RESEARCH PROJECT PLAN

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TITLE
WATER AND LEMON JUICE FOR THE PREVENTION OF CATHETER ENCRUSTATION

INTRODUCTION
A frequent complication in patients care with long-term indwelling bladder catheter is encrustation of the catheter that can lead to its obstruction by creating emergency conditions as urinary retention or incontinence (Williams & Stickler, 2008; Broomfield et al., 2009; Khan et al., 2010; Stickler & Feneley, 2010). The problem is caused by urease producing bacteria, particularly Proteus mirabilis, that colonize the catheter transforming the bacterial urease to ammonia from urea, increasing the pH of urine and forming extensive biofilm communities (Williams & Stickler, 2008; Broomfield et al., 2009; Khan et al., 2010). The pH level at which this process occurs is called nucleation pH (pH_n) (Choong et al., 2001; Broomfield et al., 2009; Khan et al., 2010). In patients who develop infections by urease producing bacteria, the voided urine pH (pH_v) may increase above pH_n levels and crystallization can occur in urine and biofilm production: in fact, the average value of pH_n in patients with catheter obstruction is 7.58 and the urine voided pH_v is 7.85 (Choong et al., 2001; Khan et al., 2010). The pH_n varied among individuals and among weeks in any single individual (Khan et al., 2010). The higher the value of urinary pH_n and the greater the safety margin between pH_n and pH_v, the longer it took catheter takes to become clogged. If pH_n value can be modified to increase the safety margin (i.e. the difference between pH_n and pH_v), there is a possible alternative solution to the inhibition of the activity of urease producing bacteria to prevent and control the development of catheter encrustation (Khan et al., 2010). Many studies have shown that with the increasing of fluid intake and citrate, also pH_n values increase to values that are not achieved even in the urine infected by bacteria such as Proteus mirabilis. This research project, based on the study of Khan et al. (2010), would be replicated in the Italian context, with a specific focus on the use of lemon juice to prevent indwelling bladder catheter encrustation and increasing the sample size.

SUMMARY
Long-term catheterization is rarely completely free of complications. Encrustation, leading to catheter blockage, is a common problem for 40-50% for patients with long-term catheters (Evans & Godfrey, 2000; Getliffe, 1994; Getliffe, 2002; Getliffe, 2003; Rew & Woodward, 2001). Studies have shown that over 70% of blocked catheters are encrusted (Getliffe, 2002; Sabbuba & Stickler, 2004; Pomfret et al, 2004).Recurrent catheter blockage is distressing to patients and caregivers, and costly to health services in terms of time and resources. However, although all catheters are susceptible to this problem, there are no effective procedures for preventing it (Morris et al., 1997). The evidence base for prevention is weak with some series suggesting that potassium citrate supplementation, increased fluid intake and lemon juice supplements all reduce the incidence and severity of catheter encrustation (Evans & Godfrey, 2000; Khan et al.,

2010). The aim of this cross-over study is to investigate that increasing fluid intake with lemon juice increases the value of pH_n and the margin safety (pH_n - pH_v) in patients with long-term indwelling catheter and Proteus mirabilis positive urinary culture. This project will be based on the study of Khan et al (2010).

OBJECTIVES

The overall goal will be to analyse the connection between fluid intake and rate of catheter change due to encrustation in patients with a long-term indwelling catheter positive to Proteus Mirabilis urinary culture.

Specific objectives will be to:

- determine the rate of catheter change due to encrustation in patients with a long-term indwelling catheter positive to Proteus mirabilis urinary culture;
- determine whether increasing the fluid intake with water and lemon juice would increase pHn and the safety margin between pHn and pHv in patients with positive Proteus mirabilis urinary culture who had recurrent catheter blockage.

Encrustation is a result of bacteria in the urine, most commonly Proteus mirabilis, that produce an enzyme called urease, which splits urinary urea into ammonia and carbon dioxide. This results in an increase of alkalinity, providing ideal conditions for the development of crystals, e.g. struvite (magnesium ammonium phosphate) and calcium phosphate. The crystal develop around the eyelets, balloon and internal lumen of the catheter (Hagen et al., 2010).

Hypothesis:

- Fluid intake of 1000 ml water with lemon juice 60 ml reduce the frequency of catheter change due to encrustation in patients with a positive Proteus mirabilis urinary culture compared to fluid intake of 1000 ml.
- Fluid intake of 1000 ml water with lemon juice 60 ml increase pHn and the safety margin between pHn and pHv in patients with a positive Proteus mirabilis urinary culture compared to fluid intake of 1000 ml.

SHORT LITERATURE REVIEW

The main indications for the positioning of a long-term indwelling bladder catheter are urinary incontinence and bladder retention chronic obstruction (Longhi, 2009; Williams & Stickler, 2008). Within these situations it is difficult to calculate a number of patients with different diseases (mainly neurological and urological) living at home or in long-term care facilities and that, independently or with the help of caregivers, must manage the catheter daily. It's not possible to accurately determine the number of patients with indwelling bladder catheter and although epidemiological data are not precise, we know from clinical practice that the problem has a certain frequency but also has a strong impact on patients quality of life. Patients with bladder catheter represent a population at risk for developing urinary tract infections (UTI) (Longhi, 2009; Fauci et al., 2009). The lenght of catheterization is the most important risk factor for bacteriuria: for each day of catheter permanence there is an increased risk from 3 to 7%, the causative agents are generally microorganisms such as Escherichia coli, Proteus, Klebsiella, Pseudomonas, Serratia, Staphylococcus, Enterococcus, Candida (Longhi, 2009). The complications of bacteriuria associated with long-term catheterization are divided into two categories represented by the symptomatic UTI, which are also observed in short-term catheterization, with fever, bacteremia and pyelonephritis (1-2% of cases), and by the UTI closely related to long-term catheterization, characterized by obstruction, urinary tract stones, periurinary local infections, chronic pyelonephritis (Longhi, 2009). A contributory cause of UTI complications related to catheterization is the presence of encrustations resulting in a catheter obstruction (Stickler & Feneley, 2010). The crystal deposits obstruct the catheter lumen causing retention or incontinence. More than 50% of patients with indwelling catheter had episodes of

encrustations and catheter obstruction (Stickler & Feneley, 2010). The problem of catheter encrustation mainly starts from infections caused by urease producing bacteria, in particular from Proteus mirabilis, that colonize catheters forming large biofilms (Williams & Stickler, 2008; Broomfield et al., 2009). Bacteriological tests confirm that Proteus mirabilis is the microorganism most frequently responsible for encrustation: the synthesis of urease by the bacteria splits urea into ammonia which then becomes ammonium, this process elevate the pH of urine for increase of ammonium salts, increase of biofilm and concentrations increase of magnesium, ammonium and carbonates that induce the formation of calcium and magnesium phosphate crystals. The continued development of these crystals obstructs the bladder catheter (Broomfield et al., 2009). The precipitation can take place simultaneously or after the microbial biofilm formation on the surfaces of catheter. The main steps of the encrustation process are: UTI with Proteus mirabilis or other urease-positive species, formation of a organic material film on the catheter surface, adhesion of urease-positive bacteria to the catheter, development of biofilms, elevation of the pH of urine and of the biofilm matrix, attraction of calcium and magnesium ions within the matrix, crystallization of calcium and magnesium ammonium phosphates induced from the alkaline environment (Broomfield et al., 2009). The continued development of biofilms blocks the catheter and slows up to block the flow of urine. In some patients the urine come out between the catheter and urethra creating incontinence, in others gives rise to urine retention that causes bladder distension, ureteral reflux up to cause pyelonephritis, sepsis and septic shock, but also more simply lesions of the bladder and urethral mucosa during catheter replacement. All types of urinary catheters are susceptible to this type of problem (Getliffe, 1994; Getliffe, 2002). The main strategies currently studied to reduce the biofilms composition and the onset of encrustations are dilute the urine by the fluid intake increasing and the increase of concentration of citrates, in example drinking lemon juice (Broomfield et al., 2009). The intake of lemon juice alkalizes the urine, the water dilutes the urine and this causes an elevation of the pH_n to values > 8.0 that exceeds the level of pH in which occurs the encrustation and the infection by Proteus mirabilis, determining its inhibition (Khan et al., 2010; Broomfield et al., 2009; Stickler & Feneley, 2010).

RELEVANCE TO UROLOGY NURSING

Patient with long-term indwelling catheter have several common complications.This intervention can prevent encrustation of catheter and, in that way, improve health-related quality of life and reduce healthcare costs. Next step will be that these ways of acting become part of the standard care training of nurses. The aim of this project is to contribute to the development of knowledge in this area, as well as to improve patient care.

METHODOLOGY

TYPE OF STUDY DESIGN

The study will be a Cross-over Trial (optional: multi-centre).
The research project is based on the study of Khan et al (2010), the authors will be contacted.
The risk of this design of study is carry over but we adopt a period of washout in relation to results of the study by Khan et al (2010). The design of the project has been chosen with the aim to investigate the connection with introducing water and lemon juice and encrustation of catheter in patient with a positive Proteus mirabilis urinary culture.

STUDY PROCEDURES

The study will be perform in the Ospedale San Raffaele srl Milan and will be approved by the local ethical committee. All patients have a long-term indwelling catheter with a positive Proteus mirabilis urinary culture will be asked to participate in this study.

- In control week baseline data will be collected on routine fluid intake in each patients.

- Patients will be randomly assigned to a sequence of two treatments, allowing a two weeks washout period at the routine fluid intake between each treatment:
  - In study arm A patients will be maintained on 1 l water in addition to the routine intake.
  - In study arm B patients will be started on 1 l water with 60 ml concentrated lemon juice in addition to the routine intake.
  - During the washout patients will be returned to the baseline fluid intake.

<table>
<tr><td>Week 1</td><td></td><td>Week 2</td><td>Week 3</td><td>Week 4</td><td>Week 5</td></tr>
<tr><td rowspan="2">CONTROL</td><td rowspan="2">Intervent randomisation</td><td>A</td><td colspan="2" rowspan="2">WASHOUT</td><td>B</td></tr>
<tr><td>B</td><td>A</td></tr>
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To assess compliance patients, fluid intake and urine output will be provide a charts to document information (24-hours fluid intake and the 24-hours urine volume will be registered every day in the scheme by the patient). Participants will be asked to collect a 24-hour urine sample on day 7 each week for sample analysis. The frequency of catheter change will be registered retrospectively. Quantitative data from the two groups will be compared. Descriptive data will be show as the mean ± SD or as the point estimate and 95% CI.

FOLLOW UP

Each patient will be observed for five weeks: all measurement (except demographics) will be done at baseline and at the end of each week. At the end of each week participants proceeded to twenty-four hour urine collection and to a compilation of the chart. The frequency of catheter change will be registered retrospectively.

SAMPLE SIZE

Simple size will be calculated in relation to the power of the study.
To give more expressive power to this study and make it more comparable could be enlarge it to multicentre. A multi centre setting will also reduce the total duration of the study.

ETHICS

The study be reported to the local ethics committee for approval and the patient will be asked to give informed consent. In case any of them regret their participation, they can decide to leave the study immediately.

STUDY POPULATION

The target population consists of all patients have a long-term indwelling catheter for greater than 3 months (urethral or sovrapubic and hydrogel coated or silicone) with positive urine cultures for Proteus mirabilis and were known to have had greater than 3 episodes of catheter blockage less than 4 weeks in duration each.

INCLUSION CRITERIA

- Patients with a long-term indwelling catheter for greater than 3 months (urethral or sovrapubic and hydrogel coated or silicone) and were known to have had greater than 3 episodes of catheter blockage less than 4 weeks in duration each.
- Positive Proteus Mirabilis urinary culture.
- Patients 18 years and older, who understand Italian language.

EXCLUSION CRITERIA

- Patients younger than 18 years.
- Patients having an urinary tract infection at baseline or less than three month ago.
- Patients needing antibiotics.
- Patients could not tolerate lemon juice.
- Patients with dysphagia.

OUTCOME MEASURES

The primary outcome is to determine whether increasing the fluid intake with water and lemon juice would increase pHn and the safety margin between pHn and pHv in patients with positive Proteus mirabilis urinary culture who had recurrent catheter blockage.

The secondary outcomes are:

- rate of catheter change due to encrustation in patients with a long-term indwelling catheter positive to Proteus mirabilis urinary culture
- daily fluid intake, daily urine output
- nucleation pH, voiding pH, safety margin (pH_n - pH_v), Ca^{++}, Mg^{++}, urinary citrate
- compliance patients

Samples analysis: urine samples will be analyzed for pH_n, pH_v, citrate, calcium and magnesium. The pH_v of urine in each patient will be measured upon sample collection using a glass electrode pH meter. Evaluation of pH_n will be based on the method described by Choong et al. (1999) in Khan et al. (2010). Urinary pH will be decreased to 5.0 by adding concentrated chloridric acid (HCl). The sample will be alkalinized in increments of 0.25 pH, at each increment it will be measured density defining the pH_n value shown on a graph also by an abrupt change in the gradient that reflects the increase in turbidity caused by the precipitation of calcium and magnesium containing salts. Citrate will be measured using a citrate assay kit (Khan et al., 2010).

STATISTICAL ANALYSIS

Data will be evaluated using computer software Statistical Package for the Social Science (SPSS).

For each urine sample pH_n minus pH_v will be calculated and termed the safety margin. A significant level of $p<0.05$ is chosen and descriptive data will be show as the mean ± standard deviation (SD) or as the point estimate and confidence interval (CI) at 95% (95% CI). The Intraclass Correlation Coefficient (ICC) will be derived for pH_n, pH_v and the safety margin to assess the steadiness of within individual measurements across the baseline and the washout periods. Most data analysis will be based on analysis of variance (ANOVA) and when specific coefficients are of particular interest, point estimates and the CI will be calculated. When the outcome of interest will not follow a well shaped normal distribution, ANOVA results are provided for reference only. The significance test of a whole variable will be preferred with respect to specific coefficient estimates. Considering the crossover design of this study the safety margin (pH_n - pH_v) will be also analyzed to test for sequence, period, treatment and carryover effects using Stata version 10.1 (Khan et al., 2010).

FEASIBILITY

TIMETABLE

November 2012–February 2013: Develop project plan for the EAUN Annual Meeting in Milan 2013 and Project plan to ethic committee
March 2013-September 2013: Inclusion of patients and create database
September-November 2013 and further: Statistics & analysis, interpretation
March 2014: Presentation of results at EAUN

BUDGET

The study should be carried out within one year.
500 EURO Information to participants, statistical costs, presentation of data, writing article
2000 EURO Cups for measuring urine, urine cultures, information material

CONCLUSION/RELEVANCE
A better knowledge of the mechanisms of catheter encrustation is the strategy to prevent important complication. It is important that we obtain more evidence in which factors are crucial to prevent catheter encrustation. In this study, we will try to find answer to these questions.

STATE ANY POSSIBLE CONFLICTS OF INTEREST
None.

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