Aus der Medizinischen Universitätsklinik und Poliklinik Tübingen

Abteilung Innere Medizin I

(Schwerpunkt: Gastroenterologie, Gastrointestinale Onkologie, Hepatologie, Infektiologie und Geriatrie)

Antimicrobial stewardship in the emergency department: a prospective cohort study

Inaugural-Dissertation
zur Erlangung des Doktorgrades
der Medizin

der Medizinischen Fakultät
der Eberhard Karls Universität
zu Tübingen

vorgelegt von
Foschi, Federico
2021

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2. Berichterstatter: Professor S. Wagner

Tag der Disputation 23.09.2021

Inhalt

Abbreviations

ASP	Antimicrobial stewardship
MRSA	methicillin-resistant *Staphylococcus aureus*
ESBL	extended-spectrum ß-lactamase
CR	carpapenem-resistant
MDR	Multidrug resistant
C. difficile	Clostridium difficile
CDI	Clostridium difficile infection
IRR	Incidence rate ratio
CI	Confidence Interval
ECDC	European Centre for Disease Prevention and Control
ED	Emergency Department
ER	Emergency room
ATB	Antibiotic
ITS	Interrupted time series
DDD	Defined daily dose
ptdays	Patients day
IDS	Infectious disease specialist
WHO	World Health Organization
LOS	Length of Stay
ICU	Intensive Care Unit
GN	Gram negative
LCG	local calibrated guidelines
HAI	hospital acquired infection

Introduction

Increasing in antibiotic resistance is an emerging issue and threat of healthcare systems worldwide. The main reasons leading to the development of resistance reside in inappropriate prescriptions and overuse antibiotics and extensive livestock[1]. All these reasons lead to a strong selection pressure and to a vertical as well as horizontal spread of resistance [2].

Due to the increased number of infections caused by multidrug-resistant (MDR) bacteria, the spectrum of untreatable infections is becoming a reality. It is estimated that more than 25,000 people die each year in Europe as a result of MDR bacterial infections and that this costs the European Union economy €1.5 billion annually [3].

Several strategies have been implemented in the last years to face this emergency: creation of databases for antibiotic use and resistance, use of new rapid diagnostic tools to shorten the identification of the mechanism/gene responsible of resistance, infection control and prevention measures, and development of antimicrobial stewardship. The latter is a coherent set of actions, which promote using antibiotics responsibly, and aims to improve the prescription´s quality as well as the appropriateness of the antibiotic therapy. An antimicrobial stewardship is a group of heterogeneous interventions, such as education programs, implementing of clinical decision support systems, restriction of specific antibiotics and of treatment duration to achieve a better use of antibiotics in the hospital setting. These strategies can be implemented with infection control tools as: hand washing, contact isolation, environmental control and barrier precautions to control the spread of MDR bacteria [4].

Antibiotic resistance threat

Despite the progress of modern medicine, which has had a strong impact both on average human survival [5] and improvement of quality of life in old age [6], resistant and MDR bacterial agents are causes of great concern. The danger of new and increasing bacterial pathogens in the number and variety of their resistances is considered not only by specialists but also by the World Health Organization (WHO) as one of the most relevant concern in the medical world. In 2017 the WHO listed 25 antibiotic resistant bacteria posing the greatest threat to human and provided indications to the research and development of new effective antibiotics. [7].

Methicillin-resistant *Staphylococcus aureus* (MRSA), extended-spectrum ß-lactamase (ESBL) producing microorganisms and carpapenem-resistant (CR) Gram-negative bacteria are on the rise worldwide, in both hospital and community settings. In most of the high-income countries the strategy to control and prevent the spread of these microorganisms are starting to become a daily practice but in the low-income countries, due to lack of funds and of infrastructure, this is not possible. Moreover, these countries often do not have the necessary screening methods and do not have nationally implemented surveillance programs. This circumstance allows an estimation of the current resistance situation in these areas of the world only to a limited extent [8].

The last ECDC surveillance report of antimicrobial resistance in Europe showed how in 2018, more than half of the Escherichia coli isolates and more than a third of the Klebsiella pneumoniae isolates were resistant to at least one antimicrobial group under regular surveillance, and combined resistance to several antimicrobial groups was frequent. Several countries reported carbapenem resistance for K. pneumonia, Pseudomonas aeruginosa and Acinetobacter species (Figure 1). MRSA isolates were decreasing in comparison with 2015 (Figure 2). [9]

Figure 1 Acinetobacter spp. Percentage (%) of invasive isolates with combined resistance to fluoroquinolones, aminoglycosides and carbapenems, by country, EU/EEA countries 2018 [9]

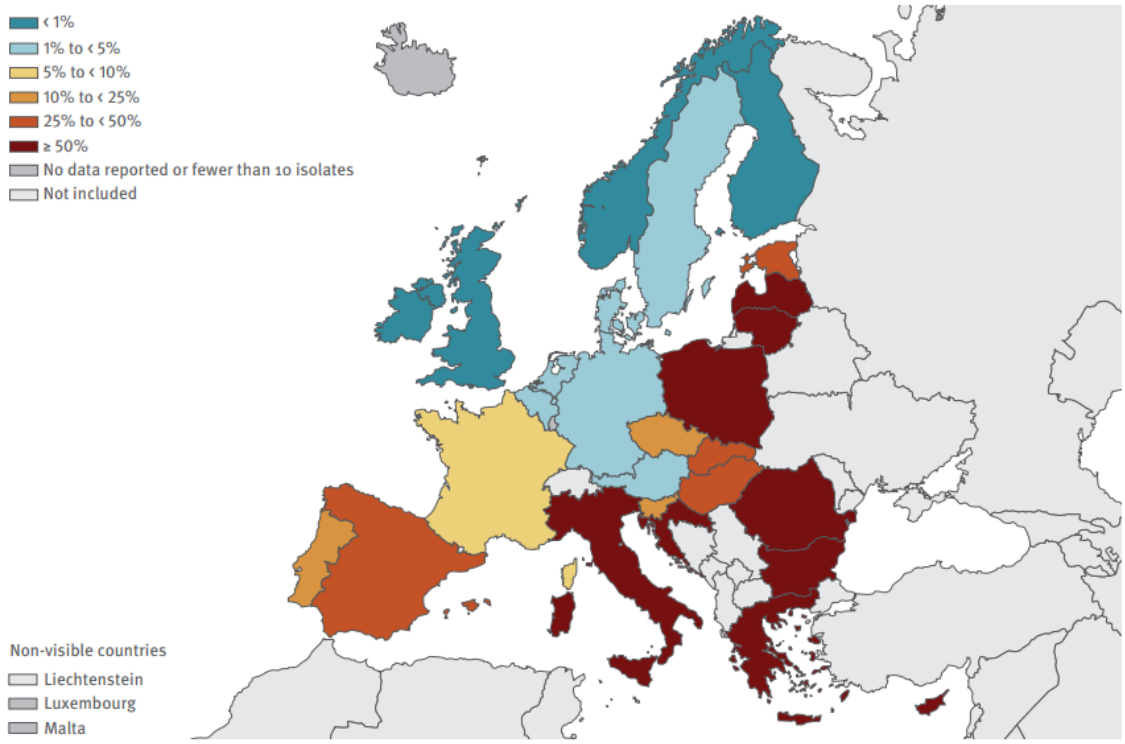
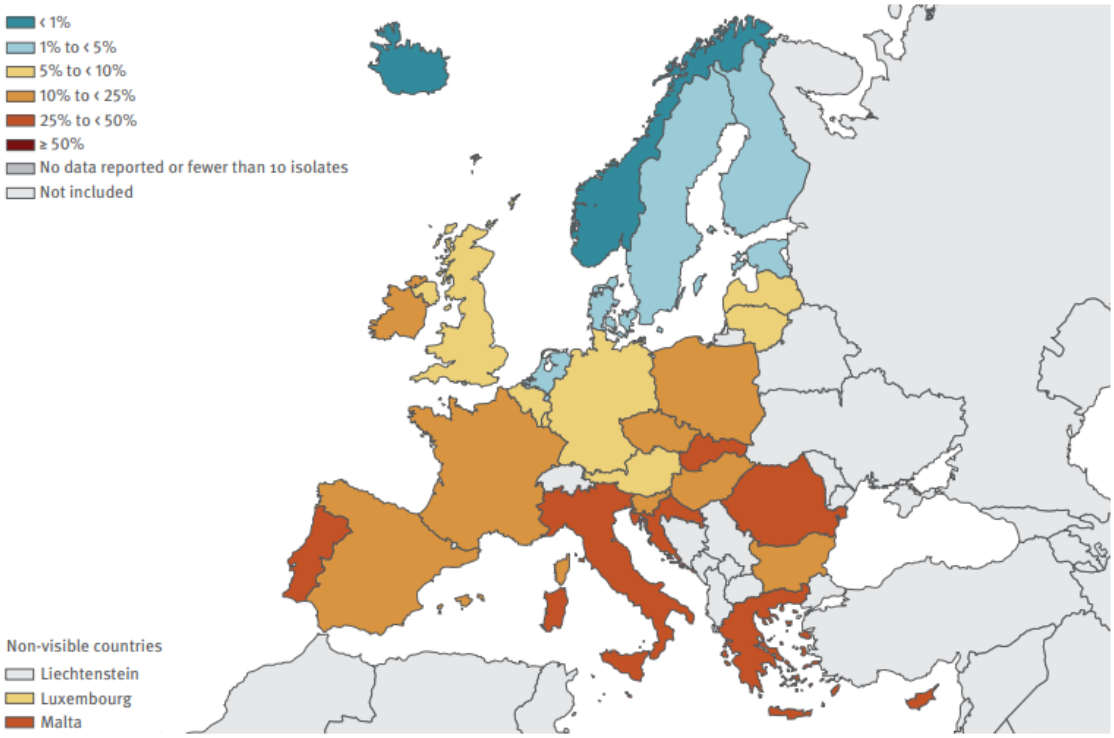


Figure 2 Staphylococcus aureus. Percentage (%) of invasive isolates with resistance to meticillin (MRSA), by country, EU/EEA countries, 2018 [9]



Antibiotic consumption

One of the most relevant cause leading to development of antibiotic resistance resides in the increased antibiotic consumption. It has been described that the overall consumption of medically used antibiotics has increased more than 30% worldwide between 2000 and 2010. This is mainly due to the increasing consumption of antibiotic substances in low-income countries [11]

Another important reason is the antibiotics consumption in the animal sector. The antibiotics used for the breeding of pigs, cattle and other sources of protein in the United States estimates roughly 80% of all antibiotics [12].

This development can also be attributed to the fact that on the one hand pet food is often already premixed with antibiotics for sale and that animal breeders use the antibiotic not only as prophylaxis but also as growth agent [8].

There are many approaches that are available today to counteract the progression of new and extensive resistance development. Using them correctly, effectively and critically questioning the use of antibiotics is a task that our society has to face. To fight this emergency, both - the development of new antibiotic substances [13] as well as the correct use of antibiotics – have to be improved.

The annual surveillance report of the ECDC on antimicrobial consumption in the EU/EEA showed how different trends in the latter are to be observed in different european countries (Figure 3 and 4) [10].

Figure 3. Consumption of antibacterials for systemic use in the community in EU/EEA countries in 2018 (expressed as DDD per 1 000 inhabitants per day) [10]

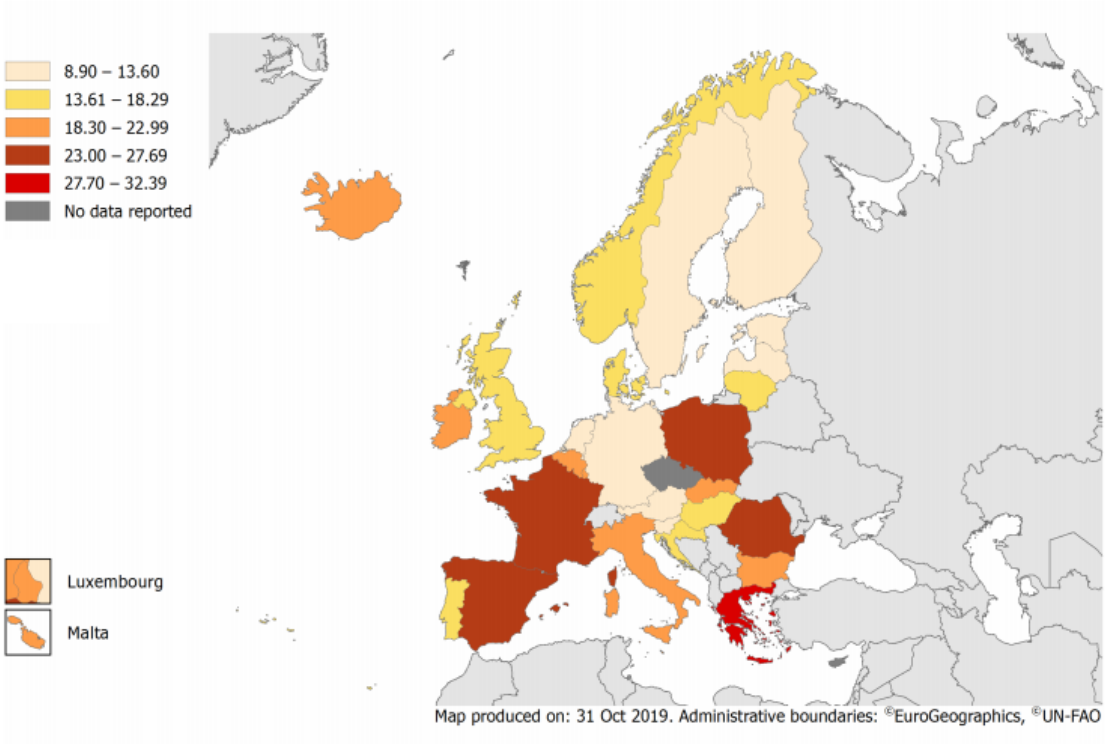


Figure 4 Total consumption (community and hospital sector) of antibacterials for systemic use in EU/EEA countries, 2009–2018 (expressed as DDD per 1 000 inhabitants per day)[10]

Country	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	Trends in antimicrobial consumption, 2009–2018	CAGR Compound annual growth rate (%)	Trend
Austria	13.6*	13.1*	12.7*	12.2*	14.2*	12.1*	12.1*	11.4*	11.9*	10.4*		-2.9%	↓
Belgium	23.9	24.9	25.4	25.6	24.2	24.0	24.4	24.2	22.8	22.3		-0.8%	↓
Bulgaria	17.3	17.2	18.3	17.4	18.6	20.0	20.1	19.2	20.5	21.0		2.1%	↑
Croatia	20.7	18.8	18.2	20.0	19.2	19.4	19.7	18.7	18.6	18.8		-1.1%	
Cyprus	29.2	26.3	26.9	25.1	23.9	22.2	26.6	28.4	28.9			-0.1%	
Czech Republic	16.6*	16.0*	16.5*	15.7*	16.9*	17.1*	17.4*					0.7%	
Denmark	16.7	17.5	18.3	17.4	17.5	17.1	17.5	17.0	16.2	15.6		-0.7%	
Estonia	11.2	11.4	12.4	12.2	12.0	11.9	12.1	12.0	11.6	11.8		0.6%	
Finland	19.6	19.7	21.5	20.6	19.6	19.1	18.1	17.4	15.7	15.5		-2.6%	↓
France	26.2	25.0	25.1	25.7	25.9	24.9	25.6	25.6	24.7	25.3		-0.4%	
Germany	13.8*	13.4*	13.1*	13.7*	14.5*	13.4*	13.1*	12.8*	12.3*	11.9*		-1.6%	↓
Greece	37.6	35.6	33.4	29.9	29.8	31.0	33.2	33.1	34.2	34.0		-1.1%	
Hungary	15.0	14.8	14.9	14.1	14.5	15.2	15.8	14.4	14.6	14.8		-0.1%	
Iceland	17.2*	19.8	19.8	19.7	19.4	17.1*	17.6*	18.2*	18.8*	20.4*		4.6%	↑
Ireland	19.0	19.0	20.8	21.0	21.6	21.0	23.0	22.0	20.9	22.7		2.0%	↑
Italy	23.7*	24.9	25.1	24.6	25.2	24.5	24.5	24.0	20.9	21.4		-1.9%	↓
Latvia	11.5	12.6	12.9	12.9	13.3	12.6	13.1	12.9	13.9	13.3		1.6%	↑
Lithuania	16.2	14.4	15.5	15.3	17.1	15.1	15.8	15.6	15.7	17.5		0.9%	
Luxembourg	25.7	25.1	25.2	25.0	25.0	23.2	23.5	22.9	22.6	22.2		-1.6%	↓
Malta	19.8	19.9	21.6	20.8	22.2	22.4	21.2	20.9	22.6	20.9		0.6%	
Netherlands	10.1*	10.9	11.0	10.9	10.5	10.3	10.4	10.1	9.8	9.7		-0.4%	↓
Norway	16.3	16.8	17.5	17.9	17.2	16.9	16.8	16.2	15.7	15.3		-0.7%	
Poland	20.1*	18.0*	18.2*	19.9*	20.5*	21.2	24.1	22.0	25.4	24.4		3.6%	
Portugal	20.4	19.9	20.6	20.1	17.6	18.0	18.8	19.0	17.8	18.6		-1.0%	↓
Romania	12.1		26.5	25.9	26.8	26.6	28.0	24.4	24.5	25.0		-0.8%	
Slovakia	23.0		21.4*	19.7	23.2	21.2	24.2	23.6	20.0	22.0		0.5%	
Slovenia	13.5	13.4	13.4	13.2	13.3	13.1	13.3	12.1	12.2	13.2		-0.3%	↓
Spain	15.7†	16.2†	16.6†	15.7†	16.2†	17.1†	17.5†	27.5	26.8	26.0		N/A	
Sweden	15.1	15.2	15.4	15.3	14.2	14.0	13.5	13.2	12.8	12.4		-2.1%	↓
United Kingdom	15.2*	16.5*	16.5*	17.7*	20.4	20.8	20.1	19.7	19.3	18.8		-1.6%	↓
EU/EEA	**20.6**	**19.7**	**20.9**	**21.0**	**21.5**	**21.1**	**21.5**	**20.7**	**20.2**	**20.1**		**-0.3%**	

The burden of antibiotic resistance

A particular challenging aspect of antibiotic resistance is the in-hospital burden of these infections. MDR bacteria and inappropriate antibiotics prescriptions are cause of increase of costs, length of stay (LOS) and mortality.

A Study from Mauldin et al [14], showed that the additional total hospital cost and LOS attributable to hospital acquired infections (HAIs) caused by MDR GN pathogens were 29.3% and 23.8% higher than those attributable to HAIs caused by antibiotic-susceptible GN pathogens, respectively.

Another study from Barrasa-Villar et al [15] concluded that the total and 30-day in-hospital mortality was significally higher in MDR infections than in in controls (24.1% vs 15.4%). The LOS increased in MDR infections, although did not achieve statistical significance. On the other hand, pooled results of Karanika et al [16] showed that antimicrobial stewardship can lead to an economic decrease when ASPs were implemented.

Well known is also the vital importance in reducing the development of adverse events occurring as a result of antibiotic therapy and the cost saving effect which results from a more appropriate use of antibiotics.

Emergency Departments (EDs) are at the crossroads of inpatient and outpatient care. They represent a critical setting for initiating interventions which could reduce inappropriate antibiotic (ATB) prescribing. Given the extremely high turnover of patients, antimicrobial stewardship interventions in the ED might affect the antibiotic use directly but they might also have an impact downstream, on other medical areas of the hospital. The ED differs from inpatient care units primarily in the need for rapid patient turnaround. Clinical decisions are often based on preliminary laboratory results and microbiological tests are seldom rapidly available. Therefore in this setting ASP have been rarely implemented and a few evidence for effectiveness is available [16-18].

Several studies showed a poor compliance to current infectious disease guidelines in the ED setting [19] and they indicate especially a misuse of broad-spectrum penicillin which can lead to increase in antibiotic resistance [20].

Measures to reduce resistance

In addition to correct prescription of antibiotic therapy, other measures may be pursued to reduce the incidence of antibiotic resistance.

A key role is played by the infection control strategies, which should be correctly put into practice both in the hospital environment, as well as by any patient contact. Every employee must comply with the hygienic basic rules [21]

Among the infection control strategies, the Hand hygiene occupies a particularly important role [13]. To carry out correctly this simple but powerful practice after each patient contact means to prevent the transfer of pathogens from patient to patient, or between staff and patients [22-24]. Also, a correct environmental cleaning and disinfection is important - especially in bacteria such as *Acinetobacter baumannii* - which can survive on surfaces for several hours or days and thus represent a source of transmission. For MRSA, decolonization has been recognized as an effective method for the prevention of endemic spread, but the feasibility of this procedure in the everyday clinical practice should be critical scrutinized [25]. These various infection control measures have already shown their positive effect on the number on infections and/or colonisation of resistant pathogens in several studies [26-28].

The increasing use of antibiotic substances promotes the development of resistance, but it also affects the costs of a health system. The implementation of an ASP can reduce the cost of antibiotic treatment and amongst other the LOS and the rate of adverse reaction [29, 30]. Moreover, the cost of isolation and treatment for patients with resistant germs or is higher [31, 32].

Antimicrobial Stewardship

“Antimicrobial stewardship refers to coordinated interventions designed to improve and measure the appropriate use of antibiotics by promoting the selection of the optimal antibiotic drug regimen, dose, duration of therapy, and route of administration. Antimicrobial stewards seek to achieve optimal clinical outcomes related to antibiotic use, minimize unintended consequences of antibiotic use, reduce the costs of health care for infections, and limit the selection for antibiotic resistant strains” [33]. Various strategies can be put into practice. The most effective are education of medical staff, restrictive and non-restrictive antibiotic policy [34], foundation of a group of specialists (these can be IDS as well as pharmacologist or microbiologist) [35, 36] to supervise and follow the antibiotic prescriptions of other physicians and to assess them and to give feedback to the medical team. Furthermore, the introduction of a computerized program may help to optimize the antibiotic prescription adapted to local resistance. Previous studies have already demonstrated the benefits of an ASP for reducing consumption [30] and costs associated with antibiotic substances [29].

Evidence on antimicrobial stewardship

The effectiveness of an ASP has been recently proven through five independent meta-analyses. Each of the five studies evaluated different outcomes. The meta-analysis published by Feazel et al, including 16 studies, demonstrated that the restrictive interventions, by limiting the use of cephalosporins and fluoroquinolones antibiotics, reduced the incidence of CDI. This is particularly important in geriatric patients who appear to benefit the most from the restriction, probably due to the high incidence of *C. difficile* in elderly patients [37].

Pooled data published by Schuts et al. focused primarily on the clinical outcome of patients, but also considered bacterial resistance rates, adverse drug reactions, and costs associated with antibiotics. The study concluded that ASPs generally have a positive effect on reduce the adverse effects of antibiotic therapy (i.e. nephrotoxicity). More than that, they suggest that an ASP could have an impact on de-escalation therapy and can improve the Prescribing of empirical

antimicrobial therapy according to guidelines; for what it concerns mortality, they showed haw it was significantlly reduced from 56% to 36% [38]. The study by Karanika et al. demonstrated the effects of an ASP on the consumption of antibiotic substances and the resistance rates of specific pathogens. They showed how the implementation of an ASP was associated with a reduction of −19.1% of antibiotic consumption. In intensive care units, the decrease was even bigger with −39.5%. They also showed a reduction in infections´ rates of MRSA, imipenem-resistant Pseudomonas aeruginosa and ESBL Klebsiella spp.. The results didn´t show any increase in infection-related 30-day mortality and infection rates after implementation of an ASP [30]. The Cochrane meta-analysis by Davey et al showed that the risk of death was similar between intervention and control groups (11% in both arms), indicating that antibiotic use can likely be reduced without adversely affecting. In this study the evidence about the effect of the interventions on reducing Clostridium difficile infections was low as well for both resistant gram-negative and gram-positive bacteria [39], but they showed how antibiotic stewardships can improve the antibiotic prescribing quality, reduce the duration of antibiotic treatment (-1.95 days) and the length of stay (-1.12 days).

The Last published meta-analysis on this topic, by Baur et al., including 32 studies and comprising 9 056 241 patient-days gave evidences that antimicrobial stewardship programs

reduce the incidence of infections and colonisations with MDR Gram negative (-51%), ESBL producing bacteria (-48%) and MRSA (-37%), as well as the incidence of *C. difficile* infections (-32%). Antimicrobial stewardship programs were showed to be more effective when implemented with infection control measures, especially hand-hygiene interventions.[40]

Antimicrobial Stewardship in the Emergency Department

The inappropriate prescription of antibiotics represents one of the most important preventable factors contributing to the spread of antibiotic resistance [41]. In order to address this issue, antimicrobial stewardship programs (ASPs) have been developed with the aim of optimizing clinical outcomes while minimizing unintended consequences [42] and have been successfully implemented in medical, surgical and intensive care units. Systematic reviews have shown, with convincing level of evidence, that the introduction of hospital wide ASPs results in reduction of antibiotic usage, [30] antibiotic resistance, [40] and adverse drug events, such as nephrotoxicity and Clostridioides difficile infections (CDIs). [37, 40]

There is a paucity of literature pertaining to ASPs in the emergency department (ED), [17, 43, 44] likely because many of the strategies commonly adopted by ASPs may be difficult to be implemented in the ED [18]. There are logistical system- and provider-level issues making the ED a critical environment for addressing interventions to reduce the inappropriate antibiotic prescription rate, [4] including ED overcrowding, [44] high turnover of patients, [18] diminished continuity of care due to high variability of practitioners, [45] and therapeutic decisions made frequently by a single ED practitioner in a rapid decision making process often without meaningful microbiologic information. [46] Furthermore, since ED sits at the interface between community and hospital, the antibiotic selection in ED has the potential to affect the antibiotic usage of both the discharged and the admitted patients with important downstream implications. In fact, antibiotic regimens started in the ED are often maintained even when another clinician has assumed care of the patient. [45]

Evidence of feasibility and impact of ASP in the ED are given from some studies made in the last years. One of these, from Borde et al, showed a decline in the mean monthly total antibiotic use density from 111 RDD per 100 patient days before the implementation of an ASP to 86 RDD per 100 patient days after starting the ASP. [17] Another study, from Dinh et al, gave evidence of a decrease in antibiotic prescription (from 3.0% to 2.2%, $P < 0.0001$) and a better compliance with guidelines before and after ASP implementation, therefore showing that the implementation of an ASP in an ED markedly decreased the number of unnecessary antimicrobial prescriptions. [43] A study from Julian-Jimenez et al, observed how the implementation of an educational ASP had an impact on the clinical outcomes of the patients. It showed an increase of appropriate antibiotic therapy, a decrease in the length of antibiotic therapy and as well a decrease in length

of hospital stay (-1.14 days). Intra-hospital mortality and total 30-day mortality were both reduced. [47]

In 2013 a “call to action” was published by May et al., advocating the implementation of ASPs within the ED due to the far-reaching consequences that prescriptions in this setting might have on patient outcomes. The statement underlined the need to shift attention to EDs to define which of the multiple antimicrobial stewardship strategies are most feasible in this setting. [4] In this context, the Centers for Disease Control and prevention promoted the development of the MITIGATE toolkit (A Multifaceted Intervention to Improve Prescribing for Acute Respiratory Infection for Adults and Children in Emergency Department and Urgent Care Settings), a six-core component framework for implementing non-restrictive intervention (mostly education and audit and feedback) in the ED. [48] Besides this example, very few guidance documents are available on this topic. Therefore, in response to this lack of evidence and in a bid to underline the relevance of the topic, the European Society of Clinical Microbiology and Infectious Diseases has recently started the process for developing clinical guidelines on ASPs in the ED.

Aim of this study was to assess the impact of a non-restrictive ASP intervention in a non-surgical ED of a tertiary university hospital on reducing the use of antibiotics and related costs. The secondary aim was to evaluate the clinical impact of the ED-based ASP intervention on the hospital-admitted patients’ group. [49]

Material and Methods

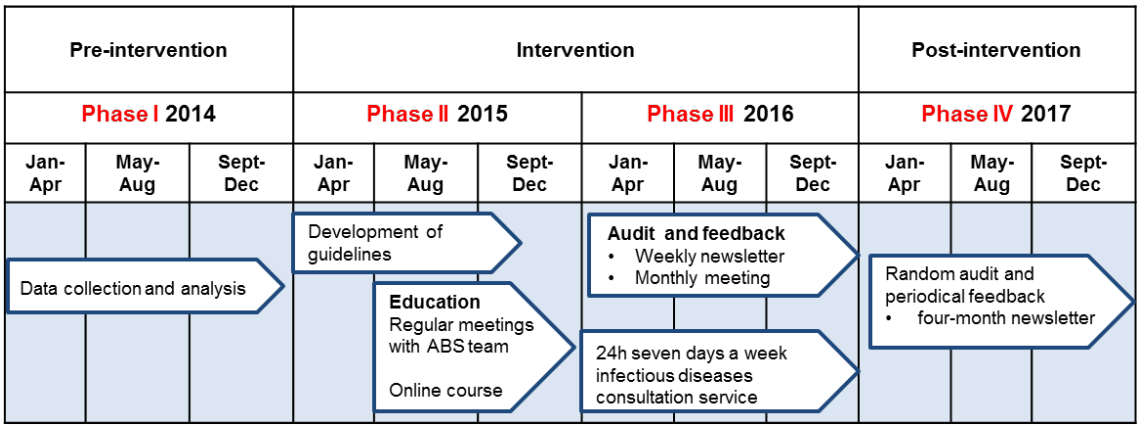
Study design and setting

We conducted a prospective quasi-experimental study using an interrupted time-series (ITS) analysis between 2014 and 2017. The study setting was the non-surgical ED of the University Hospital of Tübingen, a 1.513-bed tertiary care teaching hospital. The hospital includes different medical and surgical specialties: liver, kidney and bone marrow transplant units, a paediatric unit, a maternity ward, and a dialysis unit. The ED has 22 beds, equally distributed between the emergency room and the short term observation ward. The ED service is carried out by three personnel shifts. Two internal medicine physicians are permanently employed in the ED, whilst four senior internal medicine residents are on 6-12-month rotation. Three and two practitioners carried out the day and night shift, respectively. During the study period, there were yearly about 10.000 patient contacts, with approximatively 6000 hospitalizations. Before the ASP no official internal guidelines on antibiotic therapy and no routine infectious disease specialist visits were available for the ED. [49]

ASP implementation

The ASP was designed and carried out by a dedicated team, including two infectious diseases physicians, one infectious diseases resident, one clinical microbiology resident and two study nurses. The intervention model was exclusively non-restrictive. The ASP was composed of a one-year pre-intervention phase (Phase I), a 2-year multifaceted intervention phases (Phase II, 2015 and Phase III, 2016), followed by one year of post- intervention phase (Phase IV, 2017). A timeline of the intervention is dispayed in Figure 5.

Figure 5: Design of antibiotic stewardship program and timeline of the applied interventions[49]



The ASP program included the following core elements:

Prospective epidemiological and clinical data collection (Phase I, 2014)

Development and dissemination of guidelines on appropriate antibiotic empiric treatment (Phase II, Jan-Aug 2015). The whole ASP team developed the internal guidelines based on hospital epidemiological resistance data, on clinical and epidemiological patients' data collected in the Phase I, and on the most relevant national/international therapeutic guidelines regarding the main infectious diseases syndromes. The guidelines were made available in written pocket-sized format and distributed to the whole ED staff.

Education (Phase II, May-Dec 2015). The ASP team had weekly meetings with ED staff to discuss the validation of the guidelines and the local ecology. The ED staff carried out the on-line course "Antibiotic Stewardship: Managing Antibiotic Resistance" promoted by the University of Dundee, United Kingdom and the British Society for Antibiotic Chemotherapy (https://www.futurelearn.com/courses/antibiotic-stewardship).

Prospective audit and feedback (Phase III, Jan- Dec 2016). At least two members of the ASP-team reviewed daily each antibiotic prescription in ED, in accordance with the guidelines. The following patient data were collected and entered into a database: age, gender, underlying comorbidities, diagnosis and antibiotic prescription(s), including name, posology, length and administration route, length of hospital stay (LOS) and mortality. Microbiological data on antibiotic resistance were also gathered. The feedback was provided through weekly newsletters, reporting the compliance rate with the guidelines, the antibiotic use (expressed in daily defined dose, DDD) and the microbiological isolates with the antibiotic resistance profile. The newsletters also included the most relevant publications of the month. Additionally, weekly meetings were held focusing on the discussion of the most relevant clinical cases in which antibiotics were deemed to be inappropriate. The participation of the ED team to these meetings was strongly supported. An example of the newsletter is displayed in Figure 6.

Active infection diseases consultation service (Phase III, Jan – Dec 2016): in the second phase a specialist consultation service conducted by three infectious diseases physicians were active 24h seven days a week.

Random audit and periodical feedback (Phase IV, Jan- Dec 2017): a feedback was provided quarterly through newsletters briefly summarizing the antibiotic use.

The design of the ASP program and time line of the applied interventions are detailed in the Figure 5. [49]

Figure 6 example of a newsletter

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RETTE LEBEN

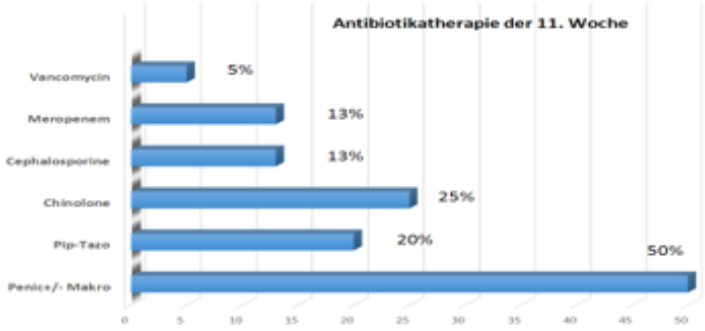
NOT- Newsletter 12.05.2016

Summary of the week 02.05.2016 - 09.05.2016

Dear colleagues of the emergency department,

Total admitted patients:168

- Patients received antibiotic(s): **40 (24%)**
- Patients received antibiotic with unclear indication: **6 (15%)**
- Patients received antibiotic without following the local guidelines: **4 (10%)**



Discussion´s Pinwall

Cave: the patients number 343XXX and 233XXX had no indication for an antibiotic therapy!

Please review the empirical therapy of the discitis for the patient number 557XXX

The following cases were not treated according to our local guidelines:

Patient-codes:

45XXXX

34XXXX

44XXXX

55XXXX

MICROBIOLOGICAL RESULTS:

Type of sample	Total	Positive n, (%)	Bacteria isolated (number)	Resistance pattern
Blood	14	3 (20)	*E.coli* (1), *S. haemoliticus* (1), *S. aureus* (1)	-
Urin	11	3 (33)	*Enterococcus* (1), *E.coli* (2)	Vancomycin resistance
Sputum	--	--	--	--
Wound	1	1 (100)	*E.coli* (1)	--
Faeces	2	0 (0)	--	--
Screening	7	2 (28)	*Enterococcus* (2)	Vancomycin resistance

Conferences and courses

Hepatitis C and HIV (CIDIC); *Wednesday, 01.June 2016, 18:00.*
Universitätsklinikum Tübingen

NOT rette aNtibiOTika RETTE LEBEN

NOT- Newsletter 12.05.2016

References of the week:

- R. Álvarez et al., Optimizing the Clinical Use of Vancomycin. Antimicrobial Agents and Chemotherapy (May 2016)
- R. K. Shields et al., Aminoglycosides for Treatment of Bacteremia Due to Carbapenem-Resistant *Klebsiella pneumoniae*. Antimicrobial Agents and Chemotherapy (May 2016)

COMIC OF THE WEEK

Taken from: http://www.beatricebiologist.com/2014/10/antibiotic-costume/

NOT-TEAM	
Prof. Dr. Tacconelli	151-8708
Dr. Kreth	82706
Dr. Foschi	151-8816
Dr. Buhl	151-9002
Miss Spohn	83679
Dr. Eisenbeis	85364

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Outcomes, measures and definitions

The primary outcome was the total monthly (oral and parenteral) antibiotic use in ED, measured as DDD per 100 patient days (DDD per 100PDs) according to the 2014 Anatomical Therapeutic Chemical (ATC) Defined Daily Dose Index delivered by the World Health Organization (https://www.whocc.no/atc_ddd_index/). Antibiotics were classified following the ATC therapeutic subgroup J01 (antibacterial for systemic use). The DDD data were retrieved from the hospital pharmacy records for the time frame January 2014 - December 2017 and reflected the monthly amount of antibiotics dispensed to the ED. To capture potential shift in use, overall DDDs were also stratified into three groups (*Access, Watch* and *Reserve*) in accordance with the 2019 World Health Organization (WHO) AWARE classification. [50] Secondary outcomes were: yearly antibiotic costs calculated in EUROs/100 PDs, and clinical outcomes including LOS, monthly CDI incidence (calculated as number of events per 100 PDs) and in-hospital all-cause mortality. The clinical outcomes were measured in the inpatients group, that includes the patients enrolled in ED ASP and admitted to the hospital. These patients were followed until hospital discharge or death. [49]

Statistical analysis

Statistical analyses were conducted using an ITS model in accordance with the Cochrane Effective Practice and Organization Care recommendations (EPOC). [51] The ITS included four period segments: pre-intervention phase I (January to December 2014), intervention phase II (January-December 2015), intervention phase III (January-December 2016) and post-intervention phase IV (January- December 2017). Estimates for regression coefficients corresponding to the effect sizes of a change in level and a change in trend along the study phases were obtained. A change in level was defined as the difference between the observed level immediately post-ASP and the predicted level by the pre-ASP trend. A change in trend was defined as the difference between the pre and post-ASP slopes. Newey-West standard errors with a maximum lag of 2 was considered for the autocorrelation structure. The other outcomes were analysed using Chi-square test and ANOVA. The trend of antibiotic costs was studied using Poisson regression. A p value less than 0.05 was regarded as significant. All statistical analyses were carried out using STATA version 14.2 (Stata Corp LLC, Texas). The methods were carried out in accordance with relevant guidelines and regulations. The informed consent was taken from all ED health-care providers involved in the study. The Ethics Committee of the University of Tübingen declared that no ethics approval was necessary since the study was considered as a quality improvement intervention. [49]

Results

Overall, the ASP intervention included 42886 patients evaluated in ED receiving an antibiotic treatment during the whole study period. The median age was 67 (± 17), with more men than women (56% vs 44%); the yearly rate of visit to the hospital was similar in the four phases, accounting for more than 10000 consultation in the ED per year.

The hospitalisation rate was about 62% throughout the four phases of the study. If hospitalised, the patients were would be admitted to one of the internal medicine wards or to the intensive care unit (Table 1).

Table 1: Number of patients received antibiotic treatment in ED and admission rate per year [49]

Study phase	**Phase I (2014)**	**Phase II (2015)**	**Phase III (2016)**	**Phase IV (2017)**	**Total**
Number of consultation in ED, n	10647	10565	10840	10834	**42886**
Discharged patients, n (%)	3871 (37%)	4317 (41%)	4009 (37%)	3911 (37%)	**16108 (37.5%)**
Hospital admitted patients*, n (%)	6776 (63%)	6322 (59%)	6831 (63%)	6923 (63%)	**26852 (62.5%)**
ED: emergency department *patients were admitted to one of the following wards: a) gastroenterology, hepatology and infectious diseases; 2) hematology, pneumology and oncology; 3) cardiology; 4) nephrology, endocrinology and angiology; and 5) intensive care unit.					

As for the overall antibiotic use, the ITS analysis showed a non-significant decrease of 31.12 DDD/100 PDs (confidence interval (CI) 95% -67.50 to 5.27, p 0.092) at the beginning of phase II and a further decrease of 7.20 DDD/100 PDs (CI 95% -40.94 to 26.54, p 0.669) at the beginning of phase III (Table 2, Figure 7) [49]. When categorizing the antibiotic use in accordance with the 2019 WHO AWARE classification, [50] an homogeneous DDD reduction in each of the AWARE antibiotic group was observed (Table 2).

Table 2 Comparison of yearly mean antibiotic DDD stratified by AWARE antibiotic group in the before-after analysis [49]

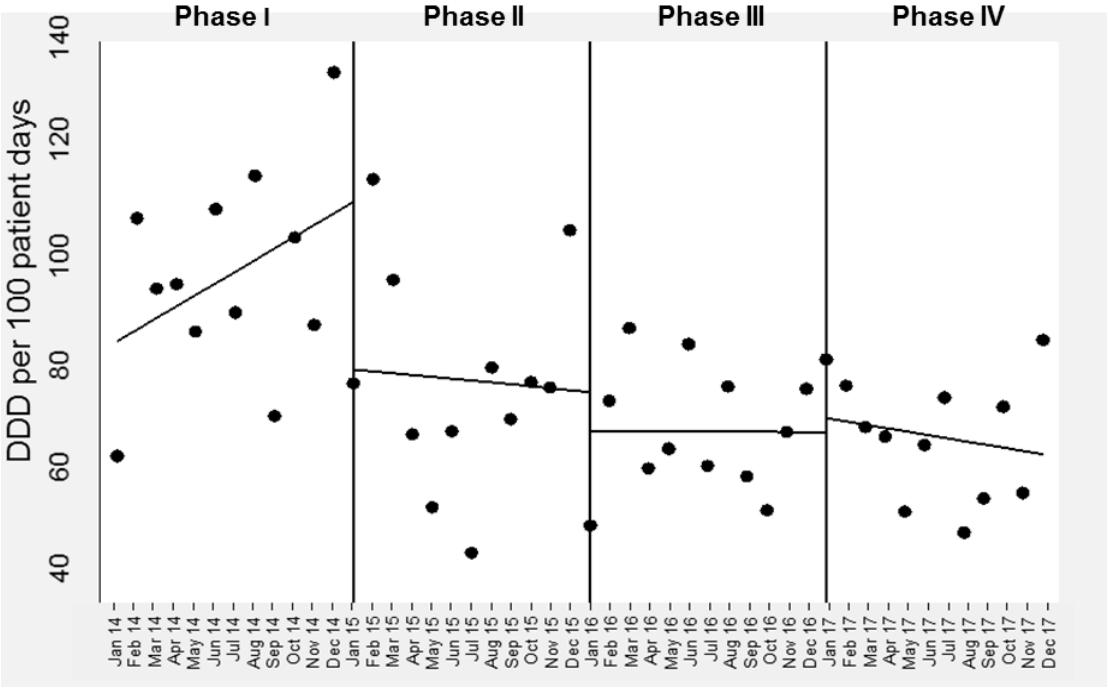
Antibiotic use expressed as DDDs/100 patient-days (standard deviation)					
AWARE Antibiotic group	**Phase I**	**Phase II**	**Phase III**	**Phase IV**	**p value**
ACCESS	64.87 (16.12)	51.15 (18.48)	33.04 (14.56)	46.44 (12.34)	0.18
WATCH	67.50 (13.23)	79.17 (20.24)	69.56 (12.99)	56.10 (14.18)	0.99
RESERVE	7.73 (1.24)	0.27 (0.92)	2.79 (3.21)	3.40 (2.76)	**<0.001**

Access group: Cefazolin, Amoxicillin, Ampicillin, Amoxicillin/Clavulanate, Ampicillin/Sulbactam, Flucoxacillin, Cotrimoxazol, Sulfadiazin, Metronidazole, Doxycicline, Clindamycin.
Watch group: Cefepim, Ceftazidim, Ceftriaxon, Piperacillin/Tazobactam, Ertapenem, Meropenem, Ciprofloxacin, Levofloxacin, Moxifloxacin, Vancomycin, Azithromycin, Clarithromycin, Erithromycin.
Reserve group: Daptomycin, Fosfomycin, Linezolid, Tigecyclin.

The antibiotic use by class was computed using Poisson regression.

Figure 7

Effect of the antibiotic stewardship implementation on the overall antibiotic use in DDD per 100 patient days in the study periods. The solid line represents the estimated slope by the segmented regression model. Abbreviation: DDD: daily defined dosis.[49]



A significant decrease in the mean yearly antibiotic cost per 100 PDs was recorded throughout the study phases, from 691.5 EUROs/100 PDs (standard deviation, SD: 263 EUROs/100 PDs) in the phase I, to 358.7 EUROs/100 PDs (SD: 189 EUROs/100 PDs) in the phase II, 262.5 EUROs/100 PDs (SD: 162 EUROs/100 PDs) in phase III and 263.3 EUROs/100 PDs (SD: 162 EUROs/100 PDs) in the phase IV ($p < 0.001$).

The ASP implementation has determined an overall decrease of LOS of the inpatients group admitted in all the five medical wards throughout the study phases. A statistical significant LOS decrease by 0.5 days, 0.7 days and 0.6 days was recorded in the gastroenterology, hepatology and infectious diseases ward (LOS phase I: 4.6 days, SD 5.1 days; LOS phase IV: 4.1 days, SD 5.1 days; $p < 0.0001$), in the hematology, pneumology and oncology ward (LOS phase I: 8.4 days, SD 7.3 days; LOS phase IV: 7.7 days, SD 7.3 days, $p < 0.0001$), and in the nephrology,

endocrinology and angiology ward (LOS phase I: 6.3 days, SD 6.8 days; LOS phase IV: 5.7 days, SD 6.8 days; p 0.006) respectively (Table 3). [49]

The implementation of the ASP program was not accompanied by significant negative effects in terms of mortality. During the study period, the all-cause mortality rate remained stable: 3.3% (213/6776) in phase I, 3.7% (238/6322) in phase II, 2.4% (259/6831) in phase III and 2.1% (224/6923) in phase IV (Table 3). [49]

Table 3: Comparison of mean monthly antibiotic costs and patient related outcomes in the ED department in the four study phases.[49]

Variable	**Phase I (2014)**	**Phase II (2015)**	**Phase III (2016)**	**Phase IV (2017)**	**p value***
Mean antibiotic costs euro/100 patient days (SD)	691.5 (263)	358.7 (189)	262.5 (162)	263.3 (162)	**0.001**
DDD (SD)	109.39 (20.27)	112.3 (34.69)	91.23 (18.69)	94.7 (20.00**)**	
In hospital all-cause mortality (n, %)	213 (3.3)	238 (3.7)	259 (2.4)	224 (2.1)	0.094
Mean length of hospital stay, days (SD) by ward					
Gastroenterology, hepatology and infectious diseases	4.6 (5.1)	4.6 (5.1)	4.2 (5.1)	4.1 (5.1)	**<0.0001**
Hematology, pneumology and oncology	8.4 (7.3)	8.2 (7.3)	7.6 (7.3)	7.7 (7.3)	**<0.0001**
Cardiology	4.5 (5.9)	4.5 (5.9)	4.7 (5.9)	4.4 (5.9)	0.112
Nephrology, endocrinology and angiology	6.3 (6.8)	6.2 (6.8)	5.8 (6.8)	5.7 (6.8)	**0.006**
Intensive care unit	2.2 (14.0)	2.0 (14.0)	2.2 (14.0)	2.0 (14.0)	0.948

DDD: defined daily doses, SD: standard deviation.
*p value for antibiotic costs computed using Poisson regression; p value for mortality computed using Chi-square test; p value for LOS computed using ANOVA.

The ITS analysis of CDI incidence showed a decreasing trend in both the intervention phases. From the phase II (change in level -0.45 CI95% -0.52 to 0.43, p 0.847), the reduction of the incidence was more remarkable during the phase II, in which the change in level further decreased by 0.23% (CI95% -0.75 to 0.29, p 0.381) and the change in trend achieved the statistical significance (change in slope -0.06, CI95% -0.10 to -0.01, p 0.014) (Table 4). [49]

Table 4: Results of the interrupted time series analysis comparing the overall antibiotic use and the incidence rate of C. difficile infection in the four study phases.*[49]*

OVERALL ANTIBIOTIC USE IN DDD per 100 patient days						
Study phase	Baseline level (β0)	Baseline slope	Change in level (CI 95%)	P value	Change in slope (CI 95%)	P value
Phase I	83.68	2.16	-	-	-	-
Phase II			-31.12 (-67.50 to 5.27)	0.092	-0.35 (-4.31 to 3.62)	0.861
Phase III			-7.20 (-40.94 to 26.54)	0.669	-0.02 (-2.16 to 2.11)	0.983
Phase IV			2.60 (-14.40 to 19.60)	0.759	-0.61 (-2.71 to 1.49)	0.562
INCIDENCE RATE OF *C. DIFFICILE* INFECTIONS per 100 patient days						
Study phase	Baseline level (β0)	Baseline slope	Change in level (CI 95%)	P value	Change in slope (CI 95%)	P value
Phase I	0.80	0.12	-	-	-	-
Phase II	-	-	-0.45 (-0.52 to 0.43)	0.847	0.04 (-0.01 to 0.09)	0.133
Phase III	-	-	-0.23 (-0.75 to -0.29)	0.381	-0.06 (-0.10 to –0.01)	**0.014**

Phase IV	-	-	0.11 (-0.31 to 0.54)	0.588	0.002 (-0.05 to 0.05)	0.946
DDD: daily defined doses. CI: confidence interval.						

Discussion

Our study demonstrated that a 4-year non-restrictive multifaceted ASP program applied in ED setting may reduce the overall antibiotic use without adversely affecting mortality. The ASP implementation was associated with a significant decrease of the antibiotic costs by two thirds after the intervention; starting from 691.5 euro per 100 patient days in the pre-intervention phase, the cost has decreased quickly by two thirds in the following phases. Among the inpatient group, a significant reduction of both LOS and CDI incidence rate has been shown, pointing out that the intervention applied in ED might have an impact downstream on other medical areas of the hospital.

Notwithstanding the several challenges hampering a successful ASP implementation, our ED-based ASP intervention has been shown to be feasible and efficacious even when no restrictive measures were adopted. The use of an entirely persuasive approach represents, in fact, a relevant strength of our ASP. In accordance with a Cochrane systematic review, the non-restrictive strategy, embedding a high potential for educational opportunities, usually results in more sustained positive effects on the clinicians' professional practice, in comparison with the restrictive approach. [16-17] In our study, the constant decrease of the overall antibiotic use, observed in each of the AWARE group (*Access, Watch* and *Reserve*), alongside the antibiotic costs might reflect a cumulative effect of the various persuasive interventions implemented stepwise. Worthy of note, the greatest decline of both outcomes was observed in phase III. The intensified "prospective audit and feedback" approach, the core element of this phase, may have played a crucial role in enhancing the clinicians' knowledge and adherence to the guidelines and consequently to an improved appropriateness of prescription.[16, 52]

The positive impact of ASPs on reducing the antibiotic use has been widely assessed in several inpatient settings. [53-55] However, very little literature is available for the ED. A German study observed a statistically significant decrease of the overall mean antibiotic use by 22% after the implementation of a non-restrictive 6-year ASP in a large academic ED. [17] A similar finding was reported in a general surgery ED in Italy. The implementation of a stewardship bundle based on education and diffusion of hospital guidelines for surgical prophylaxis and infections led to a significant drop of the antibiotic use by 18%. [56]

These findings, although promising, should be interpreted and compared with caution. The main issue, not hindering a reliable comparison of antibiotic use within and across hospitals, resides

in the lack of standardized quantity metrics for antibiotic use, which largely differ across similar settings and providers, and for specific medical populations. [57] The most common adopted metric, the DDD, is regarded as highly inaccurate [58] and might be discordant for several frequently prescribed antibiotics, since the administered dosage in clinical practice differs from the DDD suggested by the WHO. [58, 59] An addtional common metric, the days of therapy (DOT), also poses challenges in its application in the context of the ED. Given that the computation of DOT is based on the calendar days during which the patient receives antibiotic(s), this risk is that this metric is not a reliable estimate of the antibiotic use in patients that have a very short hospital stay, as usually occurs in ED.

In order to address the issue, innovative standardized evidence-based metrics for antibiotic use have been proposed. [60, 61] Among these, the Standard Antibiotic Administration Ratio (SAAR), developed by Centers for Disease Control and Prevention, seems to be the most feasible. By aggregating various patients care locations and antibiotic categories, the SAAR enables a risk-adjusted antibiotic use comparison across multiple hospitals. However, this metric is not easily applicable in European hospitals, due to the different structure of healthcare systems and the lack of shared databases with accessible electronic health records. [61]

The ASP implementation led to a significant drop in antibiotic cost by two third along the whole study period. Although not specifically assessed in the ED setting, inpatients ASPs have led to remarkable cost savings for health systems. A meta-analysis published in 2016 by Karanika *et al*., including five studies, described a cost reduction of 33.9% after ASP implementation. [30] Notably, the impact of ASPs implementation on costs saving could be even greater, despite not reliably measurable. In fact, beyond the costs referred to the direct costs of the antibiotic agents, there are several indirect expenditures that are supposed to drop alongside; [62] such as from the adverse drug events. [63]

Since the ED represents the cornerstone between community and hospital setting, we hypothesized that an appropriate antibiotic selection in ED might have a relevant impact along the entire care continuum and ED patients who were admitted to hospital would intuitively benefit. The reduction of both LOS and CDI incidence rate observed in the medical wards seems in fact to support the concept of “downstream effects”.

With regard to the LOS, a mild but sustained decrease has been shown in all medical wards throughout the study phases. Although some confounders affect this measure, the improvement of the patient care in ED, result of our ASPs, might partly explain this finding. As observed in the

clinical practice, the antibiotic therapies started in ED are frequently kept unaltered during the whole hospital stay of the patients, regardless the change of healthcare providers, mainly because of their reluctance to deescalate or even to discontinue. [45] From this perspective, the upstream selection of appropriate antibiotic treatment in ED might have a positive effect downstream in the hospital wards, leading to reduced number of antibiotic starts, shorter treatment lengths and earlier switch-to oral administration.

The CDI incidence rate showed a downward trend throughout the study phases. Interestingly, the protective effect of ASPs on CDI rate has been widely described for restrictive ASP interventions focusing on the “high risk antibiotic classes”, [64-66] whilst the efficacy of entirely non-restrictive ASP implementation has been much less investigated. [67, 68]

It is hard to evaluate how likely the CDI reduction could be directly related to the ASP implementation, since it was implemented in a different setting and, more importantly, several other co-interventions (e.g. infection control policies, hand hygiene) have been regularly employed in the hospital during the study period.

Notably, the reduction of antibiotic use was greater in Phase II, whilst the greater reduction of CDI incidence was recorded in Phase III. Since the development of CDIs is strongly related to prolonged antibiotic use, [69] it could be hypothesized that the improvement of antibiotic management might preserve the gut microbiota, [70] resulting belatedly in a reduction of CDI.

A strength of our study was the use of a Cochrane validated method to measure the antibiotic use, providing the best evidence for evaluating ASP in a quasi-experimental research setting, when a randomized trial is not applicable. [71]

Nonetheless, this study had some limitations. First, the single-center nature of the study might limit its generalizability to other ED settings, especially with different local antibiotic resistance rates. Second, the relatively small amount of DDDs per antibiotic classes did not allow to perform a reliable subgroup analysis. [39] Third, the lack of a control group not receiving the intervention did not allow appraising confounders and counterfactual outcomes.

In conclusion, the implementation of our multi-faceted non-restrictive ED-based ASP has demonstrated to be feasible and safe and may clinically benefit the hospital admitted patient group acting on LOS and CDI incidence rate. More research is needed to define the most appropriate ASPs design for the ED and the most suitable key outcome measures to reliably assess its effectiveness. [49]

Deutsche Zusammenfassung

Antibiotika Resistenz nimmt weltweit zu. Die Implementierung von Antibiotika-Stewardship-Programmen (ASPs) ist von größter Bedeutung, um den Einsatz von Antibiotika zu optimieren und die Entwicklung von Resistenzen zu verhindern, ohne den Patienten zu schädigen. Die Notaufnahme, wo Patienten zuerst eine antibiotische Therapie bekommen, ist ein entscheidender Ort für die Umsetzung des ASPs. Zurzeit sind aber die Evidenzdaten zu ASP in der Notaufnahme jedoch mangelhaft. In dieser Studie wurde ein 4-jähriger, nicht restriktiver, multi-faced ASP in der nicht chirurgischen Notaufnahme der Uniklinik Tübingen implementiert, um die Antibiotikagabe und die relative Kosten zu bewerten. Die Studie war in vier Phasen geteilt (Prospective epidemiological and clinical data collection (Phase I, 2014); Prospective audit and feedback (Phase III, Jan- Dec 2016); Active infection diseases consultation service (Phase III, Jan – Dec 2016); Random audit and periodical feedback (Phase IV, Jan- Dec 2017)). Außerdem beobachteten wir die Auswirkung einer ASP auf das Length of Stay (LOS), sowie auf den Inzidenzrate von Clostridioides difficile-Infektionen (CDI) und auf die Mortalität der Patienten, die ins Krankenhaus aufgenommen wurden. Die ASP-Implementierung war verbunden, mit einer Reduktion der Antibiotikagabe: von 31.12 DDD/100 PDs ((CI) 95% -67.50 to 5.27, p 0.092) am Anfang der Phase II und eine weitere Reduktion von 7.20 DDD/100 (CI 95% -40.94 to 26.54, p 0.669) am Anfang der Phase III (Table 2, Figure 7), sowie der Kosten: von 691.5 EUROs/100 PDs (SD: 263 EUROs/100 PDs) in der Phase I, zu 358.7 EUROs/100 PDs (SD: 189 EUROs/100 PDs) in der Phase II, 262.5 EUROs/100 PDs (SD: 162 EUROs/100 PDs) in der Phase III and 263.3 EUROs/100 PDs (SD: 162 EUROs/100 PDs) in der Phase IV ($p < 0.001$).

Ein nicht statistisch relevanter, aber anhaltender Rückgang des LOS in allen Stationen der medizinischen Klinik (Tabelle 3) und eine signifikante Reduktion der CDI-Inzidenzraten (Tabelle 4) wurden beobachtet, gleichzeitig blieb der Mortalität Rate stabil (Tabelle 3).

Zusammenfassend, die Implementierung unseres ASP hat sich als sicher erwiesen und könnte eine Verbesserung der klinischen Outcome zeigen. Weitere Studie sind erforderlich, um das am besten geeignete ASP-Design für die Notaufnahme und die wichtigsten Ergebnismaßnahmen zu ermitteln und seine Wirksamkeit zuverlässig zu bewerten.

Englische Zusammenfassung

Antibiotic resistance is increasing globally. Implementing antibiotic stewardship programs (ASPs) to optimize the everyday use of antibiotics while preventing development and progression of resistance is of utmost importance. One of the most crucial points where the implementation of these programs can have a clinical impact is the emergency room, where often the antibiotic treatments are started. The evidence-based data concerning ASPs in the emergency room are scarce. In the following study, we implemented a 4-year non-restrictive, multi-faced ASP in the non-surgical emergency room at the university hospital of Tübingen, Germany. The study was divided in four phases (Prospective epidemiological and clinical data collection (Phase I, 2014); Prospective audit and feedback (Phase III, Jan- Dec 2016); Active infection diseases consultation service (Phase III, Jan – Dec 2016); Random audit and periodical feedback (Phase IV, Jan- Dec 2017)). Additionally we assessed the impact of an ASP on the length of stay (LOS) and incidence rate of clostridium difficile infections (CDI) as well as the mortality rate in the patients' group admitted from ED to medical wards. The implementation of the ASP was linked to a reduction of antibiotic usage from 31.12. DDD/100PDs ((CI) 95% -67,50 to 5,27, p 0,0092) at the beginng of phase II and a further reduction of 7.20 DDD/100 (CI 95% -40.94 to 26.54, p 0.669) at the beginning of phase III (table 2, figure 7). The cost was reduced by 691,5€/100PDs (SD: 263 EUROs/100 PDs) in phase I to 358.7€/100 PDs (SD: 189 €/100 PDs) in phase II, 262.5 €/100 PDs (SD: 162 €/100 PDs) in phase III and 263.3 €/100 PDs (SD: 162 €/100 PDs) in phase IV ($p < 0.001$).

We also observed a non-significant yet sustained decline in LOS in all departments of the medical clinic (table 3) and a significant reduction of CDI-rates (table 4) while mortality did not significantly change (table 3).

In conclusion, that implementation of an ASP has demonstrated to be feasible and safe and might clinically benefit the hospital admitted patients' group. Further studies are required to identify the most beneficial ASP-design for emergency rooms and the key outcome measures to reliably assess its effectiveness.

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Erklärungen zum Eigenanteil:

Die Arbeit wurde in der medizinischen Klinik, Abteilung Innere Medizin I, unter Betreuung von Frau Prof. Evelina Tacconelli durchgeführt.
Die Konzeption der Studie erfolgte in Zusammenarbeit mit Frau Prof. Evelina Tacconelli.
Sämtliche Daten wurden von mir in Zusammenarbeit mit Giuseppe Marasca, Florian Kreth, Simone Eisenbeis und Michael Buhl gesammelt und zusammengestellt.
Die statistische Auswertung erfolgte durch mich in Zusammenarbeit mit Alessia Savoldi, Elena Carrara und Beryl Primrose Gladstone.
Ich versichere, das Manuskript selbständig nach Anleitung durch Alessia Savoldi und Frau Prof. Evelina Tacconelli verfasst zu haben und keine weiteren als die von mir angegebenen Quellen verwendet zu haben.

Berlin, 11.09.2020

Veröffentlichungen

Teile der vorliegenden Dissertationsschrift wurden bereits in den folgenden Publikationen veröffentlicht:

Savoldi, A., Foschi F, Kreth F, Gladstone BP, Carrara E, Eisenbeis S, Buhl M, Marasca G, Bovo C, Malek NP, Tacconelli E., *Impact of implementing a non-restrictive antibiotic stewardship program in an emergency department: a four-year quasi-experimental prospective study.* Sci Rep, 2020. **10**(1): p. 8194

Danksagung

Zunächst möchte ich mich an dieser Stelle bei all denjenigen bedanken, die mich während der Anfertigung dieser Doktorarbeit unterstützt und motiviert haben.

Ganz besonders gilt dieses Dank Frau Prof. Tacconelli, die meine Arbeit und somit auch mich betreut hat. Nicht nur gaben Sie mir immer wieder durch kritisches Hinterfragen wertvolle Hinweise – auch für Ihre moralische Unterstützung und kontinuierliche Motivation haben einen großen Teil zur Vollendung dieser Arbeit beigetragen.

Daneben gilt mein Dank Frau Alessia Savoldi, welche in zahlreichen Stunden Korrektur gelesen hat. Sie wies auf Schwächen hin und konnte als Fachfremde immer wieder zeigen, wo noch Erklärungsbedarf bestand.

Auch meine Kollegen haben maßgeblich daran mitgewirkt, dass diese Doktorarbeit nun in dieser Form vorliegt. Vielen Dank, dass Sie mir die Möglichkeit gegeben haben, bei Ihnen zu forschen und zu arbeiten.

Nicht zuletzt gebührt meinen Eltern Dank, ohne welche dieses ganze Unternehmen schon im Vorhinein niemals zustande gekommen wäre.