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Case Report

Glycopeptide-Resistant *Enterococcus Faecium* Outbreak in An Onco-Hematology Ward

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Abstract

In recent decades, there has been a worldwide increase in nosocomial infections due to multidrug resistant bacteria. The infections caused by multidrug resistant gram-positive microorganisms have a worse prognosis compared to those caused by sensitive pathogens, due in part to the fact that empirical antimicrobial treatments are not effective in a significant number of cases. In Europe, significant glycopeptide-resistant *Enterococcus faecium* (GREF) hospital's outbreaks had been detected in recent years. Even some countries have reached prevalence higher than 25%. In this study, we analyze the microbiological, epidemiological and clinical characteristics of an outbreak occurred at Guadalajara University Hospital (HUG) in Spain, which affected patients in the onco-hematology ward, as well as the preventive measures implemented for its control. The outbreak involves 28 patients, 21 as colonization and 7 infections. All isolates contained the gene vanA. The molecular results showed that the strains belong to the clone ST203, included in CC17. The 73.1% of the patients had been treated with vancomycin and teicoplanin in the 2 months prior to isolation of GREF. An early containment of the outbreak resulted from the implementation of a multidisciplinary approach by including patients contact isolation, taking colonization samples, intensifying hand hygiene, disinfection of the inanimate environment, workers training in prevention of infection transmission.

***Keywords:** glycopeptides-resistant; Enterococcus faecium; nosocomial; outbreak; onco-hematology unit.*

1. Introduction

In recent decades, there has been a worldwide increase in nosocomial infections due to multidrug resistant bacteria [1]. Although the incidence is higher in gram-negative than in gram-positive microorganisms, the latter raise a problem for the management of hospitalized patients [1]. The infections caused by gram-positive microorganisms have a worse prognosis compared to those caused by sensitive pathogens, due in part to the fact that empirical antimicrobial treatments are not effective in a significant number of cases [2].

Enterococci can be found as microbiota in the gastrointestinal and female genital tracts [3]. They are not considered highly pathogenic commensals, but they could be responsible for opportunistic infections such as bacteremia, endocarditis, intra-abdominal infections, skin and soft tissue infections and urinary tract infections [3].

Although some species of *Enterococcus* present a natural resistance to glycopeptides (*van*C genes in *Enterococcus gallinarum*, *Enterococcus casseliflavus* and *Enterococcus flavescens*), 8 genotypes of acquired resistance to glycopeptides have been described (genes *van* A/ B/ D/ E/ G/ L/ M/ N), resulting in peptidoglycan precursors with reduced glycopeptide affinity. The acquisition of resistance genes *van*A or *van*B is the most commonly described one [4]. While *van*A genes are responsible for high-level resistance to vancomycin and teicoplanin, *van*B genes confer low-level resistance to vancomycin and do not affect teicoplanin [4]. Currently, the fast propagation of glycopeptide-resistant enterococci limits treatment choices and acts as reservoir of genes, mainly *van*A and *van*B, for a possible intra- and even interspecies transfer [5] (e.g. methicillin-resistant *Staphylococcus aureus* [6]).

The increased risk of infection and/or colonization by glycopeptide-resistant enterococci has been associated to previous use of vancomycin and/or to use of multiple antibiotics, to the presence of a severe underlying disease or immunosuppression, to intra-abdominal and cardio-thoracic surgery, to the carrying of an indwelling bladder catheter or central venous catheter, and to prolonged hospital stays [7]. However, recent studies on outbreaks and endemic infections caused by enterococci suggest that patient-to-patient transmission plays an important role; such transmission has been described as being associated with direct or indirect hand contact by healthcare personnel or the healthcare environment, including monitoring devices, medical equipment and contaminated environmental surfaces [7,8].

The first isolates of glycopeptide-resistant *Enterococcus faecium* (GREF) in Europe date back to the 1980s, and they originated in hospitals in the United Kingdom [9] and France [10] and subsequent ones were originated in hospitals in the United States [11]. While in the United States, hospital infections and colonization have increased dramatically, causing outbreaks in intensive care units [12], in Europe, the EARS-Net [13] study, which is a collection of *E. faecium* from blood isolates, illustrates the large variations between different countries, even those geographically close to each other. While the prevalence of GREF is very low (<1%) in Estonia, Finland, Iceland, Malta, Sweden and France, in Romania, Croatia, Cyprus and Ireland it exceeds 25% of the isolates.

In Spain, EARS-Net detected a slight increase from 1.5 per cent in 2011[14] to 2.5 per cent in 2015 [13] although significant GREF outbreaks in hospitals were detected in recent years [15-18].

The main goal of this study is to analyze the microbiological, epidemiological and clinical characteristics of an outbreak occurred at the Guadalajara University Hospital (HUG) in Spain, which affected patients in the onco-hematology ward, as well as the preventive measures implemented for its control.

2. Methods

This study includes all cases of infection and colonization by *E. faecium* detected from October 2014 to December 2015 in the onco-hematology ward of the HUG. The HUG is a secondary hospital with 400 beds in the province of Guadalajara, Spain (255,000 inhabitants). The hospital's onco-hematology service has 35 beds and an average of 85 patients per year (average data from October 2014 to December 2015).

Once the outbreak situation was confirmed, a number of measures were established, which included the study of active surveillance in order to detect patients with GREF in the onco-hematology ward and to establish cautionary measures.

In the study of colonization, rectal swabs were taken on a weekly basis from all patients admitted at the onco-hematology ward, as well as from new patients at the time of admission. A total of 768 samples from 301 patients were processed.

The samples were introduced in the chromogenic agar medium chromID VRE (bioMerièux; Marcy-l'Etoile, France) in order to isolate the strains of GREF. The agar plates were incubated for 24-48 hours at 37ºC.

The identification and antibiogram of the isolates were done using the automated Vitek II (bioMèrieux). Sensitivity to antibiotics was interpreted as per CLSI criteria [19]. GREF isolates were sent to the Laboratory for Reference and Research on Resistance to Antibiotics of the National Center for Microbiology (CNM) for the molecular characterization about the mechanism of resistance and the molecular typing.

The glycopeptide resistance mechanism was determined by PCR amplification with primers specific to *van*A and *van*B genes and subsequent sequencing of the amplicon obtained. Molecular epidemiology was carried out by pulsed-field gel electrophoresis (PFGE) after total DNA digestion with the restriction enzyme *Sma*I and Multilocus sequence typing (MLST) (http://efaecium.mlst.net/).

A case of colonization was determined whenever GREF was isolated from a clinical specimen in the absence of symptoms or in a specific sample for colonization control. A case of infection was defined as the presence of GREF in representative cultures of the focus of infection in a patient with clinical symptoms of disease. The colonization was considered resolved whenever the patient had 3 weekly consecutive negative stool cultures for GREF. When considering risk factors, previous treatments with glycopeptides and other antibiotics such as second- or third-generation cephalosporins, aminoglycosides and metronidazole were analyzed, as well as previous stays in the onco-hematology ward.

3. Results

3.1 Description of the outbreak and control measures

The first identified case was a patient who had rectal cancer surgery in July 2012 and underwent another operation for the same tumor in September 2014. A complication ensued in the post-surgery period with secondary peritonitis and left inguinal abscess. A colostomy was placed in the left iliac fossa. A sample of the inguinal abscess was sent to the microbiology laboratory, where a GREF strain was isolated.

In December, the patient received chemotherapy sessions at the outpatient care facilities, at the same time as the second patient. This second patient was admitted at the onco-hematology ward 8 days after contact with the index case, and presented clinical urinary tract infection (UTI). A urine sample was sent to the microbiology laboratory where another GREF strain was isolated. A third case was revealed in the same ward where the second patient was recovering. Then the third patient presented an UTI by GREF.

In February and March, GREF infections were found in two more patients at the onco-hematology ward. In that moment, the outbreak was declared and the study of active surveillance began, among other measures described below. The distribution of the cases involved in the outbreak is recorded in Figure 1.

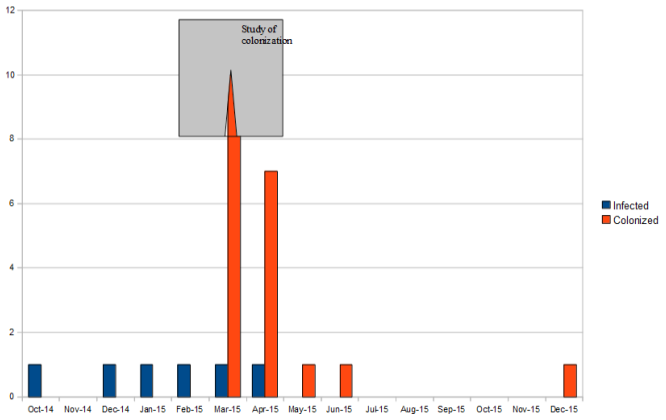

Figure 1. EFGR isolates at the onco - hematology ward from October 2014 to December 2015

From October 2014 until December 2015, GREF was isolated as a colonization (21) and/or infection (7) in 28 patients. However, 2 patients were excluded, as no epidemiological links could be established. The types of infection that were diagnosed included urinary tract infection (2), infection of skin and soft tissue (2), bacteremia (1) and intra-abdominal infection (2). These 28 patients were distributed in the onco-hematology ward (26), the intensive care unit (1) and the Internal Medicine unit (1).

In order to control the outbreak quickly and effectively from the beginning, a multidisciplinary panel was created, made up of a microbiologist, the nursing supervisor of the service involved, an hematologist, an epidemiologist, an internist and an intensive care physician, who proposed the group of measures that were implemented, and which are described below. In March 2015, the study of colonization began by collecting weekly rectal samples. A GREF carrier-status alert was created in the computer system for clinical history, in order to carry out preventive isolation for further admissions. Another measure was to restrict the patient's mobility between rooms and hospital floors. The carriers and/or infected patients were put into contact isolation whenever possible; they stayed in a private room or one shared with patient colonized by the same organism. A checklist for isolation measures was designed. The daily hygiene of the patients was carried out with 4% chlorhexidine. Training sessions were held for all the personnel at the onco-hematology service in order to improve the washing of hands.

All the material that could not be of exclusive use for a patient (thermometers, blood pressure cuff, etc.) was thoroughly cleaned with 4% chlorhexidine after use by the cleaning staff, which was specially trained for this task.

During the outbreak, the cleaning team proceeded to clean all the rooms daily with a 1% bleach solution on walls, doorknobs, carpeting, bathrooms, etc. In the case of patients in contact isolation, the cleaning was done in two shifts. The rooms intended for isolation had to be cleaned the last. In addition to this, two containers were used for disposal of contaminated materials and clothes. A form was designed to be completed by the cleaning personnel after cleaning duties to check their correct execution. Once a patient was discharged, there was a vertical terminal cleaning of the room.

3.2 Antimicrobial susceptibilities and typing

The sensitivity study determined resistance to vancomycin (MIC ≥ 32 μg/mL) and to teicoplanin (MIC ≥ 32 μg/mL) in all the isolates studied. In addition, all of them were resistant to levofloxacin (MIC ≥8 μg/mL) and synergy with gentamicin (MIC > 500 μg/mL) and streptomycin (MIC > 1,000 μg/mL). All isolates were susceptible to linezolid (MIC ≤ 2 μg/mL) as the treatment of choice in infections produced by GREF.

The molecular results showed that all isolates contained the gene *van*A. Using PFGE, a clone was detected (C1) that included 18 isolates with a single profile, and three genetically related to a genetic homology equal to or greater than 90% (Figure 2). The remaining seven isolates presented PFGE profiles unrelated to C1: four were grouped with a ≥82% genetic homology, two had the same profile and one presented an individual profile without any relation with the others (Figure 2). The analysis of five of the isolates representative of clone C1 by MLST showed that they belonged to type sequencing (ST) 203, included in clonal complex 17 (CC17). ST203 only differs in two (*atp*A and *pst*S) of the seven alleles studied at the MLST regarding the ST17.

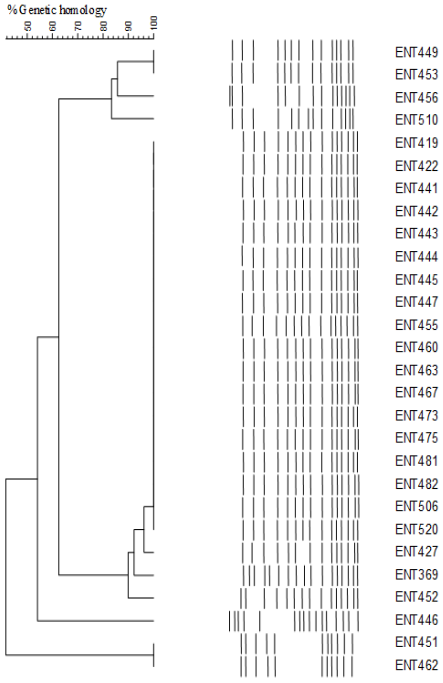

Figure 2. Dendogram that shows the genetic homology obtained by PFGE of the 28 VanA producing strains.

3.3 Patient characteristics and evolution of the outbreak

The average age of the 26 patients involved in the outbreak was 72 years, and 73% of them were men (the characteristics of the patients involved in the outbreak, excluding the 2 patients without a known epidemiological link are shown in Table 1). 73.1% of them had been treated with vancomycin and teicoplanin in the 2 months prior to isolation of GREF. Furthermore, 38.5% of the patients received a previous treatment with aminoglycosides, 38.5% were treated with third-generation cephalosporins and 3.9% with metronidazole. 26.9% of these patients had stayed at the outpatient care facilities, and the remaining 73.1% were colonized/infected during admission, whereas 65.4% of the cases (17 patients) had been hospitalized 3 to 6 months prior to the isolation of the EFGR strain, their carrier status being unknown at the time of admission during the outbreak.

Table1: Patients were coded by number according to the date of GREF isolation.

Patient ID/ Status	Disorder	Hospitalization date[a, b]	Previous vancomycin treatment	Previous hospitalization (<6 months)	First isolation +		Last isolation +		Outcome
					Date[a]	Source	Date[a]	Source	
1/Infected	Rectal adenocarcinoma	25/09/14 (26)	Yes	30/08/2014	21/10/2014	Abscess	-	-	Died
2/ Infected	Urothelial carcinoma	09/12/2014 (8)	Yes	No	17/12/2014	Urine	-	-	Died
3/ Infected	Urothelial carcinoma	10/12/2014 (7)	Yes	13/11/2014	17/01/2015	Urine	-	-	Recovered
4/ Infected	Diffuse large B-cell gastric-lymphoma	13/02/2015 (14)	Yes	25/11/2014	27/02/2015	Scab	-	-	Unknown

5/ Infected	Sigma adeno-carcinoma	5/02/2015 (35)	Yes	21/12/2014	11/03/2015	Blood	-	-	Died
6/Colonized	Small cell lung cancer	16/02/2015 (24)	Yes	24/11/2014	12/03/2015	Rectal	-	-	Unknown
7/ Colonized	Larynx epidermoid carcinoma	20/02/2015 (20)	No	No	12/03/2015	Rectal	-	-	Died
8/ Colonized	Ciliochoroidal melanoma	05/01/2015 (66)	Yes	No	12/03/2015	Rectal	-	-	Unknown
9/ Colonized	Intestinal LNH[c]T-cell	27/01/2015 (45)	Yes	02/01/2015	13/03/2015	Rectal	-	Rectal	Intermittent
10/ Colonized	Biphenotypic acute leukemia	15/02/2015 (26)	No	No	13/03/2015	Rectal	24/03/ 2015	Rectal	Recovered
11/ Colonized	Follicular LNH[c]	10/03/2015 (13)	Yes	16/06/2014	13/03/2015	Rectal	24/08/ 2015	Rectal	Recovered
12/ Colonized	Hypernephro-ma	22/03/2015 (1)	No	17/03/2015	23/03/2015	Rectal	23/03/ 2015	Rectal	Recovered
13/ Colonized	Burkitt LNH[c]	23/03/2015 (2)	No	24/11/2014	25/03/2015	Rectal	-	-	Died
14/ Colonized	Infiltrate epidermoid carcinoma	05/03/2015 (20)	No	02/02/2015	25/03/2015	Rectal	-	-	Unknown
15/ Colonized	Myelodysplas-tic syndrome	24/02/2015 (34)	Yes	22/01/2015	30/03/2015	Rectal		-	Unknown
16/ Colonized	Diffuse large B-cell brain lymphoma	02/03/2015 (36)	Yes	09/02/2015	07/04/2015	Rectal	-	-	Unknown
17/ Colonized	Myelodysplas-tic syndrome	16/02/2015 (50)	No	07/05/2013	07/04/2015	Rectal	20/04/ 2015	Rectal	Recovered
18/ Colonized	Prostate ade-nocarcinoma	01/04/2015 (6)	No	07/05/2013	07/04/2015	Rectal	-	-	Unknown
19/ Colonized	Gastric adeno-carcinoma	11/04/2015 (2)	Yes	19/02/2015	13/04/2015	Rectal	-	-	Unknown
20/ Infected	Breast cancer	15/04/2015 (1)	Yes	04/04/2015	16/04/2015	Perito-neal	-	-	Died
21/ Colonized	Multiple myeloma	19/04/2015 (1)	Yes	09/01/2015	20/04/2015	Rectal	-	-	Died
22/ Colonized	Larynx epidermoid carcinoma	22/04/2015 (6)	Yes	27/02/2015	28/04/2015	Rectal	11/05/ 15	Rectal	Recovered
23/ Colonized	High-grade lymphoma B -cell	28/04/2015 (2)	Yes	18/04/2015	30/04/2015	Rectal	-	-	Unknown
24/ Colonized	Acute myeloid leukemia	21/05/2015 (3)	Yes	17/05/2015	24/05/2015	Rectal	-	-	Unknown
25/ Colonized	Acute lymphoblastic leukemia	17/04/2015 (52)	Yes	No	08/06/2015	Rectal	06/07/ 2015	Rectal	Recovered
26/ Colonized	Acute myeloid leukemia	16/11/2015 (85)	Yes	No	21/12/2015	Rectal	-	-	Died

[a]Day/month/year.
[b]Days until first isolation are shown in parentheses.
[c]LNH: Non-Hodgking Lymphoma

During the study, 7 patients died from their respective diseases, 11 patients were not readmitted during that period and their evolution could not be followed (unknown), and 7 patients resolved the colonization (Table 1). Out of 26 patients, only one was considered an intermittent carrier after presenting positive cultures after 3 negative control cultures. In the case of the 7 patients that presented GREF-negative control cultures, and whose development could be followed, the colonization period from the date of the first detection until the third negative result, lasted between 1 and 7 months.

Six weeks after the last positive culture, the outbreak was considered concluded, although some control measures were kept such as the active search for carriers.

Discussion

The strains of glycopeptide-resistant vancomycin can colonize the human gastrointestinal tract without symptoms, persisting for long periods of time as a reservoir for transmission to other patients [7,8].

The GREF outbreak described in this study affected onco-hematological patients who had been admitted into the same ward or shared armchairs in the day hospital. The risks that lead to a patient being colonized by EFGR are firstly exposure (due to proximity to patients already colonized and/or infected, especially if they suffer from diarrhea), which is increased during a prolonged hospital stay; and secondly, the susceptibility of the host [8]. Also, a risk increase is described in the case of receptors for solid organ transplants (especially abdominal) [8]. Another risk factor that was found in our study and previously described [7,8] is previous use of vancomycin and teicoplanin. Other antibiotics that according to observations may favor colonization are second- and third-generation cephalosporins, and the aminoglycosides previously described [8].

The majority of nosocomial infections caused by *E. faecium* belong to a few clonal complexes (CC), such as CC17, CC18 and CC78, which have developed antibiotic resistance genes and virulence genes that facilitate colonization [20]. The outbreak described here was produced by the clone ST203, included in CC17. CC17 is resistant to ampicillin and fluoroquinolones [17], and has also been involved in nosocomial outbreaks by GREF in recent years [16,17,20]. Specifically, ST203 has been described previously producing GREF in Spain.

In neutropenic patients who are colonized, we need to evaluate potential sources of GREF entry in order to prevent a possible infection. Therefore, caution must be exercised when the patient is colonized by GREF in the urinary tract and must be manipulated by urological treatments (risk of bacteremia) as well as in the case of patients colonized in the gastrointestinal tract and biliary tree, especially liver transplant recipients who need abdominal surgery. At the same time, colonization of skin by GREF increases the risk of intravascular catheter-related sepsis [8].

Although our study documents a carrier status lasting up to 7 months, there are studies that observed persistence, intermittency or recurrence of GREF-positive cultures for more than one year in patients who continued to receive antibiotic treatment afterwards [21]. For this reason, having just 3 weekly consecutive negative cultures of colonization [21] does not appear to be a valid criterion to consider GREF eradicated. Although efforts have been made to decolonize patients, for example with novobiocin and tetracycline, bacitracin plus doxycycline or doxycycline with rifampicin [22], this has not always been achieved in a definitive way, as these patients may act as vectors of transmission [19] and environmental contamination [8].

In order to prevent transmission, all preventive measures possible should be applied early and effectively in any colonized patient. To confirm the outbreak, it is necessary to organize a multidisciplinary panel led by a professional with experience in outbreaks and who will act as spokesperson with the center's governing body [23]. In our hospital, the measures included, among other actions, the study of active surveillance in order to detect strains of GREF in the onco-hematological floor. The GREF surveillance cultures, by means of rectal swabs or stools, must be performed on patients who are inadvertently exposed to GREF, and more widely in the context of a possible outbreak, where sample cultures of health personnel who have been in contact with patients are not necessary because they are rarely involved in the transmission of GREF. However, the environment and the medical team cultures may be justified in order to monitor adherence to outbreak control protocols [7,21].

Adherence to handwashing procedures is essential. The centers for disease control and prevention guidelines support the use of gloves by health personnel when entering the patient's room, and bathrobes for a substantial contact with the patient or environmental surfaces in the room. Given the high rate of nosocomial infection detected in our study, we cannot overemphasize the importance of strict adherence to control measures by healthcare staff. Patients who are infected or colonized with GREF should be isolated, preferably in single rooms, as we did in our case. Some authors have suggested bringing these patients together [7]. This could be a reasonable measure for centers that may not be able to assume the economic cost of numerous individual isolations. Finally, we recommend total cleanliness in the rooms and hospital beds for patients with GREF, as well as the verification of said cleanliness.

The multidisciplinary panel must document its actions during each step of the investigation. Preliminary reports should be directed to the center's governing body, the committee for infections, the service or services affected by the outbreak and the public health agency to report on the situation [22].

Conclusion

Given the importance and potential significance of nosocomial outbreaks, it is necessary to establish mechanisms for outbreak prevention and control. Many outbreaks in health centers could have been avoided if health workers had routinely applied appropriate measures for the prevention of infections, so we recommend continued training in prevention of infection transmission. At the same time, in order to detect and control outbreaks quickly and efficiently from the beginning, each center should have a program for surveillance, prevention and control of infections that suits its particular conditions.

Conflict of Interest

The authors declare no conflict of interest.

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