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Sustained improvement in vancomycin dosing and monitoring post-implementation of guidelines: results of a three-year follow-up after a multifaceted intervention in an Australian teaching hospital

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Abstract

Introduction: Despite vancomycin being in use for over half-a-century, it is still not dosed or monitored appropriately in many centers around the world. The objective of this study was to determine the effectiveness of a multifaceted intervention to implement a vancomycin dosing and monitoring guideline across multiple medical and surgical units over time.

Methods: This was an observational before-and-after interventional cohort study. The pre-intervention period was August to December 2010-2011 and the post-intervention period was September to November 2012-2014. The implementation strategy comprised: face-to-face education, online continuing medical education, dissemination of pocket guideline and email reminder. Outcome measures included: appropriate prescribing of loading and maintenance doses, therapeutic drug monitoring, time to attain target range and nephrotoxicity.

Results: Post-implementation prescribing of loading doses increased (10.4% to 43.6%, *P*=<0.001), guideline adherent first maintenance dose (44% to 68.4% *P*=0.04), correct dose adjustment from (53.1% to 72.2%, *P*=0.009). Beneficial effects pre and post-implementation were observed for adherent timing of initial concentration (43.2% to 51.9%, *P*=0.01), concentrations in target range (32.6% to 44.1%, *P*=0.001), time to target range (median 6 to 4 days, *P*=<0.001), potentially nephrotoxic concentrations (30.7% to 20.9%, *P*=<0.001) and nephrotoxicity (10.4% to 6.8%, *P*=<0.001).

Conclusions: A multifaceted intervention to implement a vancomycin dosing and monitoring guideline significantly improved prescribing, monitoring, pharmacokinetic and safety outcomes for patients treated with vancomycin over an extended period. However, increased guideline adoption by clinicians is required to maximize and prolong the utility of this important agent.

Keywords: education; guideline; intervention; therapeutic drug monitoring; vancomycin

Introduction

Vancomycin has been in use for over half a century however we still have difficulty prescribing and monitoring this agent [1-2]. Practice recommendations have changed over time [3].To address these changes in practice and promote contemporary clinical guidance, a number of a professional societies from various nations, notably the United States, Japan and recently, China, have published vancomycin guidelines in the medical literature [4-6]. These national guidelines are in addition to the plethora of institutional vancomycin guidelines that been described in a recent systematic review [7]. Significant financial and human resources are invested into the development of transparent evidence-based clinical practice guidelines, however there is very limited information supporting these documents reflecting which implementation strategies best promote the guideline adoption.

To address guideline implementation, organisations involved with knowledge translation and guideline development including the National Institute for Health and Clinical Excellence (NICE), UK, the Scottish Intercollegiate Guideline Network (SIGN), the Australian National Health and Medical Research Council (NHMRC), the United States Institute of Medicine (IOM) and Guidelines International Network (G-I-N) provide general advice on guideline implementation [8-12]. This is important as there are numerous accounts in the literature of poor adoption of guidelines by clinicians [13-16]. Most of the peak organisations advocate for multifaceted interventions when implementing guidelines. Commonly recommended interventions by these organisations are: educational sessions [17], academic detailing [18-20], continuing medical education (CME) [21-22], provision of printed educational material [23], use of opinion leaders to endorse guidelines [24], and engaging target populations who will use the guideline [25]. However, the magnitude of effect from

Abbreviations: CME, continuing medical education; FMC, Flinders Medical Center; GIN, Guideline International Network; ICCU, Intensive and critical care unit; IOM, Institute of Medicine; JMO, junior medical officer; MRSA, methicillin-resistant *Staphylococcus aureus*; NHMRC, National Health and Medical Council; NICE, National Institute for Clinical Excellence, SIGN, Scottish Intercollegiate Guideline Network; VRE, vancomycin-resistant Enterococcus.

these interventions varies considerably and the impact these interventions have specifically when employed to implement vancomycin guidelines is unknown.

In a pilot study we implemented a vancomycin dosing and monitoring guideline, we elected to use interventions involving face-to-face education and the provision of a pocket guideline as these had limited cost implications. Despite low statistical power, the pilot produce favourable results, increasing prescribing of loading doses from 5-65% ($P = \leq 0.001$), adherent first maintenance dosages from 43-75% (P=0.04), more concentrations in target range from 27%-43.8% (P=0.04), and non-significant reductions in potentially toxic concentrations , reduced nephrotoxicity and a trend to more patients attaining target ranger sooner [26]. However, as that pilot was conducted in a single surgical unit, it was unclear if the results of the intervention would be reproducible and sustainable. Thus the objectives of the current study were to determine the effectiveness of a multifaceted intervention to implement a vancomycin dosing and monitoring guideline across multiple units over time.

Patients and methods

Study setting and design

The study was an observational cohort before-and-after interventional design. The study was conducted at Flinders Medical Centre (FMC), a 580 bed government university teaching hospital in Adelaide, Australia. The interventional cohort was all adult patients treated with vancomycin during the months, September to November over three years 2012-2014. This interval is defined as the follow-up period. A pre-implementation comparator group included all patients treated with vancomycin during the months August to December over two years 2010-2011. Ethical approval for the study granted by the Southern Adelaide Clinical Human Research Ethics Committee, Australia (approval number 123.12).

Patients

Admitted patients ≥18 years receiving vancomycin who had ≥1 vancomycin concentration result were included in the study. Patients were identified from the daily therapeutic drug monitoring report generated by the biochemistry department. Patients were excluded if they commenced treatment in the intensive and critical care unit (ICCU), receiving hemo- or peritoneal dialysis, this was due to both units having dedicated vancomycin dosing protocols.

Serum creatinine measurement and creatinine clearance calculation

Serum creatinine (S_{Cr}) concentrations were measured using Roche (Basel, Switzerland) C702 enzymatic method. Calculation of creatinine clearance (CrCl) was performed using the Cockcroft-Gault equation,

CrCl (mL/min) = {[(l40–age years) x body weight kg] / (72 x S_{Cr} mg/dL)} x 0.85 (if female) [27].

Vancomycin guideline

The vancomycin dosing and monitoring guideline for adults used in this study was based on a guideline developed for a single unit pilot study in our institution [26], later used in a broader proof of concept study across medical and surgical units [28]. The guideline largely reflected the North American consensus recommendations adapted with Australian Therapeutic Guidelines content on vancomycin [29-30]. The current study guideline was endorsed with input from institutional leaders in infectious diseases, clinical pharmacology and pharmacy, refined in early 2012 and uploaded to the institutions intranet in August 2012. *Key prescribing features were*: a loading dose of 25mg/kg at discretion of prescriber and maintenance dosing determined by CrCl (>90mL/min 1.5g 12-hourly; 60-90mL/min 1g 12-hourly; 20-59mL/min 1g 24-hourly; <20mL/min 1 g every 2-7 days with vancomycin TDM 48-hourly). *Key monitoring features were*: timing of initial trough blood sample for concentration measurement was determined by CrCl (>60mL/min required blood to be taken prior to the fourth dose; 20-59mL/min before the third dose and <20mL every 48-hourly until target (15-20mg/L) attainment) (Supplementary file 1). In the pre-implementation period there was no institutional guidance on vancomycin dosing and monitoring except for a comment on pathology result record or electronic report of a target range 15-20mg/L. This comment remained in effect for the follow-up period.

Target audience

The principal target audience of the implementation strategy was junior medical officers (postgraduate years 1 and 2) as they perform the majority of prescribing and pathology test ordering in our and many other institutions [31]. However, all medical, pharmacy and nursing staff were potential end-users of the guideline.

Interventions

There were four components to the multifaceted intervention to support the release of the guideline: 1) educational session, 2) an online continuing education module on vancomycin with knowledge assessment, 3) dissemination of printed material and 4) email reminder alert.

Education session: Learning objectives for the session were for JMOs to become familiar with the guideline and be able to dose and monitor vancomycin effectively for patients. Three identical 60-minute face-to-face educational sessions were provided to JMOs periodically through the year. The session was provided in a dedicated university teaching room in the hospital, located in close proximity to patient wards, facilitating ease of attendance. Attendance was voluntary and no incentives were offered other than lunch. The session contained information on pharmacology and indications, local audit data on vancomycin prescribing and monitoring, and MRSA prevalence. Issues of reduced susceptibility to vancomycin and minimising the development of resistance, limiting nephrotoxicity and the pharmacoeconomics of comparative agents was presented. Importantly the session included a clinical vignette with practical advice on how to dose and monitor vancomycin. The sessions were delivered by CJP a pharmacist educator who is an experienced facilitator, has expertise in clinical education, pharmacotherapy of infectious diseases and therapeutic drug monitoring. Fidelity of the content and delivery of the educational sessions was assured by CJP providing all sessions over 2012-14. One variance to this was the addition of the Infectious Diseases registrar as a co-presented at sessions in 2012.

Online continuing education: was provided to JMOs in the latter half of the hospital training year over 2012-14. The CME document was formally emailed via the Trainee Medical Officer Unit. The CME contained background information on vancomycin and how to dose and monitor vancomycin and a clinical vignette and questions. The details of this intervention have been provided in detail elsewhere [32]. An electronic copy of the guideline was also provided with the CME.

Dissemination of printed material (pocket guideline): A small pocket size version of the guideline (6cm x 10cm) compatible for attaching to hospital identification badges was provided to all JMOs. The pocket guideline was disseminated at all vancomycin educational sessions and from the Trainee Medical Officer Unit for those unable to attend. The pocket guideline was also provided to all pharmacy staff in their clinical induction.

Email alert: The Director of Medical Services sent a reminder email to all medical staff soon after the guideline was uploaded to the intranet (August 2012). The email advised staff where to locate the guideline and requested staff adherence to the guideline.

Outcome measures / process measure

Outcomes measures for vancomycin prescribing: loading doses, first maintenance dose adherent to guideline and appropriate dosage adjustment in response to concentrations outside target range, i.e. if a vancomycin concentration returned below target, was the next dose increased? Conversely, if the vancomycin concentration result was above target range, was the next dose reduced? Monitoring outcomes were proportion of vancomycin initial concentrations taken at steady-state concentration, proportion of appropriate pre-dose trough concentrations attainment of trough concentrations in therapeutic range (15-20mg/L) and time to achieve therapeutic range, and potentially nephrotoxic trough concentrations (>20mg/L). Nephrotoxicity was included as a safety outcome, defined as a rise in serum creatinine of ≥50% or 50mg/dL from baseline on two or more consecutive days of vancomycin therapy in the absence of an alternative explanation [33]. A process measure was the frequency of intranet access of the vancomycin guideline.

Power calculation and statistical analysis

The study was powered to detect similar differences in the proportion of patients within target range between pre and post intervention periods to those observed in the pilot study where we

observed a 16.9% increase from 26.9% to 43.8% [26]. Assuming a similar proportion of 26.9% at baseline, a sample size of 125 subjects in both the pre and post intervention groups (n=250 total) would be required to have 80% power to detect the same increase at a two-sided Type 1 error rate of $P<0.05$. The study had more than 90% power to detect a reduction in the median time to target range from 5 days to 3 days, similar to the changes observed in a pilot study. Differences in clinical characteristics of subjects between the pre and post-implementation phases was assessed using an independent t-test for normally distributed continuous variables and a Mann-Whitney U test for non-normally distributed data. Differences in proportions and categorical variables were assessed using 2-sample tests of proportions and chi-squared tests of association respectively. Differences in the time to reach therapeutic range since commencing vancomycin between subjects was assessed using Kaplan-Meier plots and log-rank statistics. Subjects that did not reach the therapeutic range were censored at the end of their follow-up period. All analysis was performed using Stata version 14.1 (StataCorp, Texas, USA).

Results

Patient characteristics

There were 258 subjects in the study. The interventional cohort consisted of 133 patients receiving vancomycin treatment in hospital and the pre-implementation cohort included 125 patients. Patient characteristics between the two groups were similar with exceptions in the pre-implementation group which had a longer median stay, more patients coming from residential aged care facilities, higher vancomycin-resistant Enterococcus (VRE) colonisation and more patients managed by surgical teams. More patients in the post-implementation group had comorbidity with malignancy and congestive heart failure (Table 1). There were no differences between groups for infection site or microbiological data (Table 2).

Outcomes measures

In the post-implementation group, there were significant increases in guideline-adherent prescribing of loading and first maintenance doses. The median time with interquartile range (IQR) of the first concentration attained in therapeutic target range reduced significantly from 6 (4-9) to 4 (3-6) days in the post-implementation group (*P*= <0.001) (Table 3). The time taken to reach target for all patients that had a measured concentration was significantly reduced from 25 to 13 days post-implementation (*P*= <0.001) (Fig 1). The overall duration of vancomycin therapy decreased from a median of 9 days (IQR 5-13) to 5 days (4-9) for those in the post implementation group (*P*= <0.001). The proportion of initial concentrations drawn at the correct times (i.e. vancomycin reached steady-state concentration in the serum) improved from 43.2% to 51.9% in the post-implementation group (*P*=0.01). A significantly greater number of patients post-implementation attained target trough range (15-20mg/L) 32.6% vs 44.1% (*P*= <0.001), and fewer reached potentially nephrotoxic trough concentrations (>20mg/L) with a decrease from 30.7% to 20.9% post-implementation (*P*= <0.001). The safety outcome of nephrotoxicity post-implementation was also significantly decreased from 10.4% to 6.8% (*P*= <0.001) (Table 3).

A sub-analysis was performed on those patients that attained their initial concentration within target range (n=9 pre-implementation and n=32 post-implementation) and whether they were prescribed recommended loading and initial maintenance doses. Pre-implementation only 3 patients of the 9 (3/9) 33.3% received recommended prescribing compared to 12/32 (37.5%) post-implementation (*P*=0.82). A sub-analysis was also performed on those patients that acquired nephrotoxicity (n=13 pre-implementation and n=9 post-implementation) and whether they received an appropriate initial maintenance dose. Pre-implementation 6 patients (9/13) 43.2% were prescribed appropriate initial maintenance doses compared to 5/9 (55.5%) post-implementation (*P*=0.66).

The effect changes observed for prescribing, monitoring and duration of treatment for the post implementation group were largely sustained or improved when examined by individual year for 2012, 2013 and 2014 (Table 4). A notable variant was nephrotoxicity, which had a lower incidence in 2012 and 2013 compared to pre-implementation data, however 2014 data was unchanged from pre-implementation data.

Process measure

The vancomycin guideline accessed from the hospital intranet was recorded monthly from upload in August 2012 until December 2014. The guideline was consistently accessed with a mean and standard deviation (±SD) 88.6±21.8 times per month over the follow-up period.

Discussion

In this study we demonstrated that a multifaceted intervention improved guideline-adherent vancomycin prescribing, resulting in hospital inpatients more rapidly attaining target concentrations, which have been associated with improved clinical outcomes and reduced risk of nephrotoxicity [34-35]. The findings observed in the current study were generally consistent with our pilot [26], and we showed meaningful reductions in the duration of vancomycin treatment and nephrotoxicity. We have been explicit in reporting our methodology and study design which has recently been identified as a priority when seeking to change behaviour regarding the use of antibiotics in hospitals [36], and specifically for guideline dissemination and implementation [37]. Furthermore, we have quantified the effect of our multifaceted intervention, which comprises commonly recommended strategies, specifically for the purpose of implementing a vancomycin guideline.

A major review on the effectiveness of guideline dissemination and implementation strategies found that the majority of multifaceted interventions had a median absolute improvement in care of 14.1% for reminders and 8.1% for dissemination of educational material [38]. Our study used education, dissemination of educational material and reminder email. We observed more than a four-fold increase in prescribing of loading doses, a fifty-percent rise in appropriate maintenance dosing and a thirty-percent rise in attainment of target range. We used face-to-face educational sessions as a key pillar of our implementation strategy. A Cochrane review on educational meetings and workshops in healthcare found from 30 trials, the median (IQR) difference in compliance for practice measures was a modest 6% (1.8% to 15.9%) where education was a component of an intervention compared to no intervention. Mixed interactive and didactic educational meetings had a difference median of 13.6%. The median (IQR) difference observed on patient outcomes was only 3% (0.1% to 4.0%) [17]. A Cochrane review on providing educational material to physicians when compared to no intervention showed a median (IQR) effect increase for categorical measures of 2% (0% to 11%) and a mean (range) effect increase of 13% (16% to 36%) when followed-up to 6 and 9 months

respectively [39]. We provided an electronic CME on vancomycin and a printed pocket guideline to junior doctors. The magnitude of effect for each of our interventions is unclear, however the changes in our outcome measures are considerable in excess of those reported above.

Although our study demonstrated significant improvements for most outcomes measures, that fact remains that less than half of all vancomycin concentrations were within the target range and there is still considerable room for improvement. This study focused on building prescribers knowledge of the clinical use vancomycin, and awareness of consequences to patients if vancomycin is not prescribed appropriately. The reasons why some doctors did not use the guideline are not clear. It has been reported in the literature that some doctors may lack agreement with guidelines, have a distrain for rigid medicine and guidelines may be seen as encroaching on professional autonomy and a disbelief that following the guideline will achieve the desired outcomes [15]. Furthermore, insufficient time to use guidelines, lack of peer or superiors support, have also been identified as factors influencing adherence to guidelines [16]. It is important these attitudinal factors are given greater consideration when designing implementation strategies to improve the ongoing use of vancomycin.

A strength of this study was that the implementation strategy was executed consistently and with fidelity, providing confidence in the results. The sustained effect observed over three years provides further confidence as many other studies measuring the effect of vancomycin guidelines are much shorter in duration. The finding from this study are corroborated with the process measure of intranet access of the guidelines over the same time period demonstrating a consistency of electronic access to the guideline. Considerable rigour has gone into reporting the details of our interventions, in particular the educational component to enable others to reproduce our work. We assessed our description of the educational component of the intervention against a recently published guidance for the reporting of evidence-based educational interventions in health and

found 13 of the 17 criteria were met [40]. Our study had some limitations. The study was conducted at a single centre and data was collected retrospectively. There were some significant differences in baseline characteristics that may have impacted on the results. Notably pre-implementation there were more patients from residential aged care facilities with higher rates of VRE colonization, suggesting these patients may have been more complex and frail. This in turn may have made attainment of appropriate vancomycin target concentrations more difficult. However, post-implementation more patients having malignancy and congestive heart failure may have also adversely impacted monitoring outcomes. Cancer has been reported to alter clearance of vancomycin [41], and congestive heart failure is known to decrease vancomycin clearance [42]. Potentially both these factors may have resulted in more patients failing to attain target concentration. Furthermore the longer median duration of admission post-implementation can be attributable to an unusually complex patient with a surgical site infection that was admitted for 107 days.

Whilst provider or facilitator fatigue did not feature in this study, it is possible that this may be a variable which could bias results. Future elements to add to this multifaceted intervention, could be the incorporation of guideline content into electronic prescribing as has been suggested by the IOM [8]. In recent times much has been made of pharmacokinetic/pharmacodynamic monitoring of vancomycin using area-under-the-curve (AUC) / minimum inhibitory concentration (MIC) originally derived by Moise et al. [43], and MRSA isolates with elevated MIC [44]. We elected not to promulgate AUC/MIC monitoring in our guideline nor sought to record it as an outcome measure, as a recently published study on MRSA clinical isolates from our institution found all MRSA isolates had an MIC ≤1mg/L when determined by broth microdilution [45].

These data confirm the efficacy over time of a systematic implementation strategy to improve the dosing and monitoring of vancomycin which is likely to be similarly applicable to other antimicrobial

agents and as well as to improving prescribing more broadly. Our findings provide some guidance to those tasked with allocation of resources for local guideline implementation, enabling clinicians to make informed decision when treating their patients with vancomycin.

Acknowledgements

Associate professor Matthew P Doogue, Department of Clinical Pharmacology, University of Otago, Christchurch, New Zealand for his assistance with study concept and design. Dr Marianne Martinello, The Kirby Institute for Infection and Immunity in Society, University of New South Wales, Sydney, Australia for her assistance with delivery of presentations, and Dr Alana Christensen, Dr Jolai Evans and Dr Minh Nguyen, Division of Medicine, Flinders Medical Centre, Bedford Park, Australia for their assistance with data collection.

Funding: CJP was supported by a National Health and Medical Research Council (Australia), Translating Research into Practice (TRIP) Fellowship during this study (1035960). RAM is supported by a Bear Cancer Professorial Fellowship from Cancer Council South Australia and SA Health.

Conflict of interest

All authors report no conflict of interest in relation to this work.

Supplementary material

Supplementary file 1: Vancomycin dosing and monitoring guideline for adults

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Table 1: Demographics and clinical characteristics of patients

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Figure 1: Kaplan Meier plot - time to reach therapeutic range

Table 1
Baseline characteristics of patients receiving vancomycin treatment

	Pre-implementation 2010-11 *n* =125 (%)*	**Post-implementation 2012-14** *n* =133 (%)*	***P***[1]
Characteristic			
Age, years mean (SD)	64.4 (19.2)	63.7 (19.5)	0.77
Male sex	74 (59.2)	79 (59.4)	0.54
Residence in RACF	64 (51.2)	26 (19.5)	<0.001
Prior admission to hospital ≤12 months	95 (76%)	89 (66.9)	0.07
Prior colonisation with MRO In ≤12 months			
MRSA	49 (39.2)	37 (27.8)	0.05
VRE	26 (20.8)	14 (10.5)	0.02
CrCL, mL/min mean (SD)	102.7 (60.8)	93.5 (52.5)	0.19
Weight, kg mean (SD)	81.2 (21.9)	78.1 (22.7)	0.27
Comorbidities			
Diabetes	36 (28.8)	37 (29.3)	0.86
Malignancy	15 (12)	30 (22.6)	0.03
Valvular disease	12 (9.6)	7 (5.2)	0.18
Congestive heart failure	4 (3.2)	17 (12.8)	0.005
Medication / allergic status			
Aminoglycoside	23 (18.4)	32 (24.1)	0.27
Penicillin/β-lactam allergy	39 (31.2)	34 (25.6)	0.32
Treating team			
Medical	43 (34.4)	62 (46.6)	0.04
Surgical	82 (65.6)	71 (53.4)	0.04
Days of admission; median (IQR)	10 (3-17)	13 (7.8-24.3)	0.02

*Unless otherwise stated: CrCL, creatinine clearance; IQR, interquartile range; RACF, residential aged care facility; MRO, multi-resistant organism; MRSA, methicillin-resistant *Staphylococcus aureus*; SD, standard deviation; VRE, vancomycin-resistant *Enterococcus*

[1]Using a 2-sample test of proportions.

Table 2
Infection site requiring vancomycin treatment and microbiological data

	Pre-implementation 2010-11 *n* =125 (%)*	**Post-implementation 2012-14** *n* =133 (%)*	***P***[1]
Infection site			
Bacteraemia/ cardiac	29 (23.2)	29 (21.8)	0.89
Synovial/prosthetic	23 (18.4)	9 (6.8)	0.41
CNS/cranial	11 (8.8)	2 (1.5)	0.74
Skin & soft tissue infection	39 (31.2)	44 (30.1)	0.91
Osteomyelitis	11 (8.8)	10 (7.5)	0.91
Respiratory	9 (7.2)	8 (6)	0.92
GI/abdominal infection	13 (10.4)	8 (6)	0.73
Pyrexia of unknown origin	12 (9.6)	20 (15)	0.66
Organism†			
MRSA	40 (32)	35 (26.6)	0.61
Enterococcus spp	16 (12.8)	14 (10.5)	0.85
CoNS	5 (4)	8 (6)	0.87
Staphylococcus epidermidis	10 (8)	10 (7.5)	0.97
MSSA	12 (9.6)	15 (11.3)	0.89
Other	15 (12)	15 (11.3)	0.95
No growth detected	24 (19.2)	36 (27.1)	0.48
No specimen collected	3 (2.4)	0	0.11

*Unless otherwise stated: CNS, central nervous system; GI, gastrointestinal; Spp, bacterial species; MRSA, methicillin-resistant *Staphylococcus aureus*; CoNS, coagulate negative *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; † Note some patients had infection with more than one organism

[1]Using a 2-sample test of proportions.

Table 3
Outcomes measurements of vancomycin prescribing and monitoring

	Pre-implementation 2010-11	**Post-implementation 2012-14**	***P*[1]**
	n =125 (%)*	*n* =133 (%)*	
Prescribing			
Loading dose prescribed	12 (10.4)	58 (43.6)	<0.001
First maintenance dose adherent	55 (44)	91 (68.4)	0.04
First dose adjustment correct[≠]	51/96 (53.1)	60/82 (72.2)	0.009
Days of vanco treatment; Median (IQR)	9 (5-13)	5 (4-9)	<0.001
Monitoring			
Total number of conc. per treatment days	506/977= 0.52	408/1061 = 0.38	0.12
Css. adherent timing of initial conc.	54 (43.2)	69 (51.9)	0.01
Days until first conc. in target; median (IQR)	6 (4-9)	4 (3-6)	<0.001
Potentially subtherapeutic conc. <10mg/L	48 (15)	34 (12.1)	0.71
Conc. in target range 15-20mg/L	104 (32.6)	124 (44.1)	0.001
Potentially nephrotoxic conc.>20mg/L	98 (30.7)	59 (20.9)	<0.001
Nephrotoxicity	13 (10.4)	9 (6.8)	<0.001

*Unless otherwise stated: Conc, concentration; Css, concentration steady-state achieved; IQR, interquartile range; vanco, vancomycin; [≠]first dose adjustment correct where vancomycin continuing and not in target range

[1]Using t-test for normally distributed data, Mann-Whitney U test for non-normally distributed data, and chi-squared tests for categorical data.

Table 4

Temporal outcome measures for all years of vancomycin prescribing and monitoring

	Pre-implementation	Post-implementation		
	2010-11	**2012**	**2013**	**2014**
	n=125	*n*=39	*n*=48	*n*=46
Prescribing				
Loading dose prescribed	12 (10.4)	10 (25.6)	28 (58.3)	20 (43.5)
First maintenance dose adherent	55 (44)	25 (64.1)	32 (66.7)	34 (73.9)
First dose adjustment correct[≠]	51/96 (53.1)	18/28 (64.3)	30/ 48 (62.5)	21/24 (87.5)
Days of vanco treatment; Median (IQR)	9 (5-13)	4 (4-11.5)	6 (4-10.8)	5 (3-7)
Monitoring				
Total number of conc. per treatment days	506/977= 0.52	132/345=0.38	155/411=0.38	121/305=0.40
Adherent pre-dose trough conc.	319/506 (63)	98/132 (74.2)	96/155 (61.9)	87/121 (71.9)
Css adherent timing of initial conc.	54 (43.2)	21 (53.8)	25 (50.1)	23 (50)
Days until first conc. in target; median (IQR)	6 (4-9)	4 (3-6)	5 (3.5-6)	3 (2.3-5)
Potentially subtherapeutic conc. <10mg/L	48 (15)	16 (16.3)	8 (8.3)	10 (11.5)
Conc. in target range 15-20mg/L	104 (32.6)	41 (41.8)	45 (46.9)	38 (43.7)
Potentially nephrotoxic conc. >20mg/L	98 (30.7)	18 (18.4)	23 (24)	18 (20.7)
Nephrotoxicity	13 (10.4)	3 (7.7)	1 (2.1)	5 (10.9)

*n, (%) Unless otherwise stated: Conc, concentration; Css, concentration steady-state; IQR, interquartile range; vanco; vancomycin; [≠]first dose adjustment correct where vancomycin continuing and not in target range