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# Prophylaxis with gentamicin locking of chronic tunnelled central venous catheters does not cause bacterial resistance

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## ABSTRACT

**Introduction**: Prophylaxis with gentamicin locking of chronic tunnelled central venous catheter branches in chronic haemodialysis patients reduces bacterial infections and morbidity and mortality associated with catheter bacteraemia. **Aim:** We undertook a 7-year, prospective, observational study involving 101 patients on chronic haemodialysis with catheters treated with prophylaxis to evaluate the appearance of bacterial resistance to the antibiotic in pathogens usually sensitive to its action. **Material and Methods:** A protocol of universal asepsis in catheter management. Postdialysis intraluminal locking of the branches with gentamicin at 5mg/branch + 1% heparin sodium, monitoring trough levels in the blood and modifying the dose according to the established protocol. The diagnosis of bacteraemia was based on usual criteria. The *main study variables* were: Diagnosis by the bacteriology department of bacterial resistance in pathogens sensitive to gentamicin. Diagnosis of clinical ototoxicity. *Secondary variables* were: Patients hospitalised/bacteraemia; number of bacteraemia/catheter/1000 days; infectious mortality; and catheter withdrawal/bacteraemia. Pathogens found in blood culture. **Results:** *Main variables*: We found no resistance of pathogens usually sensitive to the antibiotic or clinical ototoxicity. The mean number of months each patient remained in the study was 23 (1-84). *Secondary variables*: Three patients (3%) were hospitalised due to bacteraemia; number of bacteraemias: 8; number of bacteraemia/catheter/1000 days: 0.11; infectious mortality per bacteraemia: 1 patient (1%); catheter withdrawal due to bacteraemia: 2 (2%). No patients were diagnosed with endocarditis or spondylodiscitis. The mean trough level of gentamicin in each patient during the study was 0.17µg/ml (0.05-0.31); the mean intraluminal gentamicin locking dose per branch was 3mg (2-5), equivalent to 1.1-1.7mg/ml/branch. **Conclusions:** This 7-year, prospective observational study of 101 patients on chronic haemodialysis with tunnelled central venous catheters showed: *1)* Prophylaxis with intraluminal gentamicin locking of the catheter branches does not cause bacterial resistance in pathogens sensitive to its action. *2)* No clinical ototoxicity was seen. *3)* The lack of resistance and ototoxicity may be influenced by the gentamicin prophylaxis dose used, which was much lower than in other studies.

**Keywords:** Hemodialysis. Catheter. Bacteremia. Prophylaxis. Gentamicin. Gentamicin bacterial resistance.

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## *La profilaxis con sellado de gentamicina de las ramas del catéter venoso central crónico tunelizado no causa resistencia bacteriana*

## *RESUMEN*

***Introducción:*** *La profilaxis con sellado de gentamicina de las ramas del catéter venoso central tunelizado en hemodiálisis crónica disminuye la morbimortalidad infecciosa bacteriana asociada a la bacteriemia del catéter.* ***Objetivo:*** *Valorar en un estudio prospectivo observacional de 7 años de duración de 101 pacientes en hemodiálisis crónica con catéter tratados con profilaxis la aparición de resistencia bacteriana al antibiótico en gérmenes habitualmente sensibles a su acción.* ***Material y métodos:*** *Protocolo de asepsia universal en el manejo del catéter. Sellado intraluminal de las ramas posdiálisis con gentamicina 5 mg/rama + heparina sódica al 1%, monitorizando su nivel valle en sangre y modificando la dosis por un protocolo establecido. El diagnóstico de bacteriemia se basa en criterios habituales. Variables principales estudiadas: Diagnóstico por el servicio de bacteriología de resistencia bacteriana en gérmenes habitualmente sensibles a gentamicina. Diagnóstico de ototoxicidad clínica. Variables secundarias: Pacientes hospitalizados/bacteriemia; número de bacteriemias/catéter/1.000 días; mortalidad infecciosa y reti-*

*rada del catéter/bacteriemia. Gérmenes causantes de bacteriemia.* ***Resultados:*** *Variables principales: No observamos resistencia de gérmenes sensibles al antibiótico, tampoco ototoxicidad clínica. La media en meses en que cada paciente está incluido en el estudio es de 23 (1-84). Variables secundarias: Hospitalizados por bacteriemia, 3 casos (3%); número de pacientes con bacteriemias, 8; número de bacteriemias/catéter/1.000 días, 0,11; mortalidad infecciosa/bacteriemia, un paciente (1%); retirada del catéter/bacteriemia, 2 casos (2%). Diagnosticado de endocarditis o espondilodiscitis, ningún paciente. La media del nivel valle de gentamicina/paciente durante el estudio es de 0,17 µg/ml (0,05-0,31); la dosis media de sellado de gentamicina intraluminal/rama/paciente es de 3 mg (2-5), equivalente a 1,1-1,7 mg/ml según el volumen de la rama del catéter.* ***Conclusiones:*** *Este estudio prospectivo observacional de 7 años de duración de 101 pacientes en hemodiálisis crónica con catéter venoso central tunelizado objetiva: 1) la profilaxis con sellado intraluminal de gentamicina de las ramas del catéter no causa resistencia bacteriana en gérmenes sensibles a su acción; 2) no se observa ototoxicidad clínica; 3) la profilaxis con dosis bajas de gentamicina administrada comparada con la mayor dosis empleada en otras investigaciones puede influir en que no aparezcan resistencia y ototoxicidad.*

***Palabras clave:*** *Hemodiálisis. Catéter. Bacteriemia. Profilaxis. Gentamicina. Resistencia bacteriana a gentamicina.*

## INTRODUCTION AND OBJECTIVES

A greater rate of mortality has been shown to be associated with patients on chronic haemodialysis (HD) being treated with chronic tunnelled central venous catheters in comparison to other types of vascular accesses.[1-3] Central venous catheter-related bacteraemia (BCVC) has an important influence on bacterial infectious morbidity and mortality.[1-4] In patients on HD with a catheter, BCVC develops from a bacterial biofilm that forms on the internal surface of the catheter branches. It arises from the bacterial flora that naturally occurs on the skin around the catheter exit.[5] Previous studies and recently performed meta-analyses have demonstrated the efficacy of prophylaxis with post-HD intraluminal locking of the catheter branches with antibiotics, especially with cefotaxime and gentamicin (G) in reducing the morbidity and mortality associated with this condition.[6-16]

European guidelines for BCVC prevention, diagnosis, and treatment[17] recommend this prophylaxis, but also highlight the importance of strict universal aseptic protocols when manipulating the catheter. In our unit, G prophylaxis has been administered since July 2003, along with universal asepsis in all procedures involving the catheter.

### Objective

In a 7-year (July 2003-June 2010) prospective, observational study involving 101 HD patients with a catheter, we evaluated whether prophylaxis with post-HD intraluminal G locking of the catheter branches causes bacterial resistance in pathogens that are normally sensitive to this antibiotic, as well as the appearance of clinical ototoxicity.

## MATERIAL AND METHODS

### Patients

In the seven-year period of the study, our unit administered dialysis to 298 patients. One hundred and forty-two of them had arteriovenous fistulas, and 156 chronic tunnelled central venous catheters. We excluded 55 catheterised patients that were in the unit for less than one month (37 were transferred to other institution and 16 died due to high comorbidity), and two because of simultaneous chronic treatment with immunosuppressants and steroids. We followed 101 patients treated with prophylaxis for more than one month. The catheter was implanted in the right internal jugular vein in the vascular radiology unit, except for 4 cases in which the catheter was implanted in the right femoral vein due to exhaustion of venous access sites. HD lasted from 3.5-5 hours, each patient received 3-5 sessions per week, with ultrafiltration control monitor and bicarbonate dialysate. Some patients left the study before it was concluded: 7 for developing a fistula, 10 were transferred to another institution, 3 for receiving kidney transplants and 50 died. At the end of the study we had 31 active patients.

### Universal asepsis

All procedures involving a catheter were performed by nursing staff with the greatest level of asepsis following standard protocols similar to those previously published.[17,18]

### Prophylaxis

Post-HD intraluminal locking with 5mg of G + sodium heparin at 1%/branch/patient. In the total volume present in each branch (e.g., 2ml), one part is the amount of G to be administered from a 20mg G vial, and the other part is the 1% heparin dose, a protocol that the nursing staff carried out aseptically. In order to avoid otic iatrogenic incidents, we designed a control protocol. Trough levels of blood G content were measured weekly (normal value: 0.2-2µg/ml). If this value exceeded 0.3-0.5µg/ml, we reduced the G locking to 3mg/branch/patient; >0.5-2mg/branch.

### BCVC diagnosis

We defined BCVC as clinical improvement following treatment with antibiotics in patients that had a fever, with or without catheter removal, with positive blood cultures from peripheral

blood taken from the HD circuit,[18] excluding other infection sites. According to the NKF 2006 guidelines for vascular access in HD,[19] we also established a possible BCVC diagnosis: clinical improvement in a patient treated with antibiotics with or without catheter removal, with negative blood cultures and excluding other infection sites.

### BCVC treatment

Gram-positive pathogens are normally treated with 1g vancomycin in the first session of HD and with 500mg in consecutive HD sessions for up to 4 weeks (other antibiotic is used if the antibiogram indicates it). For gram-negative bacteria, the antibiotic indicated in the antibiogram is used for 3-4 weeks. Before the blood culture results came back, we treated all patients with vancomycin at the established dosage +G (1mg/kg weight for 3 consecutive HD sessions). Patients diagnosed with BCVC had positive peripheral blood culture results, except for one, whose symptoms disappeared with removal of the catheter.

## Main variables studied

### Ototoxicity

Hypoacusis and/or vertigo.

### Bacterial resistance to G[20]

Pathogens that are normally sensitive to G: gram-positive: *Staphylococcus aureus* and coagulase-negative, methicillin-sensitive *Staphylococcus*. Gram-negative: *Escherichia coli*, *Proteus* spp., *Serratia* spp., *Klebsiella* spp., *Enterobacter* spp., *Providencia* spp., *Shigella* spp., *Salmonella* spp., *Pseudomonas aeruginosa*, etc. The G minimum inhibitory concentration (MIC) for these pathogens is $\leq 4\mu$g/ml, which is the reference value used by the bacteriology department. We detected antibiotic resistance in the blood cultures and antibiograms, where the numerical value of MIC is expressed for each pathogen, along with the label of S (sensitive) or R (resistant).

### Secondary variables

We also measured blood trough levels of G and intraluminal locking dosage in G/patient/branch. These two variables were expressed as the sum of the relevant means for each patient. We also documented patients diagnosed with BCVC, hospitalisation due to BCVC, the number of cases of BCVC and the causal pathogen, the number of BCVC/catheter/1000 days, mortality from BCVC, and catheter removal due to BCVC. We estimated the mean, standard deviation, and range for these variables using SPSS 11.0 software for Windows.

## RESULTS

### Primary variables

We detected no bacterial resistance in the antibiogram for pathogens normally sensitive to G. MIC was $\leq 4\mu$g/ml except for two cases of BCVC caused by methicillin-resistant *S. aureus*. The blood culture was negative in one patient, and BCVC symptoms disappeared in this case when the catheter was removed. Blood cultures taken one week after the antibiotic treatment ended were negative in all patients initially diagnosed with BCVC. No patients had clinically detected ototoxicity. The mean number of months that each patient stayed in the study was 23 (range: 1-84). We treated 29 patients with prophylaxis for >30 months (29% of the total number), and they stayed in the study for a mean of 46 months (range: 31-84).

### Secondary variables

Mean age: 68±22 years (range: 21-85); 48 patients were women (47%); 33 patients were diabetic (33%). The mean trough level of G was 0.17$\mu$g/ml (range: 0.05-0.31), and was obtained by adding all values for each one. The mean intraluminal locking administered in G/branch/patient was 3mg (range: 2-5), which is equivalent to 1.1-1.7mg/ml/branch/patient, depending on the branch volume and the type of catheter used, and it represents the sum of all G locking values for each one. Seven patients were diagnosed with BCVC (7%), and 3 (3%) were hospitalised for BCVC. We observed 0.11 BCVC/catheter/1000 days, one patient died from BCVC (1%), and the catheter was removed due to BCVC in 2 patients (2%).

We did not observe BCVC in the 4 cases treated with femoral catheters. The catheter was removed due to recurrence of BCVC in one case, and due to a negative blood culture in other patient, effectively neutralising the BCVC in this patient. We observed no other BCVC complications (endocarditis, spondylodiscitis, etc.), except for one patient who died from sepsis. We observed 8 cases of BCVC; 5 of them were due to *S. aureus*, one due to *E. coli*, one due to *S. bovis*, and one case with a negative blood culture. During the first year, we diagnosed 2 cases of BCVC, two in the second year, one in the third year, one in the fourth year, one in the fifth year, one in the sixth year, and none in the seventh year.

## DISCUSSION

In previous studies and recent meta-analyses on post-HD, prophylaxis with intraluminal locking of chronic tunnelled central venous catheter branches using antibiotics (among them, G) has been shown to reduce bacterial BCVC-related

morbidity and mortality (BCVC cases/catheter/1000 days, mortality, and hospitalisations due to BCVC),[6-16] compared to patients with intraluminal locking using only heparin. Some meta-analyses have shown that G locking is the best option,[14,15] although doubts remain regarding bacterial resistance in pathogens that are normally sensitive to this antibiotic. When assessing our results, one must keep in mind a study published by Bearthar[18] with regards to health care quality in HD units, based on the number of BCVC/catheter/1000 days that is obtained considering only universal asepsis. It is excellent when this value is ≤1. In our case, universal aseptic procedures in addition to G prophylaxis achieved a value of 0.11 cases of BCVC/catheter/1000 days.

Although we cannot compare them with results from other studies, our rates of mortality, catheter removal, and hospitalisations due to BCVC over the course of the 7 years of the study are all positive results (1%, 2%, and 3%, respectively). They were achieved using G prophylaxis in addition to universal aseptic protocols. Furthermore, the absence of endocarditis, spondylodiscitis, etc. also stands out, with the exception of the patient that passed away due to sepsis. The most frequently observed pathogen was *S. aureus*, which concurs with previously published studies.[17,18] One patient had 2 different cases of BCVC due to a methicillin-resistant strain of *S. aureus*. We must also point out that 29 patients were treated with prophylaxis for more than 30 months (29% of the total), staying in the study for a mean of 46 months (range: 31-84).

Ototoxicity is a pathology that must be evaluated when treating patients with intraluminal G locking.[7,10] We measured this by testing for hypoacusis and/or vertigo. One could argue that audiometric tests would be needed, but the benefit provided by performing regular audiometric tests is questionable. The early detection of otic damage using this technique and consequent suspension of G treatment does not prevent this pathology from progressing, since G remains within the cochlea for several months. Its use is therefore impractical in clinical practice.[21] We observed no clinical ototoxicity in any of our patients and it could be attributed to the protocol we used, which ensures low trough blood levels of G, with a mean value of 0.17μg/ml (range: 0.05-0.31). As a consequence, a low dose of G locking per branch was administered, with a mean of 3mg/branch/patient (range: 2-5), equivalent to 1.1-1.7mg/ml/branch/patient, which is lower than the doses administered in previous studies[7,9,22] (Dogra[7] administered 40mg/ml/branch, McIntyre[9] 5mg/ml/branch, and Landry[22] 4mg/ml/branch). This should influence the level of toxicity due to the possibility of reduced dribbling of the antibiotic into the bloodstream from the catheter branches.

Bacterial resistance to prophylaxis with intraluminal G locking remains a point of debate. Resistance must be defined by the appearance of antibiotic resistance in pathogens that are normally sensitive to its activity. The value of MIC is an important reference value that appears in the antibiogram provided by the bacteriology department, diagnosing the sensitivity or resistance of a bacterium to an antibiotic. In our case, the MIC must be ≤4μg/ml, as referred by the bacteriology department (accompanied by the letter S or R); except for the patient with 2 different cases of BCVC due to methicillin-resistant *S. aureus* and the patient with a negative blood culture. All other cases of BCVC were sensitive to G.

Recently, in a retrospective 4-year study (October 2002 to September 2006), with 1410 patients with catheters in 8 HD different units and prophylaxis with G at a greater dose than used in our study, Landry[22] observed that the rate of BCVC/catheter/1000 days was reduced from 17 to 0.83 during the first year. From the sixth month onwards, 13 cases of BCVC due to G-resistant coagulase-negative *Staphylococcus* were diagnosed. In the following 4 years, 11 cases of BCVC were observed in 10 different patients that had G-resistant strains (7 due to *E. faecalis*), with 4 deaths, 2 cases of sepsis and admission to intensive care units, and 4 cases of endocarditis in which prophylaxis with G was stopped and prophylactic locking of the branches of the CVC with non-antibiotic medication was recommended.

In recent years, the prevalence of patients on HD with a catheter has increased,[23] which results in an increase in the number of cases of BCVC and the complications it causes to patient health in terms of infectious morbidity and mortality and economic costs (mortality, hospitalisation for endocarditis, spondylodiscitis, sepsis, catheter removal, antibiotics, etc.) The appearance of bacterial resistance to prophylaxis with G is a worrying issue when it occurs in dialysis units,[22] but the nephrologist must remember that we still do not have access to efficient non-antibiotic medications or substances that could reduce the rate of BCVC without creating resistance or causing iatrogenic incidents. It is evident that if we can reduce the number of HD patients with catheters, we will improve this issue.

In addition to G, we can lock with other antibiotics, preferably cefotaxime, or use topical prophylaxis with antibiotics such as mupirocin, which have proven effective at reducing BCVC and its complications.[10-16] We must remember the use of strict universal asepsis when using a catheter,[17,18,24] which is an essential accompaniment to prophylaxis for reducing the bacterial infectious morbidity and mortality associated with BCVC. Our experience since July 2003 administering prophylaxis from the moment the patient is admitted to our unit with post-HD intraluminal G locking using lower doses (the dosage that we recommend using) than those used in other units, such as in the Landry study,[22] does not cause bacterial resistance in pathogens that are normally sensitive to its activity. However, we must not forget the use of traditional aseptic protocols.

## CONCLUSIONS

This 7-year observational, prospective study with 101 patients on chronic HD with tunnelled central venous catheters showed that: *1)* prophylaxis with post-HD intraluminal gentamicin locking of catheter branches does not cause bacterial resistance in pathogens that are normally sensitive to this antibiotic; *2)* our treatment does not cause clinical ototoxicity, and *3)* prophylaxis with low doses of gentamicin (when compared to the higher doses cited by other studies) could have caused the absence of bacterial resistance and ototoxicity.

## *IN MEMORIAM*

This research is dedicated to the loving memory of my wife, Pepa Anaya, who was the light of my life for many years. Her light was put out and the happiness was taken from our beloved home. Rest in peace.

Juan Fernández-Gallego

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