Staphylococcus Aureus: Selective Reporting of Antibiogram Results and Its Impact on Antibiotic Use. Interventional Study with a Reference Group on the Effect of Switching from Non-Selective to Selective Antibiotic Reporting

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Abstract

Background:

Antimicrobial stewardship (AMS) strategies worldwide focus on optimised antibiotic use. Selective susceptibility reporting is recommended as an effective AMS tool, although there is a lack of representative studies investigating the impact of selective susceptibility reporting on antibiotic use.

The aim of this study was to investigate the impact of selective susceptibility reporting of *Staphylococcus aureus (S. aureus)* on antibiotic consumption. Enhancing the use of narrow-spectrum beta-lactam antibiotics such as flucloxacillin/cefazolin/cefalexin is one of the main goals in optimising antibiotic therapy of *S. aureus* infections.

Methods:

This interventional study with control group was conducted at a tertiary care hospital in Germany. During the one-year interventional period, susceptibility reports for all methicillin-sensitive *S. aureus* (MSSA) were restricted to flucloxacillin/cefazolin/oral cefalexin, trimethoprim-sulfamethoxazole, clindamycin, gentamicin and rifampin/fosfomycin; instead of reporting all tested antibiotics during the year before the intervention and in the reference clinic. The impact of the intervention was analysed by monitoring antibiotic consumption (recommended daily dose/100 occupied bed days: RDD/100 BD).

Results:

MSSA-antibiograms were reported for 2836 patients. Total use of narrow-spectrum beta-lactams more than doubled during the intervention (from 1.2 to 2.8 RDD/100 BD, $P<0.001$; $P<0.001$ compared to the reference clinic); the percentage of total antibiotic use increased from 2.6% to 6.2%. A slight, but significant increase in the use of trimethoprim-sulfamethoxazole was also observed (+ 0.37 RDD/100 BD).

There was no decrease in antibiotics withdrawn from the antibiogram, probably as a consequence of their wide use for indications other than *S. aureus* infections.

Conclusions:

As narrow-spectrum beta-lactams are not widely used for other infections, there is a strong indication that selective reporting guided clinicians to optimised antibiotic therapy of *S. aureus* infections.

As useful AMS tool, we recommend implementing selective reporting rules into the national/international standards for susceptibility reporting.

Background

Significant efforts have been made to implement antimicrobial stewardship (AMS) worldwide to improve antibiotic prescribing to prevent multidrug resistance and improve patient care. There are a number of policies, strategies and tools outlined in different guidelines [1–3] and systematic reviews [4–9] to achieve this goal. Nevertheless, the impact of each tool is unclear.

One of the recommended tools is selective reporting of antibiotics in accordance with treatment guidelines to optimize antibiotic prescribing [1–3, 10–12]. Although this is one of the tools required there is a lack of representative studies investigating the impact of selective susceptibility reporting on antibiotic use.

The aim of this study was to investigate the effect of switching antibiotic susceptibility testing for *S. aureus* from non-selective reporting of all tested antibiotics to selective reporting of recommended antibiotics. Changes in other AMS tools were minimised during that period in order to focus on the impact of antibiotic reporting.

S. aureus with its large number of pathogenicity factors causes severe infections that should be treated by optimal antibiotic therapy. Narrow-spectrum beta-lactam antibiotics such as flucloxacillin or cefazolin/cephalexin have better activity against *S. aureus* than broad-spectrum beta-lactams such as piperacillin-tazobactam, ceftriaxone or even cefuroxime [13–15]. In addition, third-generation cephalosporins or fluoroquinolones are associated with a number of side effects including *Clostridium difficile* infections and the risk of selecting multi-resistant bacteria e.g. extended spectrum beta-lactamase-strains (ESBL) or methicillin-resistant *S.aureus* (MRSA). Therefore, enhancing the use of narrow-spectrum beta-lactams is one of the main goals of AMS in *S. aureus* infections to optimize antibiotic therapy of the individual patient and to prevent the spread of multi-resistant bacteria.

Methods

This interventional study was conducted at the Helios Clinics of Schwerin, a tertiary care hospital in Germany with more than 1200 beds. Helios Clinic Duisburg, a tertiary care hospital of comparable size and structure (more than 1000 beds), served as a reference without intervention. The study was approved by the Ethics Committee of the Faculty of Medicine at the University of Rostock (A 2017 – 0149).

Intervention

From November 01, 2017 – October 31, 2018, reports on susceptibility testing (antibiogram) of all tested methicillin-sensitive *S. aureus* (MSSA) were modified in the following way: Only recommended therapeutically appropriate antibiotics for *S. aureus* infections were reported (narrow-spectrum beta-lactams: intravenous flucloxacillin/cefazolin/oral cefalexin, trimethoprim-sulfamethoxazole, clindamycin, gentamicin, rifampin/fosfomycin for combination therapy); whereas all others, especially broad-spectrum antibiotics (e.g. piperacillin-tazobactam, ceftriaxone, imipenem, meropenem, vancomycin) were excluded. The laboratory operation system (OPUS:: L by OSM GmbH, Essen, Germany) was programmed to automatically "not-report" these antimicrobials without operator intervention, in order to minimise extra effort and errors of the laboratory staff. Before the intervention, all tested antibiotics were reported on the antibiogram, predetermined by industrial panels (Table 1). Additionally, the standard advice for the therapy of *S. aureus* infections was given in every susceptibility testing report to guide the clinician's selection of the most appropriate antibiotic depending on the severity of the disease: "First choice for severe S. aureus infections/bacteraemia: high dose intravenous flucloxacillin/cefazolin (ceftriaxone/cefotaxime/vancomycin are less effective in the treatment of MSSA); mild infection/oral follow-up: cefalexin, trimethoprim-sulfamethoxazole or clindamycin depending on the indication, side effects and allergies".

Table 1 Antibiogram for *S. aureus* before and after the intervention: selective reporting of antibiotics

Non-selective antibiogram reporting:		Selective antibiogram reporting:
Penicillin	Gentamicin	**Oxacillin / Flucloxacillin**
Ampicillin/Amoxicillin	Ciprofloxacin	
Piperacillin	Moxifloxacin	**Cefazolin / Cefalexin**
Oxacillin / i.v. Flucloxacillin	Clindamycin	
Ampicillin-sulbactame	Erythromycin	**Trimethoprim-sulfamethoxazole**
Amoxicillin-clavunate	Doxycycline	
Piperacillin-tazobactam	Tigecyclin	**Clindamycin**
i.v. Cefazolin / oral Cefalexin	Vancomycin	
Cefuroxime i.v.	Teicoplanin	**Gentamicin**
Cefotaxime	Daptomycin	
Ceftriaxone	Linezolid	**Fosfomycin (combination therapy)**
Ceftazidime	Trimethoprim-sulfamethoxazole	**Rifampin (combination therapy)**
Imipenem	Fosfomycin (combination therapy)	
Ertepenem	Rifampin (combination therapy)	

The prescribing clinicians were not informed of the ongoing study.

We did not change the reporting of susceptibility testing in methicillin-resistant *S. aureus* (MRSA).

Measurement of the effect of the intervention

To measure the effect of the intervention we monitored the recommended daily dose/100 occupied bed days (RDD/100 BD) as a standardised method for measurement of antibiotic usage. To calculate RDD/100 BD, the total monthly use of every antibiotic in the entire hospital was devided by the occupied bed days and the assumed normal daily dose (Table 2: RDD for all involved antibiotics). Antibiotic consumption was compared to Helios Clinic Duisburg as a reference hospital of comparable size, where all tested antibiotics were furthermore reported on the antibiogram (antibiotic consumption data of all Helios Clinics in Germany are available on “iNAB": intranet-based statistics of antibiotic consumption). The RDD was representative of the actual dose of different antibiotics administered in both hospitals (besides dose adjustments to kidney or liver dysfunction). There were no temporary shortages of any involved antibiotics.

Table 2
Recommended daily dose (RDD) of the involved antibiotics

Antibiotic	Recommended daily dose (RDD in g)
Flucloxacillin iv	8
Ampicillin-sulbactam iv	6
Amoxicillin-clavunate po	1.75
Piperacillin-tazobactam	12
Imipenem-cilastatin iv	2
Meropenem iv	3
Cefalexin po	3
Cefuroxime iv	4,5
Cefuroxime po	1
Ceftriaxone iv	2
Trimethoprim-sulfamethoxazole iv/po	1.92/1.92
Clindamycin iv/po	1.8/1.8
Gentamicin iv	0.24
Ciprofloxacin iv/po	0.8/1
Moxifloxacin iv/po	0.4/0.4
Doxycycline iv/po	0.2/0.2
Vancomycin iv	2
Daptomycin iv	0.5
Linezolid iv/po	1.2/1.2
Fosfomycin iv	15
Rifampin iv/po	0.9/0.9

Simultaneously, we recorded the incidence of nosocomial *Clostridium difficile* infections as recommended in the IDSA guideline [2] to observe a possible secondary effect of altered prescribing habits.

The number of patients in whom *S. aureus* was detected was recorded monthly in order to have a baseline of infections for the intervention.

Other AMS interventions apart from selective reporting were avoided to minimize independent alterations in antibiotic prescribing. In particular, there was no additional consultative support by infectious disease specialists in *S. aureus* infections during the intervention.

Statistical analysis

The consumption of various antibiotics was described by the mean value, standard deviation, median and minimum-maximum (min-max not shown, but available from the author). Descriptions were recorded for both clinics for the pre- and post-interventional period, respectively (Table 3). Linear regression analysis was used to estimate the change in mean consumption post- and pre-intervention for both clinics and assessed using the t-test for independent samples, if antibiotic use in both time periods was different. The differences between post- and pre-interventional periods with regard to the mean change between Schwerin and the reference clinic was estimated, and assessed using the t-test for independent samples if the change in consumption in Schwerin and the reference clinic was equal.

Table 3

Antibiotic use (RDD/100 BD; median) pre- and post-intervention in the Helios Clinics of Schwerin and the reference clinic

	Antibiotic use (RDD/100 bed days; median)						*P*-value (difference in antibiotic use between the interventional and reference clinic during the intervention period); 95%-confidence interval)
	Interventional Clinic			Reference Clinic			
	before inter-vention	after inter-vention	RDD-Difference after-before (RDD/100 BD); *P*-value (95%-confidence interval)	before inter-ventional period	after (without inter-vention)	RDD-Difference after-before (RDD/100 BD); *P*-value (95%-confidence interval)	
Antibiotics reported **before and after the intervention**							
Flucloxacillin iv + Cefazolin iv	0.82	1.58	**+ 0,6; < 0.001** (0.35; 0.86)	0.77	0.93	+ 0.19; 0.131 (-0.06; 0.43)	**0.019** (0.07; 0.76)
Cefalexin po	0.24	1.29	**+ 1.06; < 0.001** (-0.10; 0.25)	0.11	0.18	+ 0.08; 0.383 (-0.10; 0.25)	**< 0.001** (0.71; 1.26)
Flucloxacillin iv + Cefazolin Iv + Cefalexin po	1.17	2.80	**+ 1.66; < 0.001** (1.30; 2.03)	0.85	1.19	+ 0.26; 0.141 (-0.09; 0.62)	**< 0.001** (0.91; 1.89)
Trimethoprim-sulfamethoxazole iv + po	0.69	1.05	**+ 0.37; 0.009** (0.10; 0.63)	2.11	1.40	-0.79; 0.001 (-1.24; -0.35)	**< 0.001** (0.66; 1.66)
Clindamycin iv + po	1.42	1.33	-0.07; 0.661 (-0.38; 0.25)	1.22	1.09	-0.22; 0.105 (-0.50; 0.05)	0.445 (-0.25; 0.56)
Gentamicin iv	0.36	0.35	-0.01; 0.899 (-0.19; 0.16)	0.26	0.37	+ 0.30; 0.135 (-0.10; 0.71)	0.147 (-0.74; 0.11)

BD: bed days; po: per oral; iv: intravenously

Fosfomycin iv	0.03	0.02	0.00; 0.813 (-0.03; 0.04)	0.00	0.00	+ 0.02; 0.329 (-0.02; 0.05)	0.593 (-0.06; 0.04)
Rifampin iv + po	0.47	0.66	+ 0.02; 0.908 (-0.25; 0.28)	0.30	0.41	+ 0.19; 0.101 (-0.04; 0.42)	0.308 (-0.52; 0.17)
Antibiotics not reported **after the intervention**							
Aminopenicilline/ Beta lactamase-inhibitor (Amoxicillin/Clavulanate + Ampicillin/Sulbactame iv + po)	5.53	5.98	+ 0.28; 0.415 (-0.42; 0.97)	4.40	4.30	+ 0.17; 0.540 (-0.40; 0.74)	0.805 (-0.76; 0.98)
Piperacillin-tazobactam iv	4.19	4.36	+ 0.59; 0.029 (0.07; 1.12)	5.56	5.73	+ 0.29; 0.375 (-0.38; 0.97)	0.471 (-0.53; 1.13)
Cefuroxime iv	3.55	3.29	-0.22; 0.124 (-0.51; 0.07)	1.98	1.61	-0.41; 0.007 (-0.70; -0.13)	0.332 (-0.20; 0.59)
Cefuroxime po	2.66	0.07	**-2.17;** **< 0.001** (-2.63; -1.72)	1.89	0.30	**-1.34;** **< 0.001** (-1.81; -0.87)	**0.011** (-1.47; -0.20)
Ceftriaxone iv	3.38	3.82	+ 0.36; 0.138 (-0.13; 0.85)	2.73	3.05	+ 0.14; 0.670 (-0.52; 0.79)	0.569 (-0.56; 1.01)
Imipenem/Cilastatin iv	1.35	1.24	-0.08; 0.502	2.11	2.00	-0.22; 0.167	0.473
Meropenem iv	0.58	1.01	+ 0.46; **< 0.001** (0.24; 0.68)	0.29	0.35	+ 0.09 0.252 (-0.07; 0.25)	**0.007** (0.11; 0.64)

BD: bed days; po: per oral; iv: intravenously

Imipenem/Cilastatin	1.95	2.34	+ 0.38;	2.42	2.27	-0.13;	**0.040**
+ Meropenem iv			**0.026**			0.488	(0.02; 0.99)
			(0.05; 0.72)			(-0.50; 0.24)	
Ciprofloxacin iv + po	3.17	3.44	+ 0.19;	3.81	3.33	-0.62;	0.063
			0.477			0.076	(-0.05; 1.67)
			(-0.36; 0.74)			(-1.31; 0.07)	
Doxycycline iv + po	0.36	0.67	+ 0.17;	0.13	0.52	+ 0.37;	0.273
			0.236			0.002	(-0.55; 0.16)
			(-0.12; 0.47)			(0.16; 0.58)	
Vancomycin iv	0.95	0.98	-0.02;	1.73	1.60	-0.11;	0.609
			0.828			0.438	(-0.25; 0.43)
			(-0.23; 0.18)			(-0.40; 0.18)	
Linezolid iv + po	0.33	0.36	+ 0.01;	0.44	0.35	-0.06;	0.367
			0.800			0.307	(-0.09; 0.23)
			(-0.10; 0.13)			(-0.17; 0.06)	
Daptomycin iv	0.01	0.08	+ 0.06;	0.00	0.00	+ 0.01;	0.168
			0.090			0.582	(-0.02; 0.12)
			(-0.01; 0.12)			(-0.02; 0.04)	
Total antibiotic use iv + po	43.08	45.27	**+ 2.71;**	40.89	41.52	-1.54;	**0.031**
			0.039			0.302	(0.40; 8.10)
			(0.15; 5.27)			(-4.56; 1.48)	
Total antibiotic use iv + po reduced by narrow-spectrum-beta-lactams and trimethoprim-sulfamethoxazole	42.19	43.89	+ 2.11;	40.23	40.62	-1.73;	**0.049**
			0.102			0.240	(0.02; 7.65)
			(-0.46; 4.67)			(-4.70; 1.24)	

BD: bed days; po: per oral; iv: intravenously

Incidence of nosocomial infections with Clostridium difficile (C. difficile **associated cases/100 total cases)**	0.08	0.04	-0.04 **0.006** (-0.07; -0.01)	0.23	0.23	-0.08 0.130 (-0.19; 0.03)	0.485 (-0.07; 0.15)
BD: bed days; po: per oral; iv: intravenously							

All statistical tests were two-sided and the significance level was set at 0.05. For statistical analysis, Stata/IC 14.2 Windows by Microsoft, Redmond, USA was used.

Results

The number of patients with *S. aureus* infection in the Helios Clinics of Schwerin was not significantly different during the pre- and post-interventional period (1422 pre- vs. 1413 post-intervention). That were 0.52 patients with *S. aureus* infections/colonisations per 100 occupied bed days (approximately 0.5 patients with *S. aureus*/100 BD), if the total occupied bed days of 549 511 during the observed two-year period is taken into account. The pre- and post-intervention antibiotic use of all included antibiotics in the Helios Clinics of Schwerin and the reference clinic is shown in Table 3.

1. Was there any impact of selective reporting on the use on the further on reported antibiotics (table 3, first part)?

There was a significant rise in the total use of narrow-spectrum beta-lactams in our clinic during the interventional period (+ 1.66 RDD/100 BD; $P<0.001$), and compared to the reference clinic ($P<0.001$). This increased consumption was detected for both intravenous flucloxacillin and cefazolin for severe *S. aureus* infections and oral cefalexin for less severe infections or follow-up therapy. After starting selective reporting, there was a sharp increase in the monthly use of narrow-spectrum beta-lactams (Figure 1), which was also observed in the linear regression analyses. There was no overlap of the monthly consumption of these antibiotics between the pre- and post-interventional period. No such effect was seen in the Helios Clinic Duisburg as control group, despite a slight, but non-significant increase in the use of narrow-spectrum beta-lactams over time (0.9 to 1.2; $P=0.141$).

There was also a slight, but significant increase in the use of trimethoprim-sulfamethoxazole (+ 0.37 RDD/100 BD) in contrast to a decrease in the reference clinic ($P<0.001$) (Figure 2).

No change in the use of the other four reported antibiotics: clindamycin, gentamicin and fosfomycin/rifampin (the latter exclusively used for combination therapy) was observed.

2. Was there any impact of selective reporting on the use of no longer reported antibiotics (table 3, second part)?

If we compare the interventional period with the pre-interventional period and with the reference clinic, no significant changes in the use of antibiotics not reported on the selective *S. aureus* antibiogram were observed, with the exception of a significant decrease in oral cefuroxime. At the same time, prescribing restrictions for oral cefuroxime (as another AMS tool) were implemented in both clinics due to insufficient resorption rate of approximately 50%. Thus, the decrease in oral cefuroxime cannot be stated as an isolated effect of "selectively not reporting".

When overall consumption of antibiotics in both hospitals was measured, no decreases in wide-spectrum antibiotics such as piperacillin-tazobactam, ceftriaxone or carbapenems were observed. There was even a non-significant increase in the use of piperacillin-tazobactam in both hospitals, independent of selective reporting for *S. aureus*. Carbapenems were analysed in sum as imipenem was replaced by meropenem during the investigation period due to its lower risk of seizures and expiring patent. For that reason, clinicians were forced to use meropenem instead of imipenem in most

indications (e.g. calculated sepsis therapy). For meropenem, doses higher than 3 g (=RDD) are mainly used in our hospital (often 3´2 g); thus, the consumption of meropenem in terms of patient days is probably overestimated and enhanced the total use of carbapenems during the interventional period.

Besides narrow-spectrum-beta-lactams and trimethoprim-sulfamethoxazole, there was no relevant increase in total antibiotic consumption in our clinic ($P = 0.102$), whereas there was a slight decrease in total antibiotic consumption in the reference clinic. The proportion of narrow-spectrum beta-lactams used compared to the total use more than doubled from 2.6–6.2% (Table 4) in our clinic after the intervention.

Table 4
Use of narrow-spectrum beta-lactams pre- and post-intervention and their percentage of total antibiotic use

	Helios Clinics Schwerin		**Reference Clinic**	
Antibiotic use **RDD/100 BD (median)**	Before intervention	After intervention	Before interventional period	After interventional period
Narrow-spectrum beta-lactams (flucloxacillin iv + cefazolin iv + cefalexin po)	1.17	2.80	0.85	1.19
Total antibiotics (iv + po)	43.08	45.27	40.89	41.52
Percentage of narrow-spectrum beta-lactams vs. total antibiotics	2.72%	**6.19%**	2.08%	2.87%

3. Was there any secondary effects of the intervention, e.g. on the number of nosocomial C.difficile infections as a secondary parameter for antibiotic use?

There was a significant decrease in the number of patients with nosocomial *C. difficile* infections from 0.08 to 0.04/100 total patients ($P = 0.006$) in our hospital after the intervention, but a slight increase was seen in the reference clinic. Thus, we could not show a significant reduction in *C. difficile* infections on selective antibiograms for *S. aureus*.

Discussion

Is it possible to guide clinicians to prescribe the optimal antibiotic therapy for *S. aureus* infections by solely reporting the most effective antibiotics on the antibiogram? A consulting infectious disease specialist/clinical microbiologist has a huge impact on the optimized therapy of *S. aureus* infections, but this is related to high personnel expense and is not possible in many hospitals [2, 3, 6, 16, 17]. Guiding the clinician using the antibiogram as an AMS tool could reach many more patients in a very cost-effective way. Selective antibiotic reporting is recommended by most AMS guidelines [1–3, 12, 20, 21], although the evidence is very scant: very few studies have proved a significant effect on antibiotic consumption for urinary tract infections or infections due to gram-negative pathogens [24–28] or for the use of rifampicin [29]. To our knowledge there are no studies on frequently occurring and often severe *S. aureus* infections. To date, selective reporting is poorly implemented in Europe (only in about one third of European countries), predominantly for urine cultures; only in Ireland, Turkey, the UK and Sweden is it endorsed as a standard of care by the health care authorities [19–23].

Which antibiotics are the most effective in S.aureus infections to be reported on the "selective" antibiogram?

S. aureus due to its large number of pathogenicity factors causes severe infections that should be treated with an optimal antibiotic regimen. There is broad consensus that narrow-spectrum beta-lactams such as intravenous

flucloxacillin or first generation cephalosporins (cefazolin/cefalexin) have better activity against MSSA than broad-spectrum beta-lactams such as piperacillin-tazobactam, ceftriaxone or even cefuroxime. Bacteraemia caused by *S. aureus* treated with high dose intravenous flucloxacillin or cefazolin is associated with lower mortality rates than with broad-spectrum beta-lactams or vancomycin [13–15, 30–35], and is one of the main quality indicators of AMS. Avoiding wide-spectrum beta-lactams also helps prevent side effects such as *C. difficile*-associated diarrhoea and the spread of multi-resistant bacteria. When searching the literature for specific advice on which antibiotics should be reported for a certain pathogen on a selective antibiogram, there are very few recommendations available [20, 21, 36]. There is minimum consensus that for *S. aureus* oxacillin/flucloxacillin, clindamycin and trimethoprim/trimethoprim-sulfamethoxazole (the latter for oral treatment) are the most appropriate antibiotics to report as the first step, whereas e.g. vancomycin, linezolid or broad-spectrum beta-lactams should be withheld. Oral flucloxacillin is not a suitable alternative due to its low resorption rate of about 50% in addition to its low oral maximum dose of 3 g compared with 12 g intravenously [37].

How can we measure the effect of the intervention?

We monitored the monthly consumption of different antibiotics using RDD/100 BD, a standardized method for measuring antibiotic use, which is not influenced by fluctuating patient numbers. We used RDD instead of internationally frequently used defined daily dose (DDD) [2, 38], as the RDD is based on higher daily doses, which were very close to the doses used in our investigation (Table 2). Using “Days of therapy” (DOT), favoured by IDSA guideline 2016 [2] and not impacted by individual dose adjustments, was not supported by our electronic patient files. This is probably the main limitation of our study. Analyzing statistically relevant numbers of patient records with *S.aureus* infection before and after the intervention would not have been practicable with justifiable efforts.

What could be the maximum effect of switching all antibiograms for S.aureus from reporting all tested to selectively reporting useful antibiotics?

The total number of patients with *S. aureus* infection/colonisation did not significantly change after the intervention as we detected *S. aureus* in approximately 100 patients each month. Thus, the assumed number of treatable *S. aureus* infections probably did not change during the investigation. Due to the study design, we were unable to distinguish between infection and colonisation. In relation to the occupied bed days, we found about 0.5 newly detected *S. aureus* infections/colonisations/100 BD. If one assumes that all of these patients were treated for *S. aureus* infections for 10 days, we would have the opportunity to influence a maximum of 5 days of antibiotic therapy/100 BD (5 RDD/100 BD). This value was probably much less as a significant proportion of patients may only have been colonised without an indication for therapy.

What was the impact of selective reporting on the use on the <u>further on reported</u> antibiotics?

There was a significant increase in the total use of narrow-spectrum beta-lactams such as intravenous flucloxacillin and first generation cephalosporins (intravenous cefazolin/oral cefalexin) in our clinic during the interventional period (from 1.2 to 2.8 RDD/100 BD; $P < 0.001$), and compared to the reference clinic ($P < 0.001$). No such effect was observed in the control group, despite a slight, but non-significant increase in the use of narrow-spectrum beta-lactams over time (0.9 to 1.2; $P = 0.141$), probably due to the overall AMS efforts in both clinics. Even the lowest monthly antibiotic consumption in the interventional period was higher than that in the previous year (no overlap; Fig. 1). The increase of 1.6 RDD/100 BD was particularly high compared to the maximal achievable effect caused by the relatively low rate of treatable *S. aureus* infections. The same significant increase was observed during the intervention when intravenous narrow-spectrum beta-lactams and oral cefalexin were analysed separately. Intravenous flucloxacillin and cefazolin, used in the initial therapy of severe *S. aureus* infections, were analysed as a sum because they were assessed to be equally effective

and replaced each other depending on side effects [18, 30, 31]. Their consumption doubled from 0.8 to 1.6 RDD/100 BD. This effect was not concealed by preoperative prophylaxis, as cefazolin was not used in both hospitals during that time.

There was also a striking increase in the consumption of oral cefalexin (follow-up/mild infections) during the interventional period (from 0.2 to 1.3 RDD/100 BD), significantly higher than in the reference clinic. Thus, this effect was not predominantly caused by searching for alternatives to restricted oral cefuroxime, but by selectively reporting it on the antibiogram.

Similar to cefalexin, a slight but significant increase in the use of trimethoprim-sulfamethoxazole was observed in contrast to a decrease in the reference clinic ($P < 0.001$). It is possible that we were able to detect the effect of selective reporting of this drug in *S. aureus* because trimethoprim-sulfamethoxazole was not used to calculate the therapy of urinary tract infections in both clinics due to resistance data.

There was no difference in the use of the other furthermore reported antibiotics, possibly due to its use in indications other than *S. aureus* infections.

In contrast to narrow-spectrum-beta-lactams and trimethoprim-sulfamethoxazole, there was no relevant increase in total antibiotic consumption in our hospital. The percentage of narrow-spectrum beta-lactams use compared to the total antibiotic use more than doubled from 2.6–6.2% (Table 4), whereas there was no increase in the number of patients in whom *S. aureus* was detected. As narrow-spectrum beta-lactams were not used for other infections in both hospitals (neither calculated nor according to the local guidelines), the consumption data indicate that the selective antibiogram significantly increased their use for *S. aureus* infections.

Tan *et al* [24] showed a similar significant increase in the consumption of reported antibiotics such as nitrofurantoin for targeted therapy and even for calculated therapy of urinary tract infections. Also, for urinary tract infections McNulty e*t al.* [26] demonstrated "that prescribing reverted to pre-intervention levels once the change in antibiotic reporting had stopped". We decided not to revert the antibiograms to the pre-interventional stage due to ethical reasons, and the goal to enhance the use of more effective narrow-spectrum antibiotics, along with lowering side-effects was reached.

What was the impact of selective reporting on the use of no longer reported antibiotics?

We were unable to show a significant decrease in the use of wide-spectrum antibiotics after selectively not-reporting for *S. aureus* in our clinic compared to the reference clinic, with the exception of one not caused by the antibiogram. Oral cefuroxime was rarely used in both hospitals during the interventional period (< 0.5 RDD/100 BD) due to a restriction preauthorised by the pharmacy. Intravenous cefuroxime was widely used for preoperative prophylaxis in both hospitals, which may have concealed a significant decrease in its targeted use for *S. aureus* infections. A decrease in linezolid and daptomycin consumption was not observed, as these medications in both hospitals have a restrictive prescribing policy (preauthorisation by the pharmacy/antimicrobial stewardship team).

The main reason for not detecting a reduction in the consumption of no longer reported antibiotics was their wide use for other indications than *S.aureus* infections, e.g. broad-spectrum antibiotics as piperacillin-tazobactam, ceftriaxone, carbapenems or even vancomycin for the therapy of sepsis, pneumonia or meningitis. Since the proportion of *S. aureus* infections was relatively small compared to all infections, a time-consuming evaluation of individual patient records would be necessary to prove a reduced use of broad-spectrum antibiotics for this specific indication.

Was there any impact on the number C.difficile infections?

The decrease in nosocomial *C. difficile* infections in both hospitals was probably due to multiple effects, not clearly associated with selective reporting, but with the overall epidemiological situation. Again, the proportion of *S. aureus*

infections influenced by selective reporting was low.

Conclusions

This interventional study is, to our knowledge, the first prospective study to prove the impact of selective reporting for *S. aureus* on antibiotic use. There is a strong indication that selective antibiotic reporting improves the therapy of *S. aureus* infections by enhancing the use of narrow-spectrum antibiotics.

Thus, selective reporting of recommended antibiotics is a useful AMS tool, which can be easily implemented with few personnel and technical efforts. We recommend implementing selective reporting rules in the national and international standards for susceptibility reporting.

Declarations

Compliance with ethical standards

The study was approved by the Ethics Committee of the Faculty of Medicine at the University of Rostock (A 2017-0149) and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

The manuscript does not contain clinical studies or patient data.

Competing interests

The authors declare that they have no conflict of interest.

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References

1. European Centre for Disease Prevention and Control. Proposals for EU guidelines on the prudent use of antimicrobials in humans. Stockholm: ECDC; 2017.
2. 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 Inf Dis. 2016;62:e51–e77.
3. de With K, Wilke K, Kern WV, Strauß R, Kramme E, Friedrichs A, et al. S3- Leitlinie Strategien zur Sicherung rationaler Antibiotika-Anwendung im Krankenhaus. AWMF-Registernummer 092/001 – update 2018
4. Allerberger F, Lechner A, Wechsler-Fördös A, Gareis R on behalf of ABS International. Optimization of antibiotic use in hospitals – Antimicrobial Stewardship and the EU Project ABS International. Chemotherapy. 2008;54:260–267.

5. Howard P, Pulcini C, Levy Hara G, West RM, Gould IM*, Harbarth S, et al.* An international cross-sectional survey of antimicrobial stewardship programmes in hospitals. *J Antimicrob Chemother.* 2015;70:1245–1255.
6. Schuts EC, Hulscher MEJL, Mouton JW, Verduin CM, Stuart JWTC, Overdiek HWPM, et al. Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis. Lancet Infect Dis. 2016;16:847-856.
7. Osthoff M, Bielicki J, Widmer AF, For Swissnoso. Evaluation of existing and desired antimicrobial stewardship activities and strategies in Swiss Swiss Med Wkly. 2017; 147:w14512.
8. Cunney RJ, Smyth EG. The impact of laboratory reporting practice on antibiotic utilization. Int J Antimicrob Agents. 2000;14:13-19.
9. Kaki R, Elligsen M, Walker S, Simor A, Palmay L, Daneman N. Impact of antimicrobial stewardship in critical care: a systematic review. J Antimicrob Chemother. 2011;66:1223-30.
10. 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 Inf Dis. 2007;44:159–177.
11. Morency-Potvin P, Schwartz DN, Weinstein RA. Antimicrobial Stewardship: How the microbiology laboratory can right the ship. Clin Microbiol Rev. 2017;30:381–407.
12. Duguid M, Cruickshank, M. Antimicrobial stewardship in Australian hospitals 2011. Available from https://www.savetyandqualitiy.gov.au/wp-content/uplouds/2011/01/Antimicrobioal-stewardship-in-Australian-hospitals-2011.pdf
13. Nissen JL, Skov R, Knudsen JD, Ostergaard C, Schønheyder HC, Frimodt-Møller N, Benfield T.Effectiveness of penicillin, dicloxacillin and cefuroxime for penicillin-susceptible Staphylococcus aureus bacteraemia: a retrospective, propensity-score-adjusted case-control and cohort analysis.J Antimicrob Chemother. 2013;68:1894-900.
14. Paul M, Zemer-Wassercug N, Talker O, Lishtzinsky Y, Lev B, Samra Z, Leibovici L, Bishara J. Are all beta-lactams similarly effective in the treatment of methicillin-sensitive Staphylococcus aureus bacteraemia? Clin Microbiol Infect. 2011;17:1581-6.
15. Weis S, Kimmig A, Hagel S, Pletz MW. Antibiotic Stewardship am Beispiel der *Staphylococcus aureus* Bakteriämie. Med Klin Intensivmed Notfmed. 2017;112:192-198.
16. Jump RL, Olds DM, Seifi N, Kypriotakis G, Jury LA, Peron EP, et al. Effective antimicrobial stewardship in a long-term care facility through an infectious disease consultation service: keeping a LID on antibiotic use. Infect Control Hops Epidemiol. 2012;33:1185-92.
17. Rieg S1, Peyerl-Hoffmann G, de With K, Theilacker C, Wagner D, Hübner J, et al. Mortality of S. aureus bacteremia and infectious diseases specialist consultation-a study of 521 patients in Germany. J Infect. 2009;59:232-9.
18. Bai AD, Showler A, Burry L, Steinberg M, Ricciuto DR, Fernandes T, et al. Comparative effectiveness of cefazolin versus cloxacillin as definitive antibiotic therapy for MSSA bacteraemia: results from a large multicentre cohort study. J Antimicrob Chemother. 2015;70:1539-46
19. Pulcini C, Tebano G, Mutters NT, Tacconelli E, Cambau E, Kahlmeter G, Jarlier V. On behalf of the EUCIC-ESGAP-EUCAST Selective reporting Working Group. Selective reporting of antibiotic susceptibility test results in European countries: an ESCMID cross-sectional survey. *Int J Antimicrob Agents* 2017; 49: 162-166.
20. Health Service Exucutive. Health Protection Surveillance Center. Guideline for antimicrobial stewardship in hospitals in Ireland. Available from: https://www.hpsc.ie./A-Z/MicrobiologyAntimicrobialResistance/InfectionControlandHAI/Guidelines/File,4116,en.pdf. Accessed 06 Sept 2016.

21. Svenska Läkaresällskapet. Refrensgruppen för antibiotikafragor. Available from: http://www.sls.se/RAF/. Accessed 06 Sept 2016.
22. Nathwani D. Antimicrobial prescribing policy and practice in Scotland: recommendation for good antimicrobial practice in acute hospitals. J Antimicrob Chemother. 2006;57:1189-96
23. MacKenzie FM, Gould IM, Bruce J, Mollison J, Monnet DL, Krcmery V, et al. The role of microbiology and pharmacy departments in the stewardship of antibiotic prescribing in European hospitals. J Hosp Infect. 2007;65 Suppl 2:73-81.
24. Tan TY, McNulty C, Charlett A, Nessa N, Kelly C, Beswick T. Laboratory antibiotic susceptibility reporting and antibiotic prescribing in general practice. J Antimicrob Chemoth. 2003;51:379–384.
25. Langdale P, Millar ML. Influence of laboratory sensitivity reporting on antibiotic prescribing preferences of genereal practitioners in the Leeds area. J Clin Pathol. 1986;39:233-4
26. McNulty CA, Lasseter GM, Charlett A, Lovering A, Howell-Jones R, Macgowan A, Thomas M. Does laboratory antibiotic susceptibility reporting influence primary care prescribing in urinary tract infection and other infections? J Antimicrob Chemother. 2011;66:1396-404.
27. Coupat C, Pradier C, Degand N, Hofliger P, Pulcini C. Selective reporting of antibiotic susceptibility data improves the appropriateness of intended antibiotic prescriptions in urinary tract infections: a case-vignette randomised study. Eur J Clin Microbiol Infect Dis. 2013;32:627–636.
28. Langford BJ, Seah J, Chan A, Downing M, Johnstone J, Matukas LM. Antimicrobial stewardship in the microbiology laboratory: Impact of selective susceptibility reporting on ciprofloxacin utilization and susceptibility of gram-negative isolates to ciprofloxacin in a hospital setting. J Clin Microbiol. 2016;54:2343-47.
29. Steffee CH, Morrell RM, Wasilauskas BL. Clinical use of rifampicin during routine reporting of rifampicin susceptibilities: a lesson in selective reporting of antimicrobial susceptibility data. J Antimicrob Chemother. 1997;40:595-8.
30. Paul M, Kariv G, Goldberg E, Raskin M, Shaked H, Hazzan R, et al. Importance of appropriate empirical antibiotic therapy for methicillin-resistant Staphylococcus aureus bacteraemia. J Antimicrob Chemother. 2010;65:2658-65.
31. Schweizer ML, Furuno JP, Harris AD, Johnson JK, Shardell MD, McGregor JC, et al. Comparative effectiveness of nafcillin or cefazolin versus vancomycin in methicillin-susceptible Staphylococcus aureus bacteremia. BMC Infectious Diseases. 2011;11:279.
32. Weber Z, Ariano R, Lgace-Wiens P, Zelenitzky S. Multifaced antibiotic treatment analysis of methicillin-sensitive *Staphylococcus aureus* bloodstrean infections. J Antimicrob Agents. 2016;48:674-9.
33. Kim SH, Kim KH, Kim HB, Kim NJ, Kim EC, Oh MD, Choe KW. Outcome of vancomycin treatment in patients with methicillin-susceptible Staphylococcus aureus bacteremia. Antimicrob Agents Chemother. 2008;52:192-7.
34. Stryjewski ME, Szczech LA, Benjamin DK Jr, Inrig JK, Kanafani ZA, Engemann JJ, et al. Use of vancomycin or first-generation cephalosporins for the treatment of hemodialysis-dependent patients with methicillin-susceptible Staphylococcus aureus bacteremia. Clin Infect Dis. 2007;44:190-6.
35. Chang FY, Peacock JE Jr, Musher DM, Triplett P, MacDonald BB, Mylotte JM, et al. Staphylococcus aureus bacteremia: recurrence and the impact of antibiotic treatment in a prospective multicenter study. Medicine (Baltimore). *2*003;82:333-9.
36. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing; 23rd informational supplement. CLSI document M100-S24. Wayne, PA: CLSI 2014.
37. Gath J, Charles B, Sampson J, Smithurst B. Pharmacokinetics and bioavailability of flucloxacillin in elderly hospitalized patients. J Clin Pharmacol. 1995;35:31-36.

38. Akpan MR, Ahmad R, Shebl NA, Ashiru-Oredope D. A review of quality measures for assessing the impact of antimicrobial stewardship programs in hospitals. Antibiotics (Basel).2016; 5: 5.

Figures

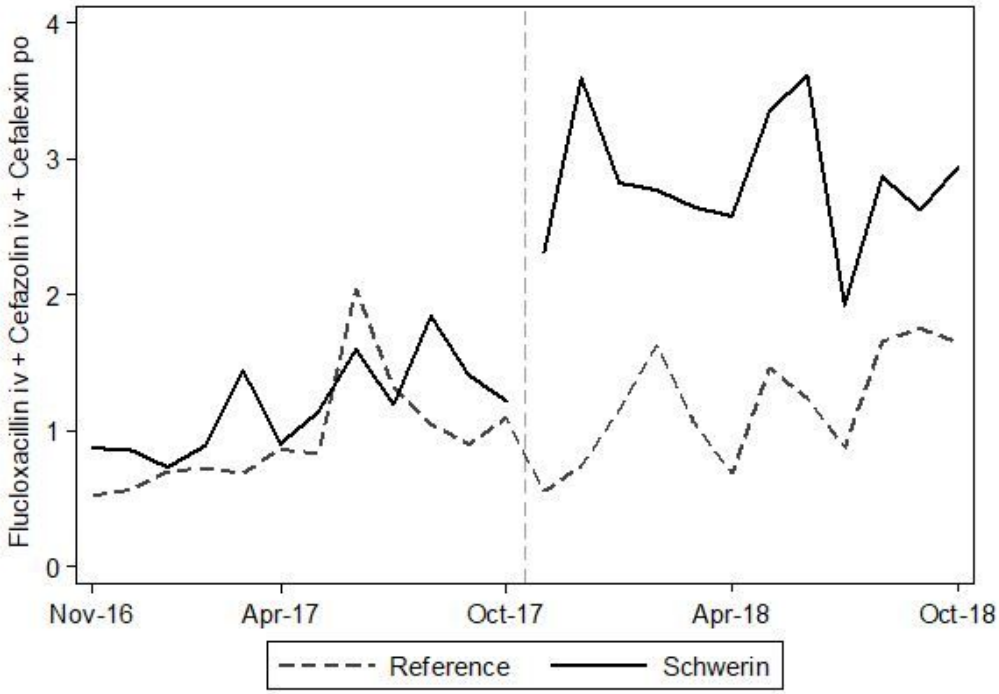

Figure 1

Monthly antibiotic use (RDD/100 BD) of narrow-spectrum beta-lactams (sum of flucloxacillin iv + cefazolin iv + cefalexin po) in the pre- and post-interventional period in the Helios Clinics of Schwerin and the reference clinic

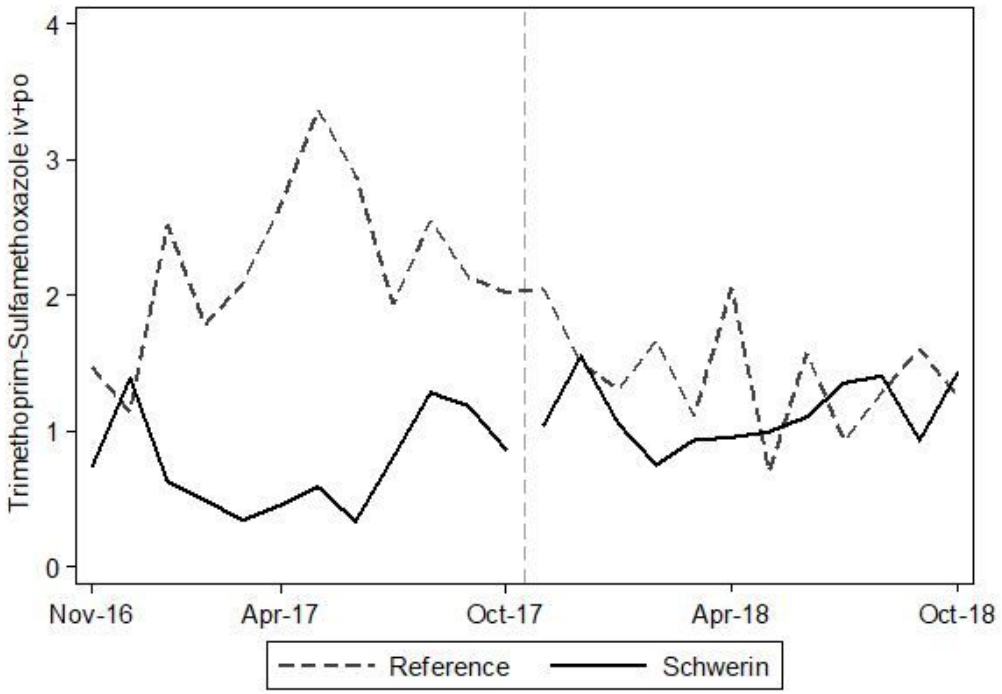

Figure 2

Monthly antibiotic use (RDD/100 BD) of trimethoprim-sulfamethoxazole in the pre- and post-interventional period in the Helios Clinics of Schwerin and the reference clinic