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Poor compliance with an antibiotic directive—A call for intensified monitoring

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ABSTRACT

Background: In April 2017, the Central Denmark Region Antibiotic Stewardship Committee issued a directive to reduce the general use of piperacillin-tazobactam and prescribe narrow-spectrum antibiotics for mild and moderate pneumonia. The directive was distributed to all regional hospital clinicians.
Methods: Electronic medical records were used to obtain de-identified details of all antibiotics administered (together with diagnosis codes) to all in-hospital patients (pre-directive and post-directive) in the nine regional hospitals. Average moving range statistical process control charts were used to analyze pre-directive and post-directive variation in antibiotic usage patterns.
Results: Upon the distribution of the directive, a period of decline of the overall usage of piperacillin-tazobactam ensued. Rather than benzylpenicillin, as recommended for pneumonia, the initial decline in piperacillin/tazobactam usage was accompanied by increased use of cefuroxime.
Conclusions: A steward-directed reduction in piperacillin-tazobactam usage was accompanied by less desirable usage of a broad-spectrum alternative. Future antibiotic stewardship initiatives will hopefully benefit from close monitoring and timely feedback to clinicians. A dialogue with clinicians based on near real-time data is predicted to improve antibiotic stewardship actions.

Background

In the Central Denmark Region, the Antibiotic Stewardship Committee has permitted the use of piperacillin/tazobactam as initial empiric treatment of severe infections with unknown etiology. An unexpected impetus that drove the Antibiotic Stewardship Committee to change this permission occurred in October of 2016. At that time, a factory explosion at Jinan, China, led to a major shortage in the raw materials necessary for manufacturing piperacillin/tazobactam (Anonymous, 2016). Thus, along with other regions around the world, the Central Denmark Region faced a 25% decline in piperacillin/tazobactam supply. This unplanned interruption of the regional *status quo* approach to piperacillin/tazobactam usage became an exceptionally useful case study in the effectiveness of stewardship directives to improve antibiotic management. Based on the directive, a retrospective analysis of detailed antibiotic usage data was performed. The aim was to evaluate the compliance with an antibiotic stewardship directive within a hospital context, with the goal of providing insights into the clinicians' responses to an urgent directive intended to alter their clinical practice.

Materials and methods

Intervention and data collection

This study was conducted from 01 January 2015 to 31 July 2017 in the Central Denmark Region, Denmark. This region in the western part of the country is the second most populous region (population was ~1.3 million at the time of intervention) (Statistics_Denmark, 2016). The intervention was a single electronic antibiotic stewardship directive sent on 10 April 2017. This directive was directly emailed to each clinician serving at a region

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hospital, regardless of their respective specialty (~3500). Furthermore, the directive was electronically and physically delivered to the department heads of each of the nine regional hospitals (136 wards with 2227 hospital beds). Department heads were asked to distribute the directive to the relevant personnel, with an appeal for compliance. The physical format was laminated cards that could be passed on to clinicians to keep in their pockets for quick reference when making antibiotic prescriptions. The directive was also designed to address a recently noted lack of compliance with national and local primary, whereby piperacillin/tazobactam was being used to treat mild and moderate pneumonia.

The Antibiotics Stewardship Committee's electronic directive was issued to specifically reduce the more than 19,000 annual piperacillin/tazobactam administration for pneumonia in the Central Denmark Region (Figure 1). The directive advised clinicians: (1) to consider the indications for using broad-spectrum antibiotics; (2) to reduce piperacillin/tazobactam usage for pneumonia treatment going forward as soon as possible; and (3) to use benzylpenicillin (preferred, or another narrow-spectrum antibiotic) for mild and moderate pneumonia. The clinicians were not restricted in their access to or usage of piperacillin/tazobactam. There was no specified target of reduction for each department or at the hospital level. No feedback data were sent directly to the departments or the individual clinicians.

This study was able to detail the regional response to an antibiotic usage directive without the need of highly detailed individual patient data. In fact, data were collected without any personal identifiers, which made tracking specific data back to a single patient impossible. Thus, this novel approach to regional clinical practice oversight ensures that robust medical care can be provided without jeopardizing individual patient data protection in any way. All antibiotic usage in hospitals throughout the Central Denmark Region are documented in the regional electronic patient records and may be extracted for further analysis by approved clinicians through the business intelligence platform. The data utilized herein were deemed exempt by the Central Denmark Region Ethics Committee because no sensitive or personally identifying information was extracted (Regionmidtjylland, 2020). This platform provided all data for the study and made it possible to evaluate the efficacy of the antibiotic stewardship directive using precise numbers of piperacillin/tazobactam and other antibiotics (e.g. benzylpenicillin and cefuroxime) administration for pneumonia. It is important to note that an administration, as used here, is not equivalent to a defined daily dose. Data were processed to ensure that "each individual administration of an antibiotic" was synonymous with "a single prescription" as depicted in the figures. This enabled true doses of antibiotics administered in the ward to be tracked and confounders, such as doses requested by clinician but not administered, to be accurately eliminated. The data were extracted from the database for every week and stratified as "usage specifically to treat pneumonia" through the reported diagnosis codes provided every time a clinician prescribed antibiotic therapy.

Statistical analyses

Average moving range (XmR or I) statistical process control (SPC) charts were used to make determinations as to whether there was a change in the usage of a given antibiotic after the intervention (Wheeler, 2003). Pre-intervention (01 January 2015–09 April 2017) data were defined as baseline for calculating the centerline (i.e. the expected consumption) as well as the upper and lower variation limits. The centerline and limits were adjusted to account for the seasonal baseline variation (e.g. annual peaks in early spring) in antibiotic administration, while enabling actual data to be presented without additional seasonal factor correction (Wheeler, 2003). Adjustments for the seasonal variation included the mean weekly antibiotic use for the same week over the baseline years. This number was built into an eight-week *moving average* calculation that smoothed usage fluctuations. The upper and lower variation limits were presented with weekly resolution and calculated by the formula: *Expected consumption in a given week +/− 2.66 X average moving range* (Wheeler, 2000). SPC chart interpretation: changes in antibiotic usage occurred post-intervention if and when the actual post-intervention data were not bounded by the baseline-defined variation limits (Anhoj, 2015). Analysis with a statistical process control does not produce *p*-values. The depicted limits reflected the statistical analyses outcomes, while the probability that a single point was outside the baseline-defined limits by chance was 1 in 370 (Mohammed et al., 2008). All statistical analyses were performed using R (Version 3.4.2) with the Qicharts2 package (R_Core_Team, 2017).

Results

To determine if the Antibiotics Stewardship Committee's directive was followed, an average moving range SPC chart of piperacillin/tazobactam administration for treating pneumonia was generated. This was performed to determine if there was a change in piperacillin/tazobactam administration coincident with the directive being issued. The first 27 months (January 2015 to mid-April 2017) presented are the baseline data (blue line), which were also used to generate the shaded range of variance on the graph. These data represent the *status quo* numbers of piperacillin/tazobactam administration for pneumonia prior to the intervention. It was observed that piperacillin/tazobactam administration (blue line) dropped below the range of random variation from intervention start in mid-April 2017 and continued into July 2017

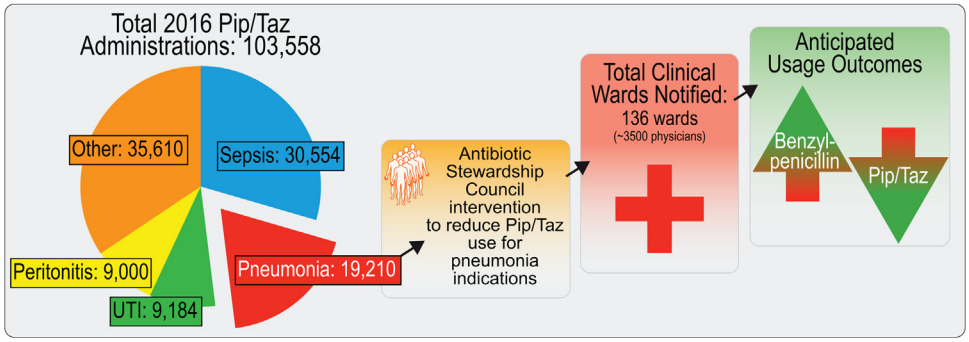

Figure 1. Study overview and workflow. Illustration of anticipated outcomes for the antibiotic stewardship directive from the Central Denmark Region Antibiotic Stewardship Council. Total numbers of piperacillin/tazobactam administrations in 2016 provide context regarding the potential impact of the directive.

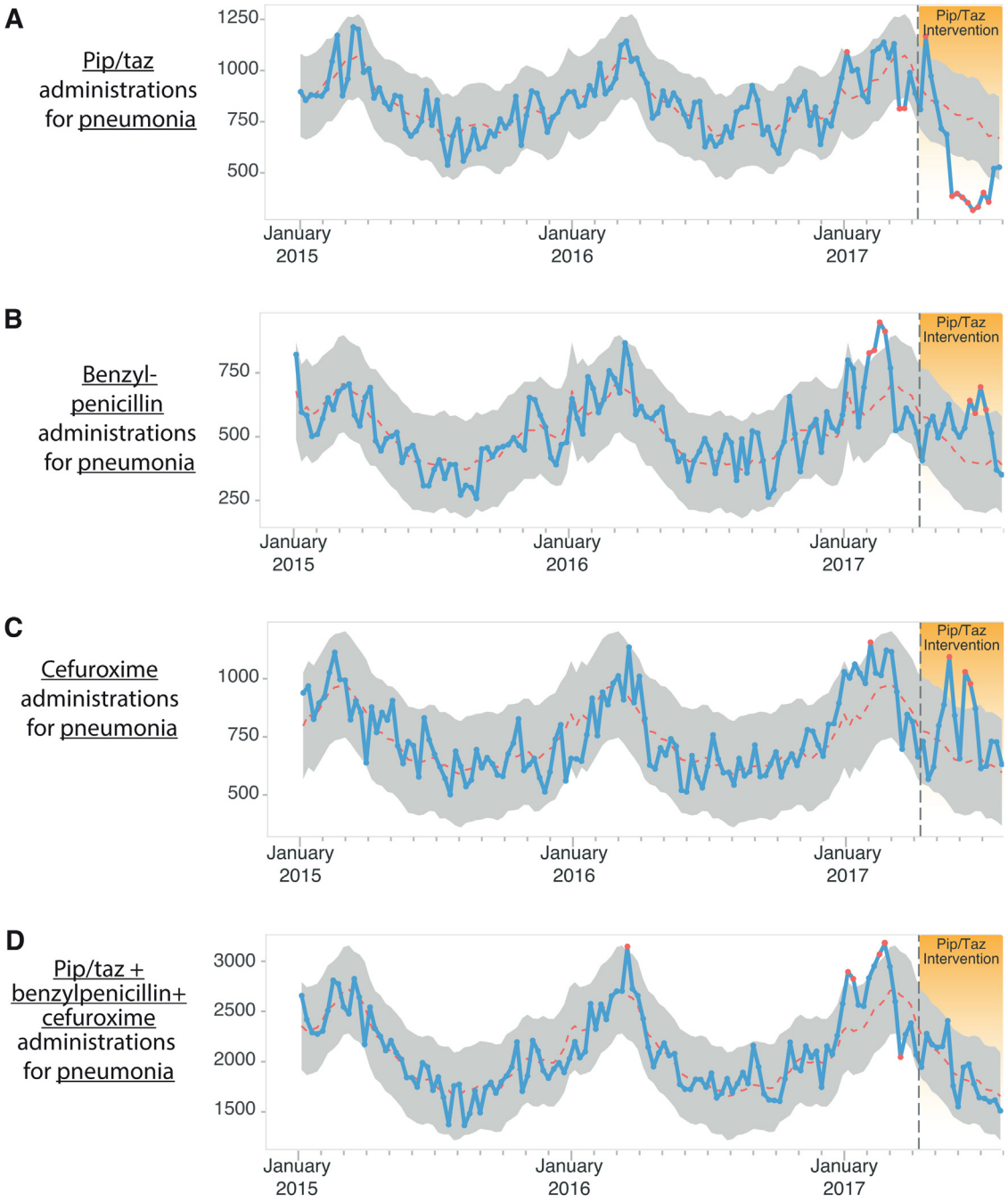

Figure 2. Benzylpenicillin usage plus cefuroxime usage compensated for reduced piperacillin/tazobactam usage during the antibiotic stewardship intervention. (A) Pneumonia-specific piperacillin/tazobactam administrations throughout the study period. (B) Pneumonia-specific benzylpenicillin administrations throughout the study period. (C) Pneumonia-specific cefuroxime administrations throughout the study period. (D) Pneumonia-specific piperacillin/tazobactam + benzylpenicillin + cefuroxime administration throughout the study period. Red dots mark changes from baseline in weekly aggregated antibiotic administration data. The red dashed line that indicates the central tendency of the pre-intervention piperacillin/tazobactam administration data is bounded by two gray lines showing the upper and lower variation limits in this parameter. The central tendency and outer limits account for seasonal changes in administrations. The vertical gray dashed line indicates the date of intervention.

(Figure 2A). Based upon these data, it was concluded that clinicians followed the directive to reduce usage of piperacillin/tazobactam for pneumonia.

Benzylpenicillin was the recommended replacement for piperacillin/tazobactam in the directive. However, benzylpenicillin administration for pneumonia did not concordantly climb with reduced piperacillin/tazobactam usage (Figure 2A and B). The benzylpenicillin average range SPC chart showed four of 16 post-intervention weeks where aggregated data were listed higher than the upper variation limit. In contrast, piperacillin/tazobactam usage dropped below variation limits for eight post-intervention weeks (Figure 2A). Thus, the benzylpenicillin administration data did not fully compensate for the decline in piperacillin/tazobactam administration. A qualitative analysis of data accounting for all antibiotics prescribed for pneumonia in the region showed that an additional replacement antibiotic option was frequently prescribed: cefuroxime. Therefore, an average range SPC chart depicting cefuroxime administration for pneumonia treatment was generated (Figure 2C). These data revealed an opposite trend in the data from the piperacillin/

tazobactam administration, which was similar to the benzylpenicillin increase but suggested earlier uptake versus benzylpenicillin (Figure 2B and C). To test if the administration of all three treatment regimens could together account for all anticipated antibiotic treatments for pneumonia during the period of intervention, a final average range SPC chart with all antibiotics graphed together was generated. In this graph, piperacillin/tazobactam + benzylpenicillin + cefuroxime usages were combined to fall within the bounds of random variation during the study period (Figure 2D). These data demonstrate that benzylpenicillin usage plus cefuroxime usage compensated for reduced piperacillin/tazobactam usage during the intervention.

Discussion

The Central Denmark Region Antibiotic Stewardship Committee sent a directive to all clinicians detailing intended changes to the usage of piperacillin/tazobactam, with a specific focus on pneumonia treatment. Encouragingly, the data showed a rapid uptake by clinicians of the Committee's recommendation to limit piperacillin/tazobactam usage for treating pneumonia. However, the data also indicated that there was an insufficient concomitant increase in benzylpenicillin administration. Benzylpenicillin was expected to increase because this drug remains the Danish Medicines Council recommended antibiotic for treating pneumonia (Birgitte Borck Høg et al., 2017). Instead, the initial decline of piperacillin/tazobactam usage was associated with increased administration of the broad-spectrum antibiotic cefuroxime. The transition from piperacillin/tazobactam to cefuroxime, instead of benzylpenicillin, reflected poor clinician uptake of this aspect of the antibiotic stewardship directive. Furthermore, the observed decline in piperacillin/tazobactam administration returned to pre-intervention levels within months of the directive being issued, without it being retracted or replaced with a newer directive. Thus, the issuing of an antibiotic stewardship directive without active management and uptake monitoring failed to yield its intended result of a lasting change in clinician prescribing patterns.

An updated Cochrane analysis showed that antibiotic stewardship interventions can safely reduce unnecessary antibiotic usage in hospitals (Davey et al., 2017) and a recent study showed that guideline-driven pneumonia empirical therapy is safe and associated with reduced mortality (Schuts et al., 2016). Despite this evidence, surprisingly low compliance with the antibiotic stewardship directive was still observed. Time pressure and high staff turnover lead doctors to habitually draw on previous experiences rather than new information when making prescriptions (Goulopoulos et al., 2019). Additionally, uncertainty of diagnoses contributes to inappropriate broad-spectrum antibiotic usage–an outcome that is undoubtedly driven by doctors' concerns for their patients' safety (Daniel Markley et al., 2017). These are challenges faced by all antibiotic stewardship committees. Furthermore, antibiotic stewardship programs are challenged by the limited amount of experiment-based data regarding the most effective techniques for modifying clinician behavior. The current observational dataset provided a unique opportunity to closely examine how clinicians in this region responded to a shortage of a commonly prescribed antibiotic combination. The data revealed that the directive did not result in a sustained change in clinical practice towards the usage of narrow-spectrum antibiotics. Analyses revealed that careful monitoring of key parameters (e.g. antibiotic dosing with ward level resolution) with a frequent interval of follow-up (e.g. daily or weekly) could rapidly detect selective uptake of directive recommendations. Similar "prospective audit and feedback" strategies have also been suggested by others (Campbell et al., 2017; Karanika et al., 2016; Rennert-May et al., 2019). Based upon the current data, it is believed that close monitoring and feedback to clinicians in hospital settings would have identified the problems with uptake of the directive and could have initiated a productive dialog with the clinicians based on near real-time data.

The major strength of this observational study was the quality of the analyzed dataset. The study had access to precise data on the numbers of each antibiotic administered and knew the indication for which the prescription was made via diagnosis codes documented by attending physicians. Usually, methods for reporting regional or nationwide antibiotic use are based on deliveries from hospital pharmacies to different clinical departments. The very precise data on the actual use of antibiotics enabled the pre-intervention pattern of usage to be analyzed and seasonal variation to be compensated for and without any additional variance that could have originated from non-administered, but ordered, doses, as could occur in cases of early discharge from the clinic or patient death.

There were also some limitations to the study. There was no mechanism in place to track whether physicians did indeed open their email and read the directive. There was no systematic follow-up with heads of department to verify that they had forwarded the stewardship directive within their groups. The study was not randomized. In this retrospective single-arm study, inclusion of a control arm based upon continued *status quo* usage of piperacillin/tazobactam without the intervention was precluded by the fact that the stewardship directive was precipitated by an acute supply chain gap for piperacillin/tazobactam. As noted in the materials and methods section, the data for the study were extracted from the electronic patient journal of the Central Denmark Region. Data were stratified to find every incident of either benzylpenicillin, cefuroxime or piperacillin-tazobactam prescribed as treatment for every diagnostic code of pneumonia. It was unable to differentiate between mild, moderate or severe pneumonia when extracting the data, which means that it could only evaluate the impact of the directive as reflected in the overall usage of the specific antimicrobials for pneumonia treatment. Likewise, the data did not account for incidences where the antimicrobial treatment had multiple targets (e.g. a patient concurrently treated for both pneumonia and sepsis). Finally, the interpretation of SPC charts was limited to whether the fluctuations in antibiotic administration were random noise or reflected a new positive tendency in lowering the usage in the underlying process. SPC charts cannot definitively assign any relationship of observed changes directly to the intervention. Rather, the temporal association of the timing of intervention and change in antibiotics usage patterns define the relationship.

Antibiotic stewardship is key to preserving society's finite antibiotic resources. This study showed that the uptake of antibiotic stewardship directives is not a given in a hospital setting. This is crucial information that, if heeded, will lead to improved rollouts of future antibiotic stewardship directives. Furthermore, it demonstrated the utility of average range SPC charts for supplying simplified near real-time monitoring of antibiotic usage. These are easily interpreted charts that will serve as valuable tools in future antibiotic stewardship program initiatives to provide efficient and sustainable practices, which will help to preserve antibiotic effectiveness globally.

Author contributions

FN and MS conceived and designed the study. FN, JTH, JDR and MS collected data. FN, JTH, JDR, PWD, and MS analyzed and interpreted data. FN, PWD and MS wrote the first manuscript draft. All authors participated in manuscript preparation. All authors approved the final manuscript version.

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Conflicts of interest

The authors declare no conflicts of interest.

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