CONCENTRATION OF ANTIMICROBIALS IN CATHETER-LOCK SOLUTIONS (CONAN). Protocol CODE: CAS110775

FINAL REPORT

Background. Conservative treatment of port-related bacteremia includes locally administered antimicrobials (*i.e.*, antimicrobial lock therapy). According to current guidelines, antimicrobial lock solutions (ALS) are replaced every day. We conducted a study to determine whether ALS could be replaced in up to 10 days of dwelling.

Methods. Patients with a non-infected, recently implanted port were randomly assigned into one of five groups of ALS with a progressively increasing dwelling time ranging from 1 to 10 days. All lock solutions were composed by heparin and an antimicrobial to achieve a concentration of vancomycin 2 mg/ml, teicoplanin 10 mg/ml, linezolid 1.8 mg/ml, daptomycin 5 mg/ml, and tigecycline 4.5 mg/ml. The primary endpoint was to determine the time when the intraluminal concentration decreased below 1 mg/ml. (ClinicalTrials.gov NCT01592032).

Results. Vancomycin and linezolid experienced a significant reduction of concentration after 3 lock-days. Daptomycin and tigecycline significantly decreased concentration after 7 lock-days but kept above 1 mg/ml. Teicoplanin did not experienced a significant reduction in concentration after 7 lock-days. No serious adverse events related to the drugs were observed in the study.

Conclusions. Antimicrobial lock solutions should be replaced in an individual basis depending on the antimicrobial agent. Vancomycin and linezolid locks should be replaced

every day. Daptomycin, tigecycline, and teicoplanin solutions keep a high antimicrobial concentration and could be used up to 7 days of dwelling.

Keywords. Catheter; Venous access port; Bacteremia; Antimicrobial lock technique; Vancomycin, Tigecycline, Linezolid, Daptomycin, Teicoplanin.

Background.

Totally implantable venous access ports are widely used in cancer patients. Port-related complications include thrombosis and infections [1]. The risk for developing catheter-related bloodstream infections (BSI) is 0.1 per 1,000 port-days [2] and frequent manipulation of the device increases the risk [3].

Almost 10% of all port carriers will develop an infective complication related to the device throughout life [4] leading to removal in 53% of cases [5]. Staphylococci are responsible for nearly 70% of all port-related BSI [6]. Treatment of non-complicated BRC consists of a combination of systemic and local antimicrobial (*i.e.*, antimicrobial lock therapy). The recommended duration of treatment is 10 to 14 days [7].

The antimicrobial lock technique (ALT) consists of the infusion of a highly concentrated antimicrobial solution into the catheter lumen to achieve the eradication of microorganisms [8]. Currently, the Infectious Diseases Society of America (IDSA), recommends that dwelling time of antimicrobial lock solutions (ALS) should not exceed 24 hours, except for hemodialysis catheters [7]. However, there is a lack of evidence to establish the optimal replacement time. Less frequent replacement of lock solutions will reduce the manipulation of the ports to one or two times during the treatment of port-related bacteremia, reducing the costs and morbidity associated with clinical care and without losing efficacy.

Based on successful clinical reports and in our own clinical experience [9–11], we designed a clinical trial to analyze the optimal replacement time for five ALS (*i.e.*, vancomycin, teicoplanin, linezolid, daptomycin, and tigecycline) instilled intraluminally into uninfected ports indwelled.

Methods

Setting and study population. The clinical trial was conducted at the University hospital Clínica Universidad de Navarra in Pamplona, Spain, from May 2012 to January 2015. End of the trial on January 28, 2015. All patients with a port implanted in our hospital were eligible for participation beginning with those with the port recently implanted. Exclusion criteria included patients with clinical or microbiologic evidence of infection with or without concomitant systemic antimicrobial therapy, a known allergy to heparin or any of the antimicrobials used in the study, systemic anticoagulant treatment, pregnancy and inability to sign the written consent. The study was approved by the local IRB (79/2010) and the Spanish Agency of Medicines and Medical Devices (EudraCT 2010-023814-29). All participants signed the informed consent. The study was registered at ClinicalTrials.gov (NCT01592032).

Main trial design. Patients were randomized in a single-blind fashion to receive one of five ALS. Lock solutions were composed of 100 IU/ml of 1% sodium heparin plus an antimicrobial to achieve a final volume of 10 ml with a concentration of vancomycin 2 mg/ml, teicoplanin 10 mg/ml, linezolid 1.8 mg/ml, daptomycin 5 mg/ml, and tigecycline 4.5 mg/ml. The concentrations of antimicrobials were the highest possible to achieve according

to the literature [12–14] and our own clinical experience [15,9,10]. All antimicrobials were reconstituted with normal saline except linezolid, which does not require reconstitution, and daptomycin, which was reconstituted with Ringer's lactate.

Randomization process was performed by a computer-generated randomized list. The research team was blind to the antimicrobial assignation. All patients were allowed to participate only once during the study.

Lock solutions were allocated increasing progressively the dwelling time, starting with 1 day, followed by 3, 5, 7 and 10 days, respectively. Each antimicrobial group was to complete 5 patients within the days of dwelling.

Before the administration of the ALS, a 10 ml blood sample was drawn to assess port sterility. After flushing with 10 ml of 0.9% sodium chloride, a volume of 5 ml of an ALS was instilled through each port. Once the ports were locked, manipulation of the devices was not allowed during the corresponding days of dwelling. After completion of dwelling time we assessed the antibiotic concentration in the first 2 ml recovered from the ports by using high-performance liquid chromatography (HPLC) (Agilent Technologies, Inc. Santa Clara, CA, USA). Additionally, we determined the concentration of urea in the samples recovered from the ports (Synchron® Clinical Systems, Beckman Coulter, Inc., Brea, CA, USA). Using the ratio of systemic urea and urea in the sample recovered from the port, we corrected the concentration of all the antimicrobials by their individual factor of dilution with blood [16]. A median antimicrobial concentration greater than 1 mg/ml in each group of ALS allowed a new process of randomization of 5 patients into the ALS groups to be dwelled for 3 days. The same methodology was used to form the groups of patients to be dwelled for 5, 7 and 10 days. The primary endpoint of the study was to assess the time required to reduce the

concentration of the antimicrobials dwelled into the ports below 1 mg/ml. A group median concentration below 1 mg/ml stopped the randomization into that ALS group.

Statistical analysis. The Kruskal-Wallis test was used to compare the antimicrobial concentrations among the groups. The Wilcoxon test was used to compare the antimicrobial concentrations at the end of dwelling time with the concentrations administered. Statistical significance was established at an alpha value of .05. All *P* values were two-tailed. The statistical analyses were performed using SPSS version 15.0.1 software (SPSS Inc., Chicago, IL, USA).

Results

Over a study period of 32 months, a total of 484 consecutive patients were assessed for eligibility (Figure 1). By the end of the study, a total of ninety-three patients have been randomized to the ALS groups as follows: eleven patients to receive vancomycin, twenty-four patients to teicoplanin, ten patients to linezolid, twenty-six patients to daptomycin, and twenty-two patients to receive tigecycline (figure 1).

There were no significant differences in the groups of patients regarding to sex, age, and underlying type of malignancy. The mean time of catheter placement before patient inclusion in the study was comparable among the groups. No port-related infections developed in the patients that received any of the lock solutions in the study. There were no serious adverse events related to the drugs used in the study.

After 1 day of dwelling, all ALS groups showed an antimicrobial concentration above 1 mg/ml. After 3 days, the group median concentrations of vancomycin and linezolid were below 1 mg/ml. Consequently, randomization of patients to both antimicrobial groups finished. The reduction in vancomycin and linezolid concentration was statistically significant (P = .043) compared to the concentration instilled. The remaining ALS groups continued receiving patients for 5, 7, and 10 days of port-lock. After 5 and 7 days, the median concentration of teicoplanin was above 1 mg/ml with no statistically significant change compared with the instilled concentration (P = .893). Daptomycin and tigecycline demonstrated a statistically significant decrease in their concentrations after 7 days of dwelling (P = .043). However, they remained above 1 mg/ml. Finally, due to the lack of patients for enrollment into the 10 days group, the study finished without completion of 10 days of dwelling time.

No serious adverse events related to the drugs were observed in the study.

In conclusion, according to our results, we propose extending the dwelling time of ports from a daily-based replacement to every 7 days when teicoplanin, daptomycin and tigecycline would be used as local treatment for port-related BSI due to CoNS. Vancomycin and linezolid replacement should be kept every 24 hours.

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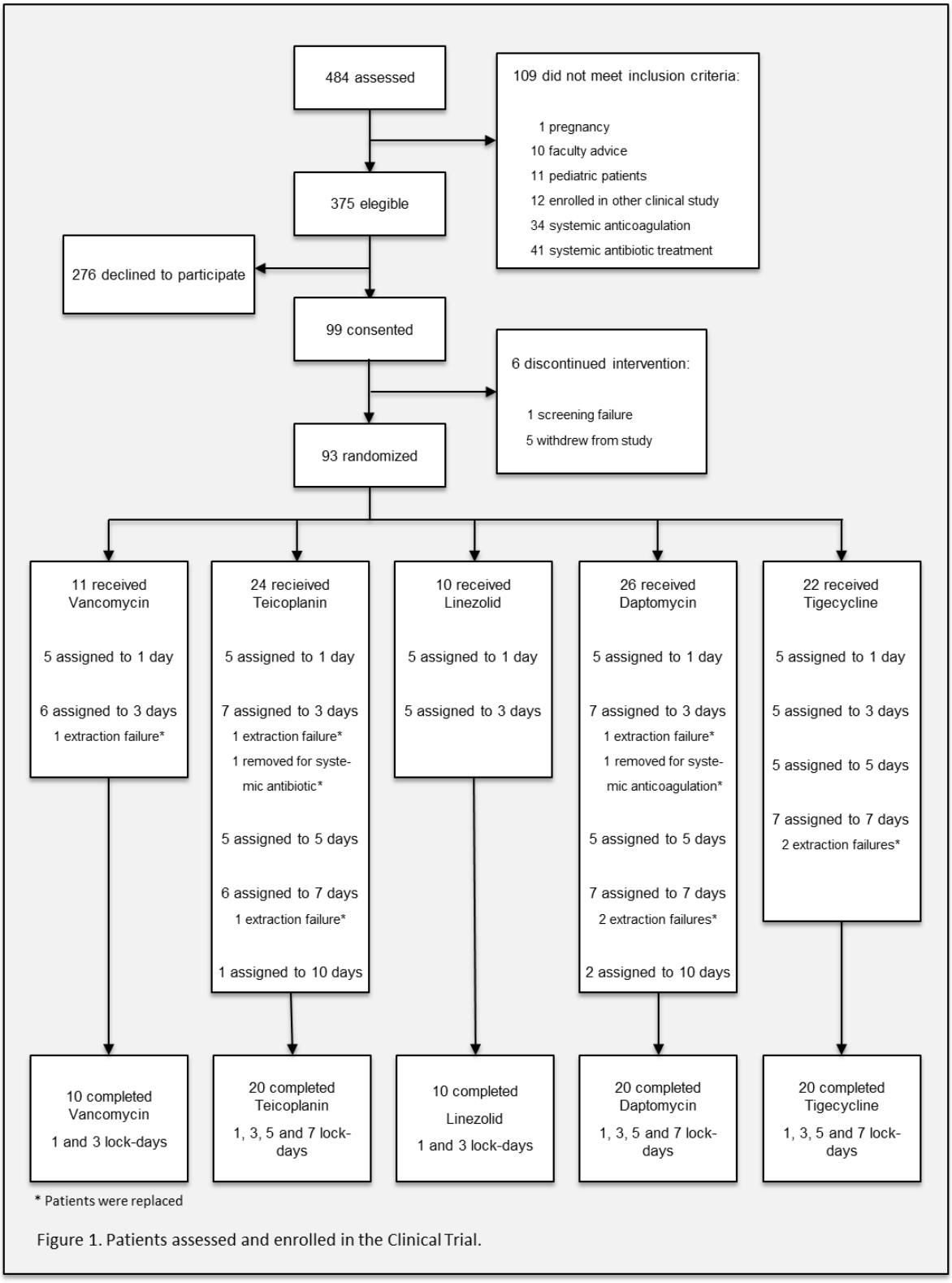

Figure 1. Patients assessed and enrolled in the Clinical Trial.