1–9.
4. Wootton DG, et al. A Haemophilus sp. dominates the microbiota of sputum from UK adults with non-severe community acquired pneumonia and chronic lung disease. Sci Rep. 2019;9(1):2388.
5. Bartlett JG. Diagnostic tests for agents of community-acquired pneumonia. Clin Infect Dis. 2011;52(Suppl 4):S296-304.
6. Egelund GB, et al. Penicillin treatment for patients with Community-Acquired Pneumonia in Denmark: a retrospective cohort study. BMC Pulm Med. 2017;17(1):66.
7. Athlin S, et al. Management of community-acquired pneumonia in immunocompetent adults: updated Swedish guidelines 2017. Infect Dis (Lond). 2018;50(4):247–72.
8. Johansson N, Kalin M, Hedlund J. Clinical impact of combined viral and bacterial infection in patients with community-acquired pneumonia. Scand J Infect Dis. 2011;43(8):609–15.
9. Holter JC, et al. Etiology of community-acquired pneumonia and diagnostic yields of microbiological methods: a 3-year prospective study in Norway. BMC Infect Dis. 2015;15:64.
10. Weiszhar Z, Horvath I. Induced sputum analysis: step by step. Breath. 2013;9(4):301–5.
11. Murray PR, EJ Baron, JH Jorgenson, Pfaller MA, Yolken RH eds. Manual of clinical microbiology 8th edition. 8th edn., ed. A. Balows. ASM Press: American Society of Microbiology. 2003.
12. Jain S, et al. Community-acquired pneumonia requiring hospitalization among U.S. adults. N Engl J Med. 2015;373(5):415–27.
13. Torres A, et al. The aetiology and antibiotic management of community-acquired pneumonia in adults in Europe: a literature review. Eur J Clin Microbiol Infect Dis. 2014;33(7):1065–79.
14. Røysted W, et al. Aetiology and risk factors of community-acquired pneumonia in hospitalized patients in Norway. Clin Respir J. 2016;10(6):756–64.
15. Stralin K. Usefulness of aetiological tests for guiding antibiotic therapy in community-acquired pneumonia. Int J Antimicrob Agents. 2008;31(1):3–11.
16. infektionsläkarföreningen, s. *Vårdprogram för samhällsförvärvad pneumoni*. 2016 [cited 2022 Jan 10th]; Available from: https://infektion.net/vardprogram/pneumoni/.
17. Neill AM, et al. Community acquired pneumonia: aetiology and usefulness of severity criteria on admission. Thorax. 1996;51(10):1010–6.
18. Anevlavis S, et al. A prospective study of the diagnostic utility of sputum Gram stain in pneumonia. J Infect. 2009;59(2):83–9.
19. Braeken DCW, et al. Shift in bacterial etiology from the CAPNETZ cohort in patients with community-acquired pneumonia: data over more than a decade. Infection. 2021;49:533.
20. Sethi S. Bacteria in exacerbations of chronic obstructive pulmonary disease: phenomenon or epiphenomenon? Proc Am Thorac Soc. 2004;1(2):109–14.
21. Cleary D et al. Pneumococcal vaccine impacts on the population genomics of non-typeable Haemophilus influenzae. Microb Genom. 2018; 4(9).
22. Metlay JP, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med. 2019;200(7):e45–67.
23. Hanson KE, et al. Molecular testing for acute respiratory tract infections: clinical and diagnostic recommendations from the IDSA's Diagnostics Committee. Clin Infect Dis. 2020;71:2744.
24. Quah J, et al. Impact of microbial Aetiology on mortality in severe community-acquired pneumonia. BMC Infect Dis. 2018;18(1):451.
25. Roger PM, et al. Risk factors for unnecessary antibiotic therapy: a major role for clinical management. Clin Infect Dis. 2019;69(3):466–72.
26. Braykov NP, et al. Assessment of empirical antibiotic therapy optimisation in six hospitals: an observational cohort study. Lancet Infect Dis. 2014;14(12):1220–7.
27. van Rijn AL, et al. Clinical implications of rapid ePlex(R) Respiratory Pathogen Panel testing compared to laboratory-developed real-time PCR. Eur J Clin Microbiol Infect Dis. 2018;37(3):571–7.
28. Wabe N et al. Impact of rapid molecular diagnostic testing of respiratory viruses on outcomes of adults hospitalized with respiratory illness: a multicenter quasi-experimental study. J Clin Microbiol. 2019; 57(4).
29. Mandell LA, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007;44(Suppl 2):S27-72.
30. Ogawa H, et al. Sputum gram stain for bacterial pathogen diagnosis in community-acquired pneumonia: a systematic review and Bayesian meta-analysis of diagnostic accuracy and yield. Clin Infect Dis. 2020;71(3):499–513.
31. Cassini A, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. Lancet Infect Dis. 2019;19(1):56–66.
32. Barlam TF, et al. Implementing an antibiotic stewardship program: guidelines by the infectious diseases society of America and the society for healthcare epidemiology of America. Clin Infect Dis. 2016;62(10):e51-77.
33. Lydon EC, et al. Validation of a host response test to distinguish bacterial and viral respiratory infection. EBioMedicine. 2019;48:453–61.

Publisher's Note

Paper II

Antimicrobial therapy of community-acquired pneumonia during stewardship efforts and a coronavirus pandemic: an observational study

Bjørn Waagsbø[1,2*], Morten Tranung[2,3], Jan Kristian Damås[4,5] and Lars Heggelund[6,7]

Abstract

Background Community-acquired pneumonia (CAP) is the most frequent infection diagnosis in hospitals. Antimicrobial therapy for CAP is depicted in clinical practice guidelines, but adherence data and effect of antibiotic stewardship measures are lacking.

Methods A dedicated antibiotic team pointed out CAP as a potential target for antimicrobial stewardship (AMS) measures at a 1.000-bed, tertiary care, teaching university hospital in Norway from March until May for the years 2016 throughout 2021. The aim of the AMS program was to increase diagnostic and antimicrobial therapy adherence to national clinical practice guideline recommendations through multiple and continuous AMS efforts. Descriptive statistics were retrospectively used to delineate antimicrobial therapy for CAP. The primary outcomes were proportions that received narrow-spectrum beta-lactams, and broad-spectrum antimicrobial therapy.

Results 1.112 CAP episodes were identified. The annual proportion that received narrow-spectrum beta-lactams increased from 56.1 to 74.4% (p = 0.045). Correspondingly, the annual proportion that received broad-spectrum antimicrobial therapy decreased from 34.1 to 17.1% (p = 0.002). Trends were affected by the coronavirus pandemic. Mortality and 30-day readmission rates remained unchanged. De-escalation strategies were frequently unutilized, and overall therapy duration exceeded clinical practice guideline recommendations substantially. Microbiologically confirmed CAP episodes increased from 33.7 to 56.2% during the study period.

Conclusion CAP is a suitable model condition that is sensitive to AMS measures. A continuous focus on improved microbiological diagnostics and antimicrobial therapy initiation is efficient in increasing adherence to guideline recommendations. There is an unmet need for better antimicrobial de-escalation strategies.

Keywords Pneumonia, Community-acquired pneumonia, Aetiology, Microbiology, Antimicrobial stewardship, Antimicrobial therapy

*Correspondence:
Bjørn Waagsbø
bjorn.waagsbo@stolav.no
[1]St. Olavs Hospital, Regional centre for disease control in Central Norway Regional Health Authority, Trondheim University hospital, Trondheim, Norway
[2]Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway
[3]Central Norway Hospital Pharmacy Trust, Trondheim, Norway
[4]Department of Infectious Diseases, St. Olavs Hospital, Trondheim University hospital, Trondheim, Norway
[5]Centre of Molecular Inflammation Research, department of Clinical and Molecular Medicine, NTNU, Trondheim, Norway
[6]Department of Internal Medicine, Drammen Hospital, Vestre Viken Hospital Trust, Drammen, Norway
[7]Department of Clinical Science, Faculty of Medicine, University of Bergen, Bergen, Norway

Introduction

Community-acquired pneumonia (CAP) is a frequent infection of the lower respiratory tract, each year accounting for millions of hospitalizations and significant morbidity and mortality worldwide [1]. A majority of cases is caused by well-known respiratory tract pathogens, but microbiological confirmation is somewhat hampered by the lack of sample harvesting, and the sensitivity and specificity of respiratory tract secretions [2].

Antimicrobial therapy is considered essential for the proper management of CAP [3]. Due to high numbers of cases, frequent misdiagnosed aetiology, and the associated mortality risk, CAP has the potential to propel antimicrobial consumption. For this reason, diagnostic and antimicrobial stewardship measures are justified, aiming at the recognition of exposure settings, acquisition, risk factors, severity assessment, and the timely initiation and de-escalation of antimicrobial therapy [4].

Antimicrobial resistance (AMR) among several respiratory tract pathogens to commonly used antimicrobials are increasing worldwide [5]. However, in a few countries, AMR still remains at relatively modest levels, as reported from particularly Scandinavian countries [6]. This favorable situation is on the other hand vulnerable to consequences of unjustified broad-spectrum antimicrobial prescriptions.

A national clinical practice guideline for the management of CAP was established in Norway in 2013. Therapy recommendations were largely consistent with those from other European countries, targeting frequently isolated respiratory pathogens. For non-severe CAP, benzyl penicillin was recommended, and for severe CAP, the addition of gentamicin or alternatively cefotaxime in monotherapy. A revision in 2020 left most recommendations unchanged, but added that CAP managed in intensive care settings should receive cefotaxime in combination with ciprofloxacin [7].

The objective of this study was to investigate antimicrobial therapy for CAP in a low AMR setting at a regional, university teaching hospital over six consecutive years during multiple and continuous antimicrobial stewardship efforts, and the interruption of a coronavirus pandemic.

Patients and methods

Study setting

A 1.000-bed university teaching hospital in Norway, accepting all patients, included patients with covid-19.

Study population

For each year from 2016 to 2021 we used hospital administration data to retrospectively identify patients ascribed with a pneumonia diagnosis at discharge. Criteria for identification were ICD-10 J13 to J18.9 as a primary diagnosis, months from March throughout May, age above 18 years, and admission to hospital antimicrobial therapy at the medical or pulmonary ward, or the intensive care unit. In order to minimize selection bias, cases ascribed with a viral aetiology to lower respiratory tract infection were not included in the criteria for identification. We chose months from March throughout May to reduce influenza virus disease influence, and to address regular hospital staffing outside of summer holiday circumstances.

To include definite CAP cases and an unequivocal study cohort, several exclusion criteria were established. Among these were hospital-acquired or ventilator-associated infections, aspiration pneumonias, pneumonia in nursing home residents, in the returned traveler, in the immunocompromised patient, and in patients diagnosed with chronic obstructive pulmonary disease, or infection in the lower respiratory tract other than pneumonia. We also excluded cases if length of stay exceeded 28 days. Criteria for clinically significant immunosuppression that were used in a recent randomized clinical trial on CAP management, were applied [8]. Exclusion criteria secured that cases investigated were likely to be diagnosed and treated according to the CAP clinical practice guideline recommendations.

Study outcomes

The primary outcome of the study was proportions of CAP episodes that received antimicrobial therapy in accordance with clinical practice guideline recommendations. This included proportions each year that received narrow-spectrum beta-lactams, and proportions that received broad-spectrum antimicrobial therapy. The clinical practice guideline recommendations are provided in the appendix.

Data collection

A study group, consisting of clinical pharmacists and an infectious diseases physician performed data collection and evaluation after each study year. Both discharge letters, medical records, radiological evaluations, and laboratory data were recovered and analyzed.

We have previously published data on an antimicrobial diagnostic strategy in the emergency room (ER) setting targeting respiratory tract specimen sampling [9]. This intervention included CAP episodes from 2016 to 2018. We then wanted to expand the knowledge on CAP management in our institution, in order to evaluate the impact of stewardship efforts on antimicrobial therapy for the ensuing years.

Laboratory procedures

In the laboratory, we used conventional techniques to secure microbiological confirmations from cultures.

Waagsbø *et al. BMC Pulmonary Medicine*   (2022) 22:379

Page 3 of 10

We also applied nucleic acid amplification techniques (NAAT) whenever this was required from the attending physician or laboratory personnel according to laboratory practice. All lower respiratory tract specimens were subjected to microscopy by a microbiologist before cultivation. The polymorphonuclear to squamous epithelial cell ratios were used to determine indications for cultivation. Laboratory personnel was uninformed of the study, seeking to maintain everyday clinical laboratory service.

Stewardship measures

Antimicrobial stewardship measures aiming at several therapy features were disseminated throughout the institution during the study period. These included, but were not limited to, both diagnostic and therapeutic aspects of CAP management. Of particular focus were disease severity assessment, timely administration of antimicrobial therapy, selection of empirical regimens, de-escalation strategies, targeted antimicrobial therapy, oral regimen conversion, and the overall therapy duration. Most efforts were directed at increasing adherence to national clinical practice guideline recommendations. A revised and updated national clinical practice guideline was available from 2020 [7], and relevant contents were transferred to local clinical practice management procedure that same year.

All measures and areas of focus were applied to clinicians through a dedicated, institutional antibiotic team consisting of an infectious disease physician, clinical microbiologist, and clinical pharmacists. Initially we offered tutoring sessions to on-call physicians in selected departments, targeting CAP management recommendations. The next year and thereafter we conducted monthly visits to the ER and selected departments, addressing on-call physicians, ward-level physicians, and nurse staffing with CAP management recommendations. We also provided yearly statistics on performance for all selected departments, and AMR reports that compared narrow-spectrum to broad-spectrum regimens. Interventions are described in detail in the appendix.

Antimicrobial therapy

We defined penicillinase-susceptible penicillins, amoxicillin, and doxycycline narrow-spectrum antimicrobials, whilst beta-lactams co-formulated with enzyme inhibitors, cephalosporins, carbapenems, and quinolones, broad-spectrum antimicrobials. The addition of gentamicin has been used for decades for severe CAP in Nordic countries, especially in cases of structural pulmonary disease. Macrolides has traditionally been indicated to cover for atypical aetiology or in case of beta-lactam allergy for non-severe CAP. According to clinical practice guideline recommendations, broad-spectrum antimicrobial therapy for CAP was indicated in cases of known renal failure, sepsis syndrome with organ dysfunction at admission, or if suspicion of CAP caused by an extended spectrum beta-lactamase (ESBL) producing pathogen. In the absence of these conditions, we defined administered broad-spectrum antimicrobial therapy unjustified.

Therapy days were measured as complete days if $\geq 50\%$ of the dosages were administered for that 24-hour dose interval. Duration of therapy was assessed using number of days prescribed with empirical and targeted antimicrobial therapy from the first antimicrobial therapy day after hospital admittance to the registered last day of therapy after hospital discharge.

Statistical analyses

Descriptive statistics were used to delineate antimicrobial therapy instituted for CAP. Empirical and targeted antimicrobial therapy were compared between study years. Especially, adherence to national clinical practice guidelines was assessed for each year. A chi-square association model was used to detect change in therapy regimens and aetiology between study years. For the comparison of means between study years, a one-way ANOVA was employed. $P < 0.05$ was used as clinical significance level.

Ethical considerations

The study was approved by the Regional Committee for Medical and Health Research Ethics (REK 2017/1439), data protection officials, and the hospital administration. Inclusion of patients was performed without consent, on the basis of a retrospective study design, assuming that all included cases received best practice as described in national clinical practice guideline recommendations. Antimicrobial stewardship measures were aimed to optimize adherence to clinical practice guidelines.

Results
Patient characteristics

Over the six-year study period, 1.839 unique hospital discharges were identified meeting the identification criterion of pneumonia as a primary diagnosis. Of these, 726 fulfilled one or more exclusion criteria and were rejected from further analyses. The remaining portion constituted 1.112 unique episodes of adult, community-acquired, hospitalized pneumonia, devoid of clinically relevant immunocompromise or chronic obstructive pulmonary disease, and of which 91% were radiologically confirmed. Clinical signs and symptoms, microbiological confirmations, and the clinical response to the instituted antimicrobial therapy were used to verify CAP-diagnosis in radiologically unconfirmed cases. Descriptive statistics for the patient population are presented in Table 1. Included episodes did not differ between years for all comparisons.
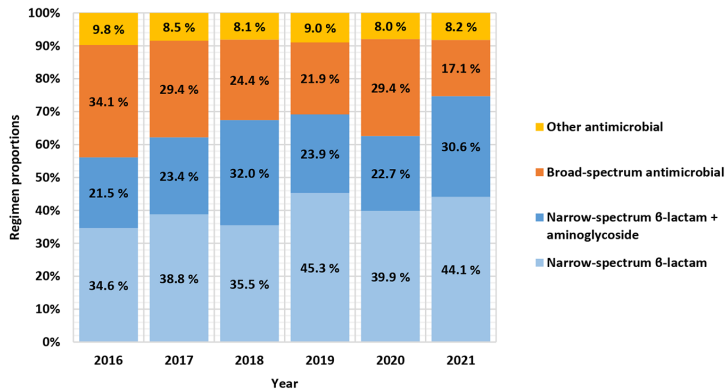
Fig. 1 Proportions of empirical regimens for CAP per year

Antimicrobial therapy

About 20% of CAP episodes had received antimicrobial therapy before hospital admission, with variations between years ranging from 17 to 23%. Prehospital prescriptions were mainly narrow-spectrum beta-lactams such as phenoxymethylpenicillin, amoxicillin, and dicloxacillin adding up to 54%, trimethoprim-sulfametoxazole to 14%, and ciprofloxacin to 12%.

Empirical antimicrobial therapy were initiated to all admitted cases on suspicion of bacterial CAP. Interestingly, a total of 16 different generic antibiotic substances were administered as the initial drug of choice, of which the majority were narrow-spectrum beta-lactams. The empirical antimicrobial therapy used for each study year is presented as proportions in Fig. 1.

As described in the method section an antimicrobial stewardship team launched several measures to actively improve diagnostic and therapy strategies. Using an association model for all regimens, a statistically significant increase in proportions that received narrow-spectrum beta-lactams, including beta-lactams combined with an aminoglycoside (Pearson chi-square $\chi^2=17.3$; df 5; p=0.004) was observed throughout the study period. The proportion increased from 56.1 to 74.4%, which represented a relative change of 32.6%. Narrow-spectrum beta-lactams were frequently combined with gentamicin, at proportions ranging from 21.5 to 32.0% between years,

and for a mean duration of 2.8 days (95% CI 2.2–3.4) for all years. The proportions that annually received gentamicin did not significantly differ (Pearson chi-square $\chi^2=9.3$; df 5; p=0.097).

Correspondingly, proportions that received broad-spectrum cefotaxime, ceftriaxone, piperacillin-tazobactam or any carbapenem declined significantly from 34.1 to 17.1% (Pearson chi-square $\chi^2=19.4$; df 5; p=0.002), which constitute a relative reduction of 49.9%. For all years combined, broad-spectrum antimicrobial therapy was administered in cases of established renal disease, sepsis-syndrome, management in the ICU setting, beta-lactam allergy, and ESBL-producing pathogen, in 12.2%, 11.4%, 6.1%, 6.0% and 0.2%, respectively. Unjustified broad-spectrum antimicrobial therapy constituted 64.1% of episodes for all years. However, a statistically significant decline per year was observed (Pearson chi-square $\chi^2=16.8$; df 5; p=0.005). There was a notable discrepancy in empirical antimicrobial therapy for the year 2020, as cefotaxime were frequently administered. Mortality and readmission rates were comparable between years, as described in Table 1.

Aetiology and resistance

Proportions of CAP episodes that were microbiologically confirmed increased from 33.7 to 56.2% during the study period. A Pearson Chi-square correlation model returned a statistically significant increase between years (χ2:

Table 1 Patient characteristics and outcomes for included CAP episodes

n	Patients	205	201	172	201	163	170	1112	0.086
Age	Mean (years)	70,5	68,5	72,8	69,0	71,1	70,4	70,3	0.196
Age group	< 50 years	11,7%	14,4%	6,4%	14,4%	11,7%	10,6%	11,7%	
	50–75 years	38,0%	42,3%	40,7%	38,8%	35,0%	38,8%	39,0%	
	> 75 years	50,2%	43,3%	52,9%	46,8%	53,4%	50,6%	49,3%	0.966
Gender	Male (%)	43,9%	51,7%	48,8%	44,8%	41,7%	41,8%	45,5%	0.299
	Female (%)	56,1%	48,3%	51,2%	55,2%	58,3%	58,2%	54,5%	
Comorbidities*	Number of conditions (median)	3	3	3	3	3	3	3	0.914
	Charlson comobidity index (median)	4	4	4	4	4	4	4	
CRB65	0–1 (%)	141 (69%)	133 (66%)	128 (74%)	147 (73%)	119 (73%)	115 (68%)	783 (70%)	
	2 (%)	51 (25%)	49 (24%)	38 (22%)	46 (21%)	35 (21%)	49 (29%)	268 (24%)	
	3–4 (%)	13 (6%)	19 (9%)	6 (3%)	8 (4%)	9 (6%)	6 (4%)	61 (5%)	0.570
ICU	Admittance (n, %)	11 (5%)	18 (9%)	14 (8%)	7 (3%)	9 (6%)	9 (5%)	68 (6%)	0.222
Ventilation	Invasive (n, %)	7 (3%)	8 (4%)	6 (3%)	9 (4%)	6 (4%)	6 (4%)	42 (4%)	0.995
	NIPPV (n, %)	18 (9%)	16 (8%)	17 (10%)	22 (11%)	16 (10%)	20 (12%)	109 (10%)	0.304
Sepsis	Without shock (n, %)	22 (11%)	16 (8%)	23 (13%)	16 (8%)	16 (10%)	14 (8%)	107 (10%)	0.740
	Septic shock (n, %)	2 (1%)	3 (1%)	3 (2%)	5 (2%)	4 (2%)	5 (3%)	22 (2%)	0.757
Length of stay	Mean (days), and (95% CI)	7.4 (6.6–8.2)	7.3 (6.7–7.8)	7.0 (6.3–7.7)	6.7 (6.2–7.3)	7.8 (7.1–8.4)	7.2 (6.5–7.8)	7.2 (6.9–7.5)	0.342
Re-admission	30 day (n, %)	16 (7.8)	11 (5.5)	6 (3.5)	12 (5.9)	6 (3.7)	8 (4.7)	59 (5.3)	0.860
Mortality	In-hospital (n, %)	22 (11%)	21 (10%)	16 (9%)	20 (10%)	18 (11%)	20 (12%)	117 (11%)	0.984
	30 day (n, %)	28 (14%)	26 (13%)	24 (14%)	22 (11%)	29 (18%)	23 (14%)	152 (14%)	0.512
	90 day (n, %)	56 (27%)	46 (23%)	42 (24%)	40 (20%)	39 (24%)	44 (26%)	267 (24%)	0.498
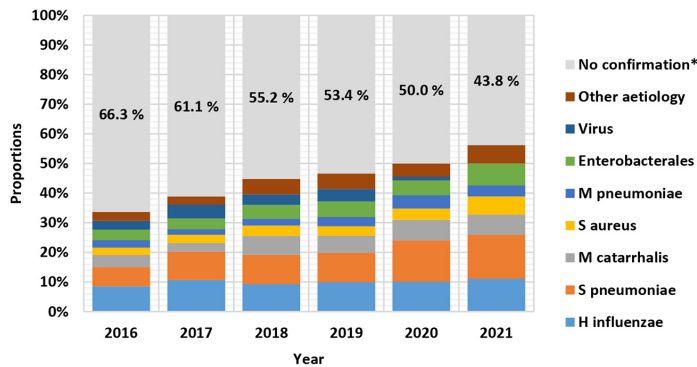
	2016	2017	2018	2019	2020	2021
No confirmation*	132	132	95	102	79	71
Other aetiology	3	4	4	7	6	7
Virus	6	10	6	8	2	0
Enterobacterales	7	8	8	10	11	14
M pneumoniae	5	4	4	6	7	6
S aureus	5	6	6	6	6	10
M catarrhalis	8	6	11	11	11	11
S pneumoniae	13	21	17	19	22	24
H influenzae	17	23	16	19	16	18

***Culture and/or NAAT negative or normal flora.**

Fig. 2 Definite CAP aetiology per year

23.431, df5, p < 0.001). Likewise, proportions of CAP episodes devoid of microbiological confirmation decreased accordingly. Respiratory tract pathogens that were most frequently detected were *S. pneumoniae, H. influenza,*
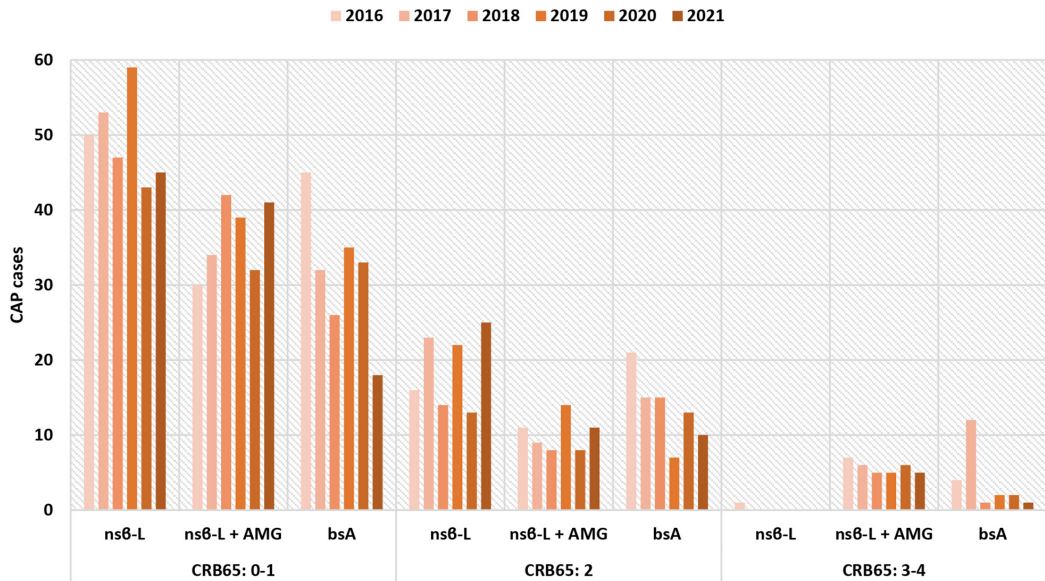
Fig. 3 Empirical antimicrobial therapy stratified by CRB65-category. Abbrevations: nsβ-L = narrow-spectrum betalactam, AMG = aminoglycoside, bsA = broad-spectrum antimicrobial

and *M. catarrhalis* that accounted for 23.8%, 22.4% and 11.9% for all years, respectively. The use of nuclear acid amplification (NAAT) tests identified 7–17% of CAP aetiology depending on inclusion year. CAP episodes with a clinically relevant positive blood culture also remained unchanged, as range spanned from 3.2 to 4.8% between years. Aetiology for CAP is presented in Fig. 2.

Proportions of microbiologically confirmed cases with an AMR phenotype were assessed. All the 116 of 116 (100.0%) *S. pneumoniae* isolates remained fully susceptible to penicillin. Among *H. influenzae* cases 19 of 109 (17.4%) were resistant to ampicillin. No cases of methicillin resistant *S. aureus* (MRSA) were reported, and among *Enterobacterales*, 2 of 53 cases (3.8%) were ESBL positive. No cases of multiresistant *P. aeruginosa* or *Legionella pneumophila* were reported.

CAP severity
Disease severity at presentation was assessed for all CAP episodes. We retrospectively applied CRB65-criteria and stratified this to the various empirical antimicrobial therapy regimens. CAP episodes that scored 0–1, 2 or 3–4 constituted 70.4%, 24.1% and 5.5%, respectively, with minimal variation between years. In the CRB65 0–1 category, a substantial proportion of CAP episodes received a broad-spectrum antimicrobial. However, this proportion declined in the study period, although statistically insignificant. Among episodes presenting within the

CRB65 3–4 category, very few received narrow-spectrum beta-lactam therapy only, while the majority received narrow-spectrum beta-lactam in combination with an aminoglycoside. Figure 3 presents the administered empirical antimicrobial regimens.

Antimicrobial de-escalation
De-escalation strategies were assessed for CAP episodes that were microbiologically confirmed and received broad-spectrum empirical antimicrobial therapy. The assessment included the timely transition from empirical to targeted antimicrobial therapy, and the transition from intravenous to oral administration route. For all CRB65 groups, broad-spectrum antimicrobial therapy was continued in 66.4% of episodes, without the transition to a more preferred narrow-spectrum therapy, although this would have been feasible in regard to antimicrobial susceptibility (AMS) testing. In 24.6% of episodes, de-escalation was applied, however, on average 1.9 days beyond the AMS reporting time point. For most CAP episodes an intravenous to oral conversion was feasible, but not performed at the AMS reporting time point. Table 2 summarizes the strategies for antimicrobial therapy from the time point of AMS testing being reported.

Duration of therapy
Prehospital therapy was excluded from duration analyses because of consistently unreliable information. Figure 4

Table 2 Antimicrobial strategies used for microbiologically confirmed CAP episodes that received broad-spectrum antimicrobial therapy

	CRB65 0–1	CRB65 2	CRB65 3–4	All groups
n	88	35	11	134
Strategy instituted at point of AMS reporting				
Broad-spectrum to narrow-spectrum B-lactam transition	28,4%	20,0%	9,1%	24,6%
Transition not recommended	6,8%	8,6%	27,3%	9,0%
Transition feasible, but continued broad-spectrum antimicrobial	64,8%	71,4%	63,6%	66,4%
Administration form instituted at point of AMS reporting				
Intravenous to oral conversion	20,5%	14,3%	0,0%	17,2%
Conversion not possible	11,4%	17,1%	45,5%	15,7%
Conversion possible, but not performed	68,2%	68,6%	54,5%	67,2%

describes the therapy duration for all included CAP episodes. The combined mean duration of therapy was 11.0 days (95% CI 10.9–11.1). Using a one-way ANOVA comparison of means returned a small but statistically significant reduction in total antimicrobial therapy duration from 11.5 to 10.2 days (p < 0.001). This reduction was largely attributed to shorter oral regimens.

Discussion

In this retrospective observational study of adult, hospitalized CAP in immunocompetent, non-COPD patients, we have investigated trends in antimicrobial therapy for six consecutive years during antimicrobial and diagnostic stewardship measures. A significant increase in proportions that received narrow-spectrum beta-lactams from 56 to 75%, and correspondingly, a decrease in proportions that received broad-spectrum antimicrobial therapy from 34 to 17% were observed. During the coronavirus pandemic year 2020, a larger extent of bacterial CAP episodes initially received third generation cephalosporins. Overall, de-escalation strategies were frequently unutilized, and therapy duration exceeded recommendations substantially. Increased focus on routine microbiological diagnostic strategies increased the absolute microbiological yield from 33.7 to 56.2% without the implementation of new laboratory methods. We found low and comparable rates of AMR. Mortality and re-admission rates between years remained unchanged, underscoring that stewardship measures seem justified in order to increase adherence to therapy guideline recommendations.

Narrow-spectrum regimens are recommended as first line therapy for hospitalized, non-severe CAP in several clinical practice guidelines [3, 7, 10, 11]. These include penicillinase-susceptible penicillins, amoxicillin, or doxycycline, whilst beta-lactams co-formulated with enzyme inhibitors, cephalosporins, carbapenems, quinolones and macrolides, are generally considered broad-spectrum antimicrobials. We have here reported a statistically
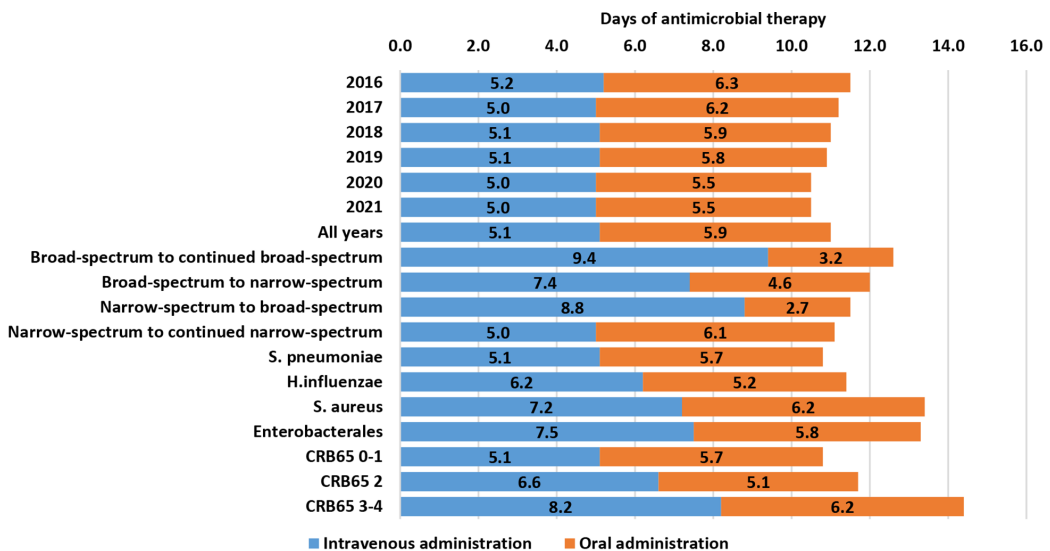
Fig. 4 Antimicrobial therapy duration stratified by years, antimicrobial therapy, aetiology and disease severity

significant increased use of narrow-spectrum, warranted beta-lactams. We believe this increase is due to the continued efforts from stewardship measures to influence on diagnostic and therapy management to this strategic patient group, as shown previously by others [8, 12]. Of note, the increase in narrow-spectrum antimicrobial therapy did not result in altered mortality or re-admission rates.

CAP management is an important subject for antimicrobial stewardship [4]. In a recent, cluster randomized intervention study from twelve hospitals in the Netherlands, broad-spectrum antimicrobial therapy for non-severe CAP were decreased from 6.5 to 4.8 days, which represents a relative reduction of 27% [8]. The 90-day mortality was comparable between the control and the intervention group at 10.9% and 10.8%, respectively. In our study, we reported proportions that received narrow-spectrum and broad-spectrum regimens, and the latter was reduced over the six-year study period from 34 to 17%, a relative reduction of nearly 50%. This result is in line with antimicrobial stewardship guideline recommendations, which favor interventions that target specific infectious syndromes such as CAP [13].

Adherence to CAP guideline recommendations is important. Several studies have provided evidence that adherence is efficacious and safe for the management of non-severe CAP [8, 12, 14, 15]. A 2017 meta-analysis showed that guideline-adherent prescriptions of hospital antimicrobial therapy increased from 43 to 58% after the implementation of stewardship interventions [12]. In our study, we noted that a wide range of empirical regimens were deployed in the ER setting at presentation, although a majority were narrow-spectrum antimicrobials. This could reflect diagnostic challenges in the ER setting, rather than non-adherence to guideline recommendations. The Dutch study also signals that even during study enrollment, physicians are reluctant to prescribe narrow-spectrum therapy for non-severe CAP, as evident by the low adherence in the control group [8]. It also showed that prescription habits during trial settings varied substantially between participating hospitals, as broad-spectrum antimicrobial therapy for non-severe CAP were unequally reduced, ranging from 17 to 39%. In our study, unwarranted and unjustified broad-spectrum antimicrobial therapy was frequently initiated and continued without a documented rationale. We were unable to point out specific reasons for this pattern. In microbiologically unconfirmed cases, we anticipate that clinical improvement while on a broad-spectrum regimen could explain reasons to defer transition. In addition, we also anticipate that if microbiologic tests provide definite or possible aetiology, several clinicians are still reluctant to make therapy transition as long as clinical improvement is observed. However, these hypotheses do not explain why non-severe CAP cases were prescribed broad-spectrum regimens in the first place.

Therapy for CAP was transiently deviating during the first pandemic year 2020, as a substantial larger proportion were prescribed cefotaxime. This could relate to insufficient evidence-based therapy recommendations for the treatment of COVID-19 with a possible concurrent bacterial superinfection at that time point. However, Norwegian health authorities rapidly deployed guidelines on COVID-19 management in April 2020. In the present study, we took active steps not to include lower respiratory tract infections with a definite or possible viral aetiology.

Adherence to CAP guideline recommendations also includes diagnostic strategies in order to provide definite or possible aetiology. We achieved a considerable increase from 33.7 to 56.2% in cases that were microbiologically confirmed. We have previously reported the results of an intervention study focusing on upscaling numbers and quality of lower respiratory tract secretions [9]. Our studies were conducted relying on standard laboratory protocols, and this leads us to conclude that interventional rather than new or extended laboratory services prevailed.

The assessment of disease severity has consistently played a key role to antimicrobial therapy approach in CAP [3]. This is also highlighted in Norwegian guideline recommendations. However, our study reveals that documented severity assessment is generally lacking and therefore under-communicated, maybe relying on a more pragmatic definition that CAP patients admitted to the ICU constitute severe cases.

De-escalation strategies are heavily recognized as a part of the global antimicrobial stewardship approach [16, 17]. Transition to narrow-spectrum, targeted antimicrobial therapy, and the timely conversion to oral formulations, were frequently unutilized among included cases in our study. Written documentation of such assessments was uniformly lacking. The optimal de-escalation strategies are to some extent studied in the ICU setting and in mechanical ventilated patients [18]. For non-severe CAP, as for several other non-severe infections, the impact of stewardship measures depends on many human and organizational factors [19, 20]. Despite evidence-based approach to target de-escalations strategies, barriers to guideline adherence exist among physicians. A more efficient strategy to overcome these barriers may be to tailor interventions to human behavioral change [20].

Therapy duration exceeded guideline recommendations substantially in our study. Comparable findings are previously reported [21–23]. The rationale for shorter duration (<6 days) for CAP, regardless of disease severity, proved non-inferior to longer (>7 days) in a recent meta-analysis comprising 21 trials which included over

Waagsbø *et al. BMC Pulmonary Medicine*   (2022) 22:379

Page 9 of 10

4.000 patients [24]. A recent, double-blind, randomized, placebo-controlled, non-inferiority trial from France showed that 3 days of beta-lactam therapy plus 5 more days of placebo, was non-inferior to 5 more days of amoxicillin-clavulanate, for CAP episodes that met clinical stability criteria [25]. Cure rates at day 15 were 77% and 68%, respectively, and incidences for adverse events were comparable. The implementation of certain clinical stability criteria in CAP, has previously been shown in a large multicenter, non-inferiority, randomized clinical trial to be a safe strategy when assessing therapy duration [26]. The observed therapy duration in our study warrants new approaches to understand reasons for deferring antimicrobial cessation.

Our observational study has limitations and some strengths. The nature of the collected data did not allow for timing of antimicrobial therapy, only dates. In addition, the availability of clinical evaluations and reasoning on empirical and targeted therapy, microbiology results, susceptibility results, disease severity, and de-escalation strategies, were largely dependent on what attending physicians found necessary to document. This may contribute to missing or misinterpretation of data. The observational nature of the study does not unequivocally state the presence of a causal relationship between the intervention implemented and the CAP management results. Previous studies have documented that a substantial proportion of patients admitted for lower respiratory tract symptoms resembling CAP, and received antimicrobial therapy for this, ultimately are diagnosed with non-infectious causes [27]. To minimize this, and to avoid cohort heterogeneity, we applied several, strict exclusion criteria. In addition, in the Dutch study, only 25% of included CAP episodes were radiologically confirmed [8], as opposed to 91% in our study. We agree that several important questions remain unanswered in CAP management, especially microbiological confirmation strategies, the role of molecular technology, and therapy optimization [28], and that randomized clinical trials are needed to clarify optimal management. However, we support observational strategies to provide effectiveness studies on guidelines adherence at an everyday clinical practice level, outside of trial settings [29].

In conclusion, antimicrobial therapy for CAP at our teaching university hospital was frequently non-adherent to national clinical practice guideline recommendations. Non-adherence was particularly frequent for empirical regimens in non-severe CAP, for the timely de-escalation to targeted antimicrobial therapy, for the timely transition to oral regimens, and for overall therapy duration. However, adherence was to a large extent modifiable. The study reaffirms CAP as an important target for antimicrobial stewardship, and CAP seem suitable for interventions to increase adherence.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12890-022-02178-6.

Supplementary Material 1
Supplementary Material 2

Data availability
The datasets generated and analysed during the current study are not publicly available due to large file sizes and complex registrations but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The protocol for each study year was evaluated and approved by the Regional Committees for Medical and Health Research Ethics, Norwegian University of Science and Technology NTNU/Regional Ethic Committee Central, Faculty of Medicine, Pb 8905, 7491 Trondheim. Approval number was 2017/1439, head of secretariat Hilde Eikemo. Data protection officials, and the hospital administration also approved the study. The study was conducted in line with the conclusion from the Regional Committees for Medical and Health Research Ethics, Central, that informed consents were not required to access or publish the data. An informed consent waiver was obtained from the St. Olavs hospital, Trondheim University Hospital. This consent waiver was evaluated by the Regional Committees for Medical and Health Research Central, before approval of the study. Consent to participate was not obtained. 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
Not applicable.

Competing interests
Author Bjørn Waagsbø is a representative to the directory group in the Norwegian Directorate of Health that seek to revise recommendations in the national clinical practice guideline for antimicrobial therapy.

Transparency declaration
None to declare.

References
1. Lallukka T, et al., GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015 (vol 388, pg 1459, 2016). Lancet, 2017. 389(10064): p. E1-E1.

2. Bartlett JG. Diagnostic Tests for Agents of Community-Acquired Pneumonia. Clin Infect Dis. 2011;52:S296–304.
3. Metlay JP, et al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med. 2019;200(7):E45–67.
4. Viasus D, et al. Antibiotic stewardship in community-acquired pneumonia. Expert Rev Anti-Infective Therapy. 2017;15(4):351–9.
5. Antimicrobial Resistance C. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet. 2022;399(10325):629–55.
6. 2020 NN-V, Usage of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Norway. 2020.
7. Health ND.o. Antimicrobial therapy in hospitals. 2020 [cited 2021 Dec 11th 2021]; Available from: https://www.helsedirektoratet.no/retningslinjer/antibiotika-i-sykehus/luftveisinfeksjoner-nedre.
8. Schweitzer VA, et al. Narrow-spectrum antibiotics for community-acquired pneumonia in Dutch adults (CAP-PACT): a cross-sectional, stepped-wedge, cluster-randomised, non-inferiority, antimicrobial stewardship intervention trial. Lancet Infect Dis; 2021.
9. Waagsbo B, et al. Diagnostic stewardship aiming at expectorated or induced sputum promotes microbial diagnosis in community-acquired pneumonia. BMC Infect Dis. 2022;22(1):203.
10. Athlin S, et al. Management of community-acquired pneumonia in immunocompetent adults: updated Swedish guidelines 2017. Infect Dis. 2018;50(4):247–72.
11. Wiersinga WJ, et al. Management of community-acquired pneumonia in adults: 2016 guideline update from the Dutch Working Party on Antibiotic Policy (SWAB) and Dutch Association of Chest Physicians (NVALT). Neth J Med. 2018;76(1):4–13.
12. Davey P, et al., Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database of Systematic Reviews, 2017(2).
13. Barlam TF, et al. Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis. 2016;62(10):e51–77.
14. Hogli JU, et al., Empirical prescribing of penicillin G/V reduces risk of readmission of hospitalized patients with community-acquired pneumonia in Norway: a retrospective observational study. Bmc Pulmonary Medicine, 2020. 20(1).
15. Wathne JS, et al. The association between adherence to national antibiotic guidelines and mortality, readmission and length of stay in hospital inpatients: results from a Norwegian multicentre, observational cohort study. Antimicrobial Resistance and Infection Control; 2019. p. 8.
16. Tabah A, et al. A Systematic Review of the Definitions, Determinants, and Clinical Outcomes of Antimicrobial De-escalation in the Intensive Care Unit. Clin Infect Dis. 2016;62(8):1009–17.
17. Aliberti S, et al. Community-acquired pneumonia. Lancet. 2021;398(10303):906–19.
18. Trupka T, et al., Enhanced antimicrobial de-escalation for pneumonia in mechanically ventilated patients: a cross-over study. Critical Care, 2017. 21.
19. Pulcini C, et al. The impact of infectious disease specialists on antibiotic prescribing in hospitals. Clin Microbiol Infect. 2014;20(10):963–72.
20. Hulscher MEJL, Prins JM. Antibiotic stewardship: does it work in hospital practice? A review of the evidence base. Clin Microbiol Infect. 2017;23(11):799–805.
21. Egelund GB, et al., Penicillin treatment for patients with Community-Acquired Pneumonia in Denmark: a retrospective cohort study. Bmc Pulmonary Medicine, 2017. 17.
22. Vaughn VM, et al. Excess Antibiotic Treatment Duration and Adverse Events in Patients Hospitalized With Pneumonia: A Multihospital Cohort Study. Ann Intern Med. 2019;171(3):153–63.
23. Aliberti S, et al. Duration of antibiotic therapy in hospitalised patients with community-acquired pneumonia. Eur Respir J. 2010;36(1):128–34.
24. Tansarli GS, Mylonakis E. Systematic Review and Meta-analysis of the Efficacy of Short-Course Antibiotic Treatments for Community-Acquired Pneumonia in Adults. Antimicrobial Agents and Chemotherapy, 2018. 62(9).
25. Dinh A, et al. Discontinuing beta-lactam treatment after 3 days for patients with community-acquired pneumonia in non-critical care wards (PTC): a double-blind, randomised, placebo-controlled, non-inferiority trial. Lancet. 2021;397(10280):1195–203.
26. Uranga A, et al. Duration of Antibiotic Treatment in Community-Acquired Pneumonia A Multicenter Randomized Clinical Trial. Jama Intern Med. 2016;176(9):1257–65.
27. Musher DM, et al. Can an etiologic agent be identified in adults who are hospitalized for community-acquired pneumonia: Results of a one-year study. J Infect. 2013;67(1):11–8.
28. Peghin M, Bouza E. Community-acquired pneumonia: is less more? Lancet Infect Dis; 2021.
29. Faraoni D, Schaefer ST. Randomized controlled trials vs. observational studies: why not just live together? Bmc Anesthesiology, 2016. 16.
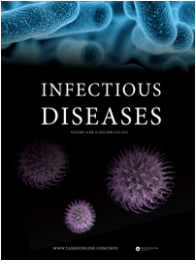
Publisher's Note

Paper III

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, Nora Stuve, Jan Egil Afset, Pål Klepstad, Skule Mo, Lars Heggelund & Jan Kristian Damås

Published online: 16 Jun 2022.

Submit your article to this journal ↗

Article views: 775

View related articles ↗

View Crossmark data ↗

ORIGINAL ARTICLE

ⅈ OPEN ACCESS ☑ Check for updates

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.

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.

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 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 %	

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)	(0.00–0.03)	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		
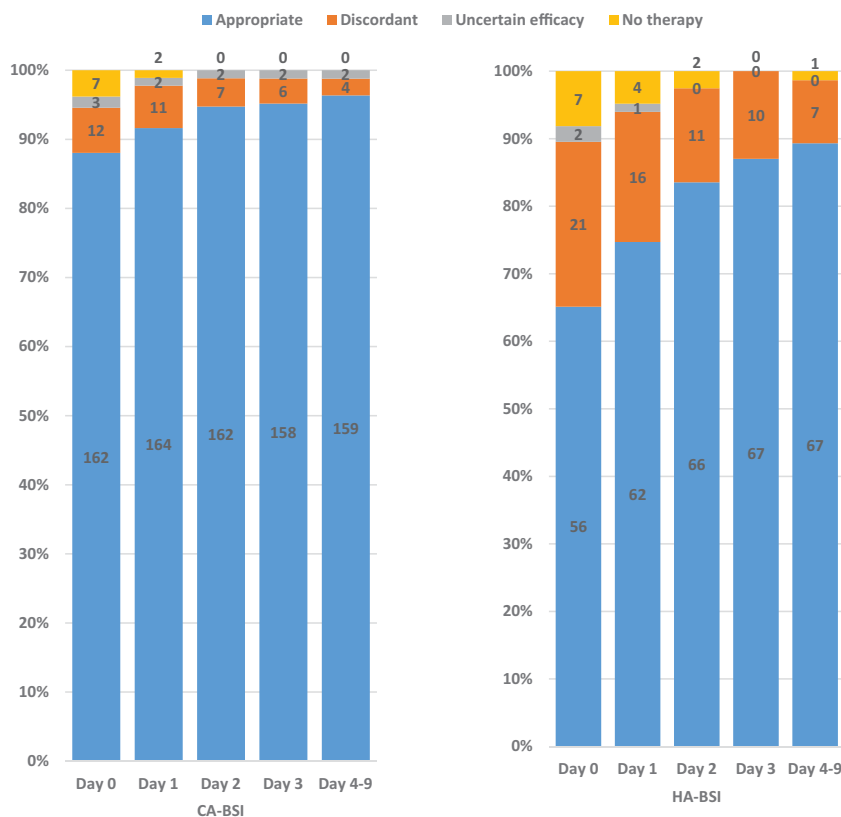
Figure 1. Coverage of empirical antimicrobial therapy according to *in vitro* susceptibility testing.

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 nonetheless put forward several comprehensive antimicrobial stewardship measures in order to preserve rational antimicrobial therapy usage and maintain the favourable 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

Funding

ORCID

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

References

[1] Goto M, Al-Hasan MN. Overall burden of bloodstream infection and nosocomial bloodstream infection in North America and Europe. Clin Microbiol Infect. 2013;19(6):501–509.

[2] Paulsen J, Mehl A, Askim Å, et al. Epidemiology and outcome of Staphylococcus aureus bloodstream infection and sepsis in a Norwegian county 1996–2011: an observational study. BMC Infect Dis. 2015;15(1):116.

[3] Wyllie DH, Crook DW, Peto TE. Mortality after Staphylococcus aureus bacteraemia in two hospitals in Oxfordshire, 1997–2003: cohort study. BMJ. 2006;333(7562):281.

[4] de Kraker MEA, Jarlier V, Monen JCM, et al. The changing epidemiology of bacteraemias in Europe: trends from the European antimicrobial resistance surveillance system. Clin Microbiol Infect. 2013;19(9):860–868.

[5] Fitzpatrick JM, Biswas JS, Edgeworth JD, et al. Gram-negative bacteraemia; a multi-Centre prospective evaluation of empiric antibiotic therapy and outcome in English acute hospitals. Clin Microbiol Infect. 2016;22(3):244–251.

[6] Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Crit Care Med. 2017;45(3):486–552.

[7] Kang C-I, Kim S-H, Park WB, et al. Bloodstream infections caused by antibiotic-resistant gram-negative bacilli: risk factors for mortality and impact of inappropriate initial antimicrobial therapy on outcome. Antimicrob Agents Chemother. 2005;49(2):760–766.

[8] Paul M, Shani V, Muchtar E, et al. Systematic review and meta-analysis of the efficacy of appropriate empiric antibiotic therapy for sepsis. Antimicrob Agents Chemother. 2010;54(11):4851–4863.

[9] Marquet K, Liesenborgs A, Bergs J, et al. Incidence and outcome of inappropriate in-hospital empiric antibiotics for severe infection: a systematic review and meta-analysis. Crit Care. 2015;19(1):63.

[10] de Groot B, Ansems A, Gerling DH, et al. The association between time to antibiotics and relevant clinical outcomes in emergency department patients with various stages of sepsis: a prospective multi-center study. Crit Care. 2015; 19(1):194.

[11] Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA. 2016;315(8):801–810.

[12] Ibrahim EH, Sherman G, Ward S, et al. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. Chest. 2000; 118(1):146–155.

[13] Plachouras D, Lepape A, Suetens C. ECDC definitions and methods for the surveillance of healthcare-associated infections in intensive care units. Intensive Care Med. 2018; 44(12):2216–2218.

[14] Jakovljev A, Bergh K. Development of a rapid and simplified protocol for direct bacterial identification from positive blood cultures by using matrix assisted laser desorption ionization time-of- flight mass spectrometry. BMC Microbiol. 2015;15(1):258.

[15] Matuschek E, Brown DFJ, Kahlmeter G. Development of the EUCAST disk diffusion antimicrobial susceptibility testing method and its implementation in routine microbiology laboratories. Clin Microbiol Infect. 2014;20(4):O255–O266.

[16] AST N. Nordic Committee on Antimicrobial Susceptibility Testing. 2021. [cited 2021 1st June 2020]; Available from: http://www.nordicast.org/index.

[17] Testing T. Breakpoint tables for interpretation of MICs and zone diameters. 2021. [cited 2020 1st June 2020]; Available from: https://www.eucast.org/clinical_breakpoints/.

[18] Helsedirektoratet. Antibiotika i sykehus. Sepsis2020. [cited 2020 15th May 2020]; Available from: https://www.helsedirektoratet.no/retningslinjer/antibiotika-i-sykehus/sepsis.

[19] Nygard ST, et al. Aetiology, antimicrobial therapy and outcome of patients with community acquired severe sepsis: a prospective study in a Norwegian university hospital. BMC Infect Dis. 2014;14:121.

[20] Mehl A, et al. Trends in antimicrobial resistance and empiric antibiotic therapy of bloodstream infections at a general hospital in mid-Norway: a prospective observational study. Bmc Infectious Diseases. 2017; 17:116.

[21] M.o.H.a.C S. Handlingsplan mot antibiotikaresistens i helsetjenesten. 2015. Helse og omsorgsdepartementet: www.publikasjoner.dep.no.

[22] Retamar P, Portillo MM, López-Prieto MD, et al. Impact of inadequate empirical therapy on the mortality of patients with bloodstream infections: a propensity score-based analysis. Antimicrob Agents Chemother. 2012;56(1):472–478.

[23] Chen H-C, Lin W-L, Lin C-C, et al. Outcome of inadequate empirical antibiotic therapy in emergency department patients with community-onset bloodstream infections. J Antimicrob Chemother. 2013;68(4):947–953.

[24] Grossman C, Keller N, Bornstein G, et al. Factors associated with suitability of empiric antibiotic therapy in hospitalized patients with bloodstream infections. J Chemother. 2017; 29(3):159–163.

[25] Kadri SS, Lai YL, Warner S, et al. Inappropriate empirical antibiotic therapy for bloodstream infections based on discordant in-vitro susceptibilities: a retrospective cohort analysis of prevalence, predictors, and mortality risk in US hospitals. Lancet Infect Dis. 2021;21(2):241–251.

[26] Seymour CW, Gesten F, Prescott HC, et al. Time to treatment and mortality during mandated emergency care for sepsis. N Engl J Med. 2017;376(23):2235–2244.

[27] Kalil AC, Johnson DW, Lisco SJ, et al. Early goal-directed therapy for sepsis: a novel solution for discordant survival outcomes in clinical trials. Crit Care Med. 2017;45(4):607–614.

[28] Tassinari M, Zannoli S, Farabegoli P, et al. Rapid diagnosis of bloodstream infections in the critically ill: evaluation of the broad-range PCR/ESI-MS technology. PLoS One. 2018; 13(5):e0197436.

[29] Timbrook TT, Morton JB, McConeghy KW, et al. The effect of molecular rapid diagnostic testing on clinical outcomes in bloodstream infections: a systematic review and meta-analysis. Clin Infect Dis. 2017;64(1):15–23.

[30] Campion M, Scully G. Antibiotic use in the intensive care unit: optimization and de-escalation. J Intensive Care Med. 2018;33(12):647–655.

[31] Garnacho-Montero J, Escoresca-Ortega A, Fernández-Delgado E. Antibiotic de-escalation in the ICU: how is it best done? Curr Opin Infect Dis. 2015;28(2):193–198.

[32] Turza KC, Politano AD, Rosenberger LH, et al. De-Escalation of antibiotics does not increase mortality in critically ill surgical patients. Surg Infect (Larchmt). 2016;17(1):48–52.

Paper IV
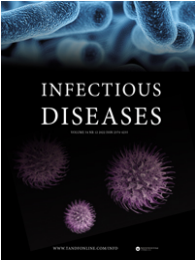
Empirical antimicrobial therapy for bloodstream infections not compliant with guideline was associated with discordant therapy, which predicted poorer outcome even in a low resistance environment

Kornelius Grøv, Erling Håland, Bjørn Waagsbø, Øyvind Salvesen, Jan Kristian Damås & Jan Egil Afset

View supplementary material 🗗

Published online: 09 Aug 2022.

Submit your article to this journal 🗗

Article views: 927

View related articles 🗗

View Crossmark data 🗗

ORIGINAL ARTICLE

Empirical antimicrobial therapy for bloodstream infections not compliant with guideline was associated with discordant therapy, which predicted poorer outcome even in a low resistance environment

Kornelius Grøv[a]*, Erling Håland[a]*, Bjørn Waagsbø[b] , Øyvind Salvesen[c] , Jan Kristian Damås[c,d,e] and Jan Egil Afset[c,e,f]

[a]Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology (NTNU), Trondheim, Norway; [b]Regional Centre for Disease Control in Central Norway Regional Health Authority, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway; [c]Department of Clinical and Molecular Medicine, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology (NTNU), Trondheim, Norway; [d]Department of Infectious Diseases, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway; [e]Gemini centre for sepsis research, Norwegian University of Science and Technology (NTNU), Trondheim, Norway, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway; [f]Department of Medical Microbiology, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway

ABSTRACT

Objectives: To characterise all bloodstream infections (BSIs) in a low antimicrobial resistance (AMR) prevalence setting with regard to the appropriateness of empirical antimicrobial therapy, compliance with the national clinical practice guideline, de-escalation practice and outcome.

Methods: A retrospective observational study including patients aged $\geq$ 18 years admitted to a university hospital in central Norway with positive blood culture in 2019.

Results: We included 756 BSI episodes in our analysis. Empirical antimicrobial therapy was in accordance with the national guideline in 534 (70.6%), and not in accordance in 190 (25.1%) of the BSI episodes. There was a statistically significant association between compliance with the national guideline and concordant empirical antimicrobial therapy ($p = .001$). De-escalation of antimicrobial therapy was possible but not done in 217 (31.1%) of the BSI episodes. Variables identified as independent predictors of discordant empirical antimicrobial therapy included hospital department, type of empirical antimicrobial regimen, bacterial species, and AMR. Independent predictors of intra-hospital case fatality rate were coverage of empirical antimicrobial therapy, CCI-score, SAPS-II score, site of infection, and type of empirical antimicrobial regimen. Furthermore, the intra-hospital and long-term unadjusted all-cause case fatality rates were increased ($p < .001$, log-rank test for overall difference in survival) for the patients who received discordant empirical antimicrobial therapy.

Conclusion: Our study shows that empirical antimicrobial therapy initiated in accordance with national guideline recommendations increases the likelihood of receiving concordant therapy. Discordant empirical antimicrobial therapy was associated with poorer outcomes, even in a setting with low AMR prevalence.

*Kornelius Grøv and Erling Håland share first authorship to this article.

Supplemental data for this article is available online at https://doi.org/10.1080/23744235.2022.2109208.

Introduction

Despite all advances in modern medicine bloodstream infection (BSI) is still a severe disease associated with high morbidity and mortality [1]. BSI is often associated with sepsis syndrome [2]. The outcome of BSI and sepsis is dependent on the prompt initiation of effective antimicrobial therapy [3,4]. Globally it is estimated that 31.5 million cases of sepsis are treated in hospitals each year, and sepsis contributes to an estimated 5.3 million deaths annually [5]. The lowest incidence of sepsis is found in Northern Europe, including Norway [5]. In Norway, it has been reported that sepsis contributed to 12.9% of hospital deaths in the period 2011–2012 [6].

Early administration of adequate antimicrobial therapy is a cornerstone in the initial management of sepsis [7]. Empirical antimicrobial therapy refers to the treatment administered before microbiological identification (ID) and antimicrobial susceptibility testing (AST), and such treatment is frequently based on clinical practice guideline recommendations, but also local empirical experience. The choice of empirical antimicrobial therapy should be broad enough to cover all likely pathogens, and therefore it might prove suboptimal for targeting the actual pathogen causing the infection [8]. Concordant or discordant therapy refers to whether or not the administered empirical antimicrobials cover the detected pathogen and the pathogen's antimicrobial susceptibility profile.

Previous studies have shown that early broad-spectrum antimicrobial therapy reduces mortality in patients with severe sepsis and septic shock, and this initial antimicrobial therapy is described as one of the most important treatments for sepsis [9]. However, the use of broad-spectrum antimicrobial therapy is also a known risk factor for the emergence of antimicrobial resistance (AMR) [10]. Early reporting of microbial ID and AST provides opportunities for early targeting and de-escalation of antimicrobial therapy which is associated with decreased antimicrobial consumption and costs [8]. De-escalation strategies have been shown to reduce the overall selection pressure for antimicrobial resistance, but have no overall effect on mortality [11,12].

The prevalence of AMR is low in Norway compared to most other countries. National surveillance on antimicrobial consumption and AMR in Norway in 2019, reported a prevalence of extended-spectrum beta-lactamase (ESBL) in Escherichia coli and Klebsiella pneumoniae isolated from blood culture of 7.1% and 5.7%, respectively [13]. The rate of resistance to gentamicin was 5.9% for E. coli and 4.4% for K. pneumoniae. The report also showed that 0.8% of Staphylococcus aureus isolated from BSI was methicillin resistant (MRSA), and 2.2% of Enterococcus species were resistant to vancomycin. The Norwegian national guideline recommends a combination of penicillin and gentamicin as empirical therapy for sepsis with unknown aetiology and infection focus [14]. This regimen covers the most common pathogenic bacteria causing BSI in Norway [13]. Recommended as alternatives to this regimen is piperacillin/tazobactam or cefotaxime.

The aim of this study was to investigate empirical antimicrobial therapy in patients with BSI admitted to a tertiary care university hospital in Norway in 2019, and proportions that were concordant or discordant. Furthermore, we wanted to describe whether the empirical antimicrobial therapy administered was compliant with the national guideline recommendations, to what extent the antimicrobial therapy was targeted and de-escalated after the AST report was received, and whether discordant empirical antimicrobial therapy affected the outcome.

Materials and methods

Study population and study design

The study population in this retrospective observational study consisted of patients aged ≥ 18 years admitted to St. Olavs Hospital, a tertiary care university hospital in Trondheim, Norway, with a positive blood culture collected in the period 01.01.2019 to 31.12.2019. All patients that had blood cultures drawn and that turned out positive during this period were evaluated for inclusion.

An episode was excluded from the study if the microbe isolated from the blood culture was not considered to be the cause of the clinical infection, there was fungal growth in the blood culture, the patient was declared terminally ill before antimicrobial therapy was started, if necessary information was missing, or the patient was transferred to another hospital before antimicrobial therapy was initiated. A study group, consisting of a medical microbiologist, an infectious disease specialist, and two medical students evaluated the AST report and concluded whether or not the isolated microbe was classified as a contaminant. Typically, blood cultures with coagulase-negative staphylococci, Corynebacterium spp, and Bacillus cereus were classified as contaminants and excluded from further analyses if there was no information in the electronic patient record indicating that the isolated microbe should be considered the cause of the current clinical infection.

Laboratory procedures

Blood cultures, normally two sets of one BACTEC Plus/F Aerobic and one BACTEC Plus/F Anaerobic bottle with up to 10 mL blood in each bottle, were collected and incubated in an automated blood culture system BD BACTEC FX (Becton Dickinson, BD Diagnostics, USA). Bacteria and yeast isolated were identified using Maldi-TOF MS on a Microflex LT mass spectrometer (Bruker Daltonics) with the MBT 7854 MSP Library, and other standard methods [15]. The standard EUCAST disc diffusion method was used to perform AST [16]. In addition, the agar gradient method with Liofilchem® MIC test strips (Liofilchem, Italy) was used for minimum inhibitory concentration (MIC) determination in selected cases. Interpretation of results was done according to breakpoints from EUCAST and NordicAST [17,18].

Definitions

A BSI episode was defined by a positive blood culture with a plausible pathogenic microorganism and concomitant clinical infection, as judged and documented by the attending physician. Positive blood culture was defined by the growth of one or more microbial species in one or more blood culture bottles. Further, a monomicrobial BSI episode was defined as growth in the blood culture of one microbial species during an episode of clinical infection, while a polymicrobial BSI episode was defined as the growth of a second microbial species in the same or subsequent blood culture bottles collected within 72 h of the first detected microbial species. A new BSI episode in the same patient was defined as growth of a new microbial species in a sample collected more than 72 h after the initial BSI episode, or if there was growth of the same microbial species in a new blood culture sampled more than 30 days after the initial BSI episode, with a period of no symptoms of infection in between [19,20].

The BSI episode was classified as hospital-acquired if the patient had been admitted to the hospital more than 48 h prior to blood culture collection [21]. A BSI episode was classified as procedure-related if the patient acquired the infection outside the hospital after having been subject to in-hospital procedures, and the clinician had concluded that it was due to this procedure. Typically, these procedures were prostate biopsies, transurethral resection of the prostate, and transurethral resection of bladder tumour. An episode was classified as community-acquired if it did not fall into either of the two first categories. Bacterial isolates belonging to the order Enterobacterales were classified as multidrug-resistant (MDR) if they were found to be resistant to three or more classes of antimicrobial drugs.

Comorbidity recorded in the electronic patient record at the time of admission was used to calculate the Charlson Comorbidity Index for each BSI episode [22–24]. The probability of survival in relation to each episode was scored according to the Severe acute physiology score (SAPS) II at the time when the blood culture was collected [25–27]. Since the information was lacking in the electronic patient journal for some of the variables, the calculation of the SAPS-II score was based on some modifications: PaO_2/FiO_2 data was not used for assessing the severity of the disease if the patient was on mechanical ventilation or CPAP ($n = 39$, 5.2%). In addition, variables with no data recorded in the electronic patient record were classified as normal based on the assumption that in the hospital routine clinicians commonly do not request data or analyses for functions where they do not suspect abnormal values and where they consider there is no clinical indication.

To describe the appropriateness of administered antimicrobial therapy, several methods were applied. The Norwegian national guideline for the appropriate use of antimicrobial therapy in hospitals was used to evaluate whether the initiated empirical regimen was compliant or not [28]. Empirical antimicrobial therapy was considered concordant or discordant depending on whether or not the patient received antimicrobial therapy that covered the detected pathogen based on ID and AST. If the microbe had not been tested for any of the given empirical antimicrobials, inferred values from antimicrobials within the same class were used, as recommended by EUCAST and NordicAST in 2019 [29]. If the AST report did not contain sufficient information for definite classification, the concordance of empirical antimicrobial therapy was classified as partial or uncertain. Targeted antimicrobial therapy was defined as any antimicrobial therapy given after the AST report was released by the microbiology department. Dosing of antimicrobial therapy was registered only for episodes with BSIs caused by *S. aureus* and treated with third-generation cephalosporins. In all other cases, dosing regimens were presumed to follow the standard regimen for each drug.

Data collection

Administrative, clinical, diagnostic, and therapy data were collected from the hospital's electronic patient

records in a spreadsheet before analysis. The information on positive blood cultures was retrieved from the laboratory information system. The study group jointly concluded how the results should be classified in case of inconsistency in recorded data, or if the data should be classified as insufficient or inconclusive.

Statistical analyses

Binomial logistic regression with the calculation of odds ratios (ORs) with 95% confidence intervals (Cis) was used to investigate the associations between episode characteristics and discordance of empirical antimicrobial therapy, intra-hospital case fatality rate, and long-term case fatality rate. Fisher's exact test was used to examine the association between compliance with the national guideline and concordance of empirical antimicrobial therapy. Log-rank test was used to compare the survival of the patients who received discordant empirical antimicrobial therapy versus the patients who received concordant empirical antimicrobial therapy. Statistical analyses were performed using IBM SPSS Statistics

(Version 27.0.1.0 Armonk, NY: IBM Corp). A p-value $<$ .05 was considered statistically significant.

Results

Episode characteristics

During the one-year study period, 924 patients had one or more blood cultures drawn that showed the growth of bacteria or fungi. Of these, 65 were excluded due to a lack of consent. Further, one or more exclusion criteria were met for 187 BSI episodes, as described in Figure 1. The remaining 756 BSI episodes were eligible for inclusion, of which 642 (84.9%) occurred as unique, single BSI incidents, and 114 (15.1%) as multiple BSI incidents with two or more BSI episodes.

Episode characteristics are presented in Table 1 and Table S1. The majority of patients with BSI episodes were admitted to a medical department (73.7%) while fewer were admitted to a surgical department (26.3%). The median age in this study was 74 years, with an interquartile range of 63–82 years. The most common
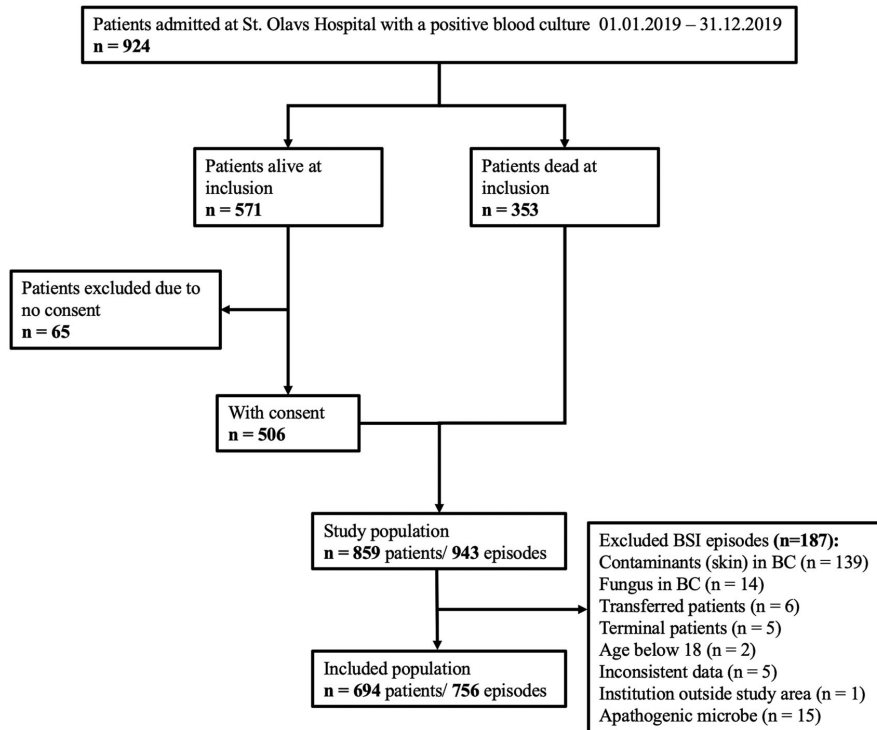

Figure 1. Flowchart showing the inclusion process and selection of patients and episodes, and the number of episodes per patient.

Table 1. Characteristics of 756 episodes of bloodstream infection.

Sex	n (%)
Male	458 (60.6)
Age	n (%)
≤49	91 (12.0)
50–74	314 (41.5)
≥75	351 (46.4)
Comorbidities	n (%)
Diabetes mellitus	
Uncomplicated diabetes mellitus	113 (14.9)
End-organ damage diabetes mellitus	18 (2.4)
Myocardial infarction	115 (15.2)
Transient ischaemic attack/cerebral vascular accident	103 (13.6)
Metastatic tumour	93 (12.3)
Congestive heart failure	86 (11.4)
Peripheral vascular disease	80 (10.6)
Connective tissue disease	72 (9.5)
Chronic kidney disease	68 (9.0)
Dementia	65 (8.6)
Localized tumour	65 (8.6)
COPD	51 (6.7)
Leukaemia	40 (5.3)
Peptic ulcer disease	37 (4.9)
Liver disease	
Mild	14 (1.9)
Moderate to severe	9 (1.2)
Lymphoma	18 (2.4)
Hemiplegia	11 (1.5)
No underlying illness	203 (26.9)
Allergies	n (%)
Penicillin	39 (5.2)
Acquisition	n (%)
Community-acquired	592 (78.3)
Hospital-acquired	148 (19.6)
Procedure-related	16 (2.1)
Site of infection	n (%)
Urinary tract	252 (33.3)
Unknown	198 (26.2)
Abdomen	115 (15.2)
Respiratory tract	100 (13.2)
Skin/soft tissue	35 (4.6)
IV catheter	20 (2.6)
Endocarditis	14 (1.9)
Bone and joint	10 (1.3)
Other	12 (1.6)
CCI-score (median (interquartile range))	5 (3–7)
Modified SAPS-II score (median (interquartile range))*	26 (21–31)
Department	n (%)
Medical	557 (73.7)
Surgical	199 (26.3)
All-cause case fatality rate	n (%)
7-day case fatality rate	39 (5.2)
30-day case fatality rate	92 (12.2)
90-day case fatality rate	155 (20.5)

*SAPS-II score variables with missing values in the electronic patient record were classified as normal.

Table 2. Microbe characteristics.

Type of microbes	n (%)	AMR, n (%)	MDR*, n (%)
Gram negative bacteria			
Escherichia coli	269 (35.6)	14 (5.2) ESBL	3 (1.1)
Klebsiella spp.			
Klebsiella pneumoniae	62 (8.2)	6 (9.7) ESBL	
Klebsiella oxytoca	17 (2.2)		
Other	3 (0.4)		
Pseudomonas spp.			
Pseudomonas aeruginosa	25 (3.3)		
Other	1 (0.1)		
Enterobacter cloacae complex	17 (2.2)		1 (5.9)
Proteus mirabilis	12 (1.6)		
Other	37 (4.9)		
Gram positive bacteria			
Staphylococcus spp.			
Staphylococcus aureus	129 (17.1)	1 (0.8) MRSA	
Other	7 (0.9)		
Streptococcus spp.			
Streptococcus pneumoniae	28 (3.7)		
Streptococcus dysgalactiae	19 (2.5)		
Streptococcus pyogenes	14 (1.9)		
Streptococcus agalactiae	14 (1.9)		
Streptococcus oralis	11 (1.5)		
Enterococcus spp.		1 (2.0) VRE	
Enterococcus faecalis	37 (4.9)		
Enterococcus faecium	10 (1.3)		
Other	2 (0.3)		
Other	56 (7.4)		
Anaerobic bacteria	69 (9.1)		

*Three strains (two *Escherichia coli* and one *Enterobacter cloacae* complex) that were ESBL producers were also classified as MDR.
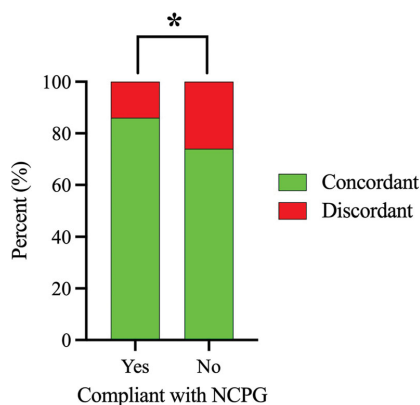
gram-positive and anaerobic pathogens constituted 443 (58.6%), 327 (43.3%) and 69 (9.1%) of the BSI episodes, respectively.

Among the *E. coli* and *K. pneumoniae* isolates, 5.2% and 9.7% were ESBL producers, respectively. Furthermore, of the 23 BSI cases with ESBL-producing bacteria, 3 strains (two *E. coli* and one *Enterobacter cloacae complex*) were also classified as MDR. *S. aureus* which was found to be methicillin resistant (MRSA) was isolated from one BSI episode (0.8%), and one of 49 (2.0%) enterococcal isolates was vancomycin-resistant (VRE).

Empirical antimicrobial therapy

Overall, 536 of 756 (70.6%) BSI episodes were prescribed empirical antimicrobial therapy in line with therapy recommendations in the national clinical practice guideline. On the other hand, 190 of 756 (25.1%) episodes were prescribed other regimens inconsistent with the guideline recommendations. For the remaining 32 BSI episodes, specific therapy recommendations were either lacking in the guideline (0.3%), the BSI episode was too complex to be ascribed to a specific therapy recommendation (0.3%), or the patient did not receive empirical antimicrobial therapy (3.7%).

The empirical antimicrobial therapy was discordant in 121 (16.0%) and concordant in 594 (78.6%) BSI episodes.

comorbidity was diabetes mellitus. Penicillin allergy was reported in 5.2% of the patients.

Microbe characteristics

Monomicrobial episodes constituted 693 of 756 (91.7%) BSIs. In 50 (6.6%) of the BSIs two different bacterial species were identified and in 13 (1.7%) three or more species were identified. The most frequently isolated bacterial pathogens were *E. coli* with 269 out of 756 (35.6%), followed by *S. aureus* with 129 out of 756 (17.1%) episodes, as shown in Table 2. Gram-negative,

Figure 2. Association between compliance with national clinical practice guideline (NCPG) and concordant empirical antimicrobial therapy. Of the episodes receiving empirical antimicrobial therapy compliant with NCPG, 452 (85.8%) and 75 (14.2%) were concordant and discordant, respectively. Of the episodes receiving empirical antimicrobial therapy not compliant with NCPG, 129 (73.7%) and 46 (26.3%) were concordant and discordant, respectively. Episodes with empirical antimicrobial therapy classified as either partial or uncertain coverage were excluded from the analysis. Asterisk indicates a statistically significant association between compliance with NCPG and concordant empirical antimicrobial therapy (Fisher's exact test, $p = .001$).

For BSI episodes, in which empirical antimicrobial therapy was compliant with national guideline recommendations, concordant and discordant therapy was observed in 452 (85.8%) and 75 (14.2%) episodes, respectively (Figure 2). In contrast, for BSI episodes not compliant with the national guideline, 129 (73.7%) and 46 (26.3%) episodes received concordant and discordant therapy, respectively. There was a statistically significant association between compliance with the national guideline and concordant empirical antimicrobial therapy (Fisher's exact test, $p = .001$).

Predictors of discordant empirical therapy were established using univariable and multivariable logistic regression analysis. Variables identified as independent predictors of discordant empirical antimicrobial therapy included hospital department, type of antimicrobial regimen, bacterial species, and antimicrobial resistance profile (Table 3 and Table S2). Third-generation cephalosporins in monotherapy were the strongest predictor of discordant empirical antimicrobial therapy among the empirical regimens, with a ten-fold increase in the rate of discordant therapy compared with narrow-spectrum penicillin combined with an aminoglycoside. Compared to narrow-spectrum penicillin combined with an aminoglycoside, all the other empirical antimicrobial

regimens had an increase in the frequency of discordant empirical therapy.

Targeted antimicrobial therapy

The mean time from blood culture sampling to the finalisation of the AST was 2.65 days (95% CI 2.53–2.76, median 2 days). The antimicrobial therapy administered after the AST results were released (hereby termed targeted antimicrobial therapy) was concordant in 697 (92.2%) of the 756 BSI episodes. However, 13 of 756 (1.7%) BSI episodes still received discordant antimicrobial therapy. For the remaining BSI episodes, empirical antimicrobial therapy was either discontinued without targeted therapy ($n = 15$, 2.0%), antimicrobial therapy was initiated with uncertain efficacy due to lack of AST ($n = 10$, 1.3%), or the patient had deceased before targeted therapy ($n = 21$, 2.8%).

De-escalation from empirical antimicrobial therapy to a more narrow-spectrum targeted regimen according to the AST report, was done in 480 (68.9%) of 697 eligible BSI episodes. In contrast, in 217 (31.1%) of 697 eligible BSI episodes, broad-spectrum antimicrobials were continued although the AST result indicated that conversion to narrow-spectrum antimicrobial therapy would have been feasible.

Case fatality rate

Discordant empirical antimicrobial therapy was significantly associated both with increased intra-hospital (Figure 3A) and long-term (Figure 3B) unadjusted all-cause case fatality rate (p-value $< .001$, log-rank test for overall difference in survival). The intra-hospital case fatality rate was 19.0% versus 7.4% for patients receiving discordant or concordant empirical antimicrobial therapy, respectively. The median follow-up time for long-time survival was 577.5 days (interquartile range 156–718.5 days).

Coverage of empirical antimicrobial therapy, CCI-score, SAPS-II score, site of infection, and type of empirical antimicrobial regimen, were identified as independent predictors of intra-hospital case fatality rate (Table 4 and Table S3). The intra-hospital case fatality rate was about three times higher for patients receiving discordant empirical antimicrobial therapy, as compared to patients receiving concordant empirical antimicrobial therapy (OR 3.01, 95% CI 1.54–5.88).

Table 3. Predictors for discordant empirical antimicrobial therapy when compared with causative bacterial species and its susceptibility profile*.

Characteristic	No. of discordant (% within category)	Univariable		Multivariable	
		Odds ratio (95% CI)	p-value	Odds ratio (95 % CI)	p-value
Acquisition					
Community-acquired (n = 563)	83 (14.7)	Ref.		Ref.	
Hospital-acquired (n = 136)	37 (27.2)	2.16 (1.39–3.37)	<.001	1.56 (0.88–2.77)	.131
Procedure-related (n = 16)	1 (6.3)	0.39 (0.05–2.96)	.359	0.43 (0.03–5.35)	.510
Overall p-value			.002		.244
CCI-score					
0–3 (n = 217)	24 (11.1)	Ref.		Ref.	
4–7 (n = 374)	68 (18.2)	1.79 (1.09–2.94)	.023	1.72 (0.95–3.11)	.072
8+ (n = 124)	29 (23.4)	2.46 (1.36–4.45)	.003	2.06 (1.00–4.24)	.049
Overall p-value			.010		.107
Department					
Medical (n = 529)	103 (19.5)	Ref.		Ref.	
Surgical (n = 186)	18 (9.7)	0.44 (0.26–0.75)	.003	0.42 (0.22–0.80)	.008
Empirical antimicrobial therapy					
Narrow spectrum beta-lactam + aminoglycoside (n = 175)	9 (5.1)	Ref.		Ref.	
Piperacillin-tazobactam (monotherapy) (n = 86)	12 (14.0)	2.99 (1.21–7.41)	.018	3.75 (1.27–11.12)	.017
3rd generation cephalosporines (monotherapy) (n = 118)	25 (21.2)	4.96 (2.22–11.07)	<.001	9.91 (3.75–26.17)	<.001
Other antimicrobial therapy with only one regimen (n = 120)	31 (25.8)	6.42 (2.93–14.09)	<.001	6.99 (2.65–18.40)	<.001
Multiple empirical regimes (n = 216)	44 (20.4)	4.72 (2.23–9.97)	<.001	7.34 (3.04–17.73)	<.001
Overall p-value			<.001		<.001
Compliant with national clinical practice guidelines for antimicrobial therapy					
Not compliant with (n = 185)	46 (24.9)	Ref.		Ref.	
Compliant with (n = 527)	75 (14.2)	0.50 (0.33–0.76)	.001	1.12 (0.65–1.92)	.682
Guidelines missing (n = 1)	0	0	1	0	1
Uncertain diagnosis (n = 2)	0	0	.999	0	.999
Overall p-value			.013		.983
Bacterial species					
Escherichia coli (n = 232)	17 (7.3)	Ref.		Ref.	
Klebsiella pneumoniae (n = 46)	2 (4.3)	0.58 (0.13–2.58)	.470	0.62 (0.12–3.21)	.570
Klebsiella oxytoca (n = 15)	1 (6.7)	0.90 (0.11–7.29)	.924	1.49 (0.17–13.14)	.720
Pseudomonas aeruginosa (n = 15)	4 (26.7)	4.60 (1.32–15.99)	.016	5.71 (1.44–22.67)	.013
Enterobacter cloacae complex (n = 14)	10 (71.4)	31.17 (8.97–111.50)	<.001	56.54 (12.80–249.78)	<.001
Proteus mirabilis (n = 9)	2 (22.2)	3.61 (0.70–18.76)	.126	7.14 (1.17–43.44)	.033
Staphylococcus aureus (n = 115)	37 (32.2)	6.00 (3.20–11.26)	<.001	9.69 (4.49–20.95)	<.001
Enterococcus faecalis (n = 23)	6 (26.1)	4.46 (1.56–12.80)	.005	11.58 (3.36–39.84)	<.001
Enterococcus faecium (n = 5)	2 (40.0)	8.43 (1.32–53.95)	.024	10.23 (1.37–76.56)	.024
Streptococcus spp. (n = 82)	0	0	.997	0	.997
Other monomicrobial (n = 103)	26 (25.2)	4.27 (2.20–8.30)	<.001	9.54 (4.20–21.65)	<.001
Polymicrobial (n = 56)	14 (25.0)	4.22 (1.93–9.20)	<.001	6.24 (4.46–15.77)	<.001
Overall p-value			<.001		<.001
Antimicrobial resistance					
No resistance to empirical therapy (n = 693)	111 (16.0)	Ref.		Ref.	
ESBL (n = 19)	10 (52.6)	5.83 (2.31–14.67)	<.001	50.92 (13.11–197.76)	<.001
VRE (n = 1)	0	0	1	0	1
MRSA (n = 1)	0	0	1	0	1
MDR (n = 1)	0	0	1	0	1
Overall p-value			.007		<.001
On antimicrobial therapy at the time when blood culture was collected					
No (n = 602)	93 (15.4)	Ref.		Ref.	
Yes (n = 113)	28 (24.8)	1.80 (1.12–2.92)	.016	1.36 (0.75–2.48)	.315

Univariable binominal logistic regression was used to find statistically significant dependent predictors. These covariates were used in a multivariable analysis to find independent predictors. The covariates that were not statistically significant in the univariable analysis are reported in Table S2.

*This table is a comparison between the BSI episodes who received discordant (n = 121) antimicrobial therapy with the BSI episodes who received concordant (n = 594) antimicrobial therapy. The BSI episodes who received partly concordant antimicrobial therapy (n = 7) or uncertain concordant antimicrobial therapy (n = 6) and the episodes who received no empirical antimicrobial therapy (n = 28) are excluded from this analysis.

Discussion

In this retrospective observational study of 756 BSI episodes over a one-year period at a tertiary care university teaching hospital in Norway with low AMR prevalence, we have shown that 70.6% received antimicrobial therapy compliant with national guideline recommendations. Of these, 14.2% were discordant. However, in BSI-episodes that received empirical antimicrobial therapy not compliant with the national guideline, 26.3% were discordant. We found a strong association between receiving a guideline-based regimen and concordant antimicrobial therapy. We have also reported that antimicrobial therapy was de-escalated, based on the AST report, to a more preferred regimen in 68.9% of BSI episodes while it was not de-escalated in 31.1% of BSI episodes. More importantly, we found that the intra-hospital
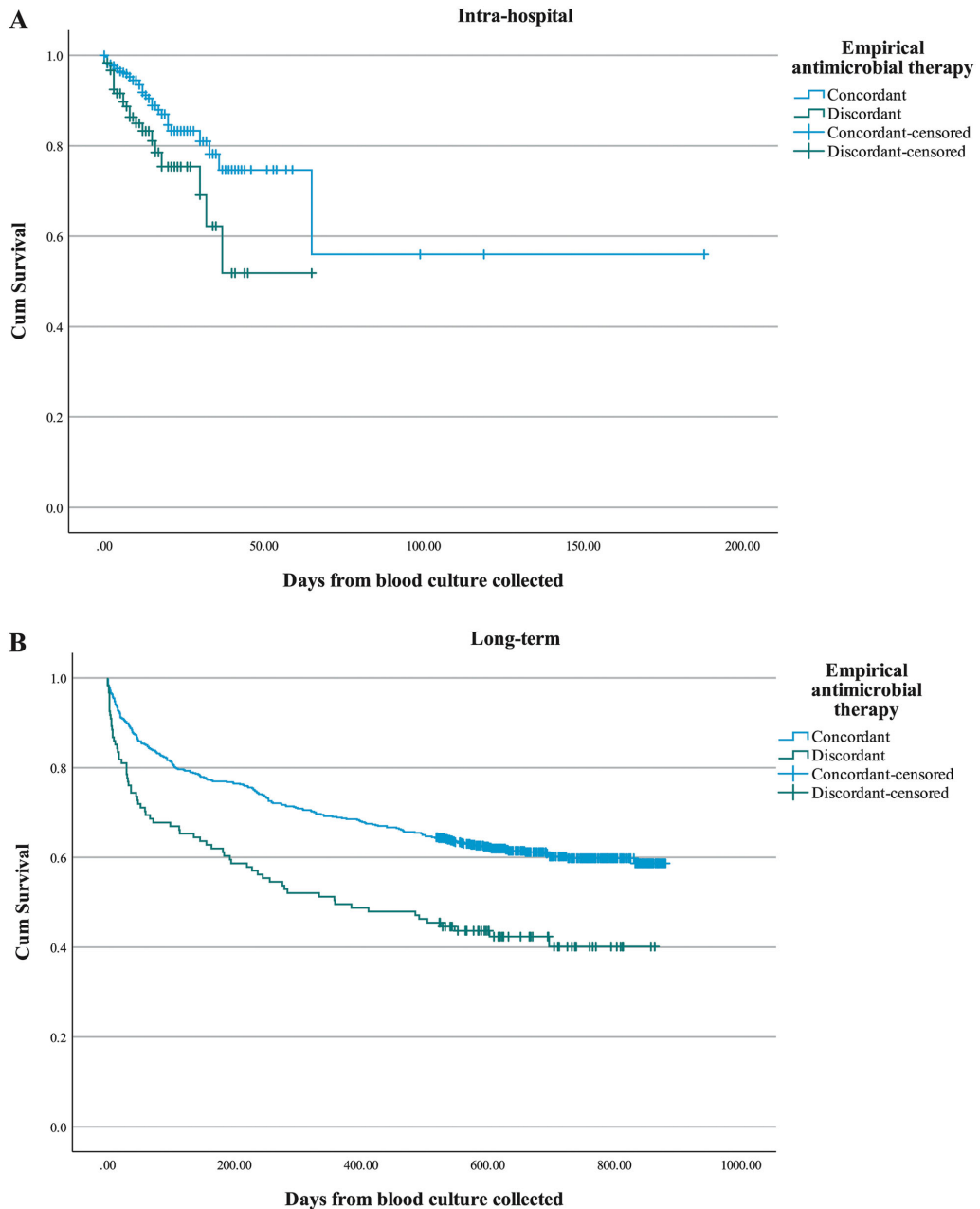
Figure 3. Kaplan-Meier plot showing the cumulative intra-hospital (A) and long-term (B) survival of patients with BSI who received concordant or discordant empirical antimicrobial therapy. BSI episodes with empirical antimicrobial therapy classified as uncertain coverage, partial coverage and no empirical antimicrobial therapy given were excluded from the analysis.

and long-term case fatality rate was significantly higher for BSI episodes that received discordant therapy.

Surveillance of AMR prevalence is of paramount importance for the validity of therapy recommendations [30]. During the two decades where we have had national systematic countrywide AMR surveillance, the prevalence of important resistant pathogens like MRSA, ESBL-producing bacteria, and VRE have been low in

Table 4. Predictors for intra-hospital case fatality rate.

Characteristic	No. of deaths (No. of death within category (%))	Univariable		Multivariable	
		Odds ratio (95% CI)	p-value	Odds ratio (95 % CI)	p-value
Concordance of empirical antimicrobial therapy					
Concordant (n = 594)	44 (7.4)	Ref.		Ref.	
Discordant (n = 121)	23 (19.0)	2.93 (1.70–5.08)	<.001	3.01 (1.54–5.88)	.001
Partly (n = 7)	0	0	.999	0	.999
Uncertain (n = 6)	1 (16.7)	2.50 (0.29–21.87)	.408	0.57 (0.02–14.08)	.730
No therapy (n = 28)	3 (10.7)	1.50 (0.44–5.16)	.520	0.48 (0.09–2.64)	.400
Overall p-value			.005		.020
CCI-score					
0–3 (n = 225)	5 (2.2)	Ref.		Ref.	
4–7 (n = 396)	43 (10.9)	5.36 (2.09–13.74)	<.001	4.11 (1.45–11.62)	.008
8+ (n = 135)	23 (17.0)	9.04 (3.35–24.40)	<.001	4.585 (1.46–14.45)	.009
Overall p-value			<.001		.022
Modified SAPS-II score					
<29 (n = 477)	23 (4.8)	Ref.		Ref.	
29–39 (n = 216)	27 (12.5)	2.82 (1.58–5.04)	<.001	1.95 (1.01–3.78)	.047
40–51 (n = 55)	14 (25.5)	6.740 (3.23–14.09)	<.001	4.19 (1.70–10.35)	.002
≥52 (n = 8)	7 (87.5)	138.174 (16.31–1170.60)	<.001	112.40 (9.64–1303.41)	<.001
Overall p-value			<.001		<.001
Site of infection					
Unknown (n = 198)	32 (16.2)	Ref.		Ref.	
Urinary tract (n = 252)	9 (3.6)	0.19 (0.09–0.41)	<.001	0.223 (0.09–0.54)	<.001
Respiratory tract (n = 100)	16 (16.0)	0.988 (0.51–1.90)	.971	1.209 (0.54–2.70)	.642
Skin and soft tissue (n = 35)	5 (14.3)	0.865 (0.31–2.40)	.780	1.230 (0.36–4.25)	.744
Bone and joint (n = 10)	0	0	.999	0	.999
IV catheter (n = 20)	0	0	.998	0	.998
Abdomen (n = 115)	6 (5.2)	0.286 (0.12–0.71)	.007	0.419 (0.14–1.29)	.130
Other (n = 12)	2 (16.7)	1.038 (0.22–4.96)	.963	2.451 (0.32–18.86)	.389
Endocarditis (n = 14)	1 (7.1)	0.399 (0.05–3.16)	.384	0.696 (0.08–6.11)	.744
Overall p-value			.002		.023
Department					
Medical (n = 557)	64 (11.5)	Ref.		Ref.	
Surgical (n = 199)	7 (3.5)	0.28 (0.13–0.62)	.002	0.70 (0.28–1.73)	.439
Type of empirical antimicrobial therapy					
Narrow spectrum beta-lactam + aminoglycoside (n = 178)	14 (7.9)	Ref.		Ref.	
Piperacillin-tazobactam (monotherapy) (n = 88)	8 (9.1)	1.171 (0.47–2.91)	.733	0.513 (0.16–1.69)	.272
3rd generation cephalosporines (monotherapy) (n = 119)	22 (18.5)	2.657 (1.30–5.43)	.007	0.869 (0.36–2.08)	.753
Other antimicrobial therapy with only one regimen (n = 123)	9 (7.3)	0.925 (0.39–2.21)	.860	0.235 (0.08–0.69)	.008
Multiple empirical regimens (n = 220)	15 (6.8)	0.857 (0.40–1.83)	.690	0.292 (0.12–0.72)	.007
No therapy (n = 28)	3 (10.7)	1.406 (0.38–5.24)	.612	0.161 (0.03–0.96)	.045
Overall p-value			.019		.014
Compliant with national clinical practice guidelines for antimicrobial therapy					
Not compliant with (n = 190)	27 (14.2)	Ref.		Ref.	
Compliant with (n = 534)	39 (7.3)	0.48 (0.28–0.80)	.005	0.523 (0.27–1.03)	.059
Guidelines missing (n = 2)	1 (50.0)	6.04 (0.37–99.43)	.208	11.907 (0.34–417.40)	.172
Unclear diagnosis (n = 2)	1 (50.0)	6.04 (0.37–99.43)	.208	0.395 (0.01–15.71)	.621
No therapy (n = 28)	3 (10.7)	0.72 (0.20–2.57)	.617	0.161 (0.03–0.96)	.045
Overall p-value			.012		.092

Univariable binominal logistic regression was used to find statistically significant dependent predictors, these covariates were used in a multivariable analysis to find independent predictors. The covariates that were not statistically significant in the univariable analysis are reported in Table S3.

Norway [13]. Based on decades of experience with clinical use combined with continued low AMR prevalence, narrow-spectrum beta-lactam therapy is still promoted in Norway for treatment of BSI and sepsis, often in combination with an aminoglycoside. The fact that 25.1% of included cases in our study were prescribed other regimens inconsistent with guideline recommendations, raises some concern. However, mechanisms that have impacted the prescribing habits among physicians were not a subject of this study.

We found a statistically significant association between compliance with guideline recommendations and concordant therapy. This finding supports that it is important to encourage the implementation of standardised therapy recommendations for specific clinical syndromes, as outlined in a previous antimicrobial stewardship guideline [31]. A recent systematic review of nine stewardship objectives from nearly 150 studies concluded that guideline-adherent empirical antimicrobial therapy was associated with a relative risk reduction for mortality of 35% [32].

Another finding is that 16.0% of BSI episodes received discordant empirical antimicrobial therapy. In a much larger American study, antimicrobial therapy was discordant in 19% of over 21.000 included BSI episodes [2]. In that study, infection with an AMR pathogen strongly predicted receiving discordant antimicrobial therapy. In our study, we also found that ESBL-producing Enterobacterales were independently associated with discordant therapy, although very few BSI episodes were due to ESBL-producing strains. Another predictor of discordant therapy was monotherapy regimens consisting of a third-generation cephalosporin or piperacillin-tazobactam, as compared to a narrow-spectrum beta-lactam in combination with an aminoglycoside. This is probably because we, according to EUCAST, classified the standard dosing of cefotaxime and ceftriaxone as insufficient to cover for S. aureus infections [17]. Of the 129 episodes with S. aureus infection in this study, 17 received a high dose of cefotaxime or ceftriaxone, while 6 received a standard dose. BSI episodes caused by Pseudomonas spp, Enterococcus spp, Enterobacter spp, Proteus spp, and as already mentioned S. aureus also predicted discordant therapy. This finding underscores that conditions other than AMR, including dosages of antimicrobial therapy, also need attention in order to reduce discordant therapy proportions.

In this study, we used clinical breakpoints for gentamicin as recommended by NordicAST in 2019. The gentamicin breakpoints were at that time classified as valid for all infections with Enterobacterales and staphylococci. In 2020 NordicAST changed its recommendation regarding gentamicin clinical breakpoints for Enterobacterales to be valid only for infections originating in the urinary tract. In addition, they stated that aminoglycoside treatment should be supported by other active treatments in case of systemic infections [33]. This study was not designed to compare results for gentamicin treatment between patients with infection origin in the urinary tract vs other site of infection. However, we believe that the results of this study are relevant despite these changes.

Early conversion from empirical to targeted antimicrobial therapy is uniformly recommended. This also applies to severe infections [34]. A recent meta-analysis concluded that antimicrobial monotherapy is non-inferior to duo therapy for severe infections, including sepsis and septic shock [35]. In our study, antimicrobial therapy was changed to pathogen-directed, targeted monotherapy with a more narrow-spectrum antimicrobial in 68.9% of eligible BSI episodes, whilst 31.1% were continued on broad-spectrum regimens. We were not able to identify reasons for deferring de-escalation strategies. Of note, 5.2% of included BSI episodes were labelled penicillin-allergic, but this can hardly explain the reasons for broad-spectrum non-targeted therapy.

Data in our study indicate that the case fatality rate was significantly increased among BSI episodes that received discordant therapy. This is consistent with several previous clinical studies [2,36–43] and reviews [34,44]. Unlike most similar studies, we applied inclusion criteria that did not select between specific pathogens or patient groups at risk but rather assessed all BSI episodes occurring over a 12-month period. The intra-hospital all-cause case fatality rate among BSI episodes receiving discordant or concordant empirical antimicrobial therapy in our study was 19.0% and 7.4% respectively. The fact that we observed such a difference in case fatality rate depending on concordance of empirical antimicrobial therapy even in a low AMR prevalence setting, is noteworthy and provides support for the importance of early concordant antimicrobial therapy.

Predictors of case fatality rate in multivariable analysis in our study were discordant empirical therapy, comorbidity, infection severity at presentation, site of infection, and choice of antimicrobial regimen. This is comparable to previous studies [2,36–43]. Of note, we were unable to assess clinical stages in sepsis, and BSI episodes presenting with especially pronounced clinical signs may have been allocated to broad-spectrum antimicrobial therapy. We therefore cannot rule out confounding by indication.

We consider it to be a strength of this study that the BSI episodes were identified based on laboratory-confirmed blood cultures systematically registered in the laboratory information system, and that the study included a high number of consecutive, unselected cases at a single centre tertiary care university teaching hospital in Norway where all types of inpatient departments and medical specialities are represented. However, there were also some limitations of this study. A subset of eligible patients still alive when the study started did not consent to participate and this may have led to the overrepresentation of diseased patients. Retrospective collection of clinical data depended on the availability and accuracy of such data in electronic patient records, and microbiology results from samples other than blood culture were not recorded in this study. Our practice of classifying missing values for the calculation of SAPS-II score as normal may have led to the underestimation of the SAPS-II score. Dosages of

antimicrobial therapy were only available on scanned paper charts and therefore difficult to access. Such information was only registered for the use of third-generation cephalosporins in staphylococcal infections in this study. In addition, it is possible in a retrospective study that factors not recorded may have influenced the results obtained. Finally, as this is a single-centre study from a low antimicrobial resistance setting, whether the results from this study can be extrapolated to international settings needs further investigation.

In conclusion, this study showed that empirical antimicrobial therapy for BSI is more concordant with AST reports if such therapy is in accordance with national clinical practice guideline recommendations. The case fatality rate was significantly higher for BSI episodes that received discordant therapy. In this study, we disclosed predictors for discordant antimicrobial therapy. Antimicrobial stewardship programmes in general encourage health professionals and authorities to assess predictors for discordant empirical antimicrobial therapy carefully and implement antimicrobial stewardship measures to facilitate therapy prescribing. Measures should include strategies that target prompt identification and AST, guideline-based initiation of therapy, and compulsory early therapy assessments. Regardless of AMR prevalence, we encourage others to investigate concordant antimicrobial therapy in order to secure rigorous clinical guideline recommendations.

Acknowledgements

Ethical considerations

The Regional Committee for Medical and Health Research Ethics, health region mid-Norway (REK midt 210524) approved the study. Deceased patients at the start of study in June 2021 were included in the study without consent, while patients still alive received a written study invitation with opportunity to withdraw from the study. A data protection impact assessment was performed and approved by the hospital before start of study.

Author contributions

This study was conceived and designed by KG, EH, BW and JEA. KG, EH and BW acquired the data. KG, EH, BW and ØS analysed and interpreted the data. The study was supervised by BW and JEA, with input from JKD. KG and EH drafted the article, which was critically revised by BW, JKD, and JEA.

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.

Funding

ORCID

Bjørn Waagsbø http://orcid.org/0000-0002-2667-7728
Øyvind Salvesen http://orcid.org/0000-0002-6145-8109
Jan Kristian Damås http://orcid.org/0000-0003-4268-671X
Jan Egil Afset http://orcid.org/0000-0003-2489-4179

Data availability statement

The datasets used and/or analysed during the current study are not publicly available due to restrictions from The Regional Committee for Medical and Health Research Ethics, health region mid-Norway (REK midt 210524).

References

[1] Goto M, Al-Hasan MN. Overall burden of bloodstream infection and nosocomial bloodstream infection in North America and Europe. Clin Microbiol Infect. 2013;19(6): 501–509.

[2] Kadri SS, Lai YL, Warner S, et al. Inappropriate empirical antibiotic therapy for bloodstream infections based on discordant in-vitro susceptibilities: a retrospective cohort analysis of prevalence, predictors, and mortality risk in US hospitals. Lancet Infect Dis. 2021;21(2):241–251.

[3] Marquet K, Liesenborgs A, Bergs J, et al. Incidence and outcome of inappropriate in-hospital empiric antibiotics for severe infection: a systematic review and meta-analysis. Crit Care. 2015;19(1):63.

[4] Paul M, Shani V, Muchtar E, et al. Systematic review and meta-analysis of the efficacy of appropriate empiric antibiotic therapy for sepsis. Antimicrob Agents Chemother. 2010;54(11):4851–4863.

[5] Fleischmann C, Scherag A, Adhikari NK, et al. Assessment of global incidence and mortality of hospital-treated sepsis. Current estimates and limitations. Am J Respir Crit Care Med. 2016;193(3):259–272.

[6] Knoop ST, Skrede S, Langeland N, et al. Epidemiology and impact on all-cause mortality of sepsis in norwegian hospitals: a national retrospective study. PLOS One. 2017;12(11): e0187990.

[7] Esposito S, De Simone G, Boccia G, et al. Sepsis and septic shock: new definitions, new diagnostic and therapeutic approaches. J Glob Antimicrob Resist. 2017;10:204–212.

[8] Berild D, Mohseni A, Diep LM, et al. Adjustment of antibiotic treatment according to the results of blood cultures leads to decreased antibiotic use and costs. J Antimicrob Chemother. 2006;57(2):326–330.

[9] Ferrer R, Martin-Loeches I, Phillips G, et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program*. Crit Care Med. 2014; 42(8):1749–1755.

[10] Abushaheen MA, Fatani AJ, Alosaimi M, et al. Antimicrobial resistance, mechanisms and its clinical significance. Dis Mon. 2020;66(6):100971.

[11] Guo Y, Gao W, Yang H, et al. De-escalation of empiric antibiotics in patients with severe sepsis or septic shock: a meta-analysis. Heart Lung. 2016;45(5):454–459.

[12] Turnidge J. Impact of antibiotic resistance on the treatment of sepsis. Scand J Infect Dis. 2003;35(9):677–682.

[13] NORM/NORM-VET 2019. Usage of antimicrobial agents and occurence of antimicrobial resistance in Norway. Tromsø/ Oslo; 2020.

[14] Antibiotika i sykehus Oslo: Helsedirektoratet; 2018. [cited 2021 9.11). Available from: https://www.helsedirektoratet. no/retningslinjer/antibiotika-i-sykehus/sepsis.

[15] Jakovljev A, Bergh K. Development of a rapid and simplified protocol for direct bacterial identification from positive blood cultures by using matrix assisted laser desorption ionization time-of- flight mass spectrometry. BMC Microbiol. 2015;15:258.

[16] Matuschek E, Brown DF, Kahlmeter G. Development of the EUCAST disk diffusion antimicrobial susceptibility testing method and its implementation in routine microbiology laboratories. Clin Microbiol Infect. 2014;20(4):O255–66.

[17] The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters, version 10.0, 2020. [cited 2021 Oct 11]. Available from: https://www.eucast.org.

[18] Nordic Committee on Antimicrobial Suceptibility Testing NordicAST; 2020. [cited 2021 Oct 11]. Available from: http://www.nordicast.org/index.

[19] Mehl A, Asvold BO, Kummel A, et al. Trends in antimicrobial resistance and empiric antibiotic therapy of bloodstream infections at a general hospital in Mid-Norway: a prospective observational study. BMC Infect Dis. 2017;17(1): 116.

[20] Mehl A, Åsvold BO, Lydersen S, et al. Burden of bloodstream infection in an area of Mid-Norway 2002-2013: a prospective population-based observational study. BMC Infect Dis. 2017;17(1):205.

[21] World Health Organization. Prevention of hospital-acquired infections: a practical guide/editors. G. Ducel, J. Fabry and L. Nicolle, 2nd. ed. World Health Organization 2002. Available from https://apps.who.int/iris/handle/10665/ 67350.

[22] Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5): 373–383.

[23] Quan H, Li B, Couris CM, et al. Updating and validating the charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol. 2011;173(6):676–682.

[24] Radovanovic D, Seifert B, Urban P, et al. Validity of charlson comorbidity index in patients hospitalised with acute coronary syndrome. Insights from the nationwide AMIS Plus registry 2002-2012. Heart. 2014;100(4):288–294.

[25] Le Gall JR, Lemeshow S, Saulnier F. A new simplified acute physiology score (SAPS II) based on a European/North American multicenter study. Jama. 1993;270(24):2957–2963.

[26] Capuzzo M, Valpondi V, Sgarbi A, et al. Validation of severity scoring systems SAPS II and APACHE II in a single-center population. Intensive Care Med. 2000;26(12):1779–1785.

[27] Beck DH, Smith GB, Pappachan JV, et al. External validation of the SAPS II, APACHE II and APACHE III prognostic models in South England: a multicentre study. Intensive Care Med. 2003;29(2):249–256.

[28] Helsedirektoratet. Antibiotika i sykehus Oslo: Helsedirektoratet; [updated 2021 May 27; cited 2021 Oct 11]. Available from: https://www.helsedirektoratet.no/ retningslinjer/antibiotika-i-sykehus#referere.

[29] NordicAST. Nordic Comittee on Antimicrobial Susceptibility Testing. [cited 2022 July 04]. Available from: https://view. officeapps.live.com/op/view.aspx?src=http%3A%2F%2Fs3- eu-west-1.amazonaws.com%2Fhl-intranet%2Ffiles%2Fb093b 042c80456a448f7e88a11f2e864a33c9202%2Fv_9_0_brytnin gspunkttabell_nordicast_no_final190325_locked.xlsx&wdOri gin=BROWSELINK.

[30] Möller V, Östholm-Balkhed Å, Berild D, et al. Antibiotic resistance among major pathogens compared to hospital treatment guidelines and antibiotic use in nordic hospitals 2010-2018. Infect Dis. 2021;53(8):607–618.

[31] Barlam TF, Cosgrove SE, Abbo LM, et al. Implementing an antibiotic stewardship program: guidelines by the infectious diseases society of america and the society for healthcare epidemiology of america. Clin Infect Dis. 2016;62(10): e51–e77.

[32] Schuts EC, Hulscher M, Mouton JW, et al. Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis. Lancet Infect Dis. 2016;16(7): 847–856.

[33] NordicAST. Nordic comittee on antimicrobial susceptibility testing. Available from: https://view.officeapps.live.com/op/ view.aspx?src=http%3A%2F%2Fs3-eu-west-1.amazonaws. com%2Fhl-intranet%2Ffiles%2F4474e596b67691fa4ee06ff89 f4d3c98f7c568d3%2F200207_v_10_0_nordicast_no_protect ed.xlsx&wdOrigin=BROWSELINK.

[34] Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med. 2021;47(11): 1181–1247.

[35] Sjövall F, Perner A, Hylander Møller M. Empirical mono-versus combination antibiotic therapy in adult intensive care patients with severe sepsis – a systematic review with meta-analysis and trial sequential analysis. J Infect. 2017; 74(4):331–344.

[36] Ju M, Huang Y, Xu X, et al. Predictors of mortality in adult patients with methicillin-resistant *Staphylococcus aureus* bloodstream infection: a meta-analysis and systematic review. Ann Palliat Med. 2021;10(8):8617–8627.

[37] Corcione S, Mornese Pinna S, Lupia T, et al. Antibiotic De-escalation experience in the setting of emergency department: a retrospective, observational study. J Clin Med. 2021;10(15):3285.

[38] Lin TL, Chang PH, Chen IL, et al. Risk factors and mortality associated with multidrug-resistant gram-negative bacterial infection in adult patients with abdominal surgery. J Hosp Infect. 2021;119:P22–P32.

[39] Baltas I, Stockdale T, Tausan M, et al. Impact of antibiotic timing on mortality from gram-negative bacteraemia in an english district general hospital: the importance of getting it right every time. J Antimicrob Chemother. 2021;76(3):813–819.

[40] Gradel KO, Jensen US, Schønheyder HC, et al. Impact of appropriate empirical antibiotic treatment on recurrence and mortality in patients with bacteraemia: a population-based cohort study. BMC Infect Dis. 2017;17(1): 122.

[41] Tang Y, Wu X, Cheng Q, et al. Inappropriate initial antimicrobial therapy for hematological malignancies patients with gram-negative bloodstream infections. Infection. 2020; 48(1):109–116.

[42] Yamaga S, Shime N. Association between appropriate empiric antimicrobial therapy and mortality from bloodstream infections in the intensive care unit. J Infect Chemother. 2018;24(4):267–271.

[43] Suppli M, Aabenhus R, Harboe ZB, et al. Mortality in enterococcal bloodstream infections increases with inappropriate antimicrobial therapy. Clin Microbiol Infect. 2011;17(7): 1078–1083.

[44] Kollef MH, Shorr AF, Bassetti M, et al. Timing of antibiotic therapy in the ICU. Crit Care. 2021;25(1):360.

NTNU
Norwegian University of
Science and Technology