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ORIGINAL PAPER

Implementing an intensified antibiotic stewardship programme targeting daptomycin use in orthopaedic surgery: a cost–benefit analysis from the hospital perspective

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Abstract
Background Hospital antibiotic stewardship (ABS) programmes offer several evidence-based tools to control prescription rates of antibiotics in different settings, influence the incidence of nosocomial infections and to contain the development of multi-drug-resistant bacteria. In the context of endoprosthetic surgery, however, knowledge of core antibiotic stewardship strategies, comparisons of costs and benefits of hospital ABS programmes are still lacking.
Materials and methods We identified a high daptomycin use for the treatment of methicillin-sensitive staphylococcal infections as a potential target for our ABS intervention. In addition, we endorsed periprosthetic tissue cultures for the diagnosis of PJI. Monthly antibiotic use data were obtained from the hospital pharmacy and were expressed as WHO-ATC defined daily doses (DDD) and dose definitions adapted to local guidelines (recommended daily doses, RDD), normalized per 1000 patient days. The pre-intervention period was defined from February 2012 through January 2014 (24 months). The post-intervention period included monthly time points from February 2014 to April 2015 (15 months). For a basic cost–benefit analysis from the hospital perspective, three cost drivers were taken into account: (1) the cost savings due to changes in antimicrobial prescribing; (2) costs associated with the increase in the number of cultured tissue samples, and (3)

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the appointment of an infectious disease consultant. Interrupted time-series analysis (ITS) was applied.

Results Descriptive analysis of the usage data showed a decline in overall use of anti-infective substances in the post-intervention period (334.9 vs. 221.4 RDDs/1000 patient days). The drug use density of daptomycin dropped by −75 % (51.7 vs. 12.9 RDD/1000 patient days), whereas the utilization of narrow-spectrum penicillins, in particular flucloxacillin, increased from 13.8 to 33.6 RDDs/1000 patient days. ITS analysis of the consumption dataset showed significant level changes for overall prescriptions, as well as for daptomycin ($p < 0.001$) and for narrow-spectrum penicillins ($p = 0.001$). The total costs of antibiotic consumption decreased by an estimated € 4563 per month ($p < 0.001$), and around 90 % of these savings were linked to a decrease in daptomycin consumption. Overall, the antibiotic stewardship programme was beneficial, as monthly cost savings of € 2575 ($p = 0.005$) were achieved.

Interpretation In this example of large endoprosthetic surgery department in a community-based hospital, the applied hospital ABS programme targeting daptomycin use has shown to be feasible, effective and beneficial compared to no intervention.

Keywords Antibiotic stewardship · Orthopaedic surgical care · Cost–benefit analysis · PJI

Abbreviations

ABS	Antibiotic stewardship
PJI	Prosthetic joint infection
MDRO	Multi-drug resistant organism

Background

In the last decades it has been demonstrated that antimicrobial resistance is driven by the increasing trend of often ill-considered use of anti-infective substances in human and veterinary medicine [1]. Hospital antibiotic stewardship programmes offer several evidence-based tools to control prescription rates of antibiotics in different settings, influence the incidence of nosocomial infections, and to contain the development of multi-drug-resistant bacteria [2–4]. In the context of endoprosthetic surgery there is little data available on potential targets and interventional trials, although the knowledge of core antibiotic stewardship strategies might be a crucial part of high-quality orthopaedic surgical care [5, 6]. The use of anti-infective substances is further complicated by the fact that this field is highly competitive for pharmaceutical companies promoting expensive anti-infective substances with special biofilm-active properties or potencies against multi-drug resistant organisms (MDROs)—like daptomycin. The limited literature regarding antibiotic stewardship interventions in endoprosthetic care reports efforts to control the incidence of hospital acquired *Clostridium difficile* infections [7] and discusses adherence to current guidelines concerning perioperative antibiotic prophylaxis in different epidemiological situations [8] as well as the management of surgical site infections [9]. There is one trial using cefepime restriction to influence resistance patterns of gram-negative healthcare-associated infections in an orthopaedic hospital, with variable effects on ciprofloxacin and carbapenem susceptibilities of gram-negative bacteria [10]. In the present study, we conduct an antibiotic stewardship programme targeting the high daptomycin use for the treatment of methicillin-sensitive staphylococcal infections in an orthopaedic surgery department. To prevent the development of daptomycin-resistant pathogens and preserve this and other substances of "last resort" for the treatment of MDROs [11] such as methicillin-resistant staphylococcal infections or vancomycin-resistant enterococcal infections. In this context, we encourage the implementation of routine infectious disease physician consultations in the field of septic surgery and prosthetic joint infections (PJI). PJI represent a serious complication, which is related to a high morbidity and costly economic side-effects for endoprosthetic departments [12–14]. In contrast to the situation in Germany, appointments of infectious disease physicians working in the field of septic surgery to ensure rational use of anti-infective substances are well established in many European and Anglo-Saxon countries. However, in Germany infectious disease patient-care is complicated by a number of regulatory issues and the lack of defined residency programmes for infectious disease physicians. As mentioned before [15], these issues are subject to the current discussion and have not yet been implemented.

Materials and methods

Ethics

The ethics committee was notified about the trial. Formal approval was not required, because the project is based on epidemiological data. Research involving human subjects, human material, specific human or personalized data was not carried out.

Setting

The intervention took place at a community-based hospital in Germany with a large dedicated endoprosthetic surgery department. The department is certified as a top level "Center for endoprosthetic surgery (EPZmax)—endoCert®", performing all types of hip, knee and shoulder

procedures—in total more than 550 total hip arthroplasties (THAP) and about 500 knee arthroplasties (TKAP) annually. The department has the status of a regional referral unit for septic and revision surgery in the context of endoprosthetic complications. The clinical spectrum is completed by specialists for paediatric orthopaedics and sports medicine. All bone and tissue specimens for microbiological culture are transferred to an external microbiological laboratory. Species results and susceptibility testings are reported online and paper based.

ABS programme

The hospital had no specific ID resources before the intervention. The ABS intervention started with the appointment of an ID-specialist, who dedicated 10 % of his work hours to the programme. The aim of the ABS programme was to reduce the unnecessary prescription of "last-resort" anti-infective substances, specifically daptomycin. The use of narrow-spectrum penicillins was encouraged as an alternative, if needed and possible. Flucloxacillin was now recommended as the first-line therapy for methicillin-sensitive staphylococcal infections. Besides the use of flucloxacillin for staphylococcal infections, we promoted the adherence to current guidelines regarding the microbiological diagnosis of PJI, emphasizing the need for and superiority of periprosthetic tissue cultures over other microbiological methods to secure the definitive diagnosis of PJI. The intervention began in February 2014. It included weekly infectious disease rounds in the department for orthopaedic surgery, consultations by phone, bedside academic detailing, revision of the local guidelines, dissemination of the new recommendations and provision of feedback on the ward- and hospital-wide evolution of antibiotic use. Furthermore, we endorsed current international guidelines on diagnosing prosthetic joint infections and perioperative anti-infective prophylaxis.

Data acquisition

Monthly antibiotic use data were obtained from the hospital pharmacy and expressed as WHO-ATC defined daily doses (DDD) and dose definitions adapted to local guidelines (recommended daily doses, RDD) to account for major discrepancies between DDD and RDD for penicillins, normalized per 1000 patient days. All DDD and RDD calculations/transformations are based on the ADKA-if-RKI national surveillance programme and definitions. Price discounts and inflation were considered in drug-expenditure calculations. The German health system provides reimbursements based on diagnosis plus extra compensation for certain complications or very expensive drugs. However, daptomycin is not included in this system. For a cost–benefit analysis from the hospital perspective, the monthly drug expenditures were monitored and adjusted for fluctuations in price by the pharmacy service. The data were administered using Microsoft® Excel software. The DRG case mix index, patient days, and data on length of stay were obtained from the hospital administration. Information regarding the total number of periprosthetic tissue samples for microbiological culture were supplied from the external laboratory facility on a monthly basis from February 2012 to April 2015. The cost of a single tissue sample sent to microbiology was approximated as the mean of cost figures used for reimbursement (~€ 50; prices vary depending on whether or not a pathogen was detected). With respect to a cost–benefit analysis of the antibiotic stewardship programme, three cost drivers need to be taken into account:

1. Intervention-related monthly cost savings due to changes in antimicrobial prescribing.
2. In addition, the monthly number of tissue samples sent for microbiological evaluation.
3. The 10 % of the appointment of an infectious disease consultant resulting in an expenditure of about € 850 per month.

Statistical analysis

Descriptive analysis of the results regarding the overall number of performed periprosthetic tissue cultures was performed using Microsoft® Excel software. The effect of the intervention on drug use densities was analysed using interrupted time-series analysis. The pre-intervention period was defined from February 2012 through January 2014 (24 months). The post-intervention period included monthly time points from February 2014 to April 2015 (15 months). Interrupted time-series analysis allows accounting for three effects of the intervention: a baseline trend as well as intervention-related level and a slope effect. Overall, our data indicate a change in the level rather than a slope change and baseline trends were not observed. In order to apply the most parsimonious regression model in the light of the limited number of observations, the final analyses included the intercept and the level changes only [16]. In detail, we applied linear regressions with Newey–West standard errors with a lag of 1 to be considered in the autocorrelation structure. All analyses were carried out using Stata 14 (StataCorp, College Station, TX, USA).

Results

Overall, use of anti-infective substances declined in the post-intervention period from February 2014 to April 2015

Table 1 Overview

	RDD/1000 PT			DDD/1000 PT		
	Mean values pre-intervention	Mean values post-intervention	Difference in %	Mean values pre-intervention	Mean values post-intervention	Difference in %
Cephalosporins	147.0	78.6	−47	252.9	128.0	−49
3. Generation cephalosporins	3.3	6.3	+90	3.3	6.3	+90
1. + 2. Generation cephalosporins	143.7	72.3	−50	249.6	121.7	−51
Penicillins	60.8	59.6	−2	145.4	171.0	+18
Broad-spectrum penicillins + BLI	4.4	4.9	+10	3.8	4.2	+10
Amino-penicillins + BLI	42.5	21.1	−50	93.4	42.4	−55
Narrow-spectrum penicillins	13.8	33.6	+143	48.2	124.3	+158
Carbapenems	2.3	0.6	−75	2.8	0.9	−69
Fluoroquinolones	34.0	37.2	+9	47.8	42.3	−12
Amino-glycosides	1.1	1.2	+5	1.5	1.6	+5
Daptomycin	51.7	12.9	−75	51.7	12.9	−75
Vancomycin	3.9	1.6	−61	3.9	1.6	−61
Rifampicin	33.1	29.6	−11	49.7	44.4	−11
Linezolid	0.8	0.2	−69	0.8	0.2	−69
Total	334.9	221.4	−34	556.6	402.8	−28

BLI beta-lactamase inhibitor

(334.9 vs. 221.4 RDDs/1000 patient days, Table 1), with an estimated intervention-related decrease of −113.5 RDDs per month ($p = 0.002$, Table 2). We detected the strongest effect, as intended, in the prescription rate of daptomycin (Table 2). The drug use density of daptomycin, measured in RDD/1000 patient days, dropped by −75 %, with an estimated intervention-related decrease of −38.78 RDDs ($p < 0.001$, Table 2). The utilization of narrow-spectrum penicillins, in particular flucloxacillin, markedly increased from 13.8 to 33.6 RDDs/1000 patient days. We observed a decrease of −47 % in the total use of cephalosporins. The overall use of pencillins, however, showed no reduction. First- and second-generation cephalosporins were prescribed less frequently in the post-intervention period (143.7 vs. 72.3 RDDs/1000 patient days), most likely due to a growing adherence to current guidelines regarding the duration of perioperative prophylaxis. There were no unfavourable side-effects; the drug densities of carbapenems and broad-spectrum penicillins like piperacillin/tazobactam showed no increasing prescription patterns (Table 2). In the interrupted time-series analysis, however, there is a slight, but not-significant increase in the use of fluoroquinolones (34.0 vs. 37.2 RDDs/1000 patient days)—mainly levofloxacin, which is most likely attributable to the changed guideline for oral therapy of staphylococcal infections, which now recommended levofloxacin, doxycycline or cotrimoxazole as preferred agents with a high bioavailability in combination with rifampicin. In the post-intervention period DRG case mix index and data on length of stay remained stable and did not influence our results (data not shown—available on request from the author).

As a result of the changes in antibiotic use, the total costs of antibiotic use decreased by an estimated € 4563.7 per month ($p < 0.001$), see Table 3. Interestingly, around 90 % of these savings were associated with daptomycin consumption, while changes in penicillin, cephalosporin or fluoroquinolone use were, at least from a cost perspective, of minor importance (Table 3).

Endorsing the rational diagnosis of PJI, we were able to increase the total number of tissue samples sent for microbiological culture in the post-intervention period. Before the intervention was initiated, there were, on average, about 8 samples taken per month, whereas in the post-interventional period this number increased to about 30 per month, with an intervention-related increase of 22.78 ($p < 0.001$), see also Fig. 1. As already mentioned above, the total number of patients per month remained stable, and there were no other changes in the infrastructure or patient morbidity which might have confounded our results. With respect to a cost–benefit analysis of the antibiotic stewardship programme, three cost drivers were taken into account:

Table 2 Interrupted time-series analysis of the antibiotic consumption data (RDD/1000 patient days)

	Total cephalosporins	3. Gen. cephalosporins	1. +2. Gen. cephalosporins	Total penicillins	Broad-spectrum penicillins + BLI	Aminopenicillins + BLI	Narrow-spectrum penicillins	Carbapenems	FQ	Aminoglycosides	Daptomycin	Vancomycin	Rifampicin	Linezolid	Total
Post-interventional level change	−68.45*** (0.000)	2.977 (0.283)	−71.43*** (0.000)	−1.225 (0.911)	0.430 (0.793)	−21.47** (0.001)	19.81*** (0.001)	−1.738+ (0.064)	3.139 (0.757)	0.0514 (0.957)	−38.78*** (0.000)	−2.397* (0.049)	−3.532 (0.615)	−0.529 (0.480)	−113.5** (0.002)
Pre-interventional level	147.0*** (0.000)	3.305* (0.014)	143.7*** (0.000)	60.80*** (0.000)	4.446*** (0.000)	42.53*** (0.000)	13.83*** (0.000)	2.319** (0.005)	34.03*** (0.000)	1.137** (0.007)	51.72*** (0.000)	3.943*** (0.000)	33.14*** (0.000)	0.770 (0.282)	334.9*** (0.000)
N	39	39	39	39	39	39	39	39	39	39	39	39	39	39	39

BLI beta-lactamase inhibitor

P values in parentheses $^{+}$ $p < 0.10$, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 3 Interrupted time-series analysis of the antibiotic costs data (in €)

	Total cephalosporins	3. Gen. cephalosporins	1. +2 Gen. cephalosporins	Total penicillins	Broad-spectrum penicillins + BLI	Aminopenicillins + BLI	Narrow-spectrum penicillins	Carbapenems	FQ	Amino-glycosides	Daptomycin	Vancomycin	Rifampicin	Linezolid	Total costs in €
Post-interventional level change	−195.0*** (0.000)	3.616 (0.277)	−198.7*** (0.000)	139.6* (0.042)	−3.343 (0.789)	−54.02* (0.018)	196.9*** (0.000)	−46.42* (0.041)	−99.25*** (0.000)	0.605 (0.771)	−4027.5*** (0.000)	−21.75* (0.026)	−213.8* (0.020)	−100.1 (0.458)	−4563.7*** (0.000)
Pre-interventional level	374.6*** (0.000)	4.134** (0.008)	370.5*** (0.000)	257.7*** (0.000)	38.38*** (0.000)	95.24*** (0.000)	124.1*** (0.000)	60.07** (0.003)	128.9*** (0.000)	1.957** (0.004)	5299.9*** (0.000)	31.48*** (0.001)	483.7*** (0.000)	140.8 (0.277)	6779.2*** (0.000)
N	39	39	39	39	39	39	39	39	39	39	39	39	39	39	39

BLI beta-lactamase inhibitor

P values in parentheses $^{+}$ $p < 0.10$, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

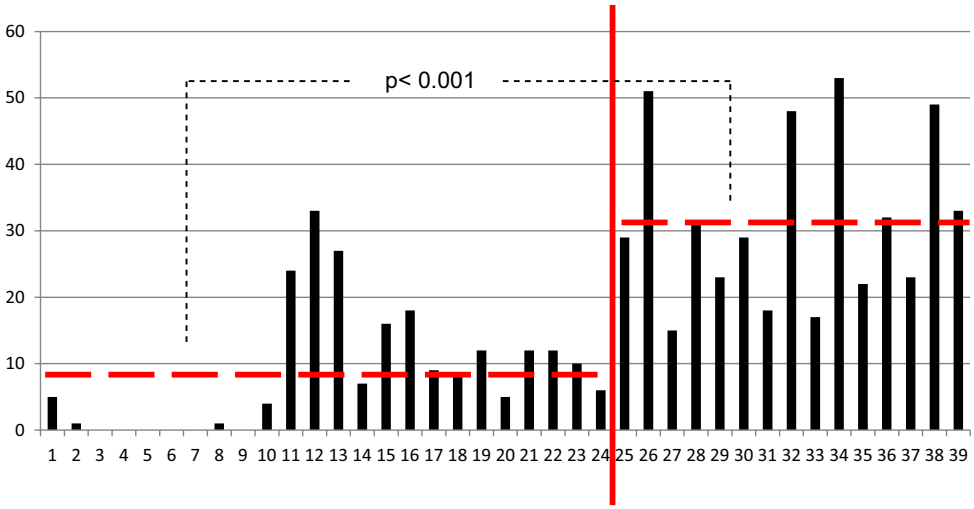

Fig. 1 Number of obtained tissue samples per month during the pre- and post-intervention period. Student's *t* test indicates a significant difference comparing the mean values in the pre- and post-intervention period (8.75 vs. 31.53; $p < 0.001$)

1. As shown in Table 2, intervention-related monthly cost savings due to changes in antimicrobial prescribing were estimated at € 4563.7 ($p < 0.001$).
2. In addition, the monthly number of tissue samples sent to microbiology showed an intervention-related increase of 22.78 ($p < 0.001$), which is associated with estimated additional costs of € 1139 (€ 50 per sample).
3. Finally, the 10 % of the appointment of an infectious disease consultant resulted in the added expenditure of about € 850 per month.

Overall, the antibiotic stewardship programme was beneficial, as a monthly cost saving of € 2575 ($p = 0.005$) could be realized. When keeping the intervention-related monthly cost savings equal, the antibiotic stewardship programme would remain beneficial until either the number of tissue samples increases to 74 each month, or the cost of the infectious disease consultant responsible reach € 3425 (which amounts ~40 % of his total salary).

Discussion

In the present study, we demonstrate that it is feasible, effective and beneficial to implement an antibiotic stewardship programme targeting daptomycin use in endoprosthetic surgical care. The prescription rate for daptomycin dropped significantly by −75 %—using persuasive and educational tools rather than restrictive measures. Recently published guidelines on the management of PJI recommend the use of narrow-spectrum β-lactam antibiotics such as flucloxacillin or nafcillin for methicillin-sensitive staphylococcal infections [17]. Despite various in vitro data on biofilm activity, superiority of daptomycin over β-lactam substances has not been shown in clinical and controlled settings [11]. It remains unclear what exactly had been responsible for the unusual high daptomycin use in treating methicillin-sensitive staphylococcal infections in the pre-intervention period in this particular department. We hypothesize that an intensified merchandizing campaign by the pharmaceutical industry might be at least in parts responsible for this phenomenon. Literature data concerning this issue indicate that there is a strong association between various merchandizing measures and the prescribing behaviours of physicians and residents [18, 19]. We observed no unfavourable side-effects of our intervention; specifically there were no unintended compensatory changes for other drug classes. The overall antibiotic consumption decreased by about 30 %. This is an appreciated effect related to an increased overall awareness in prescribing anti-infective substances and has been documented in other antibiotic stewardship trials before [20]. However, our study has several limitations. First, there are only data from a short post-interventional observation period available although the sustainability of the intervention needs to be demonstrated in a longer timeframe—preferably after 24 months [16]. Second, we did not assess the quality of prescriptions and we did not follow individual patients for outcome evaluation before and after the intervention took place. However, DRG case mix index, data on length of stay, and the overall number of patients remained stable. As published in other, earlier antibiotic stewardship trials [20, 21], these indicators might serve as a crude estimator of an unchanged patient outcome. Adverse outcomes seem very unlikely on the basis of these data. Third, there was no control department against which the observed effects could be evaluated, and we therefore cannot rule out that there were some unrelated changes occurring independent of the intervention which might have confounded our findings. Finally, the development of staphylococcal resistance patterns regarding daptomycin MICs would have been an interesting issue to follow-up. However, there is no

comprehensive dataset allowing a trend analysis available yet at this stage. Moreover, these effects are often delayed by several months.

Cost–benefit calculations are a challenging problem in the healthcare setting. In the context of hospital ABS there are no defined guidelines on how to report financial impacts of ABS interventions. A systematic review regarding financial evaluations of ABS programmes was recently published [22]. It is shown that there is still a major potential for improvement. Most studies take only drug expenditures on anti-infective substances into account (57 from 99 included studies). Only few published trials report operational costs like prices for microbiological diagnostic procedures, personal expenditures and other cost drivers which might be related with hospital ABS programmes. In the presented study, we report at least some other cost drivers than drug expenditures. However, even this remains a very basic approach to cost–benefit calculations, which is a further limitation of the study.

Conclusion

In conclusion, the present study is another example for a successful antibiotic stewardship intervention in a previously neglected clinical discipline in Germany. This intervention might serve as model for other orthopaedic departments and hospitals with a similar baseline structures. Furthermore, we would like to encourage the implementation of routine infectious disease physician consultations in this field.

Compliance with ethical standards

Conflict of interests The department of endoprosthetic surgery (SK and BS) received 2014 support from Novartis to invite a world-renown lecturer in the field of PJI.

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