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Implementation of a hospital antimicrobial stewardship program to improve vancomycin use in Cyprus: Challenges and opportunity

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SUMMARY

Background: The Republic of Cyprus is among the highest consumers of antibacterials for systemic use in Europe. The antimicrobial resistance of invasive isolates in Cyprus is also high compared to the European Union. Formal antimicrobial stewardship initiatives are scarce in Cyprus, raising an urgent need to address the challenges for implementing hospital antimicrobial stewardship.

Aim: To implement an antimicrobial stewardship program and improve vancomycin use in a tertiary care hospital in Cyprus, through implementation of a protocol for treatment and therapeutic drug monitoring (TDM) and to discuss the current challenges present in Cyprus.

Methods: Following a local audit of practices, we established a hospital antimicrobial stewardship program with limited resources, towards a model of stewardship which included a persuasive approach, education, selective reporting of antimicrobial susceptibility, providing comments on the microbiology results and regular microbiology clinical ward rounds.

Findings: By implementing our vancomycin protocol, we achieved a statistically significant improvement ($P<0.01$) in achieving vancomycin therapeutic levels over a 2-year period, while improving administration practices.

Conclusion: Meaningful steps toward implementing a local antimicrobial stewardship program are possible even in resource-limited and unfavourable settings.

Introduction

The Republic of Cyprus is historically among the highest consumers of antibacterials for systemic use in the community and hospital sector in Europe, ranking first with 28.9 defined-daily doses (DDD) per 1000 inhabitants per day in 2020 and 70.6 DDD per 100 patients in hospitals during 2016–2017 [1,2].

Moreover, high rates of antimicrobial resistance for invasive microorganisms are recorded in Cyprus. In 2019, resistance to

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vancomycin was 50% in invasive *Enterococcus faecium* isolates, resistance to aminopenicillins and fluoroquinolones was 77.1% and 43.5% respectively in invasive *Escherichia coli* isolates, and resistance to methicillin was 36.2% in invasive *Staphylococcus aureus* isolates [3].

The State Health Services Organisation (OKYPY) is the largest Healthcare provider in Cyprus, with nine hospitals and 38 health centres in all cities and provinces [4—6].

Antimicrobial stewardship initiatives are scarce in Cyprus in both public and private healthcare facilities and their implementation encounters significant challenges and barriers. Formal antimicrobial stewardship groups (ASG) or committees and related initiatives are scarce in healthcare facilities. Firstly, information governance is lacking in the majority of the hospitals possible due to an underdeveloped strategic framework for managing information at an organisational and national level. Antimicrobial stewardship groups and/or committees have not been formally established in hospitals. Furthermore, there is a relative lack of expertise related to ASP in Cyprus, with few clinically oriented medical microbiologists and infectious diseases specialists possessing relevant training and experience in developing and implementing ASP. Moreover, only a few clinical pharmacists work in hospitals, and to our knowledge, none of the pharmacists has a specialisation in antimicrobial stewardship. Another important factor is the inadequate diagnostic stewardship framework in Cyprus. With the exception of the Nicosia General Hospital and the few major private hospitals, the microbiology laboratory diagnostic services are not a comprehensive 7/7 service and are short of human resources.

A national antimicrobial guideline for surgical prophylaxis was published by the Ministry of Health in Cyprus in 2013 [7]. The level of awareness among surgeons and compliance with this antimicrobial guideline remains unknown. However, a study reported that 95% of surgical prophylaxis is administered for more than one day in Cyprus [8].

Public awareness for antimicrobial use and antimicrobial resistance in Cyprus identified a high awareness of the correct use of antimicrobials but noticed a lack of knowledge for specific indications. Approximately one-third believed that viral infections respond to antimicrobials. In addition, the vast majority (70.7%) demonstrated a lack of understanding of how antimicrobial resistance develops identified incorrectly as accurate the statement that the human body becomes resistant to the antimicrobials and not the bacteria themselves [9].

Limited progress has been made since December 2012, when the health ministry introduced the national strategic plan for dealing with multidrug-resistant organisms [10]. Recently the Ministry of Health announced plans for a new national strategy for multidrug-resistant organisms (MDRO) with the reestablishment of the national committee for infection control and AMR [11]. It remains unclear at the present time if the new strategy includes the establishment of a formal antimicrobial stewardship program (ASP) and antimicrobial stewardship groups (ASG) in the hospitals. Many countries have developed national antimicrobials guidelines to optimise their antimicrobial use and to help improve the quality of patient care and patient safety. However, a national antimicrobial policy has not been developed, and many clinicians prescribe empirical antimicrobial therapy according to guidelines and clinical practices from Greece, another country with high antimicrobial consumption and high MDRO prevalence.

Therapeutic drug monitoring (TDM) represents an undemanding tool in antimicrobial stewardship and is well established as an important part of the vancomycin therapy management. Inappropriate vancomycin dosing is associated with therapeutic failure, bacterial resistance and renal toxicity [12,13].

The aim of the current study is to implement an antimicrobial stewardship program and improve vancomycin use in a tertiary care hospital in Cyprus, through implementation of a therapeutic protocol for treatment and drug monitoring (TDM) and to discuss the current challenges present in the Republic of Cyprus.

Methods

Setting

The Limassol General Hospital is the second largest hospital of the State Health Services Organisation (OKYPY) in Cyprus and offers high-level secondary and tertiary medical care, in a wide range of clinical specialties, diagnostic and laboratory examinations.

First audit on vancomycin use

From 11 November to 8 December 2019, the microbiology department conducted the first phase of the hospital-wide vancomycin use audit. We included all vancomycin trough levels results, excluding renal patients' results during the above period. In addition, we interviewed clinicians from the intensive care unit, general medicine and general surgery on their practices regarding vancomycin administration. Eighteen clinicians were asked during a short in-person (face-to-face) interview if they (a) administered a vancomycin loading dose routinely and (b) followed a specific protocol for the administration of vancomycin.

Implementation of an antimicrobial stewardship program

Based on the first audit results, a bundle of initiatives and actions was designed and gradually implemented from February 2020 (Table I). This bundle included a protocol for the administration of vancomycin in adults, presentations of audit results and the administration protocol to clinicians and teaching seminars. The vancomycin administration protocol included (a) the routine administration of a loading dose based on actual body weight, (b) detailed (step by step) calculation of creatinine clearance based on adjusted/corrected body weight, (c) guidance for the administration of maintenance dose and frequency based on the creatinine clearance (d) guidance for therapeutic drug monitoring timing and drug administration intervals (e) detailed instructions for dosage corrections based on TDM (f) inclusion of two examples-exercises. The vancomycin protocol was both for empirical and therapeutic treatment. Our initial aim was to achieve therapeutic levels amongst patients treated with vancomycin.

The results also highlighted the need to establish a formal antimicrobial stewardship program (ASP) in the hospital. Therefore, an antimicrobial stewardship group (ASG) was established under the supervision of the Infection Control

Table I
Bundle of implemented antimicrobial stewardship initiatives and measures

Initiatives and measures	Date of competition
Establishment of Antimicrobial Stewardship Group	03/2020
Protocol for vancomycin administration in adults	06/2020
Protocol for vancomycin administration in ICU (continuous infusion)	11/2020
Formal presentations of results and vancomycin protocol to the clinicians	02/2020
Teaching — seminar	09/2020
Selective reporting of antibiotic susceptibility (Microbiology department)	03/2020
Interpretation comments on culture results (Microbiology department)	03/2020

Group (ICG). The ICG also appointed an antimicrobial stewardship lead/coordinator. The ASG was quickly established and included specialists from various disciplines (medical microbiologists, pharmacist, infectious diseases specialist/intensivist, surgeons, clinician from internal/elderly medicine, haematologist, paediatrician and two resident doctors. All members participated voluntarily. The ASG approved and published the vancomycin protocol for use in adult hospital patients in June 2020.

We presented the audit results and the bundle of recommendations to the clinicians during several official meetings on different dates and times. We aimed to provide opportunities to as many as possible clinicians to attend those meetings. The protocol for the administration of vancomycin in adults was presented during those presentations. Moreover, the results were also verbally shared and discussed with the clinical teams during the regular medical Microbiologist ward rounds in the clinics. The use of the vancomycin protocol was not compulsory for the clinicians. The two medical microbiologists and the infectious disease specialist remained at the clinicians' disposal to provide additional clarification for the protocol if required.

Table II
Vancomycin therapeutic drug monitoring

	Prior ASP (November 2019)	After ASP (October 2021)
TDM[a] Test number	111	146
TDM[a] Mean	15.93	15.19
TDM[a] Median	13.10	14.35
TDM[a] vancomycin range	0—78.4	0.1—51.5
TDM[a] range <10	37 (33%)	32 (22%)
TDM[a] range 10—20[c]	43 (39%)	83 (57%)
TDM[a] range >20—25	14 (13%)	21 (14%)
TDM[a] range >25	17 (15%)	10 (7%)
Low or high TDM range [b,c]	68 (61%)	63 (43%)
Loading dose administration	2/18 (11%)	11/17 (65%)

TDM: therapeutic drug monitoring, ASP: Antimicrobial Stewardship Program.
[a] TDM measured as μg/mL.
[b] defined as <10 or >20.
[c] *P*-value <0.01.

Table III
Vancomycin consumption (2019—2021)

Period	Pre-pandemic	COVID-19 pandemic	COVID-19 pandemic
Year	2019	2020	2021
Vancomycin DDD/100 bed days	7.95	9.56	5.52

Moreover, the microbiology department introduced a restrictive reporting of selected antimicrobial susceptibilities (e.g. carbapenems, 3rd and 4th generation cephalosporins, respiratory fluoroquinolones), selective reporting of antimicrobial susceptibility results (e.g. reporting only ampicillin, amoxicillin in susceptible *Escherichia coli*) and introduced interpretation comments (e.g. "pyuria and/or bacteriuria are common findings in urine catheter specimens. Treatment is indicated if the patient is symptomatic. In such a case, the urine catheter replacement or removal is strongly recommended").

Second audit on vancomycin use

Following the 16-month program on improving vancomycin use, we conducted a second audit between 01 and 27 October 2021. This again included recording the vancomycin trough levels and short in-person interviews of clinicians on their practices regarding vancomycin prescription.

Statistical analysis

Data were analysed for its statistical significance ($P<0.05$) using the Epi Info software (version 7.2.4.0, CDC-Atlanta).

Results

During the first phase of the study in November 2019, we recorded 111 vancomycin TDM results from 28 patients. The first audit results showed that only 39% of the samples were within the therapeutic range (10—20 mg/L). Most results were either subtherapeutic or within an increased or toxic range (Table II). Eighteen clinicians participated voluntarily in the short face-face interview, and only 11% reported that they administered a vancomycin loading dose routinely. The clinicians reported that they didn't follow a specific protocol, and for the 89% of their cases, they prescribed routinely 1g vancomycin twice daily.

Following presentation and dissemination of the first audit results and establishment of a vancomycin use protocol, the follow-up audit was conducted in October 2021. A total of 146 vancomycin TDM from 42 patients were recorded. The results showed that there was a statically significant improvement (57% vs 39%, $P<0.01$) in achieving vancomycin therapeutic levels within range (Table II).

We also observed a change in behaviour amongst the clinicians, with 65% (11 out 17) reporting that they administered a

Table IV
VRE isolates from clinical samples during 2019–2021

Year	Blood	Urine	Catheter tips	Bronchial	Wound Swab and rectal swabs	Total VRE	VRE/1000 patients	VRE/1000 bed days
2019	28	127	6	2	68	231	19.36	2.87
2020	31	56	10	7	31	135	15.44	2.08
2021	47	67	9	4	32	159	18.88	2.32

vancomycin loading dose routinely compared to 11% in November 2019. Following the implementation of the protocol, during the second half of 2020, we observed initially an increase of vancomycin consumption (Table III) during 2020 (9.56 DDD/100 bed days) in comparison to 2019 (7.95 DDD/100 bed days) followed by a reduction in the vancomycin consumption (DDD/100 bed days) in 2021 (5.52 DDD/100 bed days).

The number of vancomycin resistant Enterococci (VRE) isolates and rate (VRE cases/bed days) decreased during 2021 in comparison to 2019 (OR= 0.805, 95% CI= 0.657–0.985, $P<0.05$) as seen in Table IV.

Discussion

Following presentation and dissemination of the first audit results and establishment of a vancomycin use protocol during the second half of 2020, we were able to accomplish a statically significant improvement (57% vs 39%, $P<0.01$) in achieving vancomycin therapeutic levels within range. We also observed a change in behaviour amongst the clinicians, with 65% (11/17) reporting that they administered a vancomycin loading dose routinely compared to 11% prior (2/18). The use of the vancomycin protocol is not compulsory in our hospital. Only a proportion of the total clinical workforce (approximate 13 %) were approached and asked if they administered a vancomycin loading dose before and in the follow-up phase. Notwithstanding the limitations of our approach, we observed a significant increase ($P<0.01$) in the routine administration of a vancomycin loading dose.

We observed initially an increase of vancomycin consumption (DDD/100 bed days) during 2020 (9.56 DDD/100 bed days) in comparison to 2019 (7.95 DDD/100 patient days) and then a reduction in the vancomycin consumption during 2021 (5.52 DDD/100 patient days). The increase in vancomycin usage in 2020, the year of our vancomycin protocol introduction, could be related to the administration of an increased vancomycin loading dose (e.g. 1.5g or 2g instead of 1g) to a significant proportion of patients (>60kg) in comparison to the practice before (administration of 1g). The decrease in vancomycin usage during 2021 might be related to the permanent establishment of a clinical microbiology ward round in the intensive care unit Monday through Friday, clinical consultation on all bacteraemia hospital cases and the routine addition of an interpretation comments to the positive blood cultures with coagulase negative staphylococci isolation (e.g. "in absence of line-associated bloodstream infection, this could be a skin contaminant"). It appears that the implementation of ASP and guidelines have a favourable impact on vancomycin consumption [14,15].

Our initial aim was to achieve therapeutic levels amongst patients treated with vancomycin. Data regarding the compliance of appropriate use of vancomycin before, during, and after our intervention are unavailable. The hospital does not have a formal antimicrobial formulary or guideline for advice that would enable us to compare the compliance of antimicrobial prescriptions with guidelines.

During 2021, we observed a decrease (Table IV) in vancomycin-resistant Enterococci (VRE) cases and rate (VRE cases/1000 bed days) in comparison to 2019 (OR= 0.805, 95% CI= 0.657–0.985, $P<0.05$). Notwithstanding the reduction in VRE rate during 2020 and 2021 we noticed a statistically significant increase (in VRE bacteraemia cases and rate (OR 1.97, 95% CI 1.23–3.15, $P<0.05$). A possible explanation might include an increase in both blood culture contamination and catheter-related bloodstream infections. Contributory factors for the increased blood culture contamination could be the higher burden of workload for the care of the patients with COVID-19 and wearing personal protective equipment (PPE) that might have made the procedure of blood cultures more difficult than those without, as described elsewhere [16–19]. The increase in blood stream infections during the COVID-19 pandemic might be related to the extended length of stay [20]. Available data shows that the average length of stay (not including day cases) increased in our hospital from 6.6 days in 2019 (pre-pandemic) to 7.44 days in 2020 and 8.1 days in 2021, possible because of the care of COVID-19 patients and complex non-COVID19 patients particularly those that are severely unwell and with comorbidities [20].

The COVID-19 pandemic had an impact on the implementation and the expansion of our ASP. As a result, the initial schedule for implementing the vancomycin protocol was delayed by approximately three months. However, the impact was much greater in the ASP extension and initiatives, causing significant delays. In addition, as COVID-19 further stressed our evolving hospital ASG and ASP and resources were diverted from stewardship to traditional laboratory and clinical tasks as described elsewhere [21,22].

As already described, antimicrobial stewardship initiatives are scarce in Cyprus and their implementation encounters significant challenges and barriers. An important factor is that in countries with high antimicrobial use, antimicrobial resistance and antimicrobial prescription are essentially the outcomes or the problem of values and culture that leads to individual behaviour [23–25]. The organisation's culture (e.g. shared beliefs and values established by leaders) defines the priority within the healthcare organisation and remains one of the most crucial factors in a successful ASP intervention. Leadership commitment by the hospital administration and healthcare authorities are essential in ensuring allocation of the necessary resources to prioritise and support the antimicrobial stewardship programme (ASP).

Conclusively, this study demonstrated the implementation of ASP in a hospital with limited resources, through a persuasive approach, education, feedback, selective reporting of antimicrobial susceptibility and performing regular microbiology clinical ward rounds. Taking into account local practices, contextual setting and shortcomings can facilitate meaningful steps towards improving antimicrobial prescription even with limited resources.

CRediT author statement

Panagiotis Papastergiou: Conceptualization, Methodology, Formal analysis, Investigation, Writing - Original Draft

Constantinos Tsioutis: Writing - Review & Editing, Supervision

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Conflict of interest statement

All authors report no conflicts of interest relevant to this article.

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