Development and evaluation of a national gentamicin and vancomycin quality improvement programme

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SYNOPSIS (247 words)

Background

Scottish Antimicrobial Prescribing Group (SAPG) recommendations to reduce broad spectrum antimicrobial use led to an increase in gentamicin and vancomycin prescribing. In 2009, SAPG introduced national guidance to standardise dosage regimens, reduce calculation errors and improve the monitoring of these antibiotics. Studies conducted in 2010 and 2011 identified limitations in guideline implementation.

Aims

To develop, implement and assess the longterm impact of quality improvement (QI) resources to support gentamicin and vancomycin prescribing, administration and monitoring.

Methods

New resources, comprising revised guidelines, online and mobile app dose calculators, educational material and specialised prescribing and monitoring charts were developed in collaboration with antimicrobial specialists and implemented throughout Scotland during 2013-2016. An online survey in 2017 evaluated the use of these resources and a before (2011) and after (2018) point prevalence study assessed their impact.

Results

All 12 boards who responded to the survey (80%) were using the guidance, electronic calculators and gentamicin prescription chart; 8 used a vancomycin chart. The percentage of patients who received the recommended gentamicin dose increased from 44% to 89% (OR 10.99, CI 6.37–18.95) between 2011 and 2018. For vancomycin, the correct loading dose increased from 50% to 85% (OR = 5.69, CI 2.76–11.71) and the correct maintenance dose from 55% to 90% (OR = 7.17, CI 3.01–17.07).

Conclusions

This study demonstrated improvements in the national prescribing of gentamicin and vancomycin through the development and co-ordinated implementation of a range of QI resources and engagement with local and national multidisciplinary teams.

INTRODUCTION

The Scottish Antimicrobial Prescribing Group (SAPG) was formed in 2008 to improve antimicrobial prescribing and lead antimicrobial stewardship initiatives across NHS Scotland. The SAPG programme of work has been aligned to the UK's antimicrobial resistance strategy[1] and since 2016 to Scotland's "Realistic Medicine" agenda,[2] which aims to reduce antimicrobial-related harm, waste and variation in antibiotic prescribing practice whilst optimising individual patient management. In 2009, SAPG developed national guidance to support the use of gentamicin and vancomycin across Scotland. The guidance contained a single vancomycin guideline[3] and two gentamicin options: "in house" guidelines from NHS Greater Glasgow and Clyde (GGC guidelines[4]) and the "Hartford" guidelines.[5] The GGC guidelines arose from a consensus to avoid 36 hourly dosing and address concerns around administering high gentamicin doses to patients with renal impairment. It used a nomogram to identify patients at risk of excessive exposure. Both the gentamicin and vancomycin guidance aimed to standardise prescribing, reduce calculation errors and improve monitoring and interpretation of concentration measurements.

To determine compliance with national guidance, three studies were undertaken during 2009–2012. An initial survey found that by December 2010, 80% of health boards in Scotland had implemented the SAPG guidance and this was supported by an online calculator for gentamicin in 62% and for vancomycin in 85% of health boards (SAPG Internal Report, 2012). A point prevalence study, undertaken during February to May 2011, found that only 44% of gentamicin dosage regimens and 56% of vancomycin dosage regimens were in accordance with the SAPG guidance (SAPG Internal Report, 2012). Finally, a qualitative study, conducted between March and July 2011, found that insufficient dissemination, poor communication, unmet educational

needs and staffing issues were barriers to effective implementation.[6] Overall, these studies highlighted that the existence of guidelines was insufficient to ensure appropriate prescribing and monitoring. The present study describes the development and co-ordinated implementation of a range of quality improvement (QI) resources and evaluates their impact on clinical practice.

METHODS

Development and implementation of the quality improvement resources

The QI resources were developed by five pharmacists (the GaV team), in collaboration with antimicrobial teams across Scotland, during 2012-14. The point prevalence study from 2011 and the qualitative study[6] were used to identify areas within the guidance that required modification. A new version of the guidance was then developed, reviewed by SAPG, uploaded to the SAPG website in February 2013 and reviewed every 2 years thereafter.[7] Antimicrobial teams across Scotland were then asked to share existing educational material with the GaV team. This material informed the content of case scenarios that focused on safe prescribing, administration and monitoring. An expert review group comprising the GaV team, medical, nursing and pharmacy staff, representing seven health boards across Scotland, was then convened. Each case was reviewed by at least two group members then tested at a SAPG antimicrobial team workshop prior to being finalised. The GaV team lead (YS), working in collaboration with NHS Education Scotland (NES) and LearnPro (LearnPro Ltd®, Edinburgh, Scotland) then developed the online resource. The LearnPro® educational modules were released in August 2013 and their uptake by health boards across Scotland was monitored by NES.

During the same year, the GaV team updated the existing Excel® dose calculators for gentamicin and vancomycin according to the previous studies and feedback from antimicrobial pharmacists.

The modified calculators were validated using a database of 698 patients who had previously been prescribed gentamicin or vancomycin. Patients were aged 16-94 years, weighed 30-148 kg and their creatinine concentrations ranged from 53–822 μmol/L. The calculator was also challenged with extreme and unusual combinations of clinical characteristics.

A workshop session was held during a SAPG antimicrobial team event in 2011 to explore how documentation might be used to improve practice. Discussions focused around standardising the content and presentation of prescribing and monitoring charts. Following the workshop, a short-term working group comprising 10 medical, pharmacy and nursing staff from six health boards was established to develop national prescribing and monitoring chart templates for each antibiotic.

Evaluation of the longterm impact of quality improvement resources on gentamicin and vancomycin prescribing

A national online survey (Smart Survey Ltd, www.smartsurvey.co.uk), conducted by SAPG in July 2017, evaluated local implementation of the new resources. Questions were piloted by pharmacists from one board then the survey was emailed to antimicrobial teams in all 15 boards across Scotland.

A second point prevalence study, based on the 2011 study, was conducted during February to May 2018. A pharmacy antimicrobial specialist within each health board area was asked to organise data collection from at least two hospitals, ideally, a large teaching hospital and a district general hospital. Data were collected at times that suited each site; typically on one day in large hospitals and over 2-5 days in smaller hospitals. The following wards were included, as

appropriate: medical; surgical; medicine for the elderly; burns; renal; gynaecology; haematology; oncology; cardiology; intensive therapy and high dependency. Ward activity information was provided by the antimicrobial pharmacist. Data were collected on patients >18 years who had been prescribed treatment dose intravenous gentamicin or vancomycin on the day(s) of data collection. Prophylactic therapy, synergistic use of gentamicin, oral vancomycin and lack of access to case notes were exclusion criteria. The study was judged by the ethics coordinator to be an audit of clinical practice that did not require formal ethical review. The following data were collected: age, sex, weight, height, creatinine concentration, clinical speciality and ward. No patient identifiable data were recorded. CL_{CR} was estimated using the Cockcroft Gault equation[8] using actual weight to a maximum of ideal body weight +20%. All gentamicin and vancomycin doses prescribed and administered and concentrations measured for the current course of treatment, up to the survey date, were recorded. The first gentamicin dose administered to each patient was compared with the "correct" dose based on the relevant SAPG guidance. For vancomycin, both the loading dose and the initial daily maintenance dose were examined. As these were the same for intermittent and continuous infusions, both regimens were analysed together. Any difference ≥20% from recommended doses was defined as clinically important. Concentration measurements for both antibiotics were examined to identify whether sufficient data were available to enable interpretation, including dose times, sample times and appropriateness of timing. For vancomycin, the first trough concentration was compared with a target range of 10-20 mg/L. Odds ratios were used to compare the proportion of 'correct' doses before (2011) and after (2018) implementation of the QI resources. A two sample Student's t-test was used to evaluate differences in age, weight and CL_{CR} between the two groups. Statistical significance was set at $p<0.05$.

RESULTS

Development of quality improvement resources

The key changes to the national guidance were: introduction of a step-by-step guide that included how to use the prescribing and monitoring charts; advice on initial doses of gentamicin and vancomycin if creatinine was unknown; weight banded doses for the Hartford gentamicin guidance; how to administer vancomycin by continuous infusion; and clearer information on cautions, contra-indications and signs of toxicity.[7]

LearnPro® modules were created for the GGC and Hartford gentamicin dosing regimens (9 cases) and the intermittent and continuous vancomycin infusions (5 cases). Each module included a summary of the relevant guidance. The gentamicin cases covered prescribing and monitoring for patients with normal and abnormal weights or renal function, low or missing creatinine concentrations, ototoxicity and errors in dosing and sampling. The vancomycin cases covered normal weight and renal function, errors in the dosage regimen or sampling time, interpretation of concentration measurements and the risks of rapid infusion. In the first year after implementation in September 2013 the modules were completed 320 times, 51% by nursing staff, 34% pharmacy staff and 11% medical staff. Uptake increased to 615 in 2014-5 and 364 in 2015-6, comprising 33% nursing staff, 35% pharmacy staff and 24% medical staff. The higher levels of uptake in 2014-5 reflected a drive in two health boards to promote and monitor completion.

Modifications to the online calculators aimed to reduce risks associated with entering incorrect data by introducing limits on age, height and weight. Unusual characteristics, such as a weight >150 kg, were highlighted with a pop-up notification. Height became a mandatory field and the

calculators were colour co-ordinated (dark red for gentamicin, green for vancomycin) to reflect the prescribing and monitoring charts. Additional functionality enabled patient characteristics and recommended dosage regimens to be printed. Cross validation of the updated and existing calculators identified minor discrepancies that were easily resolved. The online calculators were launched in September 2013. In August 2016, SAPG incorporated the content of the online calculator into a mobile phone "Antimicrobial Companion" app.[7]

National prescribing and monitoring chart templates were agreed for the GGC and Hartford gentamicin dosing regimens and approved by SAPG for testing. During 2013, charts were implemented in two health boards that used the Hartford regimen and two that used the GGC regimen. User feedback was collated, summarised by an antimicrobial pharmacist from each board and reviewed by the working group. National prescribing and monitoring chart templates were then finalised in 2013 and uploaded to the SAPG website. The gentamicin chart was updated in 2015, 2017 and 2019. Each gentamicin chart documents prescribing, administration and monitoring data on one side and offers guidance on the back.[7] Two styles of vancomycin charts were initially devised: one in which each dose had to be prescribed individually; and one that allowed a fixed dosage regimen, such as 1000 mg at 8 am and 8 pm, to be prescribed for a few days. After review by antimicrobial pharmacists across Scotland and SAPG, the second option was made available for health boards to test.

Evaluation of the longterm impact of quality improvement resources on gentamicin *and* vancomycin *prescribing*

The online survey had an 80% response rate (12 of the 15 health boards) representing 99.6% of the Scottish population; smaller boards with limited use of gentamicin and vancomycin did not

194 respond. All boards used one of the SAPG gentamicin options; 10 used the GGC guidance and 2
195 the Hartford guidance. The intermittent vancomycin guidance was used by all boards; 11 also
196 used the continuous infusion guidance, typically for critically ill patients. All boards felt that the
197 SAPG guidance documents met their needs, although 30-40% had made some minor local
198 adaptations. There were requests for "*clarification of weight to use for gentamicin*", "*what to do*
199 *if a vancomycin dose is missed"* and *"timing of first maintenance dose*". Difficulty in achieving
200 vancomycin troughs of 15–20 mg/L was also raised. The SAPG online or app dose calculator was
201 used by seven boards; the remaining five used the same dose calculations but had implemented
202 local versions of these resources. All boards stated that the calculators and the SAPG gentamicin
203 chart (n = 4), or a local version of this chart (n = 8), met their needs. One board had expanded the
204 guidance on the back of the chart, another highlighted avoiding high gentamicin doses in
205 decompensated liver disease and a third was planning to update the chart to reduce the risk of an
206 incorrect dosing interval. In contrast to gentamicin, a variety of methods for recording
207 vancomycin prescribing, administration and monitoring were reported. Eight boards used a
208 vancomycin chart of which seven used a modified version of the draft SAPG chart and one a local
209 monitoring form. Although all felt the chart met their needs, one planned to add flexibility to the
210 recommended time to administer the first maintenance dose[9] and to provide advice on managing
211 delayed administration. Four boards used only the standard medicine prescribing chart. A
212 number of general comments were also received. Several supported the availability of nationally
213 endorsed guidelines; "*Think overall the standardisation has been very useful and calculators are*
214 *very well used and liked*" and "*They have been very helpful and a good example of national*
215 *guidelines working well to benefit patients.*"
216

Thirteen health boards participated in the 2011 point prevalence study (6428 occupied beds) and 12 in 2018 (6201 occupied beds). Data were available from 604 patients overall; 220 in 2011 and 384 in 2018. Between 2011 and 2018, there was an increase in the percentage of patients who were prescribed both gentamicin, from 2.2% (n = 140) to 4.0% (n = 257), and vancomycin, from 1.2% (n = 80) to 2.0% (n = 127). Table 1 summarises the patient demographics and indication for therapy. There were no differences in age, weight or renal function in patients prescribed gentamicin or vancomycin in 2018 compared to 2011. Systemic infection was the most common indication for gentamicin in 2011 and although the rate appeared lower in 2018, the incidence of 'other/unspecified' indications was high, making comparison difficult. As both studies were conducted at the same time of year, seasonal effects would not account for any differences in infection type. Skin and soft tissue, bone and joint infections were the most common indications for vancomycin. In both years, approximately one third of patients also received at least one other potentially nephrotoxic agent, typically an ACE inhibitor, angiotensin receptor blocker, nonsteroidal anti-inflammatory, vancomycin or gentamicin. There was no difference in the proportion of patients prescribed gentamicin or vancomycin who had documented liver impairment in 2011 and 2018; 10% and 5%, respectively.

The use of prescribing and monitoring charts for gentamicin increased from 37% in 2011 to 87% in 2018 and for vancomycin from 23% to 46%. These charts were typically used in addition to standard prescription charts or e-prescribing platforms. As dosage information was contained within these supplementary charts, they were legal documents that had to be signed by the prescriber. The appropriateness of the prescribed dosage regimens is summarised in Table 2. There was an increase in the percentage of patients who received the SAPG recommended gentamicin dose from 44% in 2011 to 89% in 2018, and a decrease from 23% to 4% in patients

whose initial dose varied by ≥20% from the recommendation. For vancomycin, the percentage of patients who received the correct loading dose increased from 50% to 85% and the percentage whose loading dose varied by ≥20% fell from 50% to 15%. Maintenance dose prescribing also improved with an increase in correct doses from 55% to 90% and reduction in differences of ≥20% from 36% to 10%. The incidence of inappropriate prescribing was similar across health boards.

Gentamicin concentrations were available from 74% of patients in both 2011 and 2018. Sample times ranged from 2.5 to 72 hours post dose. The percentage who had their first gentamicin concentration measured within the recommended 6 to 14 hours post-dose increased from 63% in 2011 to 75% in 2018 (OR = 1.80, 95% CI 1.07 to 3.04, p = 0.0275). Vancomycin concentrations were available from 77% of patients in 2011 and 82% of patients in 2018. There was no difference in the percentage of patients who had their first concentration checked within the recommended 48 hours from their first dose; 64% in 2011 and 66% in 2018 (OR = 1.12, 95% CI 0.57 to 2.19). However, the percentage of patients with an initial concentration of 10-20 mg/L increased from 38% to 64% (OR = 2.92, 95% CI 1.38 to 6.15).

DISCUSSION

Clinical guidelines and QI resources ideally would reflect evidence derived from rigorously conducted studies. In practice, they are generally developed via consensus.[10] In the present study, guidelines and resources were developed through meetings, workshops and face-to-face discussions. Having a dedicated team was a key enabler, along with input from the short-term working group and support from SAPG and local antimicrobial management teams, the main

stakeholders. After the 2011 point prevalence and qualitative[6] studies had identified areas for improvement around prescribing, monitoring and administration of gentamicin and vancomycin, it was concluded that having national resources would support local practice and avoid duplication of effort.

Obtaining consensus on the gentamicin and vancomycin guidance,[7] the online calculators and the content of the LearnPro® modules was straightforward as it built on resources already available within individual health boards and there was overlap in their content. Testing the LearnPro® modules during an antimicrobial team workshop enabled key stakeholders to engage with the process and provided an opportunity for feedback and refinement. Additional work was required for the national calculators to comply with the medical device regulations from the Medicines Healthcare and Regulatory Agency (MHRA).[11] NES assumed legal responsibility and CE marking was granted. The biggest challenge was agreeing the content of the gentamicin and vancomycin administration and monitoring charts as each health board used a different approach to prescribing and monitoring these antibiotics. Although it was relatively easy to achieve consensus for gentamicin, two versions of a vancomycin chart, with different pros and cons, were eventually developed and SAPG decided which one to test.

The national survey identified widespread implementation of the SAPG guidance and QI resources across Scotland and it is likely that the close engagement with local antimicrobial teams during the development process had a positive impact on this uptake. Minor local adaptations were shared and used to inform updates to the national resources. This approach facilitates continuous improvement whilst maintaining consistency of practice.

Although improvements in patient outcome should result from appropriate implementation of guidelines,[12] it has been repeatedly shown that clinicians do not always follow guidelines.[13-16] Various strategies have been recommended to address this problem, including educational meetings, dissemination of educational material and creating implementation plans for guideline introduction.[17-21] A combination approach may be the most effective.[22] The present study showed a marked improvement in the appropriateness of initial dosage regimens for both gentamicin and vancomycin between 2011 and 2018. Furthermore, as the 2018 study was conducted 4 years after full implementation, the results demonstrate a sustained improvement in practice. Improvements in the prescribing of gentamicin and vancomycin following QI interventions have been reported previously. Phillips *et al*[23] found that combining face-to-face education, online continuing education, dissemination of a new pocket guideline and an email reminder achieved a guideline adherence rate of around two thirds for vancomycin prescribing while Hamad *et al*[24] reported that implementation of an online or app-based dose calculator led to 56% of gentamicin doses, 68% of vancomycin loading and 67% of vancomycin maintenance doses being appropriate. The present study employed similar implementation tactics to Phillips *et al*[23] but also included an online calculator and specialised prescribing charts. This approach achieved adherence rates of 89% for gentamicin, 85% for vancomycin loading and 90% for vancomycin maintenance doses. These results are also markedly better than in previous audits of adherence to therapeutic drug monitoring guidelines for gentamicin and vancomycin, which consistently demonstrated poor compliance.[24-28] For example, only 58.7% of vancomycin use was in line with local guidance in a Dutch intensive care unit[26] while 34% of initial gentamicin dosing complied with Australian hospital guidelines.[27] Again, this highlights the value of the approach taken in the present study to develop an integrated package of QI resources developed by, and therefore owned by, stakeholders across the country. It also demonstrates the value of having

specialist antimicrobial pharmacists to lead local implementations. Learnpro® modules covered prescribing, administration and monitoring and could be undertaken by different professional groups. It was appropriate that health boards decided which professional groups to target the LearnPro® modules to, ensuring maximum benefit.

Key strengths of this work are demonstration of not only improvements across the whole of Scotland but also sustained improvement for 4 years after implementation of the updated guidelines and QI resources. However, the study had some limitations. Only initial doses were reviewed and the appropriateness of ongoing therapy was not determined. No efficacy or toxicity data were collected that might determine the clinical impact of the guidance. However, it is difficult to attribute clinical outcomes to guidance alone since multiple factors, including greater familiarity with the guidelines over time, affect response. Nevertheless, the increased adherence to the recommended vancomycin loading doses in 2018 led to an increase in the proportion of initial concentrations >10 mg/L, which is important because low concentrations early in therapy may reduce the chance of a good clinical outcome.[29] The study implemented a variety of QI resources and data are not available to directly link the cause and effect to any specific resource. Furthermore, how the resources were implemented was determined by individual boards and the potential influence of different implementation strategies is unknown. Another factor that was not considered was the prescribing system. There was a mixture of electronic and paper-based prescribing in the baseline and the follow-up point prevalence studies. In both cases, the paper gentamicin or vancomycin chart was used in conjunction with electronic or written prescriptions therefore it is unlikely that this limitation would have influenced the results. However, the development of electronic prescribing provides an opportunity for a fully integrated system in which the guidance, calculators and monitoring are embedded within the prescribing system.

Furthermore, new approaches to identify optimal initial doses for patients at the extremes of body weight or age can be incorporated into these systems. For vancomycin, new guidelines will be required to address changes in focus from troughs to AUC targets.[30]

Conclusions

This study has demonstrated that the initial prescribing of gentamicin and vancomycin can be substantially improved and sustained by implementing an integrated package of QI resources. Strong leadership from a dedicated team of healthcare professionals in collaboration with national and local multidisciplinary networks facilitated the success of these developments. This improvement methodology could be adapted for other areas of prescribing practice with the aim of improving the use of antimicrobial prescribing at scale within the hospital setting.

(3572 words)

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Transparency declarations

YS, AHT, JS, AC, RAS have none to declare. MB was co-investigator on a study that received grant support from Astellas Pharma Ltd (November 2014).

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Table 1 Demographic data and treatment indication for the patients who were included in point prevalence studies in 2011 and 2018

	Gentamicin		Vancomycin	
Category	2011 n = 140	2018 n = 257	2011 n = 80	2018 n = 127
Female	71 (51)	147 (57)	41 (51)	52* (41)
Male	69 (49)	110 (43)	39 (49)	74 (59)
Age (years)	62 ± 19	66 ± 18	64 ± 17	64 ± 16
Weight (kg)	74 ± 20	77 ± 23	73 ± 18	84 ± 28
Creatinine (µmol/L)	99 ± 81	90 ± 43	114 ± 96	93 ± 59
Creatinine clearance (ml/min)	72 ± 33	69 ± 33	69 ± 38	80 ± 40
Indication				
Systemic	60 (43)	63 (25)	22 (28)	18 (14)
Gastrointestinal	37 (26)	75 (29)	6 (8)	17 (13)
Urinary tract	14 (10)	47 (18)	0 (0)	0 (0)
Skin & soft tissue, bone & joint	11 (8)	11 (4)	26 (33)	54 (43)
Respiratory	11 (8)	17 (7)	8 (10)	17 (13)
Cardiovascular	1 (< 1)	1 (< 1)	7 (9)	7 (6)
Other / unspecified	6 (4)	43 (17)	11 (14)	14 (11)

Results are presented as number (%) or mean ± SD

**Sex unknown for one patient receiving vancomycin in 2018*

Table 2 Percentages of patients who received correct or incorrect initial gentamicin and vancomycin dosage regimens in 2011 and 2018

Category	2011 number (%)	2018 number (%)	OR	95% CI
Gentamicin	n= 124	n = 244		
Correct dose & frequency	55 (44)	218 (89)	11.0*	6.37 – 19.0
Overdose	31 (25)	13 (5)	0.17*	0.08 – 0.34
Underdose	38 (31)	8 (3)	0.08*	0.03 – 0.17
Dose varied by ≥20%	28 (23)	10 (4)	0.15*	0.07 – 0.31
Incorrect frequency	0 (0)	5(2)	5.72	0.31 – 104
Vancomycin Loading dose	n = 64	n = 107		
Correct	32 (50)	91 (85)	5.69*	2.76 – 11.7
Overdose	3 (5)	5 (5)	1.00	0.23 – 4.32
Underdose	29 (45)	11 (10)	0.14*	0.06 – 0.31
Varied by ≥ 20%	32 (50)	16 (15)	0.18*	0.09 – 0.36
Vancomycin maintenance dose	n = 56	n = 89		
Correct dose & frequency	31 (55)	80 (90)	7.17*	3.01 – 17.1
Overdose	13 (23)	4 (4)	0.16**	0.05 – 0.51
Underdose	12 (21)	5 (6)	0.22**	0.07 – 0.66
Varied by ≥ 20%	20 (36)	9 (10)	0.20*	0.08 – 0.49

Key: *p<0.001 ** p <0.01