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Disinfection by Sodium Hypochlorite: Dialysis Applications

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Claudio Ronco *Vicenza*

Disinfection by Sodium Hypochlorite: Dialysis Applications

Volume Editors

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Gary J. Mishkin *Gaithersburg, Md.*

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(Founded 1975 by Geoffrey M. Berlyne)

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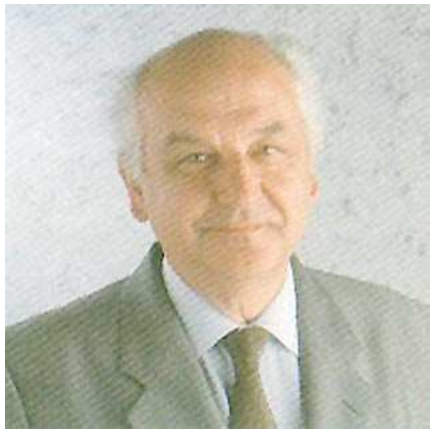
Dedication



Amuchina's history has been part of my family for over 50 years. My grandfather Pietro bought Amuchina Company from Eridania, a large Italian sugar company, in 1948.

My grandfather Pietro and my father Giorgio spent all their work and energy to improve and promote the use of Amuchina as an antiseptic and a disinfectant. Since then our mission has been the prevention of infections. After so many years of activity, we can surely say their goals were achieved.

They were always convinced of the importance of the scientific research. During their tenure, more than 400 studies have been performed and collected. In the early years, the attention was reserved principally to the treatment of wounds and burns. Later, starting in the 70s, my father was pivotal in addressing Amuchina's attention to the developing world of dialysis.

The Amuchina Study and Research Center is dedicated to Pietro. This book represents a tribute to my father Giorgio's untiring work and dedication.

Gratefully, *Disinfection by Sodium Hypochlorite: Dialysis Applications* is dedicated to his memory.

Ludovico Giavotto
Alcavis International, Inc.

Contents

Preface

Sodium hypochlorite has long been recognized for its effectiveness as an antiseptic and disinfectant. In his historic pioneering work, in which he proved in a convincing clinical trial the importance of hand disinfection, Semmelweis used sodium hypochlorite as a hand wash and disinfectant to reduce mortality from childbed fever [1]. In another historic discovery, Carrel and Dakin introduced 0.45–0.5% buffered sodium hypochlorite for the treatment of trauma wounds during the First World War [2, 3]. This solution, known as Dakin's solution revolutionized the treatment of trauma wounds and was used during and after the war. The effectiveness of sodium hypochlorite solution as an antimicrobial is unquestioned; however, its practical use in medicine had been limited due to its reduced stability. However, the method of manufacture makes the medical use of sodium hypochlorite a viable option.

Electrolytically produced sodium hypochlorite solutions, e.g. ExSept (Amuchina), differ from other commercially produced sodium hypochlorites by their method of manufacture. The electrolytic process yields a sodium hypochlorite solution that is stable at a lower pH eliminating the need to add large quantities of stabilizers, as with other sodium hypochlorites, that are both detrimental to wound healing and reduce the antimicrobial activity of the solution. The result is a highly effective antimicrobial with very good biocompatibility.

The ExSept solutions discussed herein have also been reviewed by numerous health agencies as both medical devices and medical drugs. These review agencies include, but are not limited to, the Canadian Health Ministry, Mexican Health Ministry, Italian Ministry of Health, French Ministry of Health, Swiss Ministry of Health and the US Food and Drug Administration.

This book provides the clinician with a sound understanding of how electrolytically produced sodium hypochlorite solutions differ from commercial sodium hypochlorite solutions, and presents different uses of this solution as both an antiseptic and disinfectant and to alleviate some of the stereotypes associated with the medical use of sodium hypochlorite solutions. A work from an International Faculty, presenting many different experiences with ExSept/Amuchina solutions specifically in the arena of dialysis, is included in this book. The studies present both in vitro controlled laboratory evaluations and clinical in vivo, prospective, randomized trials.

The beneficial penetration of the use of electrolytically produced sodium hypochlorite solutions in dialysis has made excellent progress; however, further advances are expected as the efficacy and safety of the product becomes more widely understood.

Claudio Ronco
Gary Mishkin

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Antisepsis

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Abstract

All dialysis treatments include a certain risk of infection because of the decreased immune defenses of the patients and because of dialytic techniques that increase the potential of microbial contamination. Peritoneal dialysis, and in particular continuous ambulatory peritoneal dialysis (CAPD), has a higher risk of infections of the peritoneum, but even of the subcutaneous tunnel. These infections are caused by environmental microorganisms principally gram-positives (*Staphylococcus epidermidis* and *Staphylococcus aureus*). We tested three active ingredients, electrolytic chloroxidizer, iodine and chlorhexidine gluconate. It is evident that because of the large spectrum of activity, the good effectiveness even at the lowest concentration, coupled with good tolerability (and to the fact of not causing allergic reactions) the electrolytic chloroxidizer appears to be an ideal antiseptic in CAPD.

All dialysis treatments include a certain risk of infection because of the decreased immune defenses of the patients and because of dialytic techniques that increase the potential of microbial contamination.

Peritoneal dialysis, and in particular continuous ambulatory peritoneal dialysis (CAPD), has a higher risk of infections of the peritoneum, but even of the subcutaneous tunnel. These infections are caused by environmental microorganisms, principally gram-positives (*Staphylococcus epidermidis* and *Staphylococcus aureus*).

Contamination of the infection sites (tunnel and peritoneal cavity) is favored by the interruption of the abdominal wall continuity, by the presence of the catheter, and by the introduction of the dialysate. The following possible affection is clearly favored by the patient conditions (uremia, malnutrition, etc.), but also:

- in case of the tunnel infection, by the continuous presence of the catheter, and
- in the case of peritonitis, by the large number of catheter-solution bag connection operations (opening and closing).

In order to reduce these complications that could require clinical intervention and could significantly limit the patient survival and the technique success, the prevention of the contamination and the destruction of the microorganisms, before entering the peritoneal cavity, are crucial.

In hemodialysis the microbial contamination can directly involve the patient (access site infections) and the extracorporeal circuit. There is the possibility to transmit even viruses to the patient or, more frequently, endotoxins through the dialysis membranes.

Many systems have been proposed to achieve the destruction of the microbial contaminants: (1) physical such as heat, UV radiation, etc., and (2) chemical. For use in PD antiseptics are favored, and not disinfectants, because disinfectants can be used on inanimate objects only and not on living tissues or with uses that could even indirectly put them in contact with living tissue.

In any case, the physical agents did not achieve a good success because of difficult practical use, more expensive or not effective. Better interest has been reserved to chemicals.

Peritoneal Dialysis

Therefore, it is easily understandable why the problem of prevention and therapy of infectious complications in patients on CAPD has attracted a lot of interest, due to the high, direct risk of infections intrinsic in this treatment.

As far as the prevention of peritonitis is concerned, consideration has been reserved to chemical agents (antisepsis). Their use has been proposed and in some extent applied in order to try to kill the micro-organisms possibly contaminating the distal end of the dialysate-bag and the external end of the peritoneal catheter, during their connection at the beginning of the exchange and during their de-connection at the end of the same. During the first years of clinical experience with CAPD, iodine tincture or chlorhexidine were sprayed at the connection sites, but with scarce efficacy and some serious untoward effects; this happened particularly for chlorhexidine, which, suspected to be responsible for a certain number of cases of encapsulating/sclerosing peritonitis, was soon completely abandoned. However, it was only with the introduction of the 'Y' set connection in the CAPD clinical practice that the use of disinfectant directly into the lines (in sufficient quantity and for time long enough to protect, above all, the external end of the catheter during the most dangerous phase of the rest between the exchanges) became somewhat popular. This was made possible

thanks to the third lateral way of the 'Y' set, through which the disinfectant could be washed to the outside with a double flush (with the fresh dialysate from the new bag and with the spent dialysate from the abdominal cavity). The disinfectant which resulted as the most suitable for this use, due to the best combination of antimicrobial efficacy and low general and local toxicity, was a chloroxidizer which not only exhibited a toxicity significantly lower than the povidone-iodine, but also with respect to other chloroxidizers, thanks to a particular production system. Our initial choice focused, ever since the late 70s, on this disinfectant because of its reported histophilic properties. Already in 1980, we published the results of our first 'in vitro' studies [1–2], which confirmed both the high antimicrobial activity and the very good tolerance. Tolerance which was confirmed clearly superior to that of the other disinfectants, as largely confirmed by other subsequent studies [3–9]. Also the high biocidal efficacy was further confirmed by us in another study [10], where we compared the action of three disinfectants (the chloroxidizer, the iodine-tincture and the chlorhexidine) against three polyresistant hospital bacterial strains (*Pseudomonas aeruginosa, Proteus mirabilis* and *Staphylococcus aureus*). The worst results were obtained with chlorhexidine, which showed, after the 5 min of contact, minimal bactericidal concentration (MBC) higher than the highest concentrations recommended by the manufacturer (but for the antisepsis of the hands). Moreover, other weak points of chlorhexidine, which caused its rapid removal from the clinical use, were its instability (we found that chlorhexidine gluconate precipitated after being transformed into chlorhexidine hydrochloride after exposure to Na^+ and Cl^- ions), and its elevated local toxicity [11]. In contrast, the other two disinfectants resulted as highly efficient, also at very low concentrations. In addition that these, contrary to the chlorhexidine, which is only bactericidal, have a wider and practically complete antimicrobial spectrum (both are also sporicidal and virucidal, and the chloroxidizer is also active against protozoa, inactivates endotoxins and pyrogens, and prevents the formation of biofilm). For both these disinfectants, due to their oxidizing nature, we found that the bactericidal activity diminished significantly after contact with broth and even more with broth plus blood (which contain reducing factors, like proteins, amino acids, glucose), but also that the residual activity was still highly effective.

As far as the therapy is concerned, the treatment of abscessed or infected cavities of the abdomen has been reserved to surgical drainage efficiency [12, 13] and to the efficacy of general antibiotic therapy [14, 15]. Cavity washing/irrigation techniques, using antiseptic solutions [16] or antibiotic solutions [17, 18] have been used less frequently. However, these techniques represent a rational and easy alternative, aimed to mechanically remove necrotic tissues, pus, coagulation/blood products, toxins coming from bacterial dissolution and,

in the meantime, to destroy the micro-organisms supporting the infection itself. We too, since the early 80s, starting from these considerations and from our initial encouraging results, continued to focus the problem of peritonitis in CAPD patients. After positive experiences on animals [19], we performed peritoneal washes with antiseptics to treat peritonitis in patients on CAPD [20]. This approach has been experienced with positive results also by other authors [3, 4]. For this use the antiseptic chosen was again the electrolytic chloroxidizer, because of its higher biocidal activity and of its lower toxicity also with respect to other chlorine-derivate products. In fact it contains higher concentrations of undissociated hypochlorous acid (the most powerful microbiocidal agent within this group) thanks to the lower pH deriving from a lower concentration of free sodium hydroxide. This last characteristic accounts in turn for the lower histological toxicity, when compared with other chlorine derivatives and with iodine products. Particularly this last, as evidenced by experiments on rats [7], when introduced into the peritoneal cavity can cause heavy lesions, up to the induction of a sclerosing/encapsulating peritonitis. Furthermore, as all hypochlorites, the electrolytic chloroxidizer solutions have the capability to reduce dense biological liquids, necrotic tissues and pus [21], which can facilitate the mechanical cleaning of abscessed cavities without damaging healthy tissues. In this sense, the large and prolonged experience use of the electrolytic chloroxidizer in the therapy of large burns [22, 23] is really important. It is evident that because of the large spectrum of activity, the good effectiveness even at the lowest concentrations, coupled with the good tolerability (and to the fact of not causing allergic reactions), the electrolytic chloroxidizer appears to be an ideal antiseptic for the many infectious problems of CAPD patients.

Extra-Corporeal Dialysis

Other than Peritoneal Dialysis, electrolytic chloroxidizer is used as well in extra-corporeal dialysis. Because of the fact that the dialytic circuit is considered an extension of the blood circuit of the patient, it is imperative to adopt universal precautions in order to avoid potential transmission of infections.

In chemical disinfection, the requirements for dialysis monitors disinfections are:

- activity versus bacteria, viruses, fungus and protozoa;
- capability to reduce pyrogens;
- capability to dissolve potential hematic residues;
- capability to stop biofilm formation;
- non-toxic or damaging for the patient and the operator;
- being easily removable;

- being easily recognizable for positive presence or for residual presence before any single use of the dialysis monitor;
- being cost-effective and ready to use.

It seems to us that the electrolytic chloroxidizer, better that any other agent, positively answer to these requirements (in particular if used after a descaling agent such as citric acid, oxalic acid or acetic acid). Furthermore, the other advantages described earlier are not satisfied by other industrial hypochlorites. In fact, because of the 1998 European new regulations concerning all medical devices, a disinfectant for dialysis apparatus must be 'CE marked'. All other industrial types of industrial formulation must be considered 'non-acceptable' (industrial bleach with non-specific claim on the label).

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Sodium Hypochlorite: History, Properties, Electrochemical Production

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Abstract

This paper analyses the evolution of hypochlorite as strong disinfectant. The electrochemical production of hypochloric acid or sodium hypochlorite represents the best method to obtain a pure product. To have a good production (as quality and quantity), it is necessary to optimize the electrochemical process with the optimal of electrocatalytic electrodes (cathode and anode) the gap between electrodes, the temperature of electrochemical cell. It is very important for the product stability during a long peirod, avoid the presence of heavy metal ions and particulate as impurity-like carbon micro-powders in suspension. It is necessary a rigorous control of the pH of final product to have the optimal disinfection power of hypochlorite solution. The most stable sodium hypochlorite solutions are those that show the following characteristics: (1) low concentration of hypochlorite; (2) pH $>$ 11.5 and $<$13; (3) absence of graphite particulate and metallic ions; (4) storage at controlled temperature $<$30ºC. Packing in containers impermeable to light.

Alcavis 100 or Amuchina for more than half a century has represented a product synonymous with disinfection; basically, it is a solution of sodium hypochlorite (NaOCl) and sodium chloride (NaCl) with a pH of about 10.

This product is produced in extremely pure and stable form in undivided electrolytic cells, and shows high disinfectant characteristics and stability over time.

Alcavis 100, Amuchina is based on NaOCl, whose history begins over two centuries ago…

The History of Hypochlorite

Some years after the discovery in 1774 of the gas called 'dephlogisticated salt spirit' by the Swedish chemist Carl Wilhelm Scheele, another chemist, the

Frenchman Claude-Louis Bertholet obtained in 1787 some bleaching solutions of this gas dissolved in water. In 1810 this gas was renamed 'Chlorine' by the Englishman Davy.

A small chemical industry in Paris directed by Leonard Alban, the 'Societé Javel', adopted the Bertholet process for the industrial production of a bleaching solution produced by dissolving gaseous chlorine (Cl_2) in water. The factory was built in 1778 on the banks of the Seine. The financial partners were a group of court nobles, and the Count of Artois, brother of King Louis XVI, gave his name to the company. In 1787 the process was modified, and the chlorine, rather than being dissolved in water (to form an unstable though very active solution of hypochlorous acid [HOCl]), was made to react in a suspension of 'washing soda'. After filtration, a solution is obtained that is still effective in bleaching and much more stable, to which Alban gave the name of 'Eau de Javel'. This product, a solution of potassium hypochlorite, had immediate success both in France and in England, in as much as it was easily transported and stored. Curiously, Bertholet initially was reluctant to accept that the chlorine molecule (called 'Oxidizing Muriatic Acid') was bi-atomic. He accepted this fact only after a publication on the subject by Davy in 1816. Bertholet established that chlorine in solution produces a molecule called 'HOCl'. Davy and Bertholet discovered, in fact, the two forms of chlorine: in aqueous solution with $pH < 7$, it is mainly HOCl; whereas, in gaseous form, it is Cl_2. In 1820 Labarraque replaced the potash solution with the more economical solution of caustic soda (NaOH) and obtained the solution of NaOCl that was called 'Eau de Labarraque', which found wide use as a disinfectant and bleaching agent.

Its uses are innumerable from industrial disinfection, to household use, but above all its germicidal properties were exploited in the food and hospital sectors.

NaOCl in itself is a relatively weak disinfectant compared to HOCl, but it functions as a reservoir for the successive formation of the acid by hydrolysis. The precise mechanism by which the HOCl kills microorganisms is not yet completely elucidated, but there are sufficient experimental data to affirm with certainty that the mechanism of action begins with permeation of the cell membrane, and thus the reaction with the enzymatic system of the microorganism attacked. NaOCl is the most widespread and commonly used household disinfectant in the world.

Sodium Hypochlorite

NaOCl is a compound that is effectively used for disinfecting water. It is used, besides, on a large scale as a detergent and surface disinfectant, bleach, deodorizer and water disinfectant. The industrial solution of NaOCl is clear, of very pale yellow color, with the characteristic odour of chlorine. In 5.5%

concentrated aqueous solution, it has a density of 1.1 kg/l. In principle, the industrial solution of NaOCl is unstable, and generates chlorine with a speed that essentially depends on the purity of the solution. This decomposition takes place by exposure to light and heat, contact with acids, and the presence of metallic ions that cause a rapid breakdown of the hypochlorite molecule. NaOCl is a strong oxidant; therefore, it reacts very strongly with inflammable compounds and reducing substances. In short, it is a weak but very reactive base and is capable of feeding and generating dangerous combustion. These characteristics are to be taken into consideration during storage, transport and use of this chemical compound. On account of the presence of NaOH in the hypochlorite solution, the pH of solutions reaches values over 12. When hypochlorite dissolves in water, it produces two different forms of similar compounds, which both play an important role in its disinfectant mechanism: extremely active HOCl and the less active hypochlorite ion (OCl^-). The pH of the solution that is produced determines the concentrations of HOCl and OCl^- that are present.

Production of Sodium Hypochlorite

NaOCl is essentially produced by two methods: chemical and electrochemical.

Chemical Method

Cl_2 is made to react with a solution of NaOH. In this way, NaOCl, NaCl and water are produced according to the reaction:

$$Cl_2 + 2NaOH \rightarrow NaOCl + NaCl + H_2O$$

This method produces solutions of high concentrations, but their purity and stability do not satisfy the quality characteristics that are necessary for their use in the food and medical sectors.

Electrochemical Method

We start with a solution obtained by dissolving NaCl, until obtaining concentrated brine. The solution is then electrolyzed in an 'undivided' cell, forming an alkaline solution of NaOCl. At the same time, gaseous hydrogen is formed. For use in food and medical disinfection, electrolytic hypochlorite is preferred, inasmuch as it is appreciably purer and more stable than the other chemical. Moreover, equipping the cell with DSA-type electrodes assures the minimal presence of chlorates and solution-destabilizing impurities like:

- suspended solids
- metallic ions
- graphite particles.

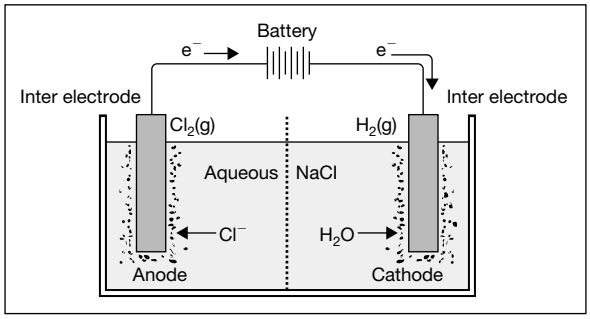

Fig.1. Electrochemical cell for NaCl electrolysis and production of chlorine.

When a salt (NaCl) solution is formed in water, sodium ions (Na^+) and chlorine ions (Cl^-) are produced according to the reaction:

$$4NaCl \rightarrow 4Na^+ + 4Cl^-$$

In the electrochemical cell, a potential difference is applied between the anode (+) and cathode (−), and the following reactions are generated at the electrodes:

At the anode, two oxidation reactions (loss of electrons) are possible:

$$2Cl^- \rightarrow Cl_2 + 2e^- \qquad E_v = 1.35\,V$$

or

$$2H_2O \rightarrow O_2 + 4H^+ + 4e^- \qquad E_v = 1.23\,V$$

At the cathode, there is a reduction reaction (gain of electrons):

$$2H_2O + 2e^- \rightarrow H_2 + 2OH^- \qquad E_v = 0.00\,V$$

The formation of undesired chlorates in the electrolytic cell is possible, either by chemical path in the 'bulk' of the solution, or by electrochemical path at both the anode and the cathode (fig. 1).

Solution: $2HClO + ClO^- \leftrightarrow ClO_3^- + 2Cl^- + 2H^+$

Anode: $2ClO^- + 3H_2O \leftrightarrow 2ClO_3^- + 4Cl^- + 6H^+ + 1.5O_2 + 6e^- \qquad E_v = 0.46\,V$

Cathode: $ClO^- + H_2O + 2e^- \leftrightarrow Cl^- + 2OH^- \qquad E_v = 0.89\,V$

Electrolysis of an aqueous solution of NaCl produces a mixture of hydrogen and Cl_2 and an aqueous solution of sodium hydroxide (NaOH).

$$2NaCl(aq) + 2H_2O(l) \rightarrow 2Na^+(aq) + 2OH^-(aq) + H_2(g) + Cl_2(g)$$

The dotted line visible in the electrolytic cell portrayed in the above figure represents a diaphragm or a membrane that prevents the Cl_2 product at the cell

anode from coming into contact with the soda-rich solution (NaOH) that accumulates in the cathode compartment. When this separation is removed from the cell, the electrolysis products of the aqueous solution of NaCl react to form NaOCl, which is the first step for producing bleaching solutions based on NaOCl, which by hydrolysis will produce HClO:

$$Cl_2(g) + 2OH^-(aq) \rightarrow Cl^-(aq) + OCl^-(aq) + H_2O(l)$$

The conversion of the salt can be optimized by running the electrolysis system with a solution of an optimal level of concentration. With the patented system employed in producing concentrated Alcavis, an optimal quantity of the product is obtained by using DSA-type electrodes with electrocatalytic coatings of oxides of precious metals and with a concentration of the brine of 180 g/l of NaOCl. For food or medical quality (i.e., greatest purity) of the electrolytic NaOCl solution, it is necessary to optimize the electrolytic solution, the electrodes and the cell, both as to surface and to inter-electrode distance.

A recent study[1] has analyzed the optimal conditions to produce NaOCl electrolytically. The electrolytic solutions must be prepared by dissolving pure NaCl (reagent grade) in distilled water. As the anode, old production cells employed graphite; to obtain solutions for medical use, the anodes in more recent cells are constructed of titanium coated with precious metals or with layers of oxides of precious metals (Pt, Ir, Ru, Os, etc.). In fact, graphite electrodes release micro- and nano-particles of graphitic carbon that are very difficult to eliminate even with sophisticated filtration methods. These impurities represent one of the main causes of instability of NaOCl, which decomposes starting from the surface of these particles, which function as catalysts for the decomposition reactions.

With DSA-type anodes (e.g., Ti/RuO_2), the solution proves particularly pure and free of particles in suspension and is stable for very long periods.

The common electrodes used in electrochemical cells for the production of NaOCl are:

Anode: graphite (not advised), titanium with a platinum coating (Ti/Pt) (good), titanium with a coating of ruthenium oxide (Ti/RuO_2) (excellent).

Cathode: graphite (not advised), stainless steel or nickel (risky[2]), Ti (good[3]), titanium coated with iridium oxide (very good).

Let us now summarize the characteristics of an electrolysis cell for production of NaOCl, analyzing some graphs obtained from the previously mentioned study, where:

[1][4].

[2]The release of Fe^{++} and Ni^{++} ions causes the solution to be unstable, with considerable rapidity of decomposition.

[3]Titanium is permeable to hydrogen, for which reason it is very valid electrochemically, but there can be drawbacks of dimensional stability of the electrodes.

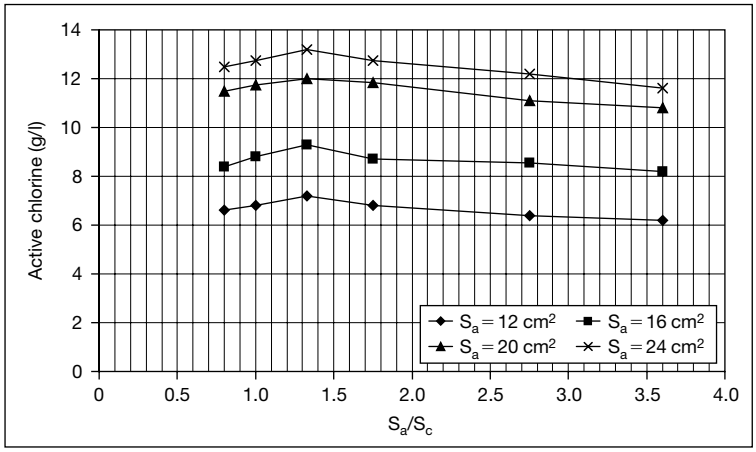

Fig. 2. Effect of S_a/S_c ratio; Ti/$TiRuO_2$ anode; Ti cathode; current density, 10 A/dm^2; NaCl concentration, 2 M; temperature, 20°C; electrolysis time, 1 h.

S_a = Anode surface
S_c = Cathode surface
AC = Active chlorine in solution

Influence of Cell Parameters

Sa/Sc Effect

Figure 2 shows the effects of the ratio of the surface areas of the electrodes on the production of active chlorine. First of all, it is noted that, with increasing S_a, AC increases in an almost linear manner, up to an optimal value. The maximum value of AC is found at an optimal value of the S_a/S_c ratio of 1.33, after which AC decreases. This is in agreement with what is described in the literature, which indicates how an $S_a > S_c$ favors the production of AC. In fact, a large S_a promotes the transformation of chloride ions into hypochlorite ions, while a small S_c works against cathodic reduction of the same hypochlorite ion.

Inter-Electrode Distance

Figure 3 illustrates the variation of AC as a function of the inter-electrode space, for an optimal value of $S_a/S_c = 1.33$. As seen in the figure, AC decreases as the distance between anode and cathode increases. The maximum AC concentration is obtained with an anode-cathode distance of 8 mm; and after 20 mm, AC decreases abruptly.

This observation is in line with the idea that a small distance should favor the conversion of Cl^- to ClO^-, inasmuch as it minimizes the ohmic potential drop and therefore increases the current density of the cell. At this point, it can

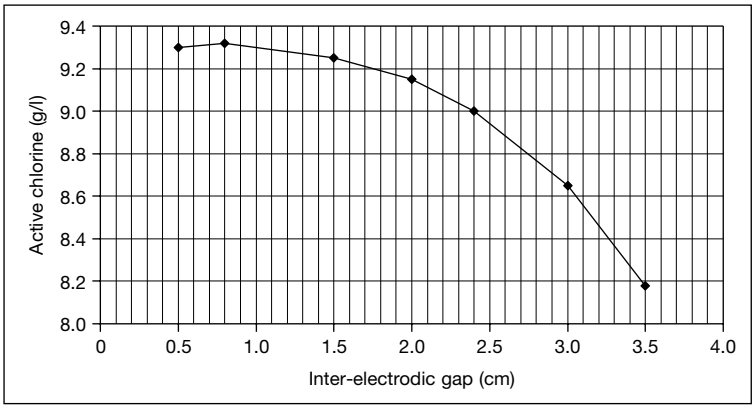

Fig. 3. Effect of inter-electrode gap; Ti/$TiRuO_2$ anode; Ti cathode; $S_a/S_c = 1.33$; current density, 10 A/dm^2; NaCl concentration, 2 M; temperature, 20°C; electrolysis time, 1 h.

be said that the optimal conversion of Cl^- into ClO^- takes place with an S_a/S_c ratio ≈ 1.33 and for an inter-electrode distance less than 0.8 cm.

The following graphs have, therefore, been obtained from tests done with the optimal cell parameters of $S_a/S_c = 1.33$, $S_a = 24\,cm^2$ and a distance between the electrodes of 0.5 cm.

Effect of Type of Cathode

The behavior of four different types of cathodes has been analyzed: graphite, stainless steel, nickel and titanium.[4] Figures 4 and 5 illustrate how AC depends on the electrolysis time and on the current density applied, respectively, using DSA electrodes of Ti/RuO_2 as anode.

The experimental curves of each figure are almost superimposable. This indicates little influence of the cathode composition on AC. However, the future of the cathode influences the behavior of the cell, acting both on the reduction reaction of the hypochlorite ions and on the cathodic overload of hydrogen development.

We can deduce from figure 4 that the active chlorine is produced at a speed of about 0.2 g/l per minute for the first 130 min of electrolysis. After that, the speed diminishes to zero, and production settles at AC = 30 g/l.

[4]For simplicity, Ti has been used rather than Ti/IrO_2, in as much as the electrochemical behavior is similar and, for the tests, the deformation is noted after time periods longer than the test period.

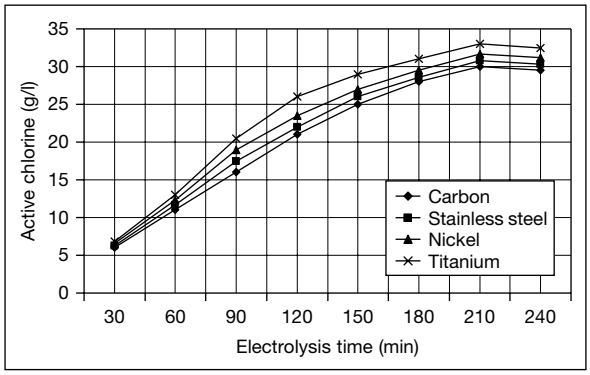

Fig. 4. Effect of electrolysis time as a function of the type of the cathode. $Ti/TiRuO_2$ anode; current density, 10 A/dm^2; NaCl concentration, 2 M; temperature, 20°C.

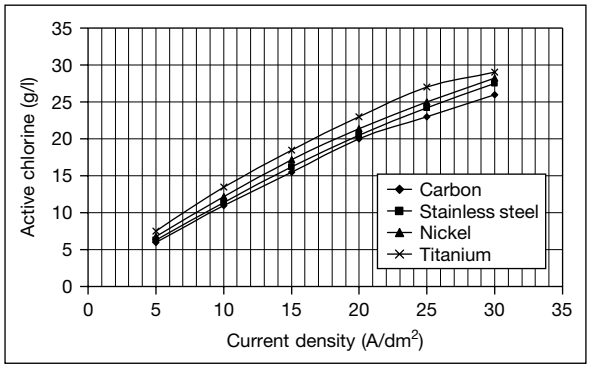

Fig. 5. Effect of current density as a function of the type of the cathode. $Ti/TiRuO_2$ anode; NaCl concentration, 2 M; temperature, 20°C; electrolysis time, 1 h.

Consequently, it is highlighted that the behavior of titanium is better than all others. Moreover, its resistance to corrosion avoids any type of pollution of the solution with metallic ions or graphite particles. However, the titanium cathode shows strong permeability to hydrogen. This generates very high mechanical tensions in its interior and causes its deformation. For this reason, cathodes of titanium coated with platinum (Ti/Pt) are preferred, or better yet with iridium oxide (Ti/IrO_2).

Effect of Type of Anode

The electrodes most used as anodes in electrolysis cells for production of hypochlorite are Ti/Pt and Ti/RuO_2, inasmuch as their perfect resistance to

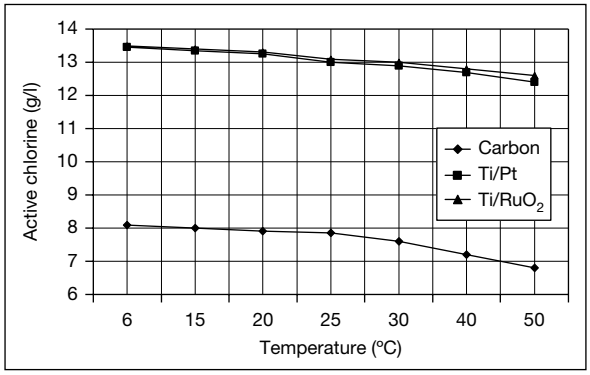

Fig. 6. Effect of temperature as a function of the type of the anode. Ti cathode; $S_a/S_c = 1.33$ cm; current density, 10 A/dm^2; NaCl concentration, 2 M; electrolysis time, 1 h.

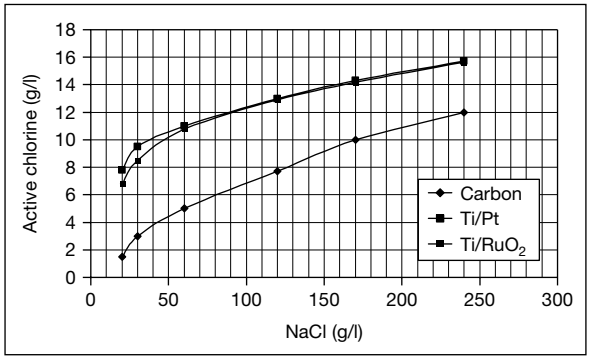

Fig. 7. Effect of NaCl concentration as a function of the type of the anode. Ti cathode; current density, 10 A/dm^2; temperature, 20°C; electrolysis time, 1 h.

corrosion permits working at high current densities. Figures 6 and 7 report the behavior of these anodes during electrolysis in comparison with traditional graphite anodes.

Effect of Cell Temperature

Figure 6 reports the variation of AC with temperature for the various types of anodes considered. The graphs shown indicate that AC is almost constant between 10 and 40°C, and then diminishes over 40°C. Consequently, it is always indispensable to work at temperatures less than 40°C to prevent the formation

of chlorates. In addition, high temperatures favor the reduction of hypochlorite. The formation of chlorate is less at $T < 40°C$, and, at alkaline values of pH, the decrease in cell current is to caused exclusively by the reduction of hypochlorite. The best yield is immediately noted, in terms of AC, from Ti/Pt and Ti/RuO_2 anodes, compared to graphite anodes.

Effect of Electrolyte Concentration

Figure 7 indicates how the cell production of active chlorine depends on electrolyte concentration. For every type of anode studied, there is an increase of AC with increase in electrolyte concentration. At concentrations over 170 g/l, the concentration of AC tends toward an asymptotic value. The cell potential diminishes with increasing concentration of electrolytes in solution, and this increase is more marked for graphite than for the other materials. As observed for the effect of temperature, the Ti/Pt and Ti/RuO_2 anodes give results appreciably better than those of graphite. However, it is known that, for industrial production of NaOCl, it is always appropriate to work with brine of high concentration.

Effect of Current Density

The effect of the variation in active chlorine production as a function of the density of applied current for the anodes is illustrated in figure 8.

For the Ti/Pt and Ti/RuO_2 anodes, the AC increases almost linearly with increase of current density. A somewhat different tendency is observed for graphite anodes. In fact, AC increases up to a maximum of about 12 g/l at 20 A/dm^2; beyond this value, it diminishes abruptly. The fact that the graphite anode could not tolerate a high current density can explain the phenomena observed. Beyond a current density of 20 A/dm^2, reactions of chlorate formation and oxygen development take the upper hand. In contrast, Ti/Pt and Ti/RuO_2 anodes bear higher current densities without problems, and concentration of AC increases, even though with lesser yields.

Effect of Electrolysis Times

Figure 9 indicates that the value of AC concentration increases in every case up to a maximum value and then decreases for prolonged periods. Indeed, for prolonged electrolysis times, the current flow drops, there is a strong development of oxygen, and transformation of Cl^- ions into ClO^- decreases, favor-

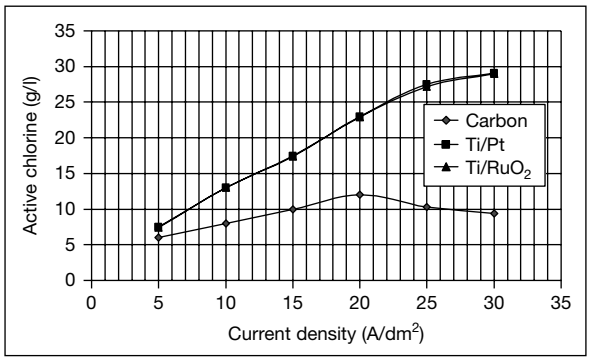

Fig. 8. Effect of current density as a function of the nature of the anode. Ti cathode; NaCl concentration, 2 M; temperature, 20°C; electrolysis time, 1 h.

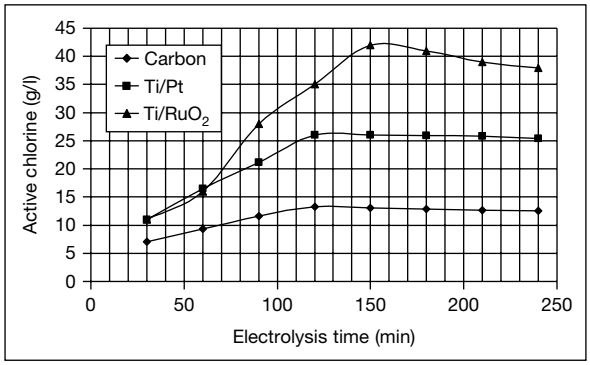

Fig. 9. Effect of electrolysis time as a function of the nature of the anode. Ti cathode; $S_a/S_c = 1.33$ cm; current density, 15 A/dm^2; NaCl concentration, 2 M; temperature, 20°C.

ing the formation of chlorate. The behavioral superiority of Ti/RuO_2 anodes in comparison to other anodes is undeniable, in as much as it is possible to employ higher currents with less production of ClO_3^-. These results confirm that the best performances, in terms of producing active chlorine and efficiency of current, were given by the Ti/Pt and Ti/RuO_2 anodes. So, the criteria of choice of anode must take into account an important factor that influences the yield of the cell, i.e., the capacity to operate with long electrolysis times. While temperature does not have a very appreciable effect, current density, electrolyte concentration and electrolysis time are the parameters that most influence the parameters of the electrochlorination reaction.

After the previous observations, some consequential conclusions can be drawn. The production of NaOCl is strictly correlated with the nature of the anode. The best result is obtained with anodes of titanium coated with ruthenium oxide; however, the operative parameters tied to NaCl concentration, current density and electrolysis time have a significant influence.

Combining all the factors in an optimal manner, it is possible to obtain, by electrochemical path in undivided cells, active chlorine concentration values up to 66 g/l with Ti/RuO_2 and 60 g/l with Ti/Pt. However, it is important to note the negative effect of current density on graphite anodes. In addition, these anodes have weak resistance to oxidation, with effects of crumbling and release of microparticles of graphite into solution. Therefore, use of these materials for producing NaOCl is not advisable, especially for food and medical use.

Electrolytic Production of Sodium Hypochlorite

The electrolytic production of NaOCl from NaCl solutions began at the end of the 1800s. The development of mercury chlorine-soda cells and diaphragm cell technologies for producing chlorine and NaOH had their development between 1883 and 1893, and their industrial use developed between 1890 and 1899. At the beginning of the 20th century, the traditional modes of producing bleaching solutions were used less and less, following the great expansion of the chlorine-soda industry, which made available great quantities of chlorine at very low prices.

Today, the industrial production of hypochlorite is carried out by absorption of (electrolytic) chlorine in a 21% solution of (electrolytic) soda.

The chlorine and soda, in turn, are produced by electrolysis of a concentrated brine of NaCl. Then the chlorine is added to the soda solution in gaseous or liquefied form. Packed or filled towers are often used, with a soda solution that descends and a flow of Cl_2 that rises in countercurrent.

Disinfection with chlorine becomes ever more complex for reasons of safety and transport. Therefore, industrial NaOCl, much more easily handled, currently represents a solution that is adopted more and more in comparison with gaseous or liquefied chlorine.

Use of Hypochlorite as a Disinfectant

Adding NaOCl to water, HOCl is formed according to the reaction:

$$NaOCl + H_2O \rightarrow HOCl + NaOH^-$$

The HOCl then separates into nascent oxygen (O*) and hydrochloric acid (HCl).

$$HOCl \rightarrow HCl + O^*$$

The O* in the atomic state is an extremely strong oxidant.

NaOCl in effective toward bacteria, viruses and fungi; it is able to disinfect with the same mechanism with which chlorine acts.

Alcavis 100 is produced by electrolytic path in optimized cells with a solution of 180 g/l of NaCl. The product has a concentration of active chlorine of about 12 g/l and a pH value of about 10. The advantage of the Alcavis product for medical use is that of being very stable, inasmuch as it is produced by a process of electrolysis of a chemically pure salt solution, with DSA electrodes, with use of correctly designed cells functioning with optimal currents so as to minimize the concentration of chlorates and maximize the stability of the NaOCl solution. In contrast to other products, it preserves its activity for much longer periods. Since NaOCl is used both to oxidize polluting organic agents and to eliminate pathogenic microorganisms, the necessary concentration of NaOCl depends on the concentration of the pollutants. It is especially necessary to know the concentration of organic pollutants in order to determine the correct concentration of hypochlorite. To decrease the use of hypochlorite in treatment of large quantities of water (sewage or purification), it is always suitable to the procedure of preliminary filtration.

Chlorine-based disinfectants act by forming HOCl. The main characteristic is the structure of the molecule, very similar to that of water (HOH ≈ HOCl); therefore, HOCl can easily cross the membrane of the pathogenic cell.

Its intracellular target is represented by the energetic metabolism enzymes of the microbe. The result is that the action of chlorine and hypochlorite on bacteria is very strong and lethal and does not offer the possibility of microbic resistance.

pH Influences Solution Activity

The pH of solutions containing active chlorine influences their disinfectant activity. When the pH of the solution diminishes, the HOCl content increases and the oxidation–reduction potential increases (fig. 10).

pH Influences Solution Stability

When the pH value drops, the stability of the hypochlorite solution drastically diminishes. This is the reason for which industrial NaOCl has added

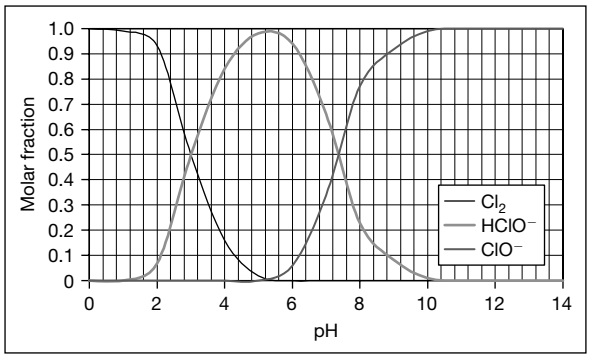

Fig. 10. Influence of pH on chlorine/hypochlorite solution equilibria.

soda. This increases its stability (not sufficiently for medical use) but significantly reduces its effectiveness and tolerability.

At about 1% concentration (typical of the Alcavis 100 product), the NaOCl solution exhibits a surface tension of 75 dyn/cm, viscosity equal to 0.968 cP, conductivity of 65.5 mS, density of 1.04 g/cm^3 and humidifying capacity equal to 1 h and 27 min. Its mechanism of antimicrobial action can be observed, verifying its chemico-physical characteristics and its reactivity with organic tissues. In fact, the strong antimicrobial effectiveness of NaOCl is based on its high pH (action of the hydroxide ions). This interferes indeed with the integrity of the cytoplasmic membrane, with irreversible enzymatic inhibition, biosynthetic alteration of cellular metabolism and phospholipid degradation observed in the lipidic hyperoxidation. For this reason, NaOCl exhibits antimicrobial activity with action on the enzymatic assets of bacteria, promoting irreversible inactivation originating with the hydroxyl ions and the action of chloramination.

So, considering the high surface tension and the antimicrobial action that can be obtained with less concentrated solutions, the best option is the use of NaOCl solutions with about 1% free chlorine (Alcavis 100 contains about 1.1% of equivalent active chlorine).

The chemico-physical characteristics of NaOCl solutions are important in order to understand their mechanism of action. The reactions of saponification, neutralization of amino acids and chloramination that occur in the presence of microorganisms and organic tissues lead to the antimicrobial process and that of elimination of organic pollutants. Antimicrobial activity is correlated with essential enzymatic sites on the bacteria, on which occurs irreversible inactivation through the hydroxyl ions and the chloramination reaction. Organic dissolution can be observed, instead, in the saponification reaction, when

NaOCl causes the degradation of lipids and fatty acids, with formation of soaps and glycerol.

NaOCl in high concentrations is very aggressive, while in lower concentrations (0.5–1%) it is biocompatible. In order to consider a substance biocompatible, it must not react or react only weakly with organic tissues for any period of time and have moderate action in the first 7 days, which decreases with time to insignificant values.

Quality of NaOCl

To specify a NaOCl solution, it is necessary to indicate that it must have zero or only traces of metallic ions of nickel, copper or iron or suspended solids (like graphite). Moreover, storage and handling of the product must be done in the correct way. There are the following advantages with these precautions:

- Low concentration of chlorates.
- Limited decomposition of the product.
- Absence of deposits on the bottom of containers and in pumps, valves, pipes, etc.
- Negligible production of oxygen.

Stability of Sodium Hypochlorite Solutions

The stability of NaOCl solutions depends on some factors:

1. Hypochlorite concentration.
2. Temperature.
3. Alkalinity and pH value.
4. Concentration of impurities that catalyze decomposition and/or production of chlorates.
5. Exposure to light.

Decomposition of hypochlorite procedures according to two main mechanisms:

$$2NaOCl \rightarrow 2NaCl + O_2 \quad (2)$$

$$3NaOCl \rightarrow 2NaCl + NaClO_3 \quad (3)$$

Let's analyze, point by point, the factors influencing the stability of NaOCl solutions.

Hypochlorite Concentration

The more concentrated the solution, the faster the decomposition. Therefore, the weaker the solution, the more stable it is.

Temperature of Solution

Decomposition due to age and temperature follows by 90% reaction (3) with production of chlorates. When hypochlorite solutions produced by chemical path (chloration of soda solutions), the high temperatures reached favor the formation of sodium chlorate with reaction (4) at the expense of hypochlorite. There is the same effect if solutions are kept stored in surroundings of high temperature.

$$6NaOH + 3Cl_2 \rightarrow NaClO_3 + 5NaCl + 3H_2O \quad (4)$$

Experience indicates that, with the final product, the temperature of 30°C should not be exceeded in order to limit the production of sodium chlorate.

Alkalinity and pH of Solution

The hypochlorite solution is to be kept at a pH between 11.5 and 12.5. A slight excess of NaOH also tends to protect the hypochlorite solution from the damaging effect of light. The minimal quantity of excess soda in normal applications is 0.3 g/l, which gives us a pH value = 11.86. For concentrated solutions of hypochlorite (15%), it will be equal to about 0.025% of the weight of the solution. For lesser concentrations and therefore for pH < 11.86, there is a more rapid decrease of the pH over time and a consequent faster decomposition of the NaOCl.

For storing dilute solutions of NaOCl, the pH must be greater than 11.86, in as much as dilution lowers it. Electrolytic hypochlorite has a natural pH over 12 and, therefore, also exhibits excellent stability from this point of view. If the pH exceeds the value of 13 (4 g/l of NaOH), there is an opposite effect, that is, there is an increase in decomposition speed.

Concentration of Impurities

Copper, nickel, iron and cobalt are catalysts of NaOCl decomposition. The metals mainly catalyze decomposition according to reaction (2) with production of O_2. Copper and iron are the ones most frequently present and must remain below 0.5 and 1 ppm, respectively, in the final solution.

Solid suspensions, as, e.g., graphite particles originating from the electrodes (if outdated cells are used) also cause the decomposition of NaOCl, in particular according to reaction (3) with formation of sodium chlorate.

Exposure to Light

Exposure to light also accelerates the process of decomposition of NaOCl in solution. Modern methods of packing and the use of opaque polyethylene bottles have practically eliminated the influence of light on the stability of solutions.

Amber or green glass bottles also have the same result.

Conclusion

In conclusion, the most stable NaOCl solutions are those that show the following characteristics:

1. Low concentration of hypochlorite
2. pH > 11.5 and <13
3. Absence of graphite particulate and metallic ions
4. Storage at controlled temperature <30°C
5. Packing in containers impermeable to light.

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Toxicity and Safety of Topical Sodium Hypochlorite

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Abstract

The safety and toxicity of sodium hypochlorite is reviewed with particular correlation to topical use. Since sodium hypochlorite is one of the most widely used chemicals in the environment, its safety has been established by long use and toxicity profile. This chapter reviews recent toxicology testing including routine systemic LD50, topical LD50, topical toxicology, irritation and sensitization. The resulting toxicity or safety profile clarifies the safe topical use of electrolytically produced sodium hypochlorite solution (ExSept, Amuchina 10%).

Historical Use of Sodium Hypochlorite

The history of the use of hypochlorite as a disinfectant and antiseptic goes back hundreds of years. It was used for the treatment of wounds and burns even before the revolutionary work of Lister and Koch. Among early uses, the Marquis de la Motte used a hypochlorite solution for the treatment of gangrene in 1732 [1]; and Paris surgeons used it for the treatment of burns, operative wounds, and ulcers [1]. As noted in the background section, Semmelweis used hypochlorite as an antiseptic hand wash to reduce the very high incidence of puerperal fever (childbed fever) during childbirth in a Vienna hospital. He ensured that his hands, and the hands of his assistants, were washed in a hypochlorite solution. He also insisted that a hypochlorite solution be used on any instruments likely to come in contact with the vaginal canal. While Semmelweis' technique resulted in a drastic decrease in the death rate from puerperal fever, his contemporaries largely ignored his work [1, 2]. Koch reported the antiseptic properties of hypochlorites in 1880 [3]; however, the widespread acceptance of hypochlorite, and recognition

of its activity in wounds, would await the work of Carrel and Dakin. The conditions of trench warfare during the First World War resulted in large numbers of casualties with wounds contaminated by soil and human and animal excrement. These conditions led to a high incidence of wound infection and gangrene [4]. Existing antimicrobial compounds such as phenol, mercuric chloride and tincture of iodine proved to be unsuitable for antiseptic treatment of large traumatic wounds. These compounds could not be used in the volume necessary to debride and disinfect the wounds without producing toxic or highly irritating effects [5]. To combat the high mortality that resulted from the wound infections of war, Nobel Laureate Dr. Alexis Carrel enlisted the aid of a noted chemist, Henry Dakin, to formulate a non-irritating solution that had significant antiseptic effect [2]. Dakin examined over 200 substances in his search for a solution that met Carrel's requirements [6]. Among the substances examined were ingredients that FDA now considers to be Category I under the First Aid Antiseptics TFM: phenol, hydrogen peroxide and tincture of iodine. Dakin rejected these substances as either too toxic or irritating (phenol and iodine) or because of insufficient antimicrobial activity (hydrogen peroxide) [5]. Dakin determined that sodium hypochlorite at concentrations of 0.45–0.5%, in a buffered solution, had the best combination of non-irritating properties and antimicrobial effectiveness.

Carrel used Dakin's solution in a specific treatment regimen that involved, among other things, irrigating debridement and use of large volumes of their hypochlorite solution on the wounds [7]. Further, the concentration of sodium hypochlorite in Dakin's solution was higher than commonly used today, so that successful use in large wound areas over a period of days constitutes significant exposure, but had its limitations [8]. Antibiotics, introduced after World War II, often do not reach bacteria in deep wounds or necrotic tissue, and often have activity against only a limited spectrum of organisms. Additionally, with widespread use of antibiotics, many resistant strains of bacteria began to appear. Because of the limitations of antibiotics, today, topical antiseptics have again increased in use [9]. Recently, McDonnell noted that '[t]here now appears to be yet another resurgence in the clinical use of Dakin's solution' [8]. Recent antiseptic uses of sodium hypochlorite cited in published literature include use for burns, wounds, pressure sores and deep ulcers.

In an article that discusses the safety of 0.1–0.5% sodium hypochlorite for the treatment of burns, Cotter notes the use of 0.05–0.2% sodium hypochlorite during the Second World War, and the recent usage of 0.08% buffered sodium hypochlorite [10]. An article by Wright, and a letter by Thomas both note recent use of sodium hypochlorite as a burn antiseptic [9, 11, 12, 26]. Bloomfield discussed the use of 0.125 and 0.25% sodium hypochlorite by hospitals for wounds, pressure sores and ulcers [13]. Articles by Lineaweaver and Kozol, and letters by Raffensperger and Barese, also note recent use of sodium hypochlorite

for wound treatment [8, 14–17, 29, 30]. An article by Slahetka [18] describes the use of 0.45–0.5% sodium hypochlorite solutions for the treatment of deep ulcers in geriatric patients.

As noted previously, sodium hypochlorite has been used for a variety of medical uses. It is one of the most widely used of all endodontic irrigating solutions. Concentrations of 2–5.25% have been recommended for this purpose [19]. In his study of five solutions, Berutti noted that '[a]lthough numerous endodontic irrigant solutions have been proposed, sodium hypochlorite has been shown to be the most effective' [20].

In addition to many medical uses, sodium hypochlorite has also been widely used for a number of non-medical uses, notably for water purification. Since its introduction, chlorination has become one of the most widely used and effective methods for providing safe drinking water to the world's population [21, 22].

The long historical use of sodium hypochlorite for wounds, burns and other medical indications, as well as the recent and current use of the ingredient as a topical antiseptic, demonstrate that sodium hypochlorite has been used for a material time and a material extent without significant evidence of toxic effects. Further assurance of the ingredient's safety is provided by its history of use for a variety of other medical and non-medical purposes.

Safety and Toxicity

These terms are consistently misunderstood, misinterpreted and confused. Toxicology is a scientific specialty that studies the effect of doses of a subject chemical administered to test animals (or in some cases, lower life forms). There are a variety of specific tests that make up a toxicity profile. They are selected based on the projected use of the formulated product (topical, oral or by injection). When the results of such a profile are examined, a judgment of safety can be made. Often included in this assessment is the inclusion of a safety factor applied to the toxic levels determined in the animal studies.

Acute Toxicity Studies

Basic dosing studies using different species and routes of administration are performed to estimate or profile the toxicity of an given chemical compound. These routes reflect potential administration of the test chemical or drug. In the case of sodium hypochlorite, the administration has been limited to topical applications to skin and burn areas, and in wound or in oral and vaginal applications, which are considered topical.

The judging of results of toxicity testing can delineate toxic from non-toxic chemicals. These acute studies reveal that sodium hypochlorite is basically a non-toxic chemical ingredient.

Early on, Amuchina (now Alcavis) commissioned a number of studies to examine the acute toxicity of sodium hypochlorite solutions by various routes of administration, including oral, intraveneous, intraperitoneal, and topical dermal application. These studies, performed by Gnemi at the Instituto di Ricerche Biomediche in Italy, were conducted on then Amuchina's 1.1% (or 11,000 ppm) sodium hypochlorite solution.

A single-dose oral toxicity study in rats was conducted by administering various amounts of 1.1% sodium hypochlorite solution resulting in dosages of 256–400 mg/kg [23]. The LD_{50} was calculated to be 290 mg/kg, with 95% confidence limits of 267 and 315 mg/kg.

A single-dose intravenous toxicity study in rats was conducted by injecting various amounts of 1.1% sodium hypochlorite solution resulting in dosages of 26.2–124.8 mg/kg [24]. The LD_{50} for intravenous administration was calculated to be 33.3 mg/kg, with 95% confidence limits of 28.2 and 39.3 mg/kg.

A single-dose intraperitoneal toxicity study in rats was conducted by intraperitoneal administration of various amounts of 1.1% sodium hypochlorite solution resulting in dosages of 26.2–150 mg/kg [25]. The LD_{50} for intraperitoneal administration was calculated to be 87.7 mg/kg, with 95% confidence limits of 79 and 97.5 mg/kg.

A single dose acute dermal toxicity study in rats was conducted by exposing shaved skin to 1.1% sodium hypochlorite solution in a dose of 50 mg/kg [26]. The test was performed by taping gauze patches to the test site, applying the solution to the patches, and leaving the patches in place for 24 h. After 14 days of observation, none of the animals showed any signs of systemic toxic effect or local irritation. The author concluded that the LD_{50} for dermal application is higher than 50 mg/kg.

Clementi examined acute dermal toxicity using rabbits instead of rats [27]. This 4-week study examined the effects of 5 and 10% concentrations of Amuchina's Electrolytic Chloroxidizer (0.055 and 0.11% or 550 and 1,100 ppm sodium hypochlorite) on intact and abraded skin. After daily administration of the test compounds for the 4-week study period, no systemic toxic effect or local irritation were observed.

These various studies indicate that sodium hypochlorite is essentially non-toxic, especially at the proposed use concentration, and for the proposed indications. For example, the oral LD_{50} for sodium hypochlorite is quite high at 290 mg/kg. In a very practical example, if this amount were to be extrapolated to an amount for a human dose, it would require that a 100-kg man consume approximately 6 l of a 0.5% solution. Also note that the acute dermal toxicity

studies demonstrated no toxic effects after the topical application of sodium hypochlorite.

Blood Levels

The 1978 Tentative Final Monograph for OTC Topical Antimicrobial Products stated that where appropriate, safety information should include studies to show expected blood levels after the use of an OTC product [28]. Sodium hypochlorite breaks down almost instantaneously on contact with blood and blood components, and therefore would not be expected to be found as sodium hypochlorite in the blood stream. Therefore, information on blood levels of sodium hypochlorite is not technically feasible. Carrel and Keen both recognized early that sodium hypochlorite solution lost its antimicrobial activity soon after contact with an open wound [6, 7, 21, 22]. More recently, Cotter et al. [10] noted that, 'because NaOCl reacts with protein and other cellular debris, its antimicrobial activity is depleted during treatment'.

Zanolo [29] examined this disappearance of activity by measuring the levels of the available chlorine in sodium hypochlorite solutions exposed to high concentrations of human and dog blood. To measure this disappearance, 8 ml of either human or dog blood was added to 2 ml of 1.1% sodium hypochlorite, and the combination was mixed for 5 s. After 5 s, the reaction was stopped with a neutralizer, and the remaining chlorine assayed. The decomposition of the sodium hypochlorite after exposure to the blood was so rapid, that no available chlorine could be measured after the 5 s of mixing.

General knowledge of sodium hypochlorite's rapid decomposition after it contacts wounds, as well as the results of the Zanolo's study, indicates that no sodium hypochlorite or de minimus amounts would be found in the blood stream as a result of topical application of sodium hypochlorite solution. Therefore, measuring blood levels would not be appropriate for this compound.

Carcinogenicity/Mutagenicity Studies

The toxicity and carcinogenicity of sodium hypochlorite has been examined extensively. Both published and unpublished studies have repeatedly demonstrated this ingredient's safety, and failed to raise any significant questions regarding acute toxicity or carcinogenicity. A number of studies that examine sodium hypochlorite's carcinogenic and mutagenic potential have been investigated by both in vitro and in vivo methods.

One of the most common worldwide uses of chlorine and chlorine containing compounds (including sodium hypochlorite) is as a disinfectant for drinking water. This use has led a number of investigators to examine the carcinogenicity of chlorinated water.

Hasegawa et al. [30] examined the effects on rats of a 104-week administration of sodium hypochlorite in drinking water at levels of 0.05–0.2%. No significant increase in incidence of any tumors was observed, leading the investigators to conclude that sodium hypochlorite showed no carcinogenic potential.

Kurokawa examined the carcinogenicity of long-term exposure to sodium hypochlorite in both rats and mice [31]. The rats were given a 104-week administration of sodium hypochlorite in drinking water at levels of 0.05–0.2%, whereas the mice underwent a 103-week administration of sodium hypochlorite in drinking water at levels of 0.05–0.1%. The authors also concluded that sodium hypochlorite was not carcinogenic in rats and mice.

Robinson et al. [32] examined hyperplasia in mouse skin after dermal exposure to sodium hypochlorite, hypochlorous acid, and to the hypochlorite ion. The stated goal of this study was to examine the potential for these compounds to promote skin cancer. The study consisted of exposing the skin of SENCAR mice to concentrations of 0.001–0.1% of various chlorine compounds. All of these compounds resulted in some degree of hyperplasia. The author's decision to use the ability of sodium hypochlorite, and its derivatives, to induce hyperplasia (thickening of the skin) as an indicator of the substance's tumor promoting capacity was based upon the 'excellent correlation' between the hyperplasiogenic activity and tumor promotion among phorbol esters. However, the author admits that this correlation does not hold true for compounds of chemical classes other than phorbol esters. Given that the correlation between skin hyperplasia and tumor promotion appears to be limited to phorbol esters, and that sodium hypochlorite is unrelated to this compound, one questions the selection of this assay as a valid indicator of sodium hypochlorite's possible carcinogenicity. One cannot conclude any positive information concerning carcinogenicity with an assay of this dubious nature.

In another study using an assay of dubious relevance, Meier examined the effect of interperitoneally administered sodium hypochlorite and its derivatives on the production of sperm-head abnormalities in mice [33]. In this study, three different in vivo tests designed to look for chromosomal damage were used to examine various disinfectant chemicals. In one of these tests, the sperm-head abnormality assay, hypochlorite ions were detected in only one of three sample groups, and were not found for other sodium hypochlorite derivatives. Further, three different assays showed no indication of mutagenic activity. Additionally,

the author admits that the meaning of a positive result in this assay was the subject of scientific debate. Therefore, a weak positive result to interperitoneally administered hypochlorite ions in an unproven assay for mutagenic activity has little bearing on the safety of sodium hypochlorite for topical use.

Amuchina (now Alcavis) commissioned two in vitro studies to examine the possible mutagenic potential of its 'Amuchina – Electrolytic Chloroxidizer,' a sodium hypochlorite disinfectant/antiseptic.

One study by Pirovano [34] was conducted using one of the most widely used of all tests for mutagenesis, the Ames assay. This assay measures the influence of a chemical compound on the spontaneous mutation rate of *Salmonella typhimurium*. In this test, mutagenic compounds showed an increase in the rate of mutations over the background or control rate. Amuchina's sodium hypochlorite solution did not increase the mutation rate, therefore, it can be concluded that it does not have mutagenic potential in tests that are often difficult when the chemical is an antimicrobial.

Pirovano [35] also conducted a second study. This study was similar to the first, but used the yeast *Saccharomyces cerevisiae* in place of *S. typhimurium* as an indicator organism. Again, Amuchina's solution did not show an increase in the mutation rate, and did not show mutagenic potential.

In sum, many studies with sodium hypochlorite have not found any demonstrated mutagenic or carcinogenic potential. Two long-term feeding studies in rats and one in mice showed no increase in the rate of tumor formation. In two standard in vitro assays, sodium hypochlorite did not show any mutagenic potential.

The study design of some authors' work discussed above strains the concept of a toxicity profile in that a rather obscure measurement of toxicity, let alone a means to examine chromosomal abnormalities, was used. Similarly, grouping chemicals other than known carcinogens like phorbal esters together for testing based on an unproven correlation between hyperplasia induction and development of skin cancer must be discounted as well-intentioned, but not reasonable.

More conventional tests for mutagenic potential show that sodium hypochlorite is not mutagenic. The carcinogenicity and mutagenic potential in vitro and in vivo have been studied as well as its toxicity using several methods of exposure, and the possible development of blood levels after topical use.

In summary, in all these studies, no adverse toxicological effects were found with sodium hypochlorite. Therefore, based on these studies as well as toxicological information accumulated during the long history of use of sodium hypochlorite, it should be considered non-carcinogenic, non-mutagenic, and essentially non-toxic for its proposed use, at use concentrations.

Topical Safety

Wound Healing and Irrigation

Ultimately, the real life topical use of sodium hypochlorite solution to reduce microbial flora involves a risk/benefit balance. The potential for adverse effects must be drawn from the studies discussed and weighed against effectiveness. The topical safety is most important since this is the normal route of administration.

It is a generalization, but a reaction often observed is that potential users may associate the odor of chlorine, its bleaching action and environmental use to conclude that sodium hypochlorite is harsh and irritating. The results of the tests discussed here belie this conclusion. If we return to Dakin and Carrel, they established effectiveness in vitro and went on to invent a method for treating the skin and large traumatic wounds for a period of days with multiple treatments per day. Their method resulted in the preservation of lives and limbs. A variety of tests show little topical toxicity. Sometimes this may be difficult to conclude from some inconclusive and ill-conceived in vitro studies. Many in vitro studies try to extrapolate from cellular models what will happen in use. These tests try to be predictive, but information from use ultimately reveals the true effects.

The human patch testing to predict sensitization and irritation have had good track records. A human irritation and sensitization test using the concentration of sodium hypochlorite in the Alcavis product, ExSept (1,100 ppm) has been conducted.

Long history of use, and published and unpublished studies, have established that buffered sodium hypochlorite solutions do not inhibit would healing and are essentially non-irritating. Studies have also shown that any irritating properties that sodium hypochlorite solutions may have are less pronounced than those exhibited by other ingredients, such as phenol and povidone-iodine (now classified as Category I under the First Aid Antiseptic TFM and in the Health-Care Antiseptic Products TFM in 1994).

As noted previously, while examining the acute dermal toxicity of sodium hypochlorite solution, both Gnemi [26] and Clementi [27] also looked for signs of skin irritation. Gnemi found no evidence of dermal reaction on intact rat skin after a 24-hour exposure to 1.1% sodium hypochlorite. Clementi noted that 4 weeks of exposure to 0.11% sodium hypochlorite solution did not produce significant irritant effect on either intact or abraded rabbit skin.

Gnemi [36] also examined the acute eye irritation effects of sodium hypochlorite. The study was conducted by administering 0.1 ml or 0.11% sodium hypochlorite solution to the eyes of rabbits. No reactions were noted during the 72-hour observation period. The author concluded that 0.11% sodium hypochlorite was not irritating to the eye.

They examined inflammatory responses from subcutaneous exposure to sodium hypochlorite in guinea pigs [19]. In these studies, open-ended tubes containing 0.9–8.4% sodium hypochlorite solution was placed under the skin of guinea pigs. After 7 and 14 days, there was no significant difference in inflammatory response between any of the sites treated with sodium hypochlorite, and the negative control sites treated with saline solution.

Cotter et al. [10] studied the effect of 0.1 and 0.5% buffered sodium hypochlorite solutions on the viability of basal cells of guinea pig skin. The basal cells of the skin were exposed to the 0.5% solution and showed no reduction in viability after 1 week, but showed a 15% decrease in viability after 2 weeks. The cells exposed to the 0.1% solution showed no loss in viability after 2 weeks. Cotter concluded that both 0.1 and 0.5% solutions would be well-tolerated by patients.

Billhimer [37] conducted a human primary irritation patch test in a clinical examination of the irritation potential of sodium hypochlorite. In this study, each test subject was exposed to three consecutive 24-hour applications of 0.11% sodium hypochlorite solution with observations taken after each application. Only transient, slight to moderate irritation was observed during the study.

Mian et al. [38] conducted a comparative clinical study of topical antiseptics for treatment of burn patients. Burn patients were treated with either a 1% silver sulfadiazine cream (a standard treatment) or a 0.05–0.11% sodium hypochlorite solution. The patients treated with sodium hypochlorite solution tolerated their treatment with less pain, had a lower incidence of dermatitis, and showed faster wound healing than those treated with silver sulfadiazine cream.

Heggers et al. [39] conducted both in vivo and in vitro examinations of the effects of sodium hypochlorite on wound healing. The in vivo portion of this investigation consisted of making full-thickness incisions in rats, and then examining the effect of 0.25 and 0.025% sodium hypochlorite solutions on these wounds. The rats were sacrificed after 3, 7 and 14 days of treatment and examined. The wounds treated with sodium hypochlorite showed little or no difference from those treated with the saline controls. The cells exposed to 0.25% solution demonstrated cell death and disruption; the cells exposed to 0.025% solution remained viable, but exhibited some cellular damage; and the cells exposed to 0.0125 showed no adverse effects. This study clearly illustrated that in vitro results do not always correlate well with in vivo results. This theoretical extension of the direct in vitro effect of sodium hypochlorite on fibroblast cells to an effect on wound healing clearly cannot be derived from this study.

Cooper et al. [40] examined the in vitro effects of three topical antiseptics on fibroblasts and keratinocytes. The test solutions were 0.125% sodium hypochlorite, 0.5% povidone-iodine, and 0.25% acetic acid. The cells were exposed to various dilutions of the antiseptic solutions. Toxicity to the fibroblasts was measured by a test system that recorded the rate of thymidine incorporation and the rate of

neutral red uptake. Toxicity to the keratinocytes was measured by the rate of neutral red uptake. With this test system, sodium hypochlorite was toxic only at the highest concentration. Sodium hypochlorite was shown, in this test, to be the least toxic to fibroblasts and keratinocytes of the three tested antiseptic solutions.

Spangberg et al. [41] examined the in vitro toxicity and antimicrobial effectiveness of seven commonly used dental endodontic antiseptic solutions. The antiseptics tested were sodium hypochlorite, chlorhexidine, three different iodine compounds, parachlorophenol and formocresol. The toxicity was measured by exposing tissue cultures of HeLa cells to various concentrations of the solutions. The antimicrobial effectiveness was determined by mixing the antiseptic solutions with various microorganisms in the presence of calf serum. All of the compounds tested proved to be toxic to the tissue culture cells at concentrations below the effective antimicrobial concentration.

Lineaweaver et al. [14] examined the effects of four topical antiseptics on wound healing by both in vivo and in vitro methods. The antiseptics were 0.5% sodium hypochlorite, 1.0% povidone-iodine, 0.25% acetic acid, and 3.0% hydrogen peroxide. In the in vivo portion of this study, 4-cm incisions were made on the backs of rats, and these wounds were irrigated with each one of the antiseptic solutions three times a day, for 4 days. After a given treatment, its effect on wound healing was measured by two testing methods: the tensile strength of the wound and determination of the rate of wound epithelialization. All of the solutions, except hydrogen peroxide, showed some inhibition of the wound healing process. The in vitro portion of the study consisted of treating cultured human fibroblasts with various dilutions of the four antimicrobial solutions. After 24 hours of exposure, all of the solutions were toxic to the fibroblasts at full strength. Sodium hypochlorite was toxic, as defined in this study, at 0.025%, but not at 0.005%. Non-toxic levels of other solutions tested were at 0.001% for povidone-iodine, 0.0025% for acetic acid, and 0.003% for hydrogen peroxide. Lineaweaver also examined the bactericidal effectiveness of the four test solutions. While all four were found to be effective as antimicrobials, only sodium hypochlorite and povidone-iodine were antimicrobial at concentrations that were not toxic to the fibroblasts after direct application to the cells.

In addition, in an in vitro study by Kozol et al. [15], the effect of sodium hypochlorite solution on neutrophil migration was used as an assay. Sodium hypochlorite solutions, down to a concentration of 0.00025%, inhibited greater than 90% of neutrophil function.

The studies by Lineaweaver and Kozol provided the suggestion that sodium hypochlorite, along with other topical antimicrobials (some of which are category I under the First Aid Antiseptic TFM), showed in vitro effects and may cause some adverse effects on wounds and wound healing. However, this evidence must be weighed together with some other relevant information and

conclusions cannot be drawn from differing assay techniques extended to rationalize effects on wound healing. From the clinical information accumulated over the years, it may be reasonably assumed that these studies place too much emphasis on in vitro methods. Carrel's early clinical work with sodium hypochlorite solutions was strongly criticized by a Dr. Almoroth Wright, who based his criticisms on results from in vitro experiments. Carrel replied that, 'experiments must be made under the real clinical conditions of the treatment, if sound conclusions are to be reached' [2]. History tells us that Carrel was right. As it turns out, the treatment developed by Wright, highly regarded on the basis of his in vitro observations, was unsuccessful in practice.

Further, Heggars recognized that the in vitro model was insufficient to provide a complete picture of the wound healing process. His study showed a drastic difference in toxicity between in vitro and in vivo models. Therefore, he states that, 'individual tissue culture toxicity assays may be misleading in that the wound milieu consists of a polycellular environment that consists of a mixture of cell types…which all contribute to the wound healing process' [39]. Heggars also recognized that, 'the cellular constituents provide a protective substance or mechanism that neutralizes the toxicity of NaOCl.' Barese and Cuono [17] also recognized the shortcomings of extrapolating results from in vitro experiments to effects in an actual wound. In a letter critical of Kozol's conclusions described above, the authors note the contradiction between sodium hypochlorite's successful clinical use and its reported adverse effects on tissue cell cultures. Like Heggars, they believed that this apparent contradiction could be explained by the difference between real wounds, and Kozol's model, and in their words, 'which bears little similarity to a real wound milieu.' As noted previously, sodium hypochlorite breaks down rapidly once exposed to blood serum, or other components of the wound environment.

Further, Barese and Cuono also questioned the composition of the 'Dakin's solution' tested by Kozol. They noted that the study did not state whether the solution was buffered, or if buffered, what buffer was used. They further noted that unbuffered sodium hypochlorite is less effective, and far more irritating (due to high alkalinity) than the buffered solution. Interestingly, Kozol [42] does not address this issue in his reply, but rather attacks the relevance of sodium hypochlorite's historical use. The Lineaweaver study also fails to detail the composition of the tested sodium hypochlorite solution [14].

It is quite likely that Kozol and Lineaweaver did, in fact, test unbuffered solutions. Many of the references that discuss the formulation of 'Dakin's solution' and 'Modified Dakin's solution,' including the orginal works by Dakin [5] and Carrel and Dehelly [6], Remington's practice of Pharmacy [43, 44], the Modern Drug Encyclopedia [45], as well as others, describe a buffered sodium hypochlorite solution. However, the USP from at least 1937 describes

'Modified Dakin's solution' as a 0.45–0.5% sodium hypochlorite solution, with no reference to any buffering. Therefore, it is possible that Kozol and Lineaweaver actually examined the effects of an unbuffered sodium hypochlorite solution instead of properly formulated Dakin's solution. Dakin himself recognized the irritating potential of unbuffered sodium hypochlorite, and developed his formulation accordingly [5]. Further, in a clinical study by Bloomfield (recognized expert in chlorine compounds), unbuffered sodium hypochlorite (also known as Milton solution) demonstrated a higher score for skin irritancy than buffered sodium hypochlorite solutions [13].

The studies discussed above indicated clearly that sodium hypochlorite is not a skin irritant and does not inhibit wound healing. All but one of the in vivo studies of sodium hypochlorite supports this conclusion. The one study to the contrary, the Lineaweaver study, does not specify whether the protocol used a buffered sodium hypochlorite solution, or a more irritating unbuffered solution. A few in vitro studies indicate that sodium hypochlorite may have adverse effects on some cell types; however, these studies fail to account for the significant differences between in vitro conditions, and the environment of an actual wound. Furthermore, even these in vitro studies demonstrate that sodium hypochlorite is no more irritating, and often less irritating, than other antimicrobials. The original Tentative Final Monograph for OTC Topical Antimicrobial Products recognized that a product that 'causes slight irritation or delays wound healing for a relatively short period can be generally recognized as safe and effective if those side effects are offset by a compensating benefit' [28].

A judgment of safety for topical use weighs the results of toxicity testing against effectiveness in reducing microbial flora to prevent infection. Several studies reported some cellular toxicity in wounds. The measure of toxic effects in theses studies as well as the actual description of products tested is open to question. These possible toxic effects were not confirmed in clinical use of studies.

Human Sensitization and Irritation Tests

The fact that sodium hypochlorite is not a sensitizer is a significant advantage that sodium hypochlorite solutions have over some other topical antiseptics. To clarify sensitization potential, Hazelton Laboratories examined 1.1% sodium hypochlorite solution using a standard test for predicting sensitization or allergic reactions, the Guinea Pig Maximization Test [46]. This test consisted of dermal and intradermal application of various concentrations of test solutions of sodium hypochlorite as an induction dose, followed 2 weeks later by a challenge dose of sodium hypochlorite solution. No reaction to the challenge dose was observed with sodium hypochlorite. The author concluded

that sodium hypochlorite was not a skin sensitizer in guinea pigs. This test has often been used as a screening test for human use and has been predictive of potential sensitization in humans. The most used predictive test procedure for topical products is a human patch test read for irritation and a patch test using induction and challenge doses to produce sensitization reactions.

Alcavis has conducted both tests with their product containing 0.1% (1,100 ppm) sodium hypochlorite.

(1) A cumulative Irritation Patch Study was conducted on the Amuchina 0.11% sodium hypochlorite, then called Amu-Skin [47]. The formulation and the vehicle were both tested for its potential to cause irritation and/or sensitization to the skin of normal volunteer subjects using a blinded, randomized, semi-occlusive 21-day cumulative irritation patch study with challenge. There was no significant irritation in the irritation phase of the study. There was no evidence of sensitization to any of the products evaluated in the challenge phase of the study.
(2) A Repeated Insult Patch Study was also performed by Amuchina (TKL Laboratories [48] performed the test). In this test, 0.1% sodium hypochlorite (Amu-Skin) was evaluated neat to determine its ability to sensitize the skin of normal volunteer subjects using a blinded, randomized, occlusive, repeated insult patch study. Under the conditions employed in this study, using 194 subjects, there was no evidence of sensitization to Amu-Skin or to the vehicle.

Sodium hypochlorite has been showed to be essentially non-irritating, and not an inhibitor of the wound healing process. Further, it has not shown any potential as a skin sensitizer. Therefore, sodium hypochlorite should be safe for the proposed indications at the proposed concentrations.

Conclusions

Many investigators have examined the potential toxic effects of sodium hypochlorite over the last 90 years of topical use. Oral, intravenous and intraperitoneal dosing has been done in animals to characterize potential toxicity coupled with evaluation of topical toxicities and effects. Probably, the most significant information for practical use is the lack of irritation and sensitization after repeated topical applications under worst case conditions and occlusion.

As has occurred with many other antimicrobial ingredients, the tension and often conflicts between the results of in vitro and in vivo studies has been reviewed. One can conclude that effects found in the laboratory model do not always translate to the real life use of a product or formulation.

It is reassuring to survey the collected information about sodium hypochlorite and to find that the conclusions reached by Alcavis from the test of time over 60 years is supported and verified by the scientific testing accumulated over these years.

Alcavis has concluded that the sodium hypochlorite products they produce are safe for their labeled uses.

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Disinfection of Dialysis Monitors

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Abstract

In recent years the concept of biocompatibility is not limited to the dialytic membranes, but has been substituted by a more general viewpoint where all the parameters of the dialytic treatment are taken into consideration: the interaction of blood-surfaces (the dialyzer in all its components and the hematic lines), the sterilization of all materials, the quality of the solutions utilized for dialysis and reinfusion.

Numerous studies have shown that the inflammatory response in dialysis is the cause of many of the side effects of dialytic treatment itself both acute and chronic. Hypoxemia, 'first use' syndrome, hypotension, allergic-anaphylactic reactions (short-term side effects); microinflammation, malnutrition, accelerated arteriosclerosis, anemia, β_2 microglobulin amyloidosis, immunodeficiency, bone mass loss (long-term side effects), have all been reported.

In this review, we will focus on the fluids utilized for hemodialysis (HD) and hemodiafiltration (HDF); we will describe the process of disinfection of the machines which produce the dialytic solutions.

Background

Until the early 60s dialytic treatment was carried out utilizing Cuprophane® membranes assembled in a plane configuration (Kiil's device) not disposable, or later assembled in a tubular shape (coiled filters); both were sterilized with ethylene oxide; the hematic lines were made from polyvinylchloride and were sterilized with ethylene oxide; dialytic solutions came from the municipal water supply often neither demineralized nor softened; the buffer utilized was bicarbonate, and glucose.

The problems coming from bacterial and endotoxic contamination were very frequent. Kiil filters were assembled manually before each dialysis session

and sterilized with formaldehyde. They had the advantage of being used in single pass; on the other hand in the coil filters, although disposable, the dialysis solution was utilized with a recirculation system and contamination was very easy.

Dialysis solution was prepared manually stagnating in large tanks, at room temperature, throughout all the dialysis (8–12 h) and was successively distributed to the various monitors through a pump and tortuous tube system. All the lines for distributing the dialysis solution, also the ones belonging to the single monitors for dialysis, were substituted frequently but this did not protect from serious side effects caused by bacteria and pyrogens. For this reason, the dialytic solutions were passed through charcoal cartridges placed in the distribution circuit immediately before the filters; results unfortunately were negative and in all dialysis centers it was usual to see patients completely covered and shivering uncontrollably during the treatment.

In 1964, Mion et al. [1] suggested substituting the buffer bicarbonate with acetate contributing to partially resolve the instability of the solutions and the bacterial contamination. At the same time production of automatic machines began for the preparation of the dialytic solutions with proportional pumps, therefore bypassing problems caused by the centralized circuits.

In the late 1960s production of hollow filters made from acetate membranes began, and some of the problems caused by the coil and plane filters were resolved (allowing miniaturization, reducing the static and dynamic volume of priming).

With the utilization of the capillary filters the concept of back-filtration began to be explored, because of the possibility of reversing the gradient of the hydrostatic pressure from the dialysate side to the blood side (without the collapse of the hematic compartment wall). For a long time, because of low ultrafiltration coefficient (KUf) of the acetate membranes, the concept of back-filtration was not understood.

At the same time demineralizators began to be utilized (ionic-exchange based resins) for treating the water, with very good results for the composition of the water but with poor results concerning the bacteric and endotoxic contamination: the resin columns represented a pabulum for germs coming from the water distribution system.

In 1970, Madsen et al. [2] proposed the utilization of reverse osmosis (RO) for the treatment of the feeding water; this technique reduces the bacteria and endotoxins in the water. This technique is comparable to the demineralizators, which is less efficient in terms of ions.

RO utilization spread and now all dialysis centers have one. RO was improved utilizing complementary systems as softeners and/or demineralizators, adopting a double osmosis system (biosmosis) and through a very accurate study of the hydraulic geometry and of the materials composing the distributing circuits.

In the 1970s with the increasing number of patients undergoing chronic dialysis, the description of problems concerning the control of the acid-base equilibrium caused by the acetate buffer and its side effects began to appear in literature: for this reason bicarbonate was utilized as buffer especially to reduce hemodynamic instability [3–7]. At the end of the 1970s, once the technical problems linked with the preparation of the dialysate solution with bicarbonate [8] were resolved, use of this buffer spread progressively although some authors even much later reported extensive case-histories showing a good control of the acid-base equilibrium with acetate (also during high-flux HD) [9].

Also in the 1970s, following research by Babb et al. [10], the necessity of having dialytic membranes with greater permeability to solutes with medium molecular weight compared to that shown with Cuprophane® was pointed out, and Rhône Poulenc produced the first synthetic membrane for dialysis with high-permeability made from polyacrylonitrile, and named PAN AN 69®, with very good biocompatibility compared to cellulose membrane; in the following years new membranes were produced, many of them with a high-hydraulic permeability: polysulfone, polymethyl methacrylate, polyamide, co-polymer of polyethylene polycarbonate and ethylene vinyl alcohol.

After the mid 1980s many problems concerning the improvement of HD seemed to be resolved: the purified water had very low bacterial and endotoxin contamination, the buffer used was bicarbonate, the dialysis solution was prepared individually with monitors equipped with ultrafiltration control, biocompatible membranes and doctors started to deal with the concept of 'dialytic dose' (Kt/V) [11, 12].

But new problems arose: synthetic membranes with high-permeability utilized for high-efficiency treatments associated with higher blood flows (Qb) caused a series of problems all related to a common hydraulic matrix: high Qb utilized, to increase Kt/V, caused an increase of the pressure in the hematic compartment of the dialyzer compared to the hydraulic permeability which in turn is high to achieve a satisfactory removal of the solutes with higher molecular weight; resulting ultrafiltration was higher than that desired, and the TMP adjustment to limit UF resulted in a high-hydrostatic pressure in the dialysate compartment of the filter.

This process causes a backfiltration resulting from the difference between the forced UF and the desired one. As a consequence, HD treatment becomes an HDF where the reinfusion solution is the dialysate solution itself. There is evidence that backfiltration occurs in all the hollow fibers of high-permeability filters [13].

The quantity of the dialysis solution has an important role. Utilizing synthetic membranes with high-permeability, which can remove β_2 microglobulin, there could be the risk of passage from the dialysis compartment to the blood.

A patient undergoing standard dialysis comes into contact at each dialysis with about 120 l of dialysis solution (500 ml/min for 240 min) which is an endotoxin reservoir. Dialysis membranes if undamaged represent a secure barrier to the transit of bacteria but not of endotoxins in the hematic compartment. In fact, even though the majority of their fragments have a molecular weight around 20–30 kDa [14], endotoxic sub-unities with a molecular weight lower than 1 kDa have been isolated and Proctor et al. [15] showed active fragments with a molecular weight of 0.711 kDa which could easily pass the dialysis membrane.

Permeability of intact endotoxins has been studied by Passavanti et al. [16] after noting the reduction of (limulus amoebocyte lysate) LAL test positivity in the plasma of septic patients undergoing dialysis with Cuprophane® and PAN membranes and the contemporaneous appearance of LAL positivity in the dialysate. This means that endotoxin derivates can filter through high-permeability and also low-permeability membranes. Also Ureña et al. [17] demonstrated a permeability to endotoxin through Cuprophane®, PAN AN 69®, and also polysulfone F-60 utilizing the lipopolysaccharide (LPS) of *E. coli* marked with ^{125}I, and Lonnemann et al. [18] showed in vitro the presence of endotoxic products which could induce activation of pro-inflammatory cytokines such as interleukine 1 during blood circulation in a filter with cellulose membrane regenerated in the presence of endotoxins in the dialysis solution.

Bicarbonate used as a buffer in the dialysis solution is worse in terms of possible contamination. Basic liquid concentrates, utilized for preparing the solutions, especially if they are in screw-top tanks not utilized in single pass, are easily contaminated by bacteria, canceling the positive effect of water treated with RO. The use of thermoformed and sealed containers to store concentrates has improved the situation [19], and further progress has been made with sterilization of the basic concentrates [20] and utilization of cartridges containing powder bicarbonate.

The last passage is the geometry and in the design of the circuits for preparing and distributing the solutions: preparation and monitoring systems with a recirculation mechanism and tortuous tubings and, stagnation make it difficult to carry out efficacious rinsing and disinfection, and this seems to play an important role in the final contamination of dialysis fluids. In 1996, Passavanti et al. [21] demonstrated the absence of bacteria and LAL negativity in water which passed the RO, absence of bacteria and LAL negativity before the monitors, and episodic bacteria presence and constant LAL positivity after the monitors. According to the authors, this means that the machines represent the most important source of contamination of the dialysate. The presence of positivity for LAL test and the absence of colony growth probably means that there is a biofilm in the hydraulic circuit which can release, during dialysis, endotoxins or

LPS fragments without a contemporary release of germs. Cappelli et al. [22] pointed out this mechanism.

Ultrafilters (polysulfone or polyamide) capable of removing bacteria and endotoxins; were introduced in the circuit this operation ensured ultra pure solutions [22–27], contributing to ameliorating overall biocompatibility of the extracorporeal treatments. For this type of intervention, protocols are necessary for the management and for disinfection of the ultrafilters; biofilms can form on the membranes of the filters exposed to continuous contamination and germs can grow with release of biofilm [22]; they can also be damaged by disinfectant and heat.

It is important that the manufacturer of the dialysis monitors tests of all the chemical agents utilized for disinfection. Since the dialysis monitor is a medical device they should follow official rules and set up CE trademarks (in particular they have to be in class II).

Synthetic membranes with high hydraulic permeability allowed evolution of the convective extracorporeal treatment whose characteristic is the depuration from medium-high molecular weight compared to standard HD where depuration is limited to low-MW solutes.

During HDF high fluxes of UF (Quf), depending on Qb, hematocrit (HCT) and total proteins and filtration fraction, allow a better depuration: bigger volumes of substitution fluids are needed and their quality and composition have to be guaranteed. The pharmaceutical companies produce 'ready to use' bags which cause many problems of management and costs; this justifies an on-line production of sterile ultrapure substitution fluids derived from dialysis solutions. Results reported in literature are positive as far as the quality of liquids is concerned [28–32].

These depuration techniques need sterile substitution of fluids because fluids are infused directly into the blood in large quantities (250–300 ml/min) in relation to the type of substitution pre- and/or post-dilution [33–37].

Sterilization and Disinfection

It is necessary to use a correct definition for some terms in current language which are sometimes confused. Sterilization is a process of removal or destruction of live pathogens, including resistant forms such as spores, while disinfection is a process of selective destruction of organisms present in a vegetative state without, however, arriving at their complete elimination. Sterilization is therefore a radical operation which is carried out in an enclosed environment: the development of the process is represented by a logarithmic curve which tends asymptotically towards zero without ever reaching it. In other words, absolute sterility is theoretically impossible to obtain and therefore

the risk of survival of microorganisms is proportionally less if their number is lower [37].

Internal Disinfection of the Dialysis Monitors

Disinfection of the monitors for dialysis, whichever method and agent used, is not a single operation but consists of a series of operations in succession which should comprise primarily a procedure of post-dialysis rinsing and pre-disinfection, then cleansing, descaling, thorough disinfection and a final post-disinfection rinse so that the machine is in perfect condition for the successive dialysis sessions.

Post-Dialysis Pre-Disinfection Rinse

This is done with the aim of removing all residue of the dialysis solution from the hydraulic circuit of the machine, and if correctly carried out for a sufficient time with adequate flux it makes a valid contribution to the removal of organic substances such as hematic traces coming from an intradialytic rupture of the filter. It is particularly important for the removal of glucose residue which, if not completely eliminated, 'caramelizes' when heat-disinfection is used and represents an ideal pabulum for germs.

Obviously, the more the hydraulic design of the circuit is appropriate, the more effective is the rinse: corners, obstructions, irregularity of the tubes (for the various materials) and areas of stagnation can negatively affect this operation as well as the successive phases.

Cleansing

The aim is to act on the biofilm which tends to form on the internal part of the hydraulic circuit of the dialysis monitor (including the external connection lines of the dialysis solution) also when the methods of heat disinfection and adequate descaling-disinfection agents are correctly utilized.

However, the technicians assigned to these machines have noted that after a certain period of use various components of the hydraulic circuit appear to be uniformly lined with a slippery substance. The same thing is sometimes found in the distribution line of the water used for preparation, especially in systems served by demineralizators.

Phillips et al. [38] have related the presence of biofilm also in monitors which have been pasteurized before each dialytic sitting and descaled with agents

containing citric acid together with formaldehyde or hypochlorite. This biofilm is composed of amorphous material where coliform *Pseudomonas* and *Micrococci* grow. It is evident that the material which composes this biofilm is able to protect these germs efficiently against the action of disinfectant agents and therefore if it is not removed, it creates an important source of contamination.

In recent years, the effect of biofilm has been recognized to be more and more important in the field of purity of the dialysis solutions. It is made up of microorganisms 'trapped' in a polymeric organic matrix of bacterial origin [39] and in HD the most favorable sites for its formation depend on the type of treatment on the distribution of water and the hydraulic circuit of the monitors, because of the contamination by bacteria present in the water, the presence of organic nutrients and because of the elevated pH of the solutions containing bicarbonate. Moreover, the existence of dead spaces, low flux or interruption of the flux (night pauses), favor the formation of biofilm. This represents the starting point of biofouling of resistance against disinfection and of the bacterial re-growth [40, 41].

Pyrogens released by the biofilm are represented not only by endotoxins, but also by short bacteric DNA fragments (oligodesoxynucleotides made of 6–20 nucleotides) capable of activating cytokines and of causing an inflammatory response [42, 43]. These fragments cannot be removed from the dialysis solution utilizing ultrafiltration, so it is necessary to disinfect the entire water supply system [42, 44].

Descaling

This aims at removing the insoluble calcium and magnesium carbonate precipitates, fragments of salts of iron and inorganic materials. These incrustations can be responsible for technical and clinical problems. The first mentioned are represented by the possible malfunction of the conducimetric pH probe, necessary for guiding the action of the concentrate pump and therefore for the correct preparation and titration of the dialysis solution, the flow meter, the electric valve, the pumps, the heating bodies, and the hematic loss detector. The second are represented by the possibility that incrustations are colonized by bacteria which find a favorable environment for their growth as happens with biofilm.

Disinfection

The aim of disinfection using a physical or chemical mechanism is to eliminate the maximum number of possible microorganisms from the hydraulic circuits of the dialytic machines in order to obtain a solution which is pure from

both a bacterial and pyrogenous point of view. This can be physical (thermic), chemical, physio-chemical, 'synergic', or 'mechanical'.

Physical (Thermic) Disinfection

This is usually done by heating potable water to a temperature between 80 and 95°C and allowing it to circulate for not less than 30–40 min. The amount of energy needed to reach and maintain such a temperature is very high, so very often the water-flow during this phase is kept at a lower level than that of normal dialysis, on average around 200 ml/min. To limit even further the absorption of energy particular precautions are taken such as the partial recirculating of hot water and the use of heat exchangers capable of recuperating part of the energy from the water before this is disposed of. It should be noted that the circulation of water maintained inside the hydraulic circuit of the monitor at these temperatures can negatively influence the efficiency and the duration of some components causing or facilitating deformations, rupture of plastic tubing, favoring movements resulting in the disconnection of elements made from materials with different dilatation coefficients.

Positive characteristics of thermic disinfection are represented by a good efficacy, as long as suitable temperatures are reached and maintained (93°C for at least 10 min) according to Werner [45], linked also to the steam activity, able to act even in absence of direct contact with the water on the various parts of the hydraulic circuit, in the absence of problems connected with eventual residue of disinfectant, and complete absence of contamination for the patient and operator likewise. Negative characteristics, other than those already mentioned connected with the reliability in time of some components, are represented by the absolute necessity of a thorough preliminary cleansing of the hydraulic circuit as the high temperature can coagulate organic deposits eventually present or 'caramelize' any glucose residue, and by the lacking action on endotoxins.

It is important to point out that heat can be used to enforce the disinfecting effect of certain chemical agents (synergic disinfection): on the whole, an increase in temperature of 10°C is capable of enforcing the effect of the disinfection and, in particular, the chemical agents which are active even in the gaseous state resulting in the strengthening of their efficacy.

Chemical Disinfection

Chemical disinfection consists of preparing, circulating and stagnating a specific solution inside the hydraulic circuits of the dialysis monitors, applying the appropriate balance between dilution and means of distribution. The outcome of the process depends on the specific nature of the agent used, on the period of action and reaching all parts to be disinfected in adequate concentration. Among the different chemical products used there can be those harmful

for the hydraulic circuit materials, others which are frothy and difficult to eliminate at the end of the cycle and still others inefficacious if in combination. For these reasons all manufacturers of dialysis monitors should specify cycles of disinfection with specific products.

The chemical agents used for disinfecting the monitors should possess characteristics of action and efficacy:

1 wide spectrum biocidal action
2 action against bacterial endotoxins
3 high power detergent and descaling
4 activity in the gaseous phase
5 absence of exhalation
6 facility of storing, preparation and use
7 safety for operators and patients
8 absence of irritant phenomena, accumulation, sensitization
9 absence of frothing
10 absence of aggressiveness towards components of the equipment
11 facility of removing by rinsing
12 eco-friendly
13 low-cost.

Formaldehyde

This is the traditional disinfectant used in HD; for many years it is represented as the first choice chemical agent. Currently, it has practically disappeared from the protocol of disinfection of the dialysis monitors. It can be used in concentrations between 1.5 and 6% and has a very wide spectrum of action being active against bacteria (including *Mycobacterium tuberculosis*), spores, fungi and viruses, including HBV, HCV and HIV. Furthermore, it is active also in the gaseous phase, acting without direct contact: it is therefore capable of acting even in the most remote angle of the hydraulic circuit. The use of this agent requires, however, a thorough preliminary cleansing as the presence of residue of organic or plasticizing substances could prevent an adequate distribution. Formaldehyde (like other aldehydes) is easily absorbed by plastic materials and in patients undergoing treatment, prolonged exposure or even repeated brief exposures can cause the appearance of auto-antibodies. This is seen especially when formaldehyde solutions are used during techniques for the re-use of filters [46, 47]. In this case, in fact, the disinfecting agent comes into direct contact with the dialyzing membrane, the potting resin of the capillary filter, and the blood ports which are all components in contact with the blood. Formaldehyde has the disadvantage of being difficult to manage, toxic and carcinogenic (at least in animals); after its use it is of utmost importance to

eliminate it completely by prolonged rinsing as it is capable of penetrating the membrane of dialysis filters, and any remaining trace can cause a series of ailments ranging from a simple burning sensation on the arm (vascular access) to cardio-circulatory problems. As it is a powerful reducing agent it can alter the state of oxidation-reduction (redox) of the erythrocytes and can cause a direct or indirect hemolysis (immunologic mechanism).

Glutaraldehyde

This is a disinfectant which acts very rapidly on an ample spectrum of pathogenic microorganisms, spores, fungi and viruses with or without lipoproteic involucres (including HBV, HCV and HIV). It is normally used in a 2% concentration and its efficacy is very similar to that of formaldehyde with less contact time, but the risk of absorption and release by plastic materials remains.

There are several types on the market: alkaline glutaraldehyde, acid glutaraldehyde and in combination. The alkaline types have a weaker odor than formaldehyde, are not corrosive, are easily removed with water but are effective for a much shorter period, not more than two weeks; the acid types, on the other hand, last months but are more difficult to eliminate. Those combined with sodic phenates utilize the synergic action and can be diluted more thus reducing the side effects [48]. Acid glutaraldehyde in a 2% concentration is also available in combination with a non-ionic surface-active agent: this combination has shown to posses good disinfectant characteristics when in contact with *Pseudomonas aeruginosa*, as well as being a detergent comparable to sodium hypochlorite, maintaining detergent action even in the presence of organic material [49].

Peracetic Acid

This acid has a rapid action in a very low concentration (0.025–0.2%) [45] against an extensive spectrum of bacteria, fungi and viruses. Commercially, it is used in combination with peroxide and hydrogen. The capacity to reduce pyrogens rapidly if used in 0.1% concentration for 30 min has been described [50]. It has an excellent descaling capacity. As with aldehydes, its efficacy can diminish in the presence of organic residue, so also in this case a preliminary cleansing of the hydraulic circuits is necessary. Many experts consider peracetic acid to be the first choice for disinfecting dialysis monitors. The greatest disadvantage is its highly corrosive power when in contact with non-ferrous metals (this can be reduced using additives such as polyphosphates or modifying the pH) while on the other hand it has no action on plastic materials such as polyvinyl or polyethylene which do not absorb it.

It is much less toxic than aldehydes because its wastes are made up of acetic acid and water and when diluted at less than 1% is not carcinogenic. In relation to the concentration it can present the risk of inflammability and explosion, therefore particular attention is needed in packing and storing.

Hypochlorite

This is an anti-oxidative agent which has the characteristic of dissolving biofilm rapidly, due to its sodium hydroxide contents. Having however a strong corrosive power, it is necessary to avoid a prolonged permanency in the dialysis machines while they are not in use. It is normally diluted in a 2.5–4.5% concentration with a pH of 11–12; on the market it is possible to find even stronger concentrations combined with anti-corrosive agents.

One of the disadvantages of hypochlorite is represented by its inactivity when organic substances are present (blood, secretions and excretion): tests show that the addition of albumin at 0.2% is able to inactivate hypochlorite even when it is used in strong concentrations [45]. It is important to point out that if not removed by adequate washing hypochlorite is capable of causing serious ailments in patients undergoing treatment such as HD.

Among the chlorine-based disinfectants the use of Amuchine® is frequent; this is a electrolytic chlorine oxidant in a hypertonic solution of NaCl (18%) containing traces of hypochlorous acid (free active chlorine 1.1%) capable of developing 174 ml of oxygen every 100 ml of solution. In relation to this composition which derives from a process of manufacture by decaustication electrolysis, this disinfectant possesses all the advantages of applicability and efficacy of common hypochlorites without presenting the disadvantages. This solution, kept away from direct light, remains stable for a longer period.

The most utilized concentrations, included in a range between 1 and 15%, have a pH ranging from 7.2 and 8, show a strong bactericidal, sporicidal, and fungicidal action, in direct relation with the presence of undissociated hypochlorous acid. The fact that these solutions do not precipitate proteins in the blood is extremely important.

In the field of chlorine-base disinfectants, further progress has been made combining an ulterior descaling action with their basic action. Two examples in this field are represented by Amuchine AMU 218® and Instrunet HD®. The first is composed of a solution with 250 ppm of active chlorine, and deprived of corrosive powers, and able to prevent the formation of encrustations in the hydraulic circuits of the dialysis monitors. It has a strong wide spectrum action and is efficacious against spores, fungi viruses and endotoxins. It does not produce froth and therefore can be easily removed during the post-disinfection rinsing cycle. The second mentioned also possesses a detergent and descaling action, as

well as a bactericidal (*Tuberculosis, Pseudomonas*), fungicide and viricide (HAV, HBV, HCV and HIV) action, and is active against endotoxins.

This agent is composed of a solution which contains 1.5% sodium chlorite and a second solution with 33.6% of lactic acid. Mixing the two components an activated solution with 1.15% of sodium chlorite and 7.75% of lactic acid is obtained and the result is the production of chloride dioxide which is the main component. The dioxide is released in the gaseous phase, and therefore is capable of reaching all the internal parts of the hydraulic circuit. Being an oxidant it shows an elevated disinfectant activity and moreover the lactic acid used in the activation maintains the pH of the solution at a very low level producing a simultaneous descaling action. The cleansing effect is guaranteed by the saponification of organic substances induced by the acid environment, together with the lowering of the surface tension of the water.

Synergic Physical-Chemical Disinfection

Heat can be used to strengthen the disinfectant effect of some chemical agents: on the whole an increase in temperature of 10°C is capable of increasing disinfection, and in particular the efficacy of the active chemical agents even in the gaseous stage is increased.

For example, the synergy between heat and chemical agents is used to advantage to obtain a descaling and disinfecting action with the use of citric acid, when appropriately diluted (12%) in water at 90°C is capable of removing precipitates of calcium and magnesium and organic deposits. Used alone, it has an excellent descaling action but does not posses a sufficient action against bacteria, protein, lipids and other organic products.

Mechanical Disinfection

As already mentioned, the increased use of a purifying method such as HDF on line requires sterile reinfusion fluids. This does not mean producing only a dialyzing solution (not directly in contact through the membrane with the blood), but to produce a liquid which is infused directly in the blood in quantities which can exceed 250–300 ml/min, according to the type of substitution (pre- and/or post-dilution) [33–36, 51–53].

The quality of the dialysate, the fundamental link in the chain of biocompatibility of the treatment, can be guaranteed by the presence of several filtering stages: microfilters or anti-bacterial filters and ultra filters. The first mentioned are normally inserted in the water circuit of the dialysis monitor entrance and are meant to capture any bacteria coming from the distribution system, while the second, which are capable of absorbing pyrogenic substances, are made for example from membranes such as polysulfone or polyamide.

Modern dialysis machines with hydraulic circuits correctly designed and manufactured both in the geometry and in the components, of reduced capacity and rigorously single pass, without flux interruption and with ample choice of cycles of chemical–thermic disinfection guarantee, on the whole, the preparation of the dialytic solution in a 'clean environment'. This could be insufficient as the system is not closed during treatment but has several 'windows' in contact with the outside world and therefore is at risk of contamination.

The most important aspect is that sterile does not mean apyrogenic and therefore correct disinfection of the hydraulic circuit may not be sufficient to guarantee the apyrogenity of the system and/or the absence of endotoxins: these could be hidden inside any biofilms present and in any case, they are difficult to eliminate even using heat [22–28, 38–43].

The only protection consists therefore in the use of ultrafilters before the dialyzers inside [51–57] and also outside [36] the monitor. It is not however sufficient to supply the machine with these ultrafilters, but it is also necessary to rigorously adhere to the periods of their substitution indicated by the supplier. These, after some time, could negatively influence the filtering powers of the membranes, reducing or even annulling these powers.

To guarantee a constantly efficacious filtering power cycles of 'spilling' should be provided. By 'spilling' we mean automatic washing of the membrane with a tangential flux or in counter-current in order to remove any substances which may have been retained, restoring in this way the effective surface of absorption. In any case the control of the dialysate quality should be always rigorous and accurate. It is necessary to provide and carry out a standardized protocol and special guide-lines are available [58–63].

Post-Disinfection Rinse

This is aimed at eliminating every residue of disinfectant solution from the hydraulic circuit mechanically and by dilution but it should be carried out also after thermic disinfection, with the purpose of eliminating the endotoxins deriving from germs which have been killed. The efficacy of a post-infection rinse, as also all the previous phases, is greater the better the 'geometry' of the hydraulic circuit is, which should be designed and made according to a correct project, capable of eliminating all deviations, areas of stagnation and presence of inaccessible zones. It is of utmost importance that the water used for post-disinfection does not represent a new contaminating agent, and therefore that it is produced and distributed by a hydraulic circuit which in turn is correctly disinfected. Moreover, all companies which produce equipment for HD should not only define specific cycles of disinfection using specific products,

but also schedule the automatic implementation (not by-passable) of an adequate rinse which guarantees the elimination of all residue of sterilizing agents. Specific tests are available on the market however, to determine whether residue of disinfectant agents is present: these tests however can present an insufficient sensitivity when used to detect residue deriving from the contemporary use of different disinfectants or, sometimes, when glucose is present. For example, for hypochlorites colorimetric tests are available to detect the presence of chlorine, for peracetic acid test using amino-iodine tests, for citric acid UV test.

External Disinfection of Dialysis Monitors

Disinfection of the hydraulic circuits of the dialysis monitors is not the sole procedure capable of guaranteeing maximum security: it is also necessary to carry out a thorough cleansing and disinfection of the external parts of the equipment before starting another dialysis session. A correct procedure includes: the operators (clothing, maneuvers, instruments) and the environment (from the dialysis room to the furnishing). Having a correctly disinfected monitor in its internal components, but operating in a contaminated environment is paradoxical.

The external surface of the equipment plays an important part in the transmissibility of infections. In the first place it is possible, and it happens frequently, that blood stains the surface of the monitors, both during the injection for vascular access and the dismantling of the hematic lines at the end of the session. Secondly, it is possible that operators use the machines (to regulate a certain parameter or to switch off an alarm) with blood-stained gloves, the consequence, for example of a preceding urgent intervention of compression of a bleeding fistula. Thirdly, it happens often that, during the disconnection of the patient, the operator, without changing gloves intervenes alternatively on the machines and on the vascular access. A very important phase is that relative to the final dismantling of the filters and of the hematic lines; a repetitive maneuver which could be carried out hurriedly without paying attention. Particular attention should be paid, therefore, to the external surface of the monitors, both at the project level (design, ergonomics, materials) and operative level (before, during and after each treatment). All buttons should be recessed and protected by a film, and knobs should not protrude, easy receptacles (especially if grained or with a rugged surface) for hematic residues or dirt. Every trace of blood should be promptly removed, and an indispensable procedure at the end of each treatment is a thorough cleansing and disinfection of all the external surfaces (in particular the support of the drip chamber) and the connections of pressure transducers) using appropriate agents. In the choice of products it is necessary to keep in mind the characteristics of the

materials of which the body of the machine and relative accessories are composed to avoid irreparable damage which could range from the simple opacity of the transparent panels to the actual 'melting' of some of the plastic components. On the whole, products containing benzene, acetone, toluene, xylene or similar solvents should be avoided. Finally external detergents and disinfectants should be used with disposable paper wipes (to be changed after use on each machine) avoiding every type of cross-contamination. Other critical components, possible causes of transmission of bacteria and/or viral cross-infections from patient to patient, are constituted by the connection of the dialytic solution in the direction of and from the filter. Both the external and internal surfaces can be easily contaminated especially in the dismantling phase of the dialyzers, when the maneuver is carried out by operators wearing soiled gloves. Moreover, at the beginning of the dialytic session, before connecting the patient the connectors could be in direct contact with the filters in the presence of heated dialytic solution for some time and therefore it is clear that they could represent an ideal carrier of bacteria and/or viruses because the configuration of their internal surface is complex.

Disinfection of connectors with Amuchine® 25% for 10–15 min at the end of each dialysis treatment followed by a generous rinse could be very useful [64] (table 1).

In table 1, we report a list of the most important incompatibilities and of the dangerous associations between chemical, disinfecting, descaling, detergent normally utilized in the dialysis centers ([65] modified). We also report their characteristics and possible toxic effects [66–68].

Acetic Acid

A colorless fluid with a pungent odor. Glacial acetic acid must be stored at temperatures >15°C to avoid crystallization. In dialysis it is used to dissolve calcium and magnesium carbonate precipitates. In a concentration of 5% it has bactericide properties (in particular against *Pseudomonas aeruginosa*); at lower concentrations it is bacteriostatic. It is not compatible with bases and reacts with hypochlorite. It is irritating for the skin (corrosive at a concentration of 30%: burns and necrosis), for the eyes (keratitis) and for the upper air passage (ulcerations), for the lungs (edema), and for the gastric apparatus (vomit, abdominal colic, diarrhea).

Citric Acid

An odorless white powder with an acid taste. Dissolved in water it is utilized to dissolve calcium and magnesium carbonate precipitates. This acid together with heat becomes also a descaler and disinfectant. It is incompatible with bases and with oxidant agents.

Table 1. Toxicity and incompatibility of the chemical agents normally utilized for detersion, descaling and internal and external disinfection of the dialysis monitors

Agent	Incompatibility	Risk with
Acids (generic)	Bases (generic)	Hypochlorite Hydrogen peroxide
Aldehydes	Acids (generic) Ammonia Phenols	Hypochlorite Hydrogen peroxide Hydrochloric acid Chlorhexidine
Alcohols	Oxidant agents Phenols	Oxidant agents Potassium
Chlorhexidine	Soaps Anionic materials	Iodine Aldehydes
Citric acid	Hypochlorite Hydrogen peroxide Bases (generic)	
Ether	Oxidant agents Alogens	Hypochlorite Hydrogen peroxide Oxygen
Phenols	Alkalis Aldehydes	Oxidant agents
Hydrogen peroxide + Peracetic acid	Concentrated alkalis Iodine	Hypochlorite Phenols Aldehydes Alcohols
Hypochlorite	Acids (generic)	Acids Nitrites Aldehydes Phenols Hydrogen peroxide Alkalis
Iodine	Phenols Alkalis	Chlorhexidine
Tensioactive agents	Chlorhexidine	

Alcohols (Ethanol, Methanol)

These are highly inflammable colorless fluids with a characteristic odor, utilized in combination with iodine or chlorhexidine. They are incompatible and can give violent reactions with oxidant agents and potassium. They are irritant to the eyes and cause corneal damage. Ingestion of methanol is toxic and

the maximal concentration tolerated is 200 ppm. Inhaling its vapor causes a violent irritation of mucosa.

Chlorhexitine

An odorless and colorless or yellow fluid. Utilized mainly as gluconate but also as acetate, it is used with alcohol for disinfecting or with water for cleansing. It is efficacious against bacteria both gram positive and negative but some of these have been described as resistant to chlorhexidine in water solution (*Pseudomonas Maltophila*). It is incompatible with soaps and with other anionic materials. It cannot be used together with iodine and aldehydes because it can produce carcinogenic products.

Diethylic Ether

A colorless fluid with characteristic odor. Very volatile and inflammable, it has a very low boiling point (35°C) and it has to be stored at cold temperatures away from the light. Its vapors are inflammable in contact with air starting from 1.8% and in oxygen it can explode starting from a concentration of 2%. For these reasons it cannot be utilized near flame or electrical devices that can produce sparks. It reacts with oxidant agents and with halogens. Diethylic ether vapors if inhaled are rapidly absorbed through the alveolar membranes. Successively it passes into the circulation and easily through cellular membranes spreading in all the tissues with accumulation in lipids. Its most important action is the depression of the nervous system: inhalation at a concentration of 1% causes analgesia, at 3% loss of consciousness and over this concentration anesthesia. It has an irritating effect on the mucosa causing hypersecretion.

Phenol

In the crystalline phase it is pink. Soluble in water it can be mixed with ether, alcohol and fats. It has to be stored at cold temperatures away from the light. Phenol is bacteriostatic at the concentrations of 0.2%, bactericide over 1% and fungicide over 1.3%. Many derivates of phenol have a better bactericide action compared to phenol itself (halogenate phenols, biphenols, alkylic derivates, resocinols). Phenolic solutions are incompatible with alkalis and with aldehydes and react strongly with oxidant agents. Phenol is rapidly absorbed and so intoxication can happen after inhalation, contact and ingestion. If there is contact it can cause burns on the skin or in the eyes in a concentration of 1%; at a concentration of 10% it causes corrosions similar to those caused with caustic agents. Inhalation of pure phenol vapors even in small quantities can cause serious lesions with edema of the glottis, hemorrhagic tracheo-bronchitis and broncopneumonia. Whatever way it is absorbed, symptoms appear very rapidly. Exposure for long periods must be avoided because it can cause: cutaneous

eruptions, digestive disturbances, nervous disturbances and myocardial hepatic and renal pathologies.

Formaldehyde

A colorless fluid with a characteristic pungent and irritant odor. Formaline is formaldehyde in solution with water at a concentration of 35–40%, it has to be stored at a temperature >15°C. It cannot be mixed with ammonia, phenol or acids and reacts with anti-oxidant agents. If it reacts with hydrochloric acid it produces carcinogenic substances. For the cells, it is a poison which combines covalently with various protoplasmatic groups and when it comes into contact with hepatic cells it becomes formic acid. It is toxic when inhaled and can cause eye damage (keratitis) upper breathing passage edema and pulmonary edema. Skin contact can cause burns and ulcerations on the hands, it can also cause sensitization. A theratogenic effect is not proved but is suspected, a carcinogenic effect is proven in animals and suspected in humans.

Gluteraldehyde

As a disinfectant agent it is superior to formaldehyde and is active against all microorganisms, also spores and viruses. It is less volatile compared to formaldehyde and for this reason it has a less aggressive odor and is less irritant when inhaled. Incompatibilities and toxic effects are similar to those of formaldehyde, although less severe for skin and mucosa but can cause sensitization phenomena. A carcinogenic effect is suspected both in animals and in humans.

Iodine

It is crystalline in shape, the color is green-violet, and it has an acrid and irritant odor. Normally, it is diluted in alcohol obtaining a dark brown-solution. It is incompatible with phenol and alkali. Iodine has a direct toxic effect on cells because it causes denaturation of proteins, similar to acids and caustics. It has a powerful action against all microorganisms and viruses. Diluted at a concentration of 1:20,000 it can destroy the majority of bacteria in 1 min and at the same concentration in 15 min can kill bacterial spores. Iodine and its derivates can cause allergic reactions resulting in anaphylactic shock: cutaneous, ocular, mucosa and upper breathing passage, lung hypersensitivity. Inhaling iodine vapors can cause symptoms similar to the ones caused by chlorine inhaling.

Sodium Hypochlorite

A colorless or slightly yellow fluid, it has the characteristic odor of chlorine. It has to be stored at cold temperatures and away from the light. Sodium hypochlorite concentration decreases during storage and for this reason solutions have to

be used in short time. There are many solutions where chlorine is present in hypochlorite form. Elementary chlorine, also in the indissociated chlorine acid form, is a very powerful biocide. At a pH of 7, the concentration necessary to kill most of the microorganisms in 15–30 s is between 0.10 and 0.25 ppm. *Mycobacterium Tuberculosis* is the only resistant microorganism: concentrations 500 times higher are needed to destroy it (50–125 ppm). It is also viricidal and amebicidal. It is a highly reactive agent and for this reason it can be bound to an organic material and if this is present its bactericide action decreases. It is incompatible with acids, and if it comes in contact with them it converts to highly toxic chlorine gas. It is not compatible with nitrites (risk of explosion), reacts with aldehydes, phenol, alkali and hydrogen peroxide. Maximum concentration of chlorine tolerated in the air is 0.5 ppm: it is a very aggressive substance and can cause acute pulmonary edema. Symptoms are burning of the eyes and of the upper breathing passage, dry cough, retrosternal pain sensation of suffocation. Concentrated hypochlorite causes damage to the skin (irritation, eczema, necrosis), eyes (irritation keratitis) lungs (edema) digestive apparatus (vomiting, abdominal colic), kidney (nephrotoxicity).

Hydrogen Peroxide

It is colorless and odorless and decomposes producing oxygen. One liter of pure hydrogen peroxide can produce 120 l of oxygen. As a disinfectant agent it is used as a solution in a concentration of 3% which produces 10 volumes of oxygen. Hydrogen peroxide is normally used mixed with peracetic acid. It has a light germicide action and is incompatible with alkali and with iodine. It can react strongly with hypochlorite, alcohols, phenol and aldehydes. Hydrogen peroxide causes burns in a concentration of 5% on the mucosa and of 10% on the skin with hyperemia, and penetrates in the lower layers of the derma. The worst burns (higher concentration of hydrogen peroxide or longer time) are similar to the ones caused by corrosive acids.

Tensioactive Agents

These agents can reduce the surface tension of interface with greasy substances; they permit the detachment and removal; they are detergents. They dissociate in water depending on the activity of the anion or of the cation; they are called anionic or cationic. The anionic ones include soaps and the cationic ones come from quaternary ammonium (the 4 atoms of hydrogen of the ammonium are substituted by radicals; at least one of these is paraffinic with high molecular weight). Anionic tensioactives are incompatible with chlorhexidine and have an antagonist action compared to the cationic ones. They are scarcely toxic (if ingested) and harmful with the only exception of potassium soaps, but they can cause sensitization and pathologic alteration of the skin after prolonged

exposure. The aggressiveness is caused by alkaline pH (between 10 and 11) and by the solvent action on the skin lipids. Cationic tensioactives are often utilized in dialysis for skin disinfection and for disinfection of the monitors. They are toxic if ingested causing inhibition of the endoglobular cholinhesterase, and have a ganglioplegic action similar to curare. Solutions with concentrations $<10\%$ can cause necrosis of the mucosa.

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Biofilm on Artificial Surfaces

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Abstract

Biofilms are microbial communities quite different from planktonic cells and most of common microbiological concepts had to be updated in recent years. The peculiar capacity to resist to disinfectants and antibiotics results in biofilms being a public health problem mainly when modern medical devices are used. All artificial surfaces used in medicine may be prone to biofilm attachment and could therefore represent a cause of acute or chronic infectious diseases. Uremic patients are at higher risk from biofilms as not only traditional causes, such as indwelling catheters, but also hemodialysis apparatuses contribute to bacterial exposure. Chemical or physical disinfections have been demonstrated partially active on sessile microorganisms and biofilm avoidance remains the goal to assure an adequate quality of dialytic treatment.

Biofilm represents a community of microorganisms attached and growing on a solid surface. Bacteria, fungi, yeasts, protozoa and other microorganisms may aggregate to form biofilm. Microorganisms are enveloped in an extracellular matrix of polymeric substances while biofilm is characterized by structural heterogeneity, genetic diversity, and complex community interactions.

Biofilm develops on virtually all surfaces submerged in or exposed to some aqueous solutions irrespective of whether the surface is biological (plants and animals) or inert (glass, plastics, metal, stones). It forms particularly rapidly when the solution contains an abundant nutrient supply. The main component of biofilm is water (97%) organized in channels carrying, by convection, bulk fluid to the community, containing microbial live and dead cells (15%), exopolysaccharides (85%) and a small amount of macromolecules such

as bacterial DNA, proteins and other products of bacterial lysis [1]. The initial event in biofilm formation is the adhesion of free-floating microbes to surfaces through weak, reversible van der Waals forces. If the microorganisms are not immediately separated from the surface they can anchor themselves more permanently using cell adhesion molecules such as surface proteins, pili and fimbriae. Some human proteins such as connective matrix (collagen) or plasma (fibronectin and fibrinogen) adsorbed on the biomaterial surface are recognized by specific staphyloccal membrane adhesins, defined as Microbial Surface Components that Recognize Adhesive Matrix Molecules (MSCRAMM), and seem to be determinant for initiating the colonization process [2]. The first microbes begin to synthesize an exopolysaccharide and proteic matrix (slime) that holds the biofilm together and helps in deposition of other cells by providing more varied adhesion sites. The compositions of extracellular polysaccharide matrixes are different between microbe species and play an important role in determining the final architecture of biofilms. The main component of bacterial extracellular matrix is cellulose, but in addition to cellulose other polysaccharides are now recognized as important components. *Staphylococcus epidermidis* and *Staphylococcus aureus* produce polysaccharide intercellular adhesion (PIA) or the related poly-*N*-acetyl glucosamine polymer whose synthesis is regulated by the ica locus. PIA supports cell-to-cell contact by means of multilayered biofilm. Now it is recognized that PIA-like polymers are produced by several gram-negative bacterial species (e.g., *E. coli* MG1655) [3].

Only some species are able to attach to a surface on their own, while others are often able to anchor themselves to the matrix or directly to earlier colonists. Once colonization has begun the biofilm survives by its own life, growing through a combination of cell division, recruitment and detachment.

The polymeric matrix of microbial origin protects the cells within it, facilitates the communications among microbes through chemical and physical signals, and provides a physical and chemical barrier to the diffusion of antimicrobial substances and to environmental insults.

Biofilm is a dynamic complex system that evolves according to local microenviromental conditions (hydrodynamics and biochemical conditions, thickness, shear stress and possibly others) and has a spatial heterogeneity (channels, towers) that is linked to the type of bacteria and differs in relation to oxygen limitation, pH, nutrient access and growth rates.

Biofilm and Medical Devices

Microorganisms in a sessile phase exhibit a distinct phenotype with respect to gene transcription, growth rate and ability to resist antimicrobial or

Table 1. Medical devices associated with biofilm infections

Catheters	Implants	Devices
Central venous catheters	Pacemakers Arteriovenous shunts	Biliary stents
Arterial catheters	Spinal implants	Ureteral stents
Pulmonary artery catheters	Penile implants	Mechanical heart valves
Umbilical catheters	Breast implants	Fracture fixation devices
Peritoneal dialysis catheters	Orthopedic prostheses	Joint prostheses
Urinary catheters	Cochlear implants	Vascular grafts and assist devices
Nasogastric tubes	Neurosurgical stimulators	Intrauterine devices
Gastrostomy tubes	Middle ear implants	Intraocular and contact lenses
Enteral feeding tubes	Dental implants	Coronary stents
Endotracheal tubes	Voice prostheses	Intracranial pressure devices
Tracheostomy tubes	Implanted monitors	Suture material

disinfection treatments from planktonic (freely suspended) organisms and therefore pose a public health problem.

Biofilm, as a matter of fact, is involved in acute and chronic infectious diseases and has been described in human and experimental pathology such as native valve endocarditis, otitis media, bacterial chronic rhinosinusitis, COPD, chronic urinary infections, bacterial prostatitis, osteomyelitis, dental caries, biliary tract infections, Legionnaire's disease and amyloidosis.

Modern medicine is largely based on medical devices support and their surfaces, even if from many different materials, represent a possible site of microorganism adhesion with biofilm formation. Table 1 reports medical devices documented to be biofilm contaminated with consequent clinical sequelae. When a medical device is microbiologically contaminated, biofilm formation depends on several variables, bacteria and non-bacteria dependent. Main variables are: type and number of microorganism, type and physicochemical characteristics of surface, flow rate, components (nutrients, antimicrobials) and temperature of liquid through the device. The rapid growing of scientific knowledge on the matter is documented by an increasing number of published reviews dealing with biofilm and related problems [4–11].

Biofilm and Dialysis

Uremic patients are at high risk of acquiring a biofilm related illness as it usually takes some time to reach stage 5 of CKD and in the course of treatment

several medical devices could be used. Intravascular or urinary catheters represent the most frequent cause of medical device related pathologies, but it is during the phase of chronic kidney replacement therapy that uremic patients are at higher risk. During chronic hemodialysis infections, with related inflammatory events activation, may take place not only from vascular access but also from dialysis apparatus [12]. Even in the absence of standardized collection methods, biofilm has been detected in the hydraulic circuits of hemodialysis machines particularly in low-flux sections, loops and ultrafilters. In this biofilm, the concentrations of bacteria and endotoxins can range from 1.0×10^3 to 1.0×10^6 cells/cm^2 and 1–10 EU/cm^2, respectively. Several constituents of cell wall of viable or not viable microorganisms can be released into the dialysate, including high molecular weight substances (>100,000 Da) as well as low molecular weight ones (<1,000 Da) or DNA fragments [13]. These molecules can stimulate circulating and membrane adherent leukocytes to release pro-inflammatory cytokines (IL-1β, TNF-α), important co-causal factors of the chronic micro-inflammatory condition of the hemodialysis patients. This specific chronic induction of pro-inflammatory cytokines could contribute to the MIA syndrome or to EPO resistance in dialysis patients [12].

Dialysis monitors are at risk of microbiological contamination from different entrances. Feeding water from water treatment system, concentrate salts and drain backflow are well-documented causes while critical is the water pipe connecting distribution loop with individual hemodialysis monitor where biofilm may take place during water stagnant phases (e.g., during the night).

Of note, microbiological controls (either bacteria or endotoxins), performed on water for dialysis or dialysate according to even most recent standards [14], evaluate contamination from planktonic bacteria but not from sessile microorganisms and only testing the levels of cytokines inducing substances are related to biofilm and to hazards for patient health [15].

Therefore to prevent biofilm, in the absence of assurances for a satisfactory microbial level, proper disinfection protocols for the complete water distribution system, including connecting pipes and dialysis monitors, must be instituted in each dialysis unit (figs. 1–7).

Biofilm and Disinfection in Dialysis

Disinfection enters the quality assurance program in dialysis and represents part of the various anti-inflammatory treatment strategies adopted to improve outcome in these patients.

Several liquid chemical germicides or physical disinfectant techniques are commercially available and choice is based not only on effectiveness but also

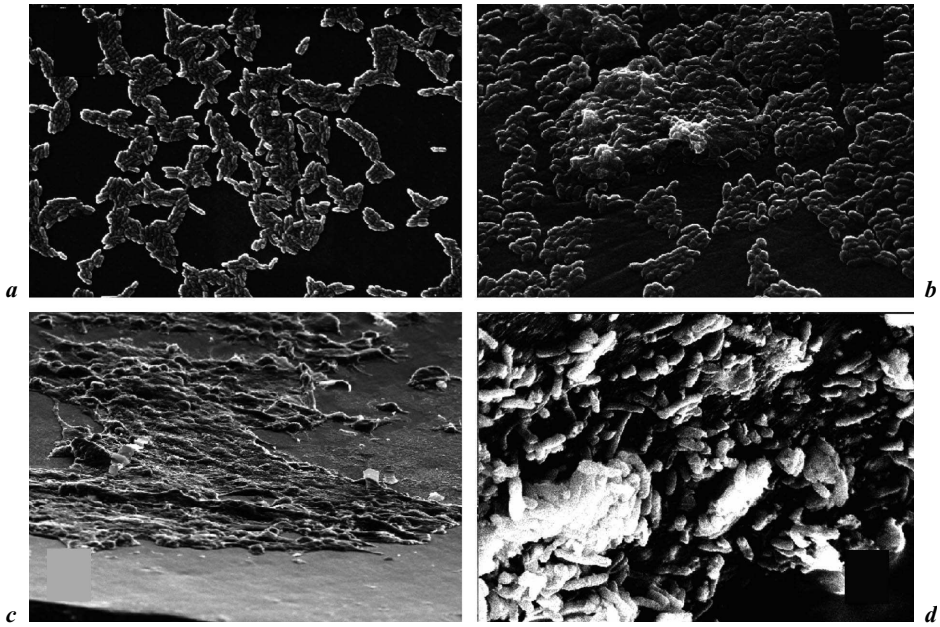


Fig. 1. Subsequent phases of biofilm formation with bacterial deposition (***a***), attachment (***b***), growing (***c***) up to a mature biofilm (***d***) onto a silicone tube from a dialysis monitor hydraulic circuit.

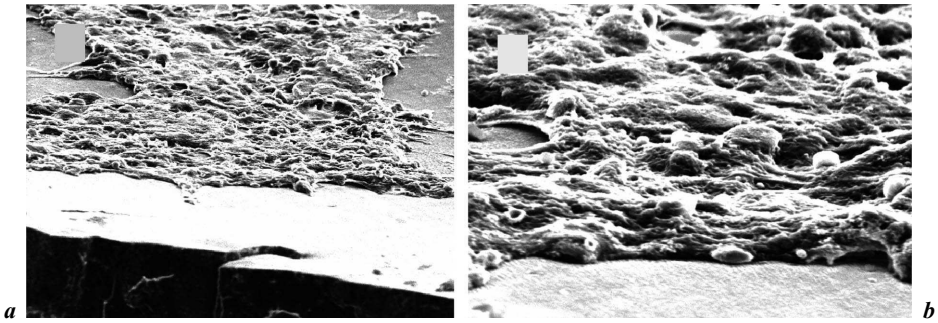


Fig. 2. Biofilm presence on a peritoneal dialysis catheter removed because of peritonitis caused by colonization.

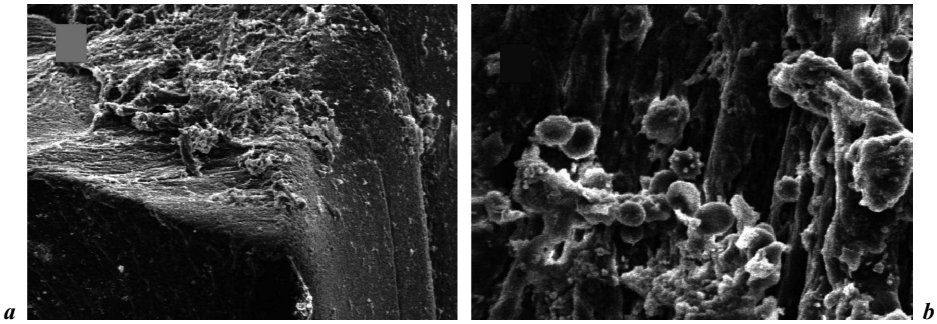


Fig. 3. Ureteral stent showing biofilm, cellular debris and erythrocytes at different magnifications.

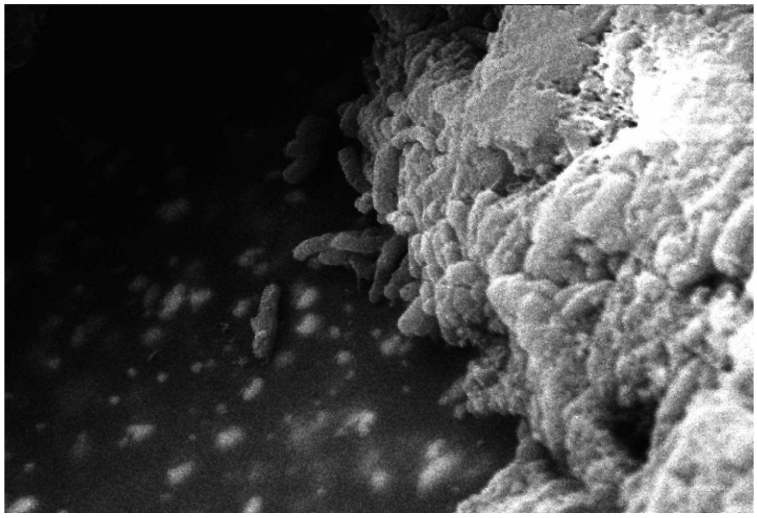
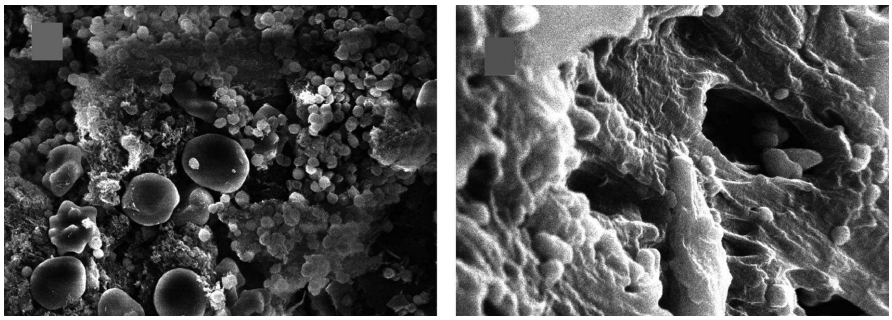


Fig. 4. Biofilm on a urinary catheter with bacteria released from biomass.

on effects in term of tolerability on piping and accessories materials as reported in table 2.

Today, as a matter of fact, disinfectants in dialysis are considered as class II devices and therefore regulated by FDA in the US and CE mark application directives in Europe. Therefore disinfection is a part of the maintenance procedure validated by device manufacturers, and health care professionals need to comply with suggested and validated protocols [16].



a ***b***

Fig. 5. Central venous catheter showing biofilm deposition with erythrocytes included in the matrix.

Fig. 6. A filtration membrane from water treatment system with inorganic (crystals) and bacterial deposition.

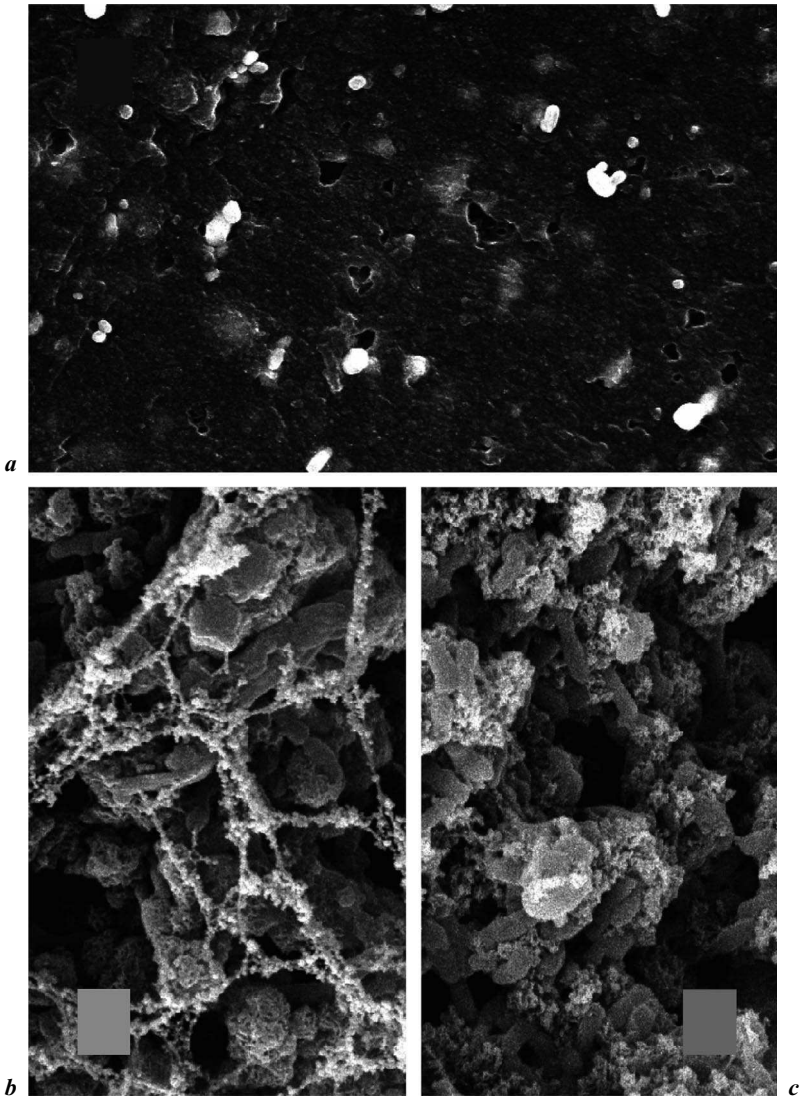


Fig. 7. Biofilm presence on a water treatment system showing PVC piping irregular surface and bacterial deposition (***a***). Mature biofilm with inorganic salts deposition found in a low flux zone of a dialysis monitor (***b***, ***c***).

Table 2. Disinfectants used in dialysis for water treatment systems and monitors with compatibility for piping material

	Water treatment system	Monitors	Compatibility
Chemical			
Hypochlorites	X	X	PVC, PVDF, PEX, PP, PE
Peracetic acid	X	X	PVC, PVDF, PEX, PP, PE, ABS
Chlorine dioxide		X	PVC, PVDF, PEX, PP, PE
Formaldehyde	X		PVC, PVDF, PEX, PP, PE, SS
Ozone	X		PVC (low concentration), PVDF, SS
Physical			
Ultraviolet irradiators	X		nr
Hot water (>80°C)	X	X	PVDF, PEX, SS

ABS = Acrylonitrile butadiene styrene; nr = not reported; PE = polyethylene; PEX = cross-linked polyethylene; PP = polypropylene; PVC = polyvinylchloride; PVDF = polyvinylidene fluoride; SS = stainless steel.

The importance of biofilm avoidance in dialysis disinfection procedures has been demonstrated as it causes a bacterial regrowing after some hours from a standard disinfection and it affects efficiency of both chemical or heat disinfections [17]. In search of optimal treatment for a combined action on microorganisms and biofilm several research papers describe effects from chemical disinfection alone or in conjunction with some physical treatment. Hypochlorite has offered a concentration dependent effect on biofilm removal, but only autoclaving is able to obtain a complete biofilm removal [18, 19].

When comparing some oxidizing, non-oxidizing and surfactant agents, chemicals, associated with mechanical treatment, have been reported to be weak agents in biofilm removal and some of them may cause even an increase in biofilm mechanical stability [20]. Ultraviolet treatment too, seems of little impact as it is unable to modify pathogen adhesion on biofilm within a water distribution system [21]. An effective procedure to remove biofilm from tubing surface of monitors previously disinfected with peroxyacetic and citric acid has been described with an enzyme/detergent combination leading to a complete detachment of the biomass [22]. In presence of biofilm the efficacy of both chemical and physical conventional disinfection procedures on hemodialysis monitors is significantly reduced for both CFU and endotoxins. Chemical disinfectants such as peracetic acid, hydrogen peroxide and hypochlorite used alone at concentrations of clinical practice cannot effectively remove the biofilm in experimental conditions. The penetration of a disinfectant into the

biofilm appears to be the major rate-limiting factor and it is postulated that only the outermost layers of the biofilm is affected by disinfectant because diffusion into the biomass is impeded by the polysaccharide matrix. Hydrogen peroxide and citric acid for their detergent effect have a better microbial detachment efficacy, but a lower bactericidal activity compared with peracetic acid and hypochlorite. The combination of a chemical with detergent effect (such as citric acid) and a chemical with high disinfectant activity (such as hypochlorite) offers better results on reduction of CFU, but still results as incompletely efficient in cell detachment from tubing surfaces. As a result, the endotoxin concentration is not effectively reduced and residual biofilm allows re-growing and a new colonization.

Isolated heat disinfection at temperatures between 70 and 95°C, as in most hemodialysis apparatuses, cannot remove biofilm and produces a lower reduction of CFU when compared to chemical disinfectants such as hypochlorite and peracetic acid. When heat is combined with chemical detergent agents it has a better efficacy on CFU reduction, but it is still unable to completely eradicate biofilm [23].

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Compatibility of Electrolytically Produced Sodium Hypochlorite Solutions on Long-Term Implanted Dialysis Catheters

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Abstract

More than 20% of the world's population use a catheter for dialysis, despite guidelines limiting their use. Although the structure and design of the catheters differ by manufacturer, the material used in central venous catheters and peritoneal dialysis catheters are the same across manufacturers. Given the long-term use of these catheters in the dialysis population, the good compatibility of the antiseptics and disinfectants used on the catheters is imperative to prevent failure and cracking of the catheter material. Tensile strengths of commercially available catheters were measured after exposure to commonly used disinfectants. The tensile strength was then compared between the catheters by analyzing the displacement vs. force (N) curves produced during the evaluation. A total of 44 catheter lumens were evaluated. The electrolytically produced sodium hypochlorite solution, Alcavis 50/ExSept Plus, was the only solution shown to be compatible with all three catheter materials resulting in a deviation of less than 10% for each of the different catheter types. Electrolytically produced sodium hypochlorite solutions were the only solutions in this study that did not alter the physical properties of any of the catheters after long-term exposure.

Long-term implanted catheters continue to be an important tool for the administration of dialysis. In the United States, for example, there is a prevalence of 20% catheter use for hemodialysis (HD), while all peritoneal dialysis (PD) patients require an implanted catheter [1]. This results in more than 90,000 dialysis patients in the United States using a long-term catheter. Prevalence of long-term catheter use throughout the world may be even greater dependent on the proportion of patients on PD and availability of vascular surgical teams to prepare fistulas [1, 2].

Patients with either a HD central venous catheter (CVC) or PD catheter (PDC) are at an elevated risk of skin infection at the exit site of the catheter or below the skin in the catheter tunnel. CVCs are at risk of bacteremia, if bacteria are introduced into the lumen of the catheter and migrates into the blood stream. Similarly, PDCs are at risk of peritonitis if bacteria enter the inner lumen of the catheter and reach the peritoneal cavity.

Proper handling of the catheter and aseptic technique are required to reduce risks of infection. Routine dressing changes, antisepsis at the exit site, cuffed catheters, proper disinfection prior to accessing and careful manipulation of the catheter are powerful tools for reducing exit site, tunnel and blood stream infections. Maki showed that in the short-term, approximately 1 week, bacteremia is likely a result from the insertion procedure with a lesser risk from hub contamination [3]. However, Sitges-Serra and Linares et al. suggest that the risks of bacteremia are greatest as a direct result of hub contamination. This was their conclusion in a study population that had catheters in place on average for approximately 3 weeks [4, 5].

Several studies have demonstrated that the use of electrolytically produced sodium hypochlorite (ESH) solutions for the chronic care of implanted dialysis catheters (CVC and PDC) can reduce the rate of infection. Benefits of the use of ESH for exit site antisepsis for CVC care has recently been demonstrated by Astle and Jensen [6], while Mishkin et al. [7], Wahdwa et al. [8] and Mendoza [9] have demonstrated the benefits of ESH for routine PDC exit site care. Furthermore, advantages using ESH solutions in reducing bacteremia and peritonitis rates have also been demonstrated by Astle et al. [6] and Mishkin et al. [7].

The benefits of ESH for routine long-term catheter care at the exit site and connection sites (ex. hub and cap disinfection and transfer set change disinfection) have been clinically demonstrated. However, a common obstacle of good catheter care is the compatibility of an antiseptic or disinfectant with the catheter material. The Center for Disease Controls' Guideline for the Reduction in Intravascular Catheter Related Infections, recommendations for the routine care of 'Dialysis CVC' states: 'ensure the cleaning solutions are compatible with the catheter materials' [10].

CVC and PDC exit site care is performed thrice weekly and daily, respectively. Disinfection of the catheter hubs and connectors is also performed before and after every treatment. Given a life expectancy of a catheter of 6 months, this results in a minimum of 78 applications of the antiseptic or disinfectant to both the skin and catheter material. It is imperative that the antiseptic or disinfectant be safe and effective to the patient as well as compatible with the catheter materials. There is ample evidence that ESH solutions are safe, non-irritating and non-sensitizing, and effective [6, 7, 11–13]. The compatibility of the catheter materials with different antiseptics and disinfectants will be reviewed.

PDCs are usually made out of silicone as are the transfer sets used with PDCs. CVCs however are usually made from one of three different materials: (1) silicone (similar to PDC); (2) Tecoflex® polyurethane (Noveon), or (3) Carbothane® polyurethane/polycarbonate copolymer (Noveon) [14]. Although the structure and design of the catheters differ by manufacturer, the material used in CVC and PDC catheters are the same across manufacturers.

The safety testing of catheters is similar around the world and follows ISO 1055501:1995(E) guideline. The use of antiseptics and disinfectants on catheters potentially affect the safety of the catheter by degrading the structural integrity of the catheter material, (ex. lumen) or the integrity at each juncture of the catheter (ex. luer connector to extension, extension to hub, hub to lumen, etc). ESH is listed as a recommended disinfectant/antiseptic by numerous catheter manufacturers, having passed the ISO standards above, for all three available catheter materials. This makes ESH unique in that it is the only antiseptic routinely used that is compatible with all materials. As a rule of thumb, it is recommended that povidone iodine only be used with polyurethane based catheters and alcohol containing products only be used with silicone based products. The newer material Carbothane copolymer claims to be compatible with all antiseptics and disinfectants commonly used.

A modified evaluation of the ISO standards was performed in order to compare the affects of ESH on the three different materials used for dialysis catheters. In addition, we evaluate the affects of different antiseptics on dialysis catheters to assess changes in physical properties such as lumen strength.

Method

Exposure to Disinfectant

Catheter lumens were cut at the juncture and completely submerged in the test disinfectant for 48 h. Disinfectant was flushed through each lumen to ensure the disinfectant contacted both the external and internal part of the lumens. After 48 h, each catheter lumen was removed from the disinfectant and rinsed with normal saline. Table 1 displays the catheter model, manufacturer and material. Table 2 shows the catheter models and disinfectants tested.

Tensile Strength Testing

Tensile strength was evaluated using an ATS 900 (Applied Test Systems) device which was connected to an IBM PC for data acquisition (fig. 1). Unique grips were made in order to properly grasp both ends of the lumen to minimize any damage at the connection sites (fig. 2). A segment of 6 cm was used for each catheter. The ATS 900 was then programmed to elongate the lumens at a rates of 25 mm per minute. As the lumen was being stretched, displacement (mm) and force (N) were recorded every second and stored in a database on the PC.

Three samples of each catheter type in each solution were evaluated.

Table 1. Catheters tested

Catheter	OEM	Material	Subclass
Hemoglide®	Bard®	Polyurethane	Tecoflex®
Hemosplit®	Bard®	Polyurethane	Carbothane®
Hickman®	Bard®	Silicone	–
Cannon Cath II®	Arrow®	Polyurethane	Tecoflex®
Xpresso®	Spire®	Silicone	–

Carbothane® and Tecoflex® are manufactured by Noveon Thermedics Polymer Products.

Table 2. Solutions tested

Catheter	Saline (Control)	Alcavis 50/ ExSept Plus	Povidone iodine	Alcohol 70% IPA
Hemoglide®	Y	Y	–	Y
Hemosplit®	Y	Y	Y	Y
Hickman®	Y	Y	–	Y
Cannon Cath II®	Y	Y	–	–
Xpresso®	Y	Y	–	Y

Analysis

Tensile strength was compared between the catheters by analyzing the displacement vs. force (N) curves produced during the evaluation. In order to evaluate differences caused by exposure to different antiseptics/disinfectants, the deviation percentage of the resultant force at each elongation length were calculated. An average deviation greater than 10% when compared to the control lumen (only exposed to saline) was considered significantly affected by the antiseptic/disinfectant. Catheters were only compared with the same catheter exposed to saline, not across different catheters.

Results

A total of 44 catheter lumens were evaluated (only two Hemosplit® with povidone iodine were evaluated). The average maximum displacement for each catheter type in each solution is presented in table 3. Significance in displacement was reached for Alcavis 50 on the Cannon Cath II® catheter, however this is not significant since the catheter exposed to Alcavis 50 ESH had reached maximum displacement as limited by the ATS 900 system.

Fig. 1. ATS 900 meter with computer.

The final force (N) reached as the catheters were stretched is displayed in table 4. Significance was reached for both polyurethane based materials tested that were exposed to alcohol. The Carbothane yielded a greater force vs. displacement curve than Tecoflex, although only achieving 40% of the force for the same catheter exposed to saline or Alcavis 50. The Carbothane catheter appears to be stronger than the Tecoflex catheter.

Evaluation of the curves were performed by assessing the deviations from the control. Table 5 shows the average deviations from the saline control. Again, the Carbothane and Tecoflex catheters exposed to 70% isopropyl alcohol resulted in significant deviations from the control by approximately 50%. None of the other solutions tested affected the characteristic displacement vs. force curve by more than 10% on average.

The ESH solution Alcavis 50 was compatible with all three catheter materials resulting in a deviation of less than 10% for each of the different catheter

Fig. 2. Unique grips were designed to minimize tearing at the connection sites.

Table 3. Catheter displacement (mm)

Catheter	Material	Saline (Control)	Alcavis 50/ ExSept Plus	PI	Alcohol
Hemoglide® (Bard)	Polyurethane Tecoflex®	494 ± 93	565 ± 9	–	469 ± 63
Hemosplit® (Bard)	Polyurethane Carbothane®	310 ± 72	323 ± 86	362 ± 65	374 ± 21
Hickman® (Bard)	Silicone	496 ± 90	456 ± 37	–	370 ± 83
Cannon Cath II® (Arrow)	Polyurethane Tecoflex®	512 ± 29	462 ± 23*	–	–
Xpresso® (Spire)	Silicone	374 ± 38	466 ± 66	–	397 ± 59

*$p < 0.05$, compared to saline control.

Table 4. Catheter resultant forces (N)

Catheter	Material	Saline	Alcavis 50 (ExSept Plus)	PI	Alcohol
Hemoglide® (Bard)	Polyurethane Tecoflex®	242 ± 14	228 ± 4	–	51 ± 6*
Hemosplit® (Bard)	Polyurethane Carbothane®	215 ± 9	211 ± 23	229 ± 32	81 ± 9*
Hickman® (Bard)	Silicone	54 ± 7	54 ± 5	–	49 ± 5
Cannon Cath II® (Arrow)	Polyurethane Tecoflex®	268 ± 27	254 ± 37	–	–
Xpresso® (Spire)	Silicone	82 ± 5	84 ± 8	–	78 ± 7

*$p < 0.05$, compared to saline control.

Table 5. Average deviations: comparing the curves

Catheter	Material	Saline	Alcavis 50 (ExSept Plus)	PI	Alcohol
Hemoglide® (Bard)	Polyurethane Tecoflex®	NA	8.1 ± 5.4	–	52.5 ± 8.7*
Hemosplit® (Bard)	Polyurethane Carbothane®	NA	1.1 ± 14.4	7.0 ± 9.5	49.3 ± 5.7*
Hickman® (Bard)	Silicone	NA	7.0 ± 9.6	–	1.9 ± 9.4
Cannon Cath II® (Arrow)	Polyurethane Tecoflex®	NA	7.7 ± 5.2	–	–
Xpresso® (Spire)	Silicone	NA	0.5 ± 16.1	–	7.8 ± 17.2

*>10% deviation, considered significant.

types. Figures 3, 4, and 5 display the resultant curves for the different antiseptics and disinfectants. You will notice that the resultant curve for ESH is nearly identical to the curves from those catheters exposed to normal saline for all three materials tested.

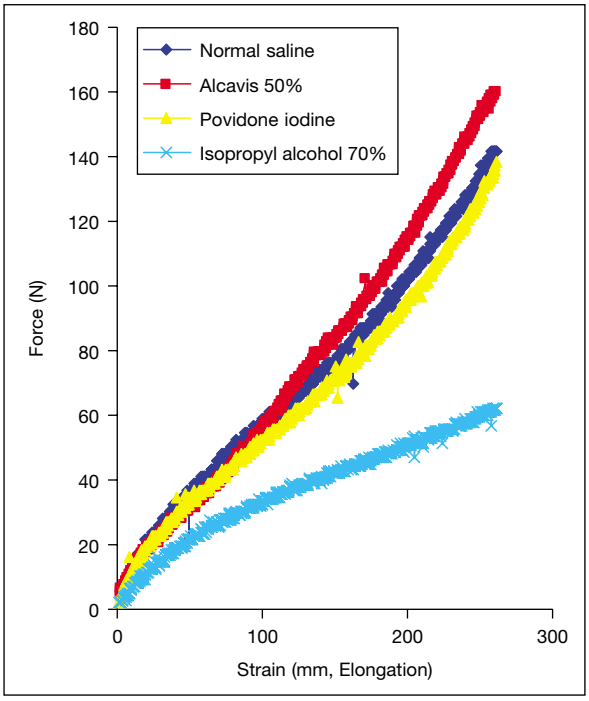

Fig. 3. Bard Hemosplit® Carbothane® catheter in different disinfectants.

Discussion

Concerns of incompatible antiseptic and disinfectants are commonly raised by catheter manufacturers, clinic staff and even regulatory agencies such as the CDC [10]. The frequency of reported complications is low, however, this does not mean catheter degradation is not a common problem in the clinics, only that it is not commonly reported.

It is common that a clinic will have many patients from several different nephrologists, different hospitals and different interventional radiologist or surgeons. It is therefore, very likely that there will be several different catheters from different manufacturers and of different materials. This is where the risk of degradation is greatest since identifying the catheter material is not a simple feat.

The catheter manufacturers provide a list of compatible antiseptics and disinfectants in their instructions for use. However, the name of the catheter and manufacturer are not commonly found on the catheter making identification

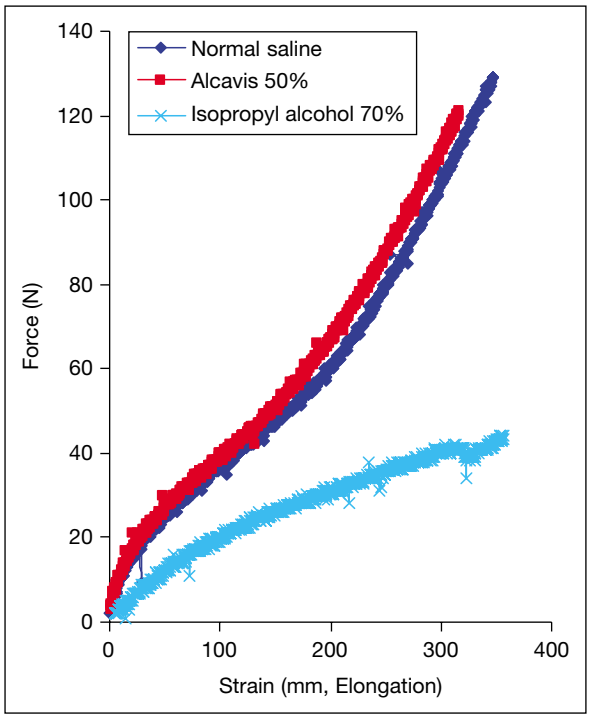

Fig. 4. Bard Hemoglide® Tecoflex® catheter in different disinfectants.

nearly impossible. Recently, some manufacturers are putting contraindicated solution markers on the actual catheter extensions to help minimize the risk of using the wrong solution and damaging the catheter.

As mentioned previously, the catheter manufacturers perform their own testing on the compatibility of their catheters with different solutions. This testing follows the ISO 10555–1 standards and consists of measuring the force that is required to break a catheter at each segment, separately. The minimum force acceptable is a force between 3 and 15 N, dependent on outside diameter of test piece. To evaluate the affects of disinfectants, the catheters are tested after being placed in solution for either extended periods of time, ex. 48 h, or placed in solution for 10 min and then removed with this step repeated every other day for 60 days, simulating actual use.

Since it has already been proven, by the dialysis catheter manufacturers, that ExSept and Alcavis 50 ESH are compatible solutions with all types of materials, this study aimed to evaluate the physical affects of different solutions

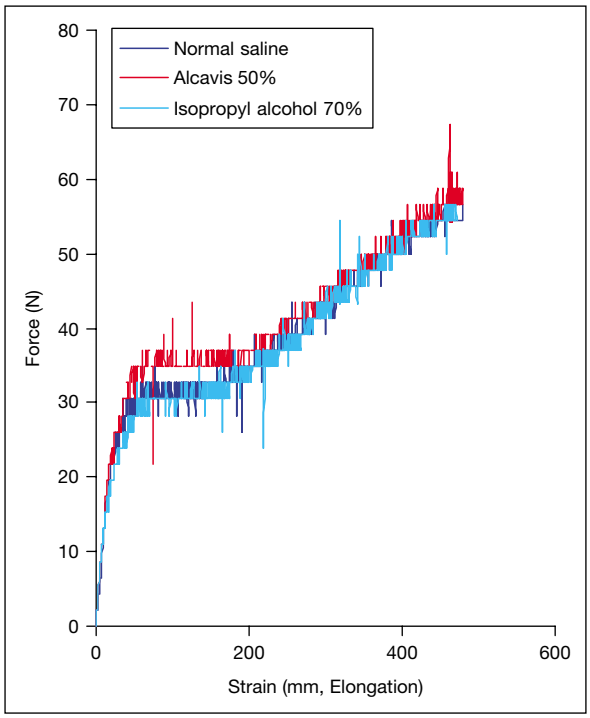

Fig. 5. Bard Hickman® Silicone catheter in different disinfectants.

on the different catheter materials. This was performed by soaking the catheters for 48 h in solution, then rinsing with saline and recording the displacement to force curves for different catheters and materials. A possible limitation of this study is that the catheters were placed in solution and filled with the solution for a period of 48 h. Normally, the antiseptic or disinfectant is in contact with the catheter for a period of not more than 10 min and then air dried. This step is then repeated every other day for as long as the catheter is in place. In addition, the inner lumen of the catheter is rarely exposed to the antiseptic/disinfectant solution (lock solutions were not evaluated in this study). However, a 48 h soak is a similar contact time to 28,810-min exposures and is, therefore, an acceptable challenge to the catheter material.

It has been clearly demonstrated in this study that ESH solutions are the only solutions that do not alter the physical properties of any of the catheters after long-term exposure. This was evident by the less than 10% deviation in the resultant displacement vs. force curves measured compared to a saline exposed control. Alcohol was clearly compatible with silicone catheters, however appears to affect the physical properties of both polyurethane based catheters.

The Tecoflex catheters do list alcohol containing solutions as contraindicated. The Carbothane catheters, which exhibited a similar deviation when exposed to alcohol, do not list alcohol as a contraindication. This is because, even though there were physical changes with alcohol exposure, the strength of the catheter was well within the ISO guidelines. The strength of Carbothane and compatibility with different solutions was also confirmed by Ash [15].

Given that ESH solutions have been shown in this study, by the manufacturers of the dialysis catheters and by decades of historical use, to be compatible with all catheter types and all catheter materials, it would be best practice to incorporate ExSept and Alcavis 50 into routine catheter site and catheter care. ESH solutions will permit ease of mind in catheter compatibility as well as safety and effectiveness as an antiseptic and disinfectant for dialysis patients throughout the world.

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Hemodialysis Catheter Exit Site Care

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Abstract

Tunneled, cuffed central venous catheters are used extensively throughout the hemodialysis patient population as a permanent arterio-venous access. One of the major complications associated with these devices is infection. The strategies aimed at reducing catheter-related infection include nurse-patient ratio, use of barrier precautions, hand washing, ointments, dressings, and skin antiseptics. The intent of this paper is to examine the types of skin antiseptics and compare their effectiveness.

Though the arterio-venous fistula is the access of choice for the hemodialysis patient, a significant number of these patients initiate treatment with tunneled, cuffed, central venous catheters (CVCs). Kapoian and Sherman [1] reported a 5% use of CVCs in 1980 that increased to 30% in 1993. By the year 2000, 200,000 patients in the United States were receiving hemodialysis with 54,000 people starting therapy annually. Rundback and Malloy [2] reported that 20% of those patients initiated dialysis through the use of a tunneled, cuffed catheter. Further, the number of catheters still in use 1 month after initiation of dialysis rose from 15% to almost 40%.

Central Venous Catheters

Tunneled, cuffed catheters were developed in 1987 [3]. Since their inception, CVCs have become an access of convenience; easily inserted and available for use within minutes. Maturation or healing time is not necessary; rather, these devices may be used immediately after radiological verification. They are inserted into deep veins such as the jugular, subclavian, or femoral veins and are advanced into the vena cava. They may be placed percutaneously at the

bedside thereby eliminating the need for expensive and often unavailable operating room time. CVCs are essential for those patients requiring emergency dialysis or patients who are described as access failure, having used up the vessels required to create a permanent access. These devices can serve as a bridge for new fistulae waiting maturation or as a backup to the fistulas that require ligation due to high output states or steal syndrome [4]. Not only are these catheters readily available, but the survival rates of the CVCs are reported to be 75% at 1 year and 50% at 2 years, thereby allowing them to become an alternate form of long-term access to the arterio-venous fistula and graft [5, 6]. CVCs are used as a permanent access in children, the elderly, morbidly obese, or in diabetic patients whose blood vessels are not suitable for the creation of a permanent, internal, arterio-venous fistula or graft.

Complications of Central Venous Catheters

Procedure related complications of CVCs occur in approximately 7% of cases and include pneumothorax, hemothorax, air embolism, and procedure-induced sepsis [2]. Long-term complications, however, contribute to high mortality rates in this patient population [7]. They include thrombosis, stenosis, occlusion, and infection.

Thrombosis may occur as a result of tissue trauma at the time of catheter placement. Any disruption in the endothelium triggers a change in the blood flow, the vessel wall and patient coagulability. Endothelial inflammation of the traumatized vessel precipitates vasoconstriction and platelet aggregation with resultant formation of thrombus [8]. Thrombus associated with the CVC may present in numerous forms: as a mural, intraluminal, atrial, catheter tip, central venous thrombosis, or fibrin sheath [3]. In a mural thrombus, the clot forms at the catheter tip and attaches to the vessel wall. This is thought to be due to the movement of the catheter tip resulting in trauma to the vessel wall. Atrial thrombus presents as a mass in the right atrium and is believed to be an extension of a mural thrombus [3]. Intraluminal thrombus occurs within the catheter lumen as a result of the presence of blood or an inadequate heparin priming volume of the catheter lumen. Catheter tip thrombus is the formation of clot in the side holes or at the tip of the catheter. Central venous thrombosis presents as engorged chest wall veins and swelling of the ipsilateral extremity. Fibrin sheath is a sleeve of fibrin that surrounds the catheter starting at the point where the catheter enters the vessel. It may extend down the catheter and eventually covers the tip. All types of thrombus will contribute to catheter dysfunction wherein extracorporeal blood flow is inadequate to perform hemodialysis [3]. Treatment may include thrombolysis, catheter stripping, or catheter exchange [2].

Central vein stenosis with occlusion begins at the time of catheter insertion as a result of the trauma of passing a large dialysis catheter through the vein wall. A fibrin sheath forms at the site of insertion progressing down the length of the catheter to the tip. The fibrin is reported to transform into fibrous tissue which stimulates intimal hyperplasia creating the stenosis and possible occlusion. The incidence of central vein stenosis is reported to be between 5 and 17% [9]. Symptoms include swelling of the ipsilateral extremity, edema involving the upper chest, head and neck, and the presence of engorged chest wall veins. If severe, the edema can cause decreased mobility and pain. Treatment is balloon angioplasty with or without stent placement.

Catheter-Related Infection

The infection associated with CVCs is of primary concern because catheter-related sepsis represents the most frequent life-threatening complication [10]. Catheter-related infections can be described as a colonized catheter, exit site infection, tunnel infection, infusate-related blood stream infection, and catheter-related blood stream infection [4]. The potential sources of the infection are the skin, catheter hub, infusate, and the catheter. A colonized catheter infection is described as growth of greater than 15 colony-forming units (cfu) (semiquantitative culture) or 10^3 cfu (quantitative culture) from a proximal or distal catheter segment in the absence of accompanying clinical symptoms [11]. A local catheter-related infection might comprise an exit site infection or a tunnel infection. The Center for Disease Control (CDC) Guidelines [12] described an exit site infection as inflammation around the insertion site that consists of erythema, warmth, tenderness, induration, or purulence within 2 cm of the skin at the exit site of the catheter. The incidence of exit site infections ranges from 1.2 to 2.2 per 1,000 catheter days [13]. They may result from inadequate skin disinfection at the time of catheter placement, incorrect suture material or technique, improper site care by dialysis staff, or patient hygiene. Treatment is usually antibiotic coverage without the need for catheter removal. A pocket infection is erythema and necrosis of the skin over the reservoir of a totally implantable catheter, or purulent exudate in the subcutaneous pocket containing the reservoir [12]. A tunnel infection is characterized by erythema, tenderness, and induration in the tissues overlying the catheter more than 2 cm from the exit site. Tunnel infections are relatively uncommon with an incidence of 0.12 per 1,000 catheter days [13]. Treatment involves catheter removal and antibiotic coverage.

Infusate-related bloodstream infection is a rare cause of catheter-related sepsis. It is defined as isolation of the same organism from infusate and from

separate percutaneous blood cultures, with no other identifiable source of infection [10]. Infusate-related blood stream infections should be suspect when sepsis occurs in an otherwise low-risk patient receiving an intravenous solution, or when there is a cluster of primary bloodstream infections with an unusual organism. Organisms may contaminate infusate by several mechanisms: during manufacture, solution preparation, handling by health care workers or by retrograde contamination from a contaminated catheter [2, 14].

Central venous catheter-related blood stream infection rates range from 8 to 43% [15]. The rate of septicemia for cuffed catheters is dependent upon the patient's comorbid conditions, history of previous bacterial infections, immunosuppression, and the length of time the catheter is left in place. Sepsis is primarily a result of bacterial or fungal strains that colonize the catheter hub [16–19]. The hub is often contaminated by the hands of the medical personnel during frequent manipulations of the catheter [17, 20]. Approximately 40% of central venous catheter infections are due to *Staphylococci*, 30% to Gram-negative bacilli, 12% to *Candida* and 12% to *Enterococci* [21, 22]. The implicating evidence is isolation of the same organism from a culture of a catheter segment and from the blood of the patient, with accompanying clinical symptoms of blood stream infection and no other apparent source of infection. In the absence of laboratory confirmation, if there is resolution of clinical sepsis within 48 h of catheter removal during which time the patient does not receive antibiotics, the catheter is implicated as the source of infection [13]. The patient may present with signs and symptoms of systemic infection ranging in severity from minimal to life-threatening. Fever and shaking chills are typical. Nausea, vomiting, back pain, headache, myalgia, arthralgia, and changes in mental status may also occur. The patient may develop hypotension. Some patients present to the dialysis unit with little or no evidence of infection and then develop symptoms after initiation of dialysis via the CVC, suggesting a release of bacteria or endotoxin from a sequestered source [13]. Infectious complications may include osteomyelitis, endocarditis, epidural abscess, septic arthritis, or death [22]. Saad [13] and Tanriover et al. [23] reported catheter-related infections of 3.4–5.5 episodes per 1,000 catheter days.

Strategies for the Prevention of Catheter-Related Infection

The literature has reviewed a number of preventative strategies employed to reduce catheter-related infection. They include: low nurse-patient ratio, maximal sterile barriers, use of topical ointments, appropriate catheter dressings, and type of skin antiseptics.

Nurse-Patient Ratio

The literature appears to be consistent in its support of an educational program and/or specialized team of individuals dedicated to the care of intravascular devices [15, 24, 25]. In a cohort study of surgical intensive care unit patients with CVC associated blood stream infections, the corresponding patient to nurse ratio was reviewed by Fridkin et al. [26]. They hypothesized that an increase in the patient to nurse ratio, in combination with an increase in the total parental nutrition use, may have placed time constraints that prevented the nurse from caring for the CVCs properly. During an outbreak of CVC blood stream infections a high patient to nurse ratio was identified. In a study by Maki [11] a decrease in infection rates associated with CVCs occurred with the implementation of vascular access teams. These reports indicate that increased time, care, and attention paid by individuals dedicated to a single task may result in fewer infectious complications.

Maximal Sterile Barriers

Use of maximal barriers and careful hand washing prior to and during the insertion of a CVC are reported to the most important steps in preventing catheter-related infections [11, 20, 27, 28]. A maximal sterile barrier involves wearing sterile gloves, a mask, gown, and using a large drape. Darouiche and Radd [15] reported a four-fold decrease in the rate of pulmonary artery catheter bacteremia and a more than six-fold decrease in the rate of CVC sepsis following the use of maximal sterile barriers during the insertion of CVCs.

Topical Ointments

Theoretically, the application of topical ointments should confer some protection against microbial invasion [11]. In the study by Levin et al. [29] where the treated group ($n = 63$) received povidone-iodine ointment with the dressing changes and the control group ($n = 66$) used dry dressings for CVC exit site care, there was a reported 93% relative reduction of septicemia in the treated group. In a comparative study of a polyantibiotic and iodophor by Maki and Band [30] ($n = 827$ catheters from 381 patients), the rates of catheter-related septicemia was too low to make a valid comparison. The conclusions were that the polyantibiotic offered some protection against catheter-related infection but only marginally.

Dressings

Microorganisms that colonize the skin are responsible for most of the infections that occur around catheter exit sites. Improper handling of the device by staff may also contribute to the infectious process. The dressings that cover the exit site could therefore have considerable influence on the incidence of nosocomial

infection. The purpose of an intravascular site dressing is to prevent trauma to the catheter wound and the cannulated vessel as well as to prevent extrinsic contamination of the wound [19, 31]. Numerous studies have been carried out in an attempt to identify the most appropriate dressing for intravascular access sites.

Criteria for insertion site dressings includes: they should be sterile, capable of moisture prevention, allow visible inspection, cost-effective, easy to apply and fix to the insertion site, and easy to remove [32]. The traditional dressing is gauze, covered by non-sterile tape. It does not allow visible inspection but allows the passage of organisms when wet, and should be changed daily. This increases the amount of manipulation of the device and could potentially encourage contamination of the hub. The alternative to the gauze dressing is the transparent polyurethane dressing. Specific types of transparent dressings have been proven to be more effective in their physical properties, particularly moisture vapor transmission rates, oxygen transmission and cutaneous adherence [33]. Further, patients are permitted to shower with transparent dressings in place.

The disadvantage associated with transparent dressings is greater cost, difficult removal, poor adherence to the skin over the catheter, and leakage due to drainage from the exit site wound. To obviate the disadvantage of cost, these dressings are left in place for up to 7 days or longer. The concern is whether transparent dressings left on for prolonged periods of time increases the risk of catheter-related infection. The literature presents conflicting results. In the studies by Maki et al. [34]; Richardson [35]; Claeys and Degrieck [36]; Wille et al. [37]; and Besley [38], leaving the transparent dressings for 7 days did not increase the incidence of catheter-related infections when the OpSite 3000 transparent dressing was used. Most of these studies took place in an ICU setting with the study periods being less than 3 weeks in total. In a study by Bijma et al. [39], 206 CVCs were studied over a 7-month-period in a surgical ICU. During the study, transparent dressings were replaced by gauze dressings and colonization rates were greatly reduced (206 CVCs in 128 patients, $p < 0.025$).

Skin Antiseptics

Skin cleansing of the insertion site is regarded as one of the most important measures for preventing catheter-related infection. Disinfectant agents use alcohols, chlorine and chlorine components, and iodines. Commonly used disinfecting agents include povidone-iodine, chlorhexidine, alchohols, and electrolytic chloroxidizer.

Povidone-Iodine

Iodine solutions employ a wide microbiological activity when formulated with free iodine [16]. Povidone-iodine is the most widely used form of

iodophor compound. The 10% solution is known as Betadine. It is frequently used in hospitals as a disinfectant. Iodophors are effective against most bacteria and viruses but less effective against fungi. It is not sporicidal and is inactivated by organic compounds such as blood and serum protein [40]. It is important to allow the skin surface to dry to achieve its effectiveness. The time recommended is 3–5 min. Further, povidone-iodine can be irritating to the skin causing skin breakdown thereby opening a portal for microorganisms.

Chlorhexidine

Chlorhexidine gluconate, a cationic bisbiguanide, was developed in England in the early 1950s and was introduced into the United States in the 1970s. It is a chlorophenol biguanide with a broad antimicrobial spectrum. It is thought that chlorhexidine produces enzymatic reactions within the cell that result in protein denaturation and inactivation of nucleic acids [16]. Chlorhexidine is active against many Gram-positive and to a slightly lesser degree Gram-negative bacteria. Chlorhexidine is supplied in various concentrations of 0.5% with 70% alcohol, 2%, and a 4% detergent. It has greater residual activity than alcohol alone and is not inactivated by the presence of blood or human protein [19, 38–40]. There is minimal absorption through the skin. Anaphylactic reactions with bronchospasms and generalized urticaria are very rare and are associated with use on mucous membranes. In a prospective, randomized trial by Fuchs et al. [41], three different methods of catheter exit site care were studied in a peritoneal dialysis population for 14 months. The solutions used included chlorhexidine gluconate and water, dilute sodium hypochlorite solution, and povidone-iodine. The study failed to demonstrate that one method of care was superior to another. In the prospective, randomized study by Mimoz et al. [42], chlorhexidine gluconate and 10% povidone-iodine were compared in all ICU patients during the 15-month study requiring a CVC or arterial catheter. The chlorhexidine solution was superior in preventing catheter colonization and catheter-related sepsis due to Gram-positive bacteria (5 vs. 20 [$p < 0.001$] and 2 vs. 10 [p 0.001], respectively), whereas the chlorhexidine was not superior in preventing Gram-negative infections (7 vs. 4 [$p = 0.5$] and 4 vs. 2 [$p = 0.8$], respectively). Maki [19] compared three antiseptics for disinfection of 668 central venous and arterial catheters. Chlorhexidine was associated with the lowest incidence of local catheter-related infection and catheter-related bacteremia in comparison to alcohol and povidone-iodine. Traore et al. [43] compared povidone-iodine to chlorhexidine in two groups of 22 healthy subjects and concluded that both antiseptics are equal in bactericidal activity at 0 time, 30 s, 3 min, and 2 h. There is high alcohol content in the chlorhexidine solutions, which has damaging effects on some catheter materials, thereby restricting its use.

Alcohols

The majority of alcohol-based hand antiseptics contain isopropanol, ethanol, n-propanol, or a combination of these products. Ethyl alcohol (ethanol) and isopropol are not considered high-level disinfectants though they are frequently used to clean small surfaces such as rubber stopped vials. Alcohol is used as a disinfectant with rapid action against a broad spectrum of microorganisms. However, once evaporated, the alcohol has no long-lasting antimicrobial effect. They act by denaturing or altering the molecular structure of the bacterial proteins, destroying the cell. They are rapidly bactericidal, viricidal, and tuberculocidal but they do not destroy bacterial spores nor do they penetrate protein rich material such as blood [16]. Optimal concentrations range from 60 to 90%. Alcohol dries and irritates the skin. The combination of alcohol and iodine is used as a tincture which delivers rapid and sustained antimicrobial action, but the iodine often causes skin irritation and staining. The alcohol gel with 5% iodine has equal effectiveness as a high concentration of alcohol and is less irritating to the skin [44, 45]. In a study by Traore et al. [43], where an iodine alcohol solution and iodine scrub was compared to a chlorhexidine alcohol solution and chlorhexidine scrub, the results were comparable for all four groups.

Electrolytic Chloroxidizer

Electrolytic chloroxidizer, otherwise known as Amuchina, is a chlorine-based solution with a 17% sodium chloride component and 0.057% sodium hypochlorite. ExSept® is the 5 or 10% dilution of Amuchina. It is said to be effective against all spectrums of pathogens including Gram-positive, Gram-negative bacteria, viruses and spores. Amuchina is similar in molecular size and structure to water, and because it does not present with an electrical charge, the undissociated hypochlorous acid may easily cross the microbial cell membrane. Its intracellular targets are enzymes containing sulfhydril groups involved in aerobic and anaerobic pathways. The action of hypochlorous acid on these enzymes consists in irreversible oxidation of the thio-group, thus abolishing enzymatic action and resulting in the destruction of the bacteria (ExSept unpublished manuscript).

Amuchina is reported to be non-toxic, non-irritating [46, 47]. Roveda et al. [48] conducted a controlled randomized study on 48 patients comparing the antiseptic properties of Amuchina (ExSept 10%) to 10% povidone-iodine. Both antiseptics produced an immediate reaction in bacterial load during a single application, however, the absolute values were more significant with ExSept ($p < 0.05$). Jones and Mulberry [49] repeated the study with 24 female

Table 1. Exit site infections

Exit site infections	Group (n)		Total	p-Value
	Chlorhexidine	ExSept®		
Negative culture	59	52	111	0.553
Clinical signs and positive culture	3	5	8	
Clinical signs	2	0	2	
Total	64	57	121	

volunteers, 12 per group. The bacterial flora of the skin and abdomen were studied. Both products produced an immediate large reduction of bacteria at the abdominal area but Amuchina appeared more effective than povidone-iodine at the axillar area ($p < 0.05$). Cruz et al. [50] conducted a similar study comparing skin surface bacterial counts of three groups of 9 voluntary patients and found no difference between products ($p < 0.05$). No side effects occurred suggesting Amuchina was well-tolerated. In 1989, a Canadian clinical trials group lead by Churchill et al. [51] conducted a multi-center trial comparing the Y-set, which used Amuchina 50% as the in-line disinfectant and compared it to the standard peritoneal dialysis systems. There was a 61% risk reduction with Amuchina, however accidental infusions into the peritoneal cavity related to patient error caused moderate to severe abdominal pain for patients. DeVecchi et al. [52] used Amuchina as an in-line disinfectant in some Y-systems to prevent exogenous peritonitis. The results were inconclusive because the researchers suggested that glucose in solution, in combination with organic compounds like peritoneal dialysate, could reduce the bactericidal effect of the product. Therefore, it could not be determined as to what the clinical role of Amuchina was with the Y-set. In the study by Astle and Jensen [4], the standard 0.5% chlorhexidine with 70% alcohol ($n = 64$) was compared to ExSept 10% ($n = 57$) as a skin and hub disinfectant in 111 hemodialysis CVCs, 10 (8.26%) patients developed exit site infections: 5 from each group (table 1). Two episodes of bacteremia occurred in the study: one per group (table 2). 91.7% of the patients developed skin colonization: 56 patients in the cholorhexidine group and 55 in the ExSept group (table 3). Of the 10 patients who had exit site infections all were colonized. The microorganism primarily responsible for colonizing the skin was coagulase-negative *Staphylococcus*. In conclusion, ExSept 10% was comparable to chlorhexidine 0.5% with 70% alcohol for the incidence of catheter-related infections. However, ExSept is less costly and has less catheter-associated damage such as catheter cracking (tables 1–3).

Table 2. Bacteremic episodes

Culture results	Group (n)		Total
	Chlorhexidine	ExSept®	
Positive	1	1	2
Negative	61	56	117
Possible	2	0	2
Total	64	57	121

Table 3. Skin colonization of exit sites

Colonization	Group (n)		Total	p-Value
>15 cfu	56	55	111	0.069
<15 cfu	8	2	10	
Total	64	57	121	

cfu = colony forming units.

Infection is a well-documented complication associated with CVCs for hemodialysis. It is imperative that strict aseptic technique is adhered to and all strategies employed in an effort to reduce or prevent infections associated with these catheters. Preventative care will also ensure the added benefit of reduced costs of hospitalizations. It is a primary concern that health care providers continue to study and search for methods to protect the patients from preventable infections.

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Effectiveness of Sodium Hypochlorite in the Prevention of Catheter Related Infections

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Abstract

Vascular access in hemodialysis is a major point of concern in the management of chronic patients. Although arteriovenous fistula remains as the access of first choice, tunneled central venous catheters are still commonly used. Infection remains the principal cause of catheter dysfunction or loss. Many protocols have been used in order to prevent exit site infections and bacteremia. We describe our experience with the use of sodium hypochlorite, an electrolytic chloroxidizer used as a topical disinfectant. It has been shown to be active against a broad spectrum of potential pathogens and has other specific advantages compared to other cleansing agents, including its non-toxic, non-irritating nature and its low cost. We conclude that sodium hypochlorite solution in different concentrations (10 and 50%) is effective in preventing exit site infections and bacteremia associated with tunneled central venous catheters in chronic hemodialysis patients.

Vascular access management represents a major clinical concern in chronic hemodialysis (HD) patients, because its efficiency considerably affects dialysis adequacy and patient morbidity and mortality [1, 2]. While native arteriovenous fistula is considered the access of choice for HD, some specific conditions (acute renal failure, inadequate or exhausted vessels and reduced life expectancy) oblige the use of central venous catheters (CVC) or arteriovenous grafts [3, 4].

Catheter infections are common among chronic HD patients, with an incidence of 18.4/1,000 days among temporary catheters, and 13.6/1,000 days in

tunneled cuffed catheters [5]. Catheter infection can occur following transmission of hand or aerosolized bacterial contaminants. *Staphylococcus aureus* is the leading cause of catheter exit site infection (ESI) and bacteremia in HD patients [6, 7]. Bacteremia and tunnel tract infections are the leading causes of catheter loss [8, 9]. The KDOQI guidelines for catheter care include treating the exit site with a skin disinfectant, either chlorhexidine or povidone-iodine, followed by ointment of povidone-iodine or mupirocin [10]. This has been shown to reduce the incidence of ESI. However, certain manufacturers have indicated that the glycol constituents of ointment should not be used on their polyurethane catheters. Mupirocin ointment and certain preparations of povidone ointment contain polyethylene glycol.

Sodium hypochlorite is an electrolytic chloroxidizer, and solutions are used as a topical disinfectant. Chlorine is the active ingredient with a pH of 9.5–10.5. Sodium hypochlorite 50% solution (Amuchina, Italy) contains chlorine (0.55%), and costs less than 10% povidone-iodine or 4% chlorhexidene. It has been shown to be active against a broad spectrum of potential pathogens. In addition, it has some specific advantages compared to other cleansing agents: it cannot be contaminated by bacteria, it is non-toxic and non-irritating, it improves tissue growth, and does not cause sclerosant encapsulating peritonitis [11, 12]. Sodium hypochlorite Y-connector systems have been shown to reduce peritonitis rates by 61% compared to standard systems [13]. Sodium hypochlorite 50% has been effectively used for the prevention of ESI in children treated with chronic peritoneal dialysis (PD) [12]. It was reported to be more effective than 10% povidone-iodine and as effective as 4% chlorhexidine, but with fewer adverse effects, such as local skin irritation. A second group of investigators have also found sodium hypochlorite 50% to be as effective as 10% povidone-iodine for transfer set changes [14]. Furthermore, sodium hypochlorite 3% solution, which costs even less than the 50% preparation, has been found to be as effective in the prevention of ESI in children [12]. Similarly, our own experience with PD patients has demonstrated that with sodium hypochlorite 50% packs in addition to systemic and local antibiotic therapy is effective treatment for ESI, and helped avoid peritoneal catheter removal and need for temporary HD. These packs were left in place for 3 min each day for 2 weeks, after which usual povidone-iodine dressings were resumed.

To our knowledge, there has been no study evaluating the use of sodium hypochlorite for tunneled cuffed CVC in chronic HD patients. In 2004, we used sodium hypochlorite 10% as part of our routine exit site care for tunneled cuffed catheters. Standard catheter care in our center adheres to the KDOQI guidelines. Having noted encouraging results with our PD population, we implemented a policy change in January 2005; thereafter, sodium hypochlorite 50% solution was used.

We compared the incidence of ESI/colonization and catheter-associated bacteremia in the two time periods to assess the efficacy of sodium hypochlorite 50 vs. 10% solution used for routine exit site care in the prevention of these outcomes. Data on these endpoints are routinely prospectively collected as part of center policy. For catheters, blood cultures from both the arterial (red) and venous (blue) ports and exit site swab cultures were performed routinely on a monthly basis, and whenever infection was suspected. Bacteremia was treated with intravenous antibiotics for 4–6 weeks. ESI, as indicated by the presence of erythema, tenderness or purulent discharge, were treated with systemic antibiotics for 2–4 weeks. All systemic antibiotic therapy was based on the culture and sensitivity results. Exit site swab cultures positive for *Staphylococcus epidermidis* without erythema, tenderness or purulent discharge were considered colonization, and no intervention is performed. In the absence of obvious signs of ESI, exit site swab cultures which grew Gram-positive organisms other than *S. epidermidis* were treated locally with Vancomycin packs left in situ over the exit site for 20 min during the HD treatment for 10 consecutive treatments. Exit site swabs which grew *Candida* were always treated with systemic antifungal therapy, based on culture and sensitivity results. No tunnel infections occurred during the observation period.

Data were collected on 37 tunneled CVCs between January and December 2004 (Group A, sodium hypochlorite 10%) and 41 tunneled CVCs in January and December 2005 (Group B, sodium hypochlorite 50%). We compared the incidence-density of ESI/colonization and bacteremia in Groups A and B using chi-square test. A two-sided p-value <0.05 was considered statistically significant.

Results are summarized in table 1. In Group A, 24 catheters had 81 positive exit site swab cultures, or 1 positive site culture per 77 catheter-days. In Group B, 20 catheters had 64 positive exit site swab cultures, or 1 positive site culture per 115 catheter-days. There was a significantly lower incidence of positive exit site cultures with the use of sodium hypochlorite 50%. A significant proportion of these positive exit site cultures were colonization with *S. epidermidis*. The difference between the two preparations of sodium hypochlorite appeared to be largely due to a reduction of exit sites positive for *S. epidermidis*. Considering only ESI involving other organisms, Group A had 1 ESI per 445 catheter-days and Group B had 1 ESI per 435 catheter-days ($p = 0.54$). The cultured microorganisms are listed in table 2. With regards to blood cultures, in Group A, 7 catheters lead to 11 positive blood cultures, or 1 bacteremia episode per 567 catheter-days. Although there were fewer bacteremia episodes in Group B (1 per 1,478 catheter-days), this did not reach statistical significance.

Eighty six percent of the cultures grew Gram-positive organisms, while Gram-negative organisms accounted for 8.7%. The most common organism was

Table 1. Incidence of positive cultures with use of Amuchina 10 and 50%

	Group A	Group B	p-Value
Skin disinfectant	Amuchina 10%	Amuchina 50%	
Total catheter days	6,241	7,389	
Positive exit site cultures	81	64	0.02
Infection	14	17	1.00
Colonization	67	47	0.001
Positive blood cultures	11	5	0.08
Peripheral	2	2	1.00
Arterial port	7	2	0.09
Venous port	2	1	0.59
Total	92	69	0.004

Table 2. Identified microorganisms

	Group A Amuchina 10%		Group B Amuchina 50%	
	Exit site culture	Blood culture	Exit site culture	Blood culture
Gram-positive				
Staphylococcus epidermis	71	4	46	0
Coagulase negative *Staphylococcus* (other than *S. epidermidis*)	2	1	1	0
Staphylococcus aureus	5	2	5	0
Corynebacterium sp.	2	0	1	0
Gram-negative				
Pseudomonas aeruginosa	0	0	2	4
Proteus mirabilis	2	1	0	0
Enterobacter cloacae	0	3	0	0
Enterobacter amnigenus	0	0	1	1
Other				
Candida sp.	4	0	3	0

S. epidermidis, followed by *S. aureus*. Candidal infections accounted for 4.3% of all infections. Our findings are congruent with the literature. *S. aureus* and *S. epidermidis* are reported to be the most common causes of CVC related infections (60%) [15, 16]. Other Gram-positive and Gram-negative account for 25%. Among fungi, an important role is played by *Candida albicans* and *Candida*

parapsilosis (15%). Many individuals are nasal bearers of *S. aureus*, making them an important factor in the spread of this kind of infection [15]. In contrast, *S. epidermidis* is usually an opportunist, but in the presence of a foreign body it becomes pathogenic. The frequent association between coagulase negative Gram-positive bacteria and biomaterials demonstrate its ability to adhere and colonize the polymeric materials [4]. Candidal species are usually present in human cavities, but become virulent only in case of an immunodepressed state, as in Chronic Kidney Disease Stage 5. Recently, Enterococci are considered as emerging causative agents of intravascular catheter related blood stream infections: they are the fourth most common cause of blood infections in Europe.

On closer evaluation of our data, we detected a slightly higher incidence of positive exit site cultures during July–August 2004. There was one positive exit site culture per 66 catheter-days and one bacteremia episode per 617 catheter-days. This incidence was higher than in January–June 2004, although the difference did not reach statistical significance: during this earlier period, there was one positive exit site culture per 91 catheter-days and one bacteremia episode per 518 catheter-days (vs. July–August 2004, $p = 0.15$ and 1.00, respectively). This increase coincided with light construction work in our HD unit. Most likely this external factor contributed to the increased frequency of infections, although every effort was made to maintain aseptic technique during catheter handling. When this period was excluded from analysis, the difference in incidence of infection between Groups A and B was no longer significant. Excluding exit site cultures which grew *S. epidermidis*, Group A had one ESI per 621 catheter-days, while Group B had one ESI in 435 catheter-days ($p = 0.64$). In a high-risk environmental situation as we encountered with construction work during January–June 2004, it is possible that a higher concentration of sodium hypochlorite, i.e. 50%, may be more effective in reducing the risk of infections. Unfortunately, we were unable to test this hypothesis, as we only started using sodium hypochlorite 50% after the construction work was completed.

Our results show that the use of sodium hypochlorite 50% appeared to be more effective than 10% solution in reducing the incidence of positive exit site swab cultures associated with tunneled CVCs in chronic HD patients. However, the effect was largely due to a reduction in colonization with *S. epidermidis* with the use of the 50% preparation. In terms of true ESI and bacteremia, there was no significant difference between them. This is in agreement with the findings of Grosman et al. [12] in PD patients. The potential advantages of a lower concentration of sodium hypochlorite solution include cost savings and perhaps less local skin irritation. However, we cannot exclude the possibility that sodium hypochlorite 50% is more effective in high-risk situations such as the one as we have described.

In conclusion, catheter-related infections remains of vital concern in the management of chronic HD patients, and prevention of these is an important objective of HD care providers. We conclude that sodium hypochlorite solution is effective in preventing ESI and bacteremia associated with tunneled CVCs in chronic HD patients.

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Use of Sodium Hypochlorite in Peritoneal Dialysis: The Genesis of the 'Y' Set and Beyond

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Abstract

The 'Y' set introduced in the clinical practice in the early 80s with the aim of reducing the peritonitis rate in patients on continuous ambulatory peritoneal dialysis, successfully revolutioned the philosophy of the connection system catheter-container of dialysate, which was the main way of bacterial contamination of the peritoneal cavity. In fact, while the previous connection systems had focused the attention on the reduction of the possible contaminating acts, the 'Y' system, taking into account the fact that soon or later a failure could occur even with the most skilled and compliant patient, introduced the possibility to kill the bacteria with a disinfectant and to remove it and the killed bacteria together with the bacteria eventually still surviving, by flushing the contaminated area. This goal was achieved thanks to a 'Y' shaped connector, having a third way connected to the discharge bag/container, besides the two connected to the new bag and to the catheter. From the 'Y' set have originated all the currently used continuous ambulatory peritoneal dialysis connection systems, where the 'Y' is mounted on the bag side (double-bag systems). However in these systems the disinfectant is no longer used, due to the fear of possible untoward effects on the peritoneal membrane. The groundlessness of this position and the possible further advantages of the use of a disinfectant in combination with the 'Y' are discussed and new 'Y' systems preventing every possibility of accidental entry of disinfectant into the peritoneal cavity are presented.

Background

In the late 70s, the introduction of the system suggested by Oreopoulos et al. [1], i.e. the 'wearable enrolled 2-l plastic bag system', made possible the wide practical clinical application of the new, more efficient, continuous ambulatory peritoneal dialysis (CAPD) schedule proposed by Popovich et al. [2],

diffusion previously prevented by the unacceptably high peritonitis rate of one episode every 4–6 weeks [3], deriving from the high number of the possibly contaminating acts inherent in the use of two 1-l glass bottles for 4–5 exchanges per day (fig. 1). The main advantage of the system proposed by Oreopoulos et al. consisted in the significant reduction of the number of risky steps (down to 1/4 vs. the glass bottles system) (fig. 2).

However, even with the system proposed by Oreopoulos et al. the results were only partially satisfactory: in fact, the peritonitis rate, after the significant initial drop to one episode every 8–11 months [4–8], stabilized at this level notwithstanding a huge number of tentative technical improvements and in spite of rigid selection criteria. This was derived from the fact that even the unique deconnection-connection act was however at very high risk, because it took place at the end of the exchange and the first subsequent obligatory act was the filling of the abdomen, with no way to flush out the possible contaminating bacteria, which were thus almost obligatorily dragged into the peritoneal cavity. Once there, remaining undisturbed many hours until the next exchange and with optimal growth conditions (physiological temperature, rich pabulum consisting of glucose from dialysate and amino acids and proteins leaked across the peritoneal membrane) they had the best possibility to multiply and to generate peritonitis. The persistence of a relatively high peritonitis rate coupled with the other weak point of the system, i.e. the aesthetical hindrance arising from the need to wear permanently the empty bag and the long transfer set, continued to prevent significantly a wider diffusion of the CAPD. Thus, there was still a clear need for a new system which could overcome both these limitations.

The Perugia 'Y' Set with Disinfectant

The search for a new connection system for CAPD started from the consideration that in the system proposed by Oreopoulos et al. there was no possibility to remove the bacteria after the possible contamination of the connection and before the filling of the abdomen and that, as a consequence, the only way to reduce the peritonitis rate was the accurate and paroxysmal prevention of the contamination [9], because, once this had occurred, peritonitis was almost unavoidable. But, sooner or later, even the most skilled patient could contaminate the connection site. Thus, it resulted from the beginning clearly mandatory to search for a complete revolution in the philosophy of the connection, switching it from the prevention of the contamination to the possibility to remove and/or kill the bacteria after the contamination and before their entering into the peritoneal cavity. This goal was achieved [10] by mounting a 'Y' shaped prosthesis filled with disinfectant on the external end of the peritoneal catheter (fig. 3).

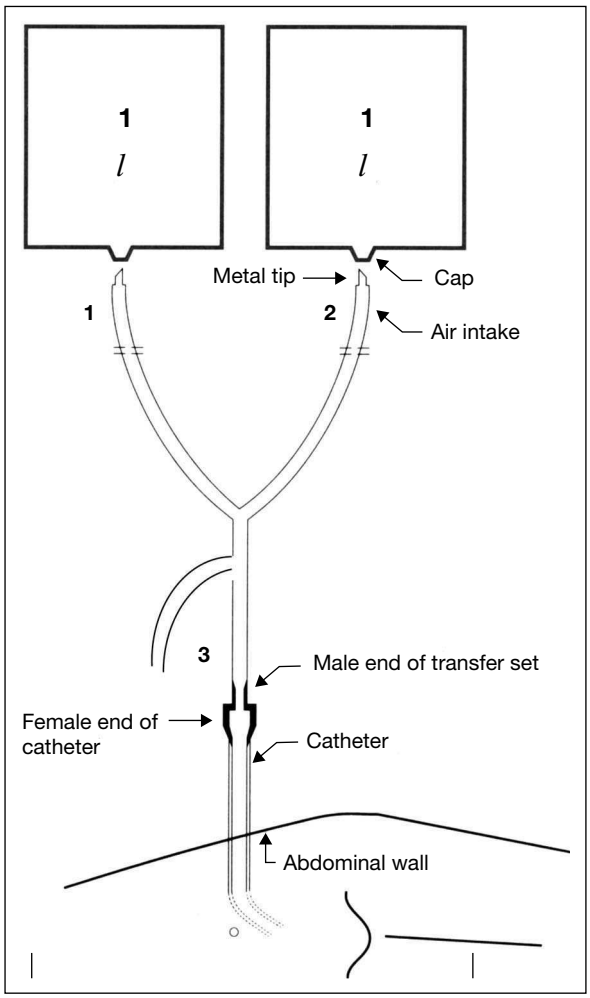

Fig. 1. Glass bottles. Primitive system employed for the initial clinical experience with CAPD. Very high number of possible microbiological contaminations at every exchange, represented by two connections between the punching end of the transfer-set and the rubber cap of the glass bottles (1 and 2); the connection between the distal end of the transfer-set and the external end of the peritoneal catheter (3); the final de-connection of the transfer-set from the catheter and closure of it with a cap. A further possibility of contamination derived from the air necessarily entering into the bottles in order to enable the out-flow of the dialysate from the rigid container.

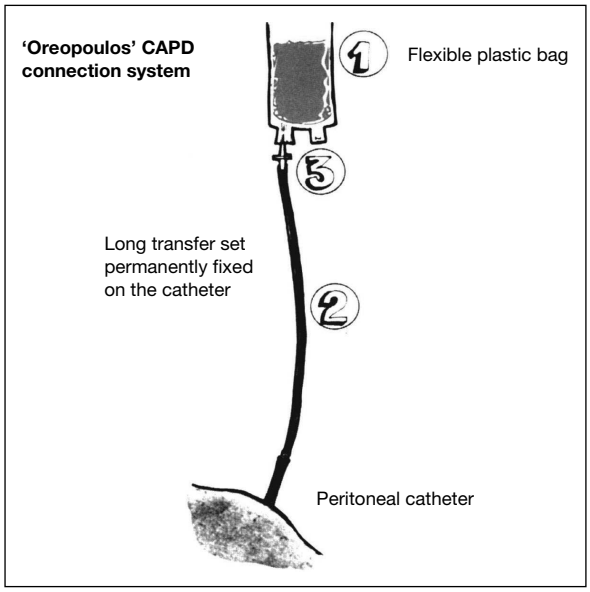

Fig. 2. Oreopoulos connection system for CAPD. Week points of the system: need to wear permanently the empty bag (1) and the long transfer-set (2); persistence of a relatively high risk of infection in spite of the sharp reduction of the number of contaminating acts per exchange to just one (the connection of the new bag (3) to the transfer-set), because: (a) the first act after the connection of the new bag (i.e. after the possible contamination) was obligatorily the filling of abdomen; (b) there was no way to perform a flushing of the connection in order to wash away the contaminating micro-organism.

Besides the two ways of the prosthesis used for the connection to the catheter and to the bag with fresh dialysate, the third way enabled the discharge to the outside of the fresh and of the spent dialysate after the connection and before the filling of the abdomen, and, for the same reason, made it possible to use a disinfectant at the connection site.

The Protective Effect of the 'Flushing before Filling' Enabled by the 'Y' Set

The protective effect of the 'Y' set against the risk of peritonitis depends essentially on the possibility of flushing the connection site with a bolus of fresh solution after the possible contaminating act, i.e. the connection of the new bag to one branch of the 'Y' on the catheter, thus removing the possible contaminating micro-organisms from the connection site and from the tubing,

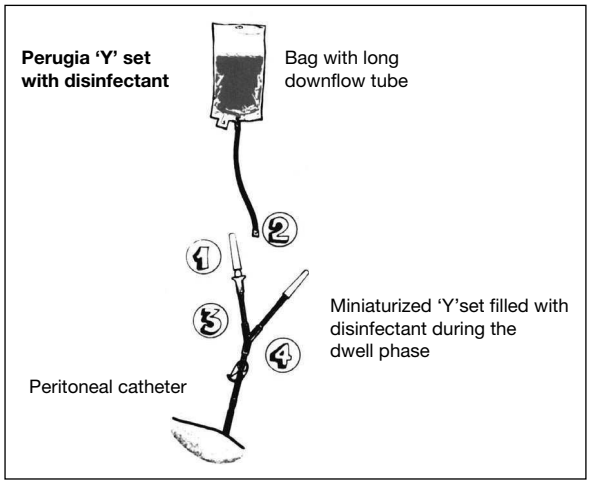

Fig. 3. Perugia or 'Y' connection system for CAPD. The four significant advantages of this system were: no need to wear permanently the empty bag and the transfer-set; the third way of the 'Y' set enables (a) the connection of new bag – 'Y' transfer set as first and not last step; (b) the removal (even if not always complete) of the contaminating micro-organisms by a bolus of fresh dialysate and then by the discharge of the spent dialysate; (c) the safe use of a disinfectant into the prosthesis during the rest phase, thanks to the possibility of removing it before the refilling of the abdomen.

pushing them through the second branch toward the drainage bag (fig. 4). This protective action is completed and reinforced by the subsequent flushing with the spent dialysate, which can be drained after the connection is made, again thanks to the third lateral way of the 'Y' (fig. 5).

The efficacy of the flushing per se in removing the bacteria from the connecting tubes has been for the first time studied and proved by the group from Perugia, with an in vitro study [10], and subsequently confirmed by others [11–14].

However, the efficacy of the simple flush before fill was not absolute, i.e. the system permits a significant reduction of the bacterial count but does not guarantee the certainty of a constant complete removal of all micro-organisms [10–13]. This is particularly true for bacteria, like *Staphylococcus aureus* and *Pseudomonas aeruginosa*, which are removed only 50% or less of the time with the flush alone, because of their high capability to adhere to the tubes thanks to their pili and flagella, and to produce a biofilm in which the bacteria are retained, thus escaping the action of the flush [12, 15–16]. But a certain rate of failure occurs also for the *Staphylococcus epidermidis*, even if at a lower rate. The rate of failure, however, 'increases significantly with all bacteria and especially for

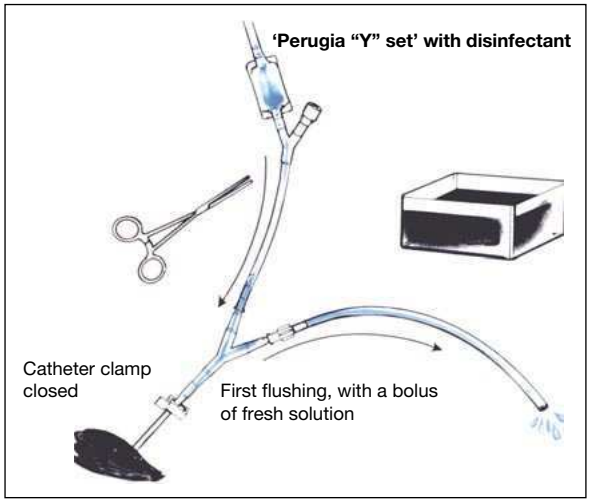

Fig. 4. First flushing of the 'Perugia 'Y' set' CAPD connection system. First flushing of the 'Y' set, with a bolus of fresh dialysate (about 100 ml).

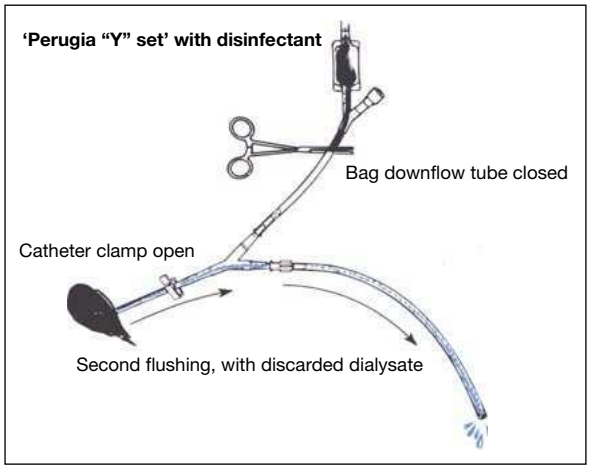

Fig. 5. Second flushing of the 'Perugia "Y" set' CAPD connection system. A second, more important flushing is performed with the 2 l of spent dialysate.

S. epidermidis, when the flushing is not performed soon after the possible contamination, allowing a prolonged contact time of the micro-organisms with the tubes [12, 13]. This is the case of the last, most risky step (de-connection of the empty bag and closure of the catheter with a cap) in the 'Y' disconnect systems without disinfectant.

The Contributory Effect of the Disinfectant

Why Use a Disinfectant

The rationale for the use of a disinfectant in combination with the flush resides in the fact that the positive effect of the sole flush is not absolute and, as already discussed, has a certain number of failures. Thus, adding a disinfectant to the flush eliminates or significantly reduces the rate of the failures by killing the contaminating micro-organisms [10] and by reducing the biofilm formation and inhibiting the growth of biofilm-adherent bacteria microcolonies [12] during the interval between the exchanges, the most dangerous phase. Another reason supporting the use of disinfectant is the lack of convincing studies supporting an equal efficacy in preventing peritonitis of the simple flush vs. the combination flush + disinfectant.

Which Disinfectant?

The ideal disinfectant for the disinfection of the CAPD connection should have the following requisites:

- high efficacy against all infectious pathogens (every kind of bacteria, viruses, protozoa, fungi), at concentrations far below the ones with possible toxic effect for the patient and after a reasonably short contact time;
- preserved efficacy even after contact with residues of glucose and amino acids, as it can occur in the clinical practice;
- no or low local and general toxicity, i.e. absence of serious damage to the patient and to the peritoneal membrane, even in the case of accidental entry into the peritoneal cavity;
- good long-term compatibility with the components of the connection system;
- cheapness.

Regarding the efficacy, already from the very beginning, we directed our interest toward the chloroxidizers, reported in the literature as bactericidal, virucidal, sporicidal. After repeated in vitro studies [17, 18], we confirmed that the most potent disinfectant is hypochlorite, which disclosed the lowest minimum bactericidal concentration against various micro-organisms, when compared with iodine tincture and chlorhexidine [18]. It proved to be efficient even at very low concentrations (5% or even less). Furthermore, the effect is achieved very rapidly: in fact, the contact time required to kill all bacteria was extremely short (30–60 min).

Due to the possibility that the contact of the oxidizing disinfectants with substances with reducing power, like glucose, proteins, amino acids (as can occur in CAPD), could reduce their antibacterial efficacy, we tested in this respect the disinfectants after dilution at different concentrations with solutions

containing glucose or amino acids or culture broth. We found [18] that the reducing activity of glucose does not interfere with the bactericidal action of the disinfectant at concentrations as low as 10% even after a contact time of 24 h. At lower concentrations, down to 3%, the bactericidal activity of the disinfectant is reduced but only with exposure time higher than 30 min. An inhibitory effect more pronounced is exerted by the contact with amino acids and broth, but limited to concentrations below 10%. However, the inhibitory effect is less pronounced than for iodine tincture.

The activity of chlorhexidine, which was not affected by contact with reducing agents, was significantly lower.

Regarding the innocuousness and safety, again our preference was, already from the start of our experience, for the chloroxidizers and precisely for a particular one, Amuchina, which, thanks to its original production process (partial electrolysis of a solution of NaCl), does not contain the toxic/irritating residues of the conventional chemical production process and has a lower caustic alkalinity. It is thus much better tolerated by tissues, even in presence of wounds and/or inflammation and does not interfere with the process of healing, which, on the contrary, is improved at the point that has been qualified with the adjectives 'histophilic' and 'eudermic' [19–21]. The very low general and local toxicity of Amuchina has been further confirmed by us with experiments in animals [17] and in animals and man [22] and more recently by others in another study [23] which showed that while povidone-iodine caused severe mesothelial injury, Amuchina at similar dilution did not. The safety of the use of this disinfectant for the disinfection of the 'Y' CAPD connection is even more evident when we consider the small quantity used and that an accidental injection of it usually occurs during the final refilling of the connector in the case of uneffected closing of the clamp on the catheter, when the abdominal cavity has been refilled with the 2 l of fresh dialysate, which will allow a very high dilution. In fact, our long-lasting clinical experience confirmed the rarity and the relative innocuousness of such possible accidents, which usually produce a mild abdominal pain which disappears rapidly after few rapid exchanges, without signs of chemical peritonitis or functional consequences on the peritoneum. This has been further confirmed by a study [24] which found no difference at all in the ultrafiltration between the patients experiencing or not the accidental injection of Amuchina, and before or after this.

The compatibility of Amuchina with the components of the connection system (connector on the bag and above all 'Y' set which remains filled with the disinfectant for most of the time) has proved to be excellent, to the point that the 'Y' could be left in place for up to 6 months without problems.

The cheapness of the system results not only from the relatively low cost of the disinfectant but also from the fact that, thanks to the efficacy and to the

compatibility of the same, the 'Y' can be reused for a long time, avoiding the need for expensive disposable 'Y' sets.

In conclusion, based on the above reported data and considerations, we are still firmly convinced (and more than 25 years ago) that the ideal disinfectant for CAPD Connections is Amuchina, which has at the highest level all the basic requisites for that function.

Clinical Results

With the 'Y' set connection with disinfectant, we achieved in our patients on CAPD a dramatic reduction in the peritonitis rate [25]. Our results were repeatedly confirmed by a high number of studies from other Italian centers which soon adopted this system [26–29]. But, in spite of the fact that the majority of these studies were prospective and controlled, it took a certain time before the system could be validated outside Italy, but at least it came from a prestigious study group [30].

Limitations of the Conventional 'Y' Set with Disinfectant

Notwithstanding the very good results in preventing peritonitis, the original 'Y' set system retained some limitations, which have been responsible for the progressive replacement with the 'Y'-derived systems (i.e. double-bag system) without disinfectant.

A first limitation was the persistence of a certain percentage (even if low) of failures arising from: (a) the difficulty to obtain a constantly certain and efficient disinfection of the distal end of the down-flow tube of the new bag, not protected by the disinfectant, and (b) the possible loss of efficacy of the disinfectant left inside the prosthesis during the intervals between the exchanges, as a consequence of the prolonged exposure to the reducing action of the glucose and amino acids contained in the residues of the dialysate remaining in the 'Y' set.

A second limitation was the fear for the possible injection of disinfectant into the abdominal cavity (even if extremely rare and without major consequences).

Optimization of the 'Y' Set with Disinfectant

In order to overcome the first limitation, i.e to completely eliminate every possibility of failure we proposed a new system called '*Double Y*' [31, 32] and

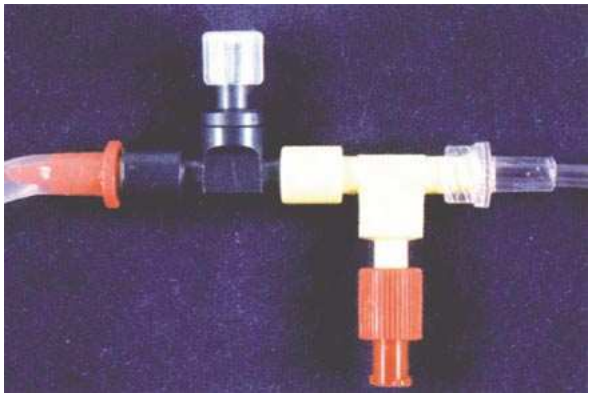

Fig. 6. 'Double Y' CAPD connection system with disinfectant. On the left side, the first 'Y' mounted on the distal end of the new dialysate bag, with the still intact breakable-membrane and the lateral way to be used for the injection of disinfectant at the beginning (soon after the connection with the catheter, being the clamp on this still closed) and at the end of the exchange (after the refilling of the abdomen and the closure of the clamp on the catheter and before its de-connection and closure with the cap). On the right side, the second 'Y' mounted on the catheter, with the lateral way to be connected with the drainage bag, which will collect not only the spent dialysate, but also the redundant disinfectant during the injections and the disinfectant washed away with the flush of fresh solution and with the spent dialysate.

consisting of two connectors, each with three ways, and mounted respectively one on the catheter (as the original Y) and the other on the distal end of the down-flow tube of the bag (fig. 6). Through the lateral way of the 'Y' on the catheter can be injected with a syringe fresh and surely effective disinfectant, which can be drained into the collecting bag through the lateral way on the distal end of the new bag. With this procedure, at the beginning of the new exchange, all the inner surface of the connection, not only on the catheter but also on the bag side, is washed with a sufficient quantity of disinfectant, ensuring an efficient disinfection even against heavy contaminations, as it was clearly proved by our in vitro experiments [31]. Through the same way, at the end of the exchange, the 'Y' on the catheter could be refilled with fresh disinfectant, ensuring also an efficient antimicrobial defense during the interval.

Afterwards, in order to overcome the second limitation, i.e. to avoid every possibility of injection of disinfectant into the abdominal cavity, we proposed [33] a new device which, thanks to a special slider, closes automatically the catheter line when the disinfectant is allowed to flow through the connection toward the discharge bag (figs. 7, 8). Furthermore, in order to overcome the

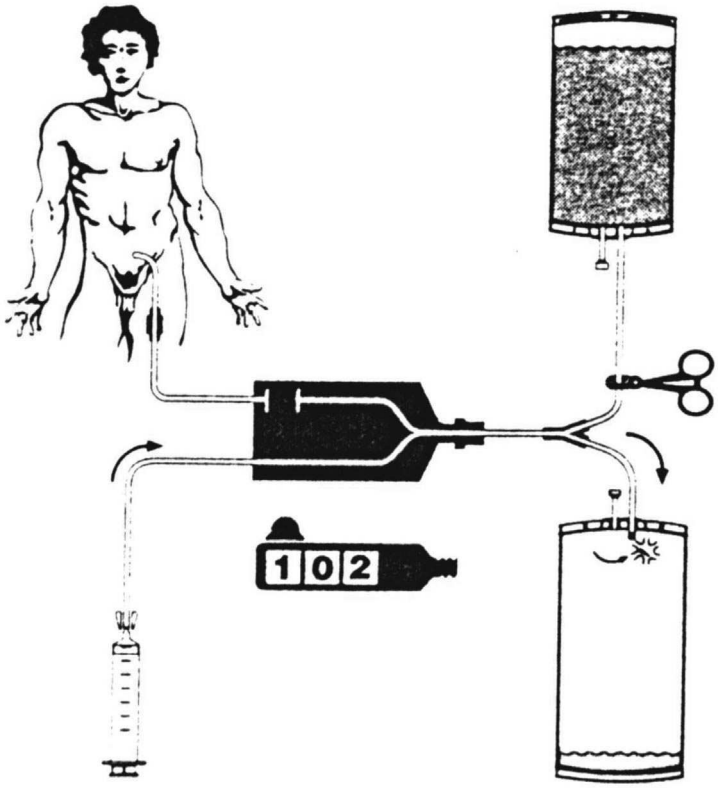

Fig. 7. 'Double Y' CAPD connection system with automatic prevention of accidental intraperitoneal injection of disinfectant. First injection of disinfectant at the beginning of the exchange, to disinfect the system after the connection bag-catheter: the slider in position 1 closes the way to the peritoneal cavity and opens the one to the drainage bag (still empty).

operational difficulties which a minority of patients could encounter in spite of the simplicity of the system, a small, portable, electromechanical device [34] was set up, which performs automatically the various operations performed by the patient in the manual version.

Conclusions

During the last 15 years, the worldwide adoption of the CAPD connection systems derived from the original 'Y' system enabling the 'flushing before filling' (mainly in the form of 'double-bag' systems, where the 'Y' is in the bag

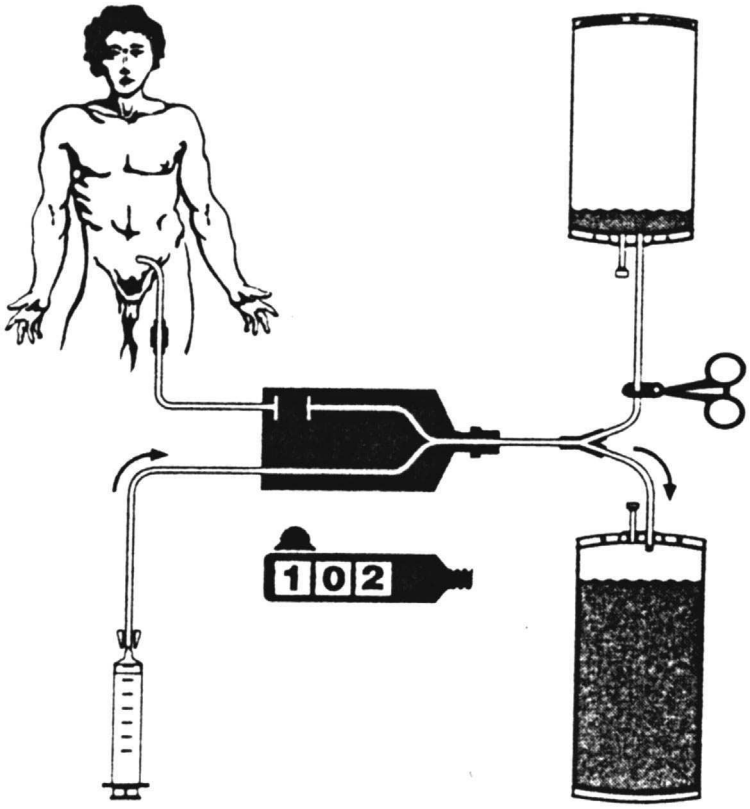

Fig. 8. 'Double Y' CAPD connection system with automatic prevention of accidental intraperitoneal injection of disinfectant. Second injection of disinfectant, at the end of the exchange, to refill the 'Y' on the catheter for the interval phase: the slider again in position 1 closes the way to the peritoneal cavity and opens the one to the drainage bag (already filled with the spent dialysate).

side) has stabilized the peritonitis rate in this type of treatment at levels surely acceptable. However, peritonitis still remains one of the most frequent complications of CAPD and certainly the most serious, both for the clinical consequences (morbidity and mortality) and for the technique survival. Furthermore, the fear for this complication is still the most important obstacle to a wider diffusion of this kind of treatment. The main reason for the persistence of this still relatively high peritonitis rate resides in the fact that in order to simplify the maneuver and, above all, to avoid the hypothetic risk of possible toxic effects of an accidental entry of disinfectant into the peritoneal cavity, the use of this has been abandoned. However, this choice seems at present no longer justified on

the basis of the following considerations: (1) we have accumulated a large body of evidence that the disinfectant proposed for this use, Amuchina, has a very low degree of general and local toxicity, at the point that it has been also utilized for peritoneal washing; (2) new systems have been set up, which guarantee an almost absolute certainty of complete disinfection and avoid any possibility of accidental entry of disinfectant in the peritoneal cavity; (3) for the less skilled patients an electromechanical device is now available; (4) the further reduction of the peritonitis rate achievable with this new connection systems utilizing a proper disinfectant could be of great importance, not only under the clinical aspect, but also for a safer and wider diffusion of this kind of treatment, what could have a considerable positive social-economic impact in view of the growing number of uremic patients.

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Exit-Site Care in Peritoneal Dialysis

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Abstract

Exit-site infection (ESI), tunnel infection and associated peritonitis are major causes of morbidity and catheter loss in chronic peritoneal dialysis patients. Meticulous exit-site care is vital in preventing ESI. Avoiding trauma to the exit-site and daily cleaning of the exit-site with a dedicated antimicrobial soap is essential for the longevity of the peritoneal dialysis catheter. Antibiotics cream and disinfectant agents including povidone-iodine, chlorhexidine, electrolytic chloroxidizing solutions (Amuchina 10% – ExSept Plus, Amuchina 5% – ExSept) are useful to keep the resident micro-organisms inhibited. ESI rates in peritoneal dialysis patients treated with Amuchina 10% (ExSept Plus) and Amuchina 5% (ExSept) for the exit-site care are similar or lower compared to povidone-iodine or chlorhexidine. Electrolytic chloroxidizing (Amuchina 10% – ExSept Plus and Amuchina 5% – ExSept) solutions for exit-site care are effective for prevention and treatment of ESI.

Access to the peritoneal cavity using an indwelling permanent and trouble-free catheter is a key factor in the success of peritoneal dialysis (PD). However, catheter exit-site infection (ESI) and tunnel infection (TI) remain the major cause of increased morbidity, prolonged antibiotic therapy, recurrent peritonitis, and catheter failure. The frequency of infection can be reduced by scrupulous exit-site care. Exit-site care begins even before the catheter is implanted. The ultimate goal of the exit-site care is to keep the exit-site clean, dry, scab-free, crust-free, and painless and non-inflamed [1, 2]. The PD exit-site care will be discussed as below in this chapter:

(1) Exit-site care pre-implantation of PD catheter.
(2) Early exit-site care post-implantation during healing phase.
(3) Chronic exit-site care of healed exit-site.

Exit-Site Care Pre-Implantation of PD Catheter

Determination of the Exit-Site

The exit-site should be identified and marked on the skin. This should be done in collaboration with the patient, the surgeon, the nephrologist, and the experienced PD nurse. The exit-site should be placed laterally either above or below the belt line, and it should not lie on a scar or in abdominal folds. It should be determined with the patient in an upright (seated or standing) position. Local trauma and hematoma during catheter placement should be avoided. The exit-site should be round and the tissue should fit snugly around the catheter. Sutures around the exit-site increase the risk of infection and should be avoided. The downward-directed exit-site is associated with significantly lower catheter related peritonitis [3]. Prophylactic antibiotics given at the time of catheter placement decreases the risk of infection [4, 5]. Vancomycin (1 g IV, single dose) at the time of catheter insertion is found to be superior to cephalosporin (1 g IV, single dose) in preventing early peritonitis [6]. Eradication of nasal *Staphylococcus aureus* carriage significantly reduces ESI [7].

Early Exit-Site Care Post-Implantation During Healing Phase

The optimal care of the PD catheter exit-site after catheter implantation is not known. The goal of immediate post-operative catheter care is to minimize bacterial colonization of the exit and tunnel during the healing period. However, no consensus exists regarding specific procedures, the use of dressings, methods of immobilization of PD catheter, or the use of cleansing/disinfectant agents at the exit-site.

Dressings

After implantation, the exit-site should be covered with sterile gauze. Transparent occlusive dressings should not be used alone because the drainage can pool at the exit-site and in the sinus. Thus gauze dressings can wick the drainage away from the exit and keep the exit-site dry. The surgical dressing should not be changed for several days unless there is obvious bleeding or signs of infection. The dressings should be changed no more than once a week. The dressing changes following catheter implantation should be restricted to specially trained staff [8]. Aseptic technique using face masks and sterile gloves is recommended for post-implantation exit-site care [9]. Patients should avoid submerging the exit-site during healing to avoid colonization with water-borne organisms. If the exit-site gets colonized with bacteria, more frequent dressing changes should be done [10].

Immobilization

The catheter should be immobilized using a dressing or tape. It is advisable to prevent torquing movement and to minimize handling of the catheter until the exit-site and tunnel are completely healed. This will reduce the incidence of trauma and promote tissue growth. This period usually lasts at least 4–6 weeks [11]. Although a number of devices for catheter immobilization are available, the immobilizer has not been shown to be more effective than tape or dressings in preventing exit infection [12].

Cleansing Agents and Disinfectants

Povidone-iodine and hydrogen peroxide have been used for cleaning the exit-site post-operatively. These are cytotoxic and can cause tissue damage and delay clean wound healing [13]. Care should be taken to keep them out of the exit-site sinus. Alternately normal saline or pure soap has been used for post-implantation care [8, 14]. However, there are no prospective, controlled studies to assess outcomes.

Chronic Exit-Site Care of Healed Exit-Site

Although sterile dressings are recommended until the exit is well-healed, there is no clear consensus as to when patients may begin to shower or change to chronic exit-site care. When the exit-site can be classified as good or equivocal, then showering and chronic care are appropriate [10]. The primary goal of exit-site care is to prevent ESIs and TIs. Exit-site care should include: (1) assessment of the exit-site; (2) cleansing the exit-site; (3) anchoring or immobilizing the catheter; and (4) protecting the exit-site and tunnel from trauma [9].

Assessment of the exit-site by visual inspection and palpation of the tunnel should be a routine part of exit-site care for both health care professionals and patients. Initial patient education should include how to assess the exit-site, signs and symptoms of ESI, and when to notify the PD clinic of exit-site problems. The optimal frequency of exit-site care has not been established. However, frequent cleansing is essential to reduce resident bacteria, and daily care is recommended. Exit-site care should also be repeated more than once a day if the exit becomes grossly dirty or wet. Good hand washing prior to exit care is critical to avoid cross contamination. Optimal chronic exit-site procedures for peritoneal catheters are undetermined. The few controlled studies have focused primarily on the use of dressings or the use of cleansing agents for exit care.

Dressings and Immobilization

Chronic exit-site care in adults showed a similar incidence of ESI in groups with and without dressings [15, 16]. The use of dressings for chronic care is based on anecdotal experience or individual preference. Theoretically, the use of dressings may help to keep the exit clean, protect it from trauma, and help to stabilize the catheter. Furthermore, dressings are indicated for all patients when the exit is infected or likely to become grossly contaminated. Gauze dressings are used most frequently, but semipermeable dressings and occlusive dressings are also used. The catheter should always be kept immobile to prevent pulling and trauma to the exit-site, which may lead to infection.

Antibiotics

The use of mupirocin cream at the exit-site has been shown to lower significantly *S. aureus* ESIs and peritonitis [7, 17, 18]. Although mupirocin cream is effective against *S. aureus*, it does not have activity against *P. aeruginosa* [19]. In a randomized double blinded trial comparing daily use of mupirocin cream (2%) and gentamicin cream (1%), the reduction in *S. aureus* ESIs were similar in both groups. In addition, there was a significant reduction of *P. aeruginosa* infection in the gentamicin group [20].

Cleansing Agents and Disinfectants

Antibacterial soap and water are routinely used to clean the exit-site. Povidone-iodine, chlorhexidine and electrolytic chloroxidizing solutions have been used as disinfectants for the routine care of exit-site and PD connection site to prevent or treat ESI/TI and catheter related peritonitis [21–25]. Povidone-iodine application in comparison to pure soap has been shown to reduce infection [24, 25].

An electrolytic chloroxidizing (Amuchina 10% – ExSept Plus) is a clear aqueous liquid that contains 1.15 g/l of sodium hypochlorite, 1.7 g/l of sodium chloride and has a pH of 9, thereby producing long-lasting stability. Non-clinical studies in two animal species over a substantial dose range of Amuchina 10% (ExSept Plus) revealed no potential toxic response [26, 27]. The Minimal Inhibitory Concentration has been found to range from 0.15 to 3.7% in vitro studies with a broad range of micro-organisms [28]. It has been shown to have bactericidal activity in vitro within 1 min against broad range of micro-organisms. Irritation and sensitization have been found to be similar to 0.9% NaCl solution.

In a single center randomized trial, Amuchina 10% (ExSept Plus) solution was compared with povidone-iodine 10% solution for exit-site care in 50 ESRD patients receiving PD. The patients with new catheter 4 weeks following catheter placement or with current catheter with no infection were included into

Table 1. Demographics and ESI/TI

Variables	Amuchina 10%	Povidone 10%
No patients	25	25
Patient-months	130	109
No diabetics	12	8
Mean age:years	59	53
No ESI	5	7
No ESI-PD	0	1
No catheter loss	0	1
No patients:irritation	14	6
No patients:scab	17	13
ESI/TI*	0.52	0.60

*Episode/patient/year.
ESI = Exit-site infection; PD = peritoneal dialysis; TI = tunnel infection.

the study. All patients underwent double-cuff coiled swan neck catheters implantation surgically with downward exit-site at lower abdomen below the belt line. The patients received cefazolin 1 g IV peri-operatively. All patients underwent exit-site care training session and received written instructions. They were instructed to shower daily and to clean the exit-site with a dedicated soap and water followed by an application of Amuchina 10% or povidone- iodine 10% with one to two cotton tip applicators. The exit-site was then air dried and covered with gauze dressing. Exit-site was examined at least once a month for drainage, crust, pain, swelling, induration or irritation. Drainage was sent for gram stain, culture and sensitivity. Catheter ESI was defined by purulent discharge and erythema with or without tenderness.

The mean age, months on PD, method of dialysis (CAPD/CCPD), and number of diabetic and non-diabetic patients were not statistically different (table 1). ESI/TI rates were lower in the Amuchina group (0.52 episode/patient/year) in comparison to the povidone group (0.60 episode/patient/year). No catheter was lost in the Amuchina group. Local irritation and scab formation were more common in the Amuchina group [21].

Since with the use of Amuchina 10% solution, there was a higher incidence of local irritation at the exit-site in comparison to povidone-iodine 10%, the subsequent study evaluated randomly Amuchina 5% (ExSept) solution comparing povidone-iodine 10% for exit-site care in PD [22]. Thirty nine PD patients were studied over a period of 470 patient-months. Eighteen PD

Table 2. Demographics and ESI/TI

Variables	Amuchina 5%	Povidone 10%
No patients	18	21
Patient-months	164	161
No diabetics	5	6
Mean age:years	55	60
No ESI	10	10
No ESI-PD	2	2
No catheter loss	3	1
No patients:irritation	11	7
No patients:scab	12	14
ESI/TI*	0.66	0.59

*Episode/patient/year.

patients received exit-site care with Amuchina 5% solution and 21 received exit-site care with povidone-iodine 10% solution. Protocol used in this study was similar to the previous study using Amuchina10% solution for the exit-site care. The mean age, months on PD, number of diabetic and non-diabetic patients were not different (table 2). The ESI/TI rates were 0.66 episode/patient/year in the Amuchina group and 0.59 episode/patient/year in the povidone-iodine group, respectively (table 2). The ESI/TI rates were not statistically different between two groups. Eleven patients in the Amuchina group had varying degrees of irritation at the exit-site while there were seven in the povidone-iodine group. The scab formation at the exit-site was in equal distribution (table 2). The frequent occurrence of local irritation and scab formation with the use of antiseptic agents including hydrogen peroxide, sodium hypochlorite, chlorhexidine and povidone solution has been reported at the catheter exit-site in PD patients [29, 30]. A retrospective study showed a significant reduction in infection rates (1.8 vs. 3.2/1,000 days; $p < 0.05$) with ExSept Plus and Alcavis 50 in comparison to povidone-iodine for both exit-site care and PD connection sites [31]. ExSept Plus has been found to be of similar efficacy compared to chlorhexidine for exit-site care of central venous catheters in hemodialysis patients [32].

In conclusion, both Amuchina 10% (ExSept Plus) and Amuchina 5% (ExSept) solutions for daily exit-site care are as effective as povidone-iodine 10% for prevention and treatment of ESI. However, local irritation and scab formations at the exit-site with the use of these disinfectant solutions are of concern.

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Successful Use of Sodium Hypochlorite Pack Plus Systemic and Local Antibiotic Therapy for the Treatment of Pseudomonas Infection of Peritoneal Dialysis Catheter Exit-Site

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Abstract

Peritoneal catheter exit-site and tunnel infections remain critical problems in patients undergoing peritoneal dialysis. Catheter-related peritonitis occurs in about 20% of patients and exit-site infections are responsible for catheter removal in more than one-fifth of the cases. For the last 2 years in the Department of Nephrology, San Bortolo Hospital, Vicenza, Italy, we have been treating exit-site infections caused by *Pseudomonas* with sodium hypochlorite packs as well as systemic and local antibiotic therapy. Considering the encouraging results obtained on *Pseudomonas* infection, we decided to utilize the same schedule for the treatment of exit-site infections caused by other germs which are generally difficult to eradicate to prevent peritonitis and catheter removal. Between 2003 and 2004, 10 patients contracted infection of the exit-site. All patients underwent a swab test because of the reddening and the purulent secretion of the exit-site. The swab resulted positive for *Pseudomonas* in 7 patients, *Corynebacterium* sp. in 2 patients, and *Candida albicans* in 1 patient. All patients were treated with systemic antibiotic therapy or antifungal therapy, local sodium hypochlorite 50% packs. After 15 days all patients were submitted to a swab test of the exit site. In all patients, the swab test resulted negative after 15 days and 1 month, and they could continue peritoneal dialysis. This procedure avoided peritoneal catheter removal and temporary switch to hemodialysis in all patients with exit site infection. The mechanism of action is related to the wide antimicrobial spectrum and the rapid action of sodium hypochlorite possibly creating a protective barrier on the exit-site.

Table 1. Characteristics of Amuchina® product

Amuchina® (sodium hypochlorite)	Sodium hypochlorite
Stability	Stable for 30 months
Efficacy	Wide spectrum of activity for gram+, gram−, viruses (HBV, HIV, HCV), fungi, spores with low-time of action and short-time of contact
Safe	No injuries on skin and mucosae

Peritoneal catheter exit-site and tunnel infections remain critical problems in patients undergoing peritoneal dialysis (PD) and often lead to catheter removal and treatment failure. Catheter-related peritonitis occurs in about 20% of patients on continuous ambulatory PD (CAPD). Exit-site infections are responsible for catheter removal in more than one-fifth of the cases [1]. In most cases infections begin at the exit-site and then, along the catheter length, can reach the peritoneum with consequent peritonitis. For this reason, early removal of the catheter is considered a safe and protective approach.

Catheter removal is an important complication, because it determines the necessity to switch the patient to hemodialysis and suspend PD for a relatively long period of time.

For the last 2 years in our department, we have treated exit-site infections caused by *Pseudomonas* with sodium hypochlorite packs as well as systemic and local antibiotic therapy. Considering the encouraging results obtained on *Pseudomonas* infection [2], we decided to utilize the same schedule for the treatment of exit-site infections caused also by other germs generally difficult to eradicate such as *Corynebacterium* sp. and *Candida albicans*). This action was undertaken in order to prevent peritonitis and catheter removal.

In this paper, we summarize the experience of the past 3 years in which we obtained the complete resolution of *Pseudomonas* infection of the peritoneal catheter exit-site by treating the patients with systemic antibiotic therapy together with Amuchina® 50% (hypochlorite and sodium chloride) packs left in place for 3–5 min, and dressing with iodine pack (table 1).

Methods

The study began in May 2003, in the Peritoneal Dialysis Unit of the Department of Nephrology, Dialysis and Transplantation of San Bortolo Hospital, Vicenza, Italy. In 2003, 6 patients with *Pseudomonas* infection of the exit-site were treated with IM antibiotic therapy (imipenem + cilastatin 500 mg/day) for 10 days according to the antibiogram results plus

Table 2. Application of Amuchina packs for different germs

Germs	CFU per ml	KE, %	Product concentration %	Time (min)			
				30″	1′	5′	15′
Staphylococcus aureus	10^8	100	5	X	X		
Staphylococcus faecalis	10^8	100	5	X	X		
Escherichia coli	10^8	100	5	X	X		
Klebsiella pneumoniae	10^8	100	5	X	X		
Proteus vulgaris	10^8	100	5	X	X		
Pseudomonas aeruginosa	10^8	100	5	X	X		
Mycobacterium smegmatis	10^8	100	0.5	X	X	X	
Candida albicans	10^8	100	0.31–0.62	X	X	X	
Herpes simplex virus	*	>99.9	3	X	X	X	X
Poliovirus	10^8 PFU	>99.99	0.75	X	X	X	X
HIV-1	*	>99.999	1.5	X			
Hepatitis A virus	*	*	1.5	X			
Hepatitis B virus	*	*	1.5	X			
Hepatitis C virus	*	>90	3	X	X	X	
Salmonella typhi	4×10^6	100	2	X			

Amuchina (sodium hypochlorite) packs that were left in place for 3–5 min each day for 2 weeks. Every day the dressing was prepared with iodine pack (table 2).

In the period 2004–2005, 15 patients contracted infection of exit-site. All patients underwent a swab test because of the reddening and the purulent secretion of the exit-site discovered at the physical examination. The swab resulted positive for *Pseudomonas aeruginosa*, *Clostridium difficile*, *Corynebacterium* sp. and *C. albicans*.

All patients were treated with IM antibiotic therapy or antifungal therapy according to the antibiogram and their residual renal function; hypochlorite-sodium chloride 50% packs that were left in place for 3 min each day for 2 weeks, and subsequently the dressing was prepared with iodine package.

The patients were treated either with APD or CAPD.

Results

Treatment as described was continued for 2 weeks and after this period the efficacy evaluation was carried out in all patients.

After 2 weeks of treatment all patients were submitted to a swab test of the exit-site that resulted negative. Another swab test was repeated after 1 month confirming the negativity. In this way, we were able to avoid catheter removal from these patients, maintaining PD therapy, thanks to the negativity of the exit-site to the infection. These results are remarkable in the sense that generally

such conditions may result in peritonitis leaving no alternative to catheter removal.

Conclusions

These data suggest that the combined procedure [Amuchina (Sodium Hypochlorite) packs, systemic and local antibiotic therapy and iodine pack] in patients with *Pseudomonas* infection of the exit-site may permit to avoid peritoneal catheter removal and patient switch to temporary hemodialysis. These results allow the continuation of PD therapy guaranteeing further confidence of the patient with this treatment. The association of local dressing with iodine pack and the sequential Amuchina (sodium hypochlorite) application seems to be helpful. The reason of the success of this multiple therapeutic approach may be related to the wide spectrum (gram+, gram–, mycobacterium, virus, spore and fungi) of activity and the rapid action.

These characteristics probably may avoid further infections creating a protective barrier on the exit-site.

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Disinfection of Lines and Transfer Sets in Peritoneal Dialysis

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Abstract

Peritoneal dialysis (PD) exchanges require sterile equipment, supplies, and technique. Sterility may be maintained with single use. However, when equipment such as lines and transfer sets are used repeatedly, disinfection techniques become a critical aspect in preventing infectious complications. Techniques available for disinfection of lines and transfer sets in PD will be reviewed.

One measure of peritoneal dialysis (PD) success is a decrease in infection rate. Contaminants from external sources enter the peritoneal cavity via the intra-luminal or peri-luminal paths. Disinfectant can be used to prevent bacteria migration during an exchange due to touch contamination, which would enter along the intra-luminal path or from infections at the exit site, or tunnel, which would enter along the peri-luminal path. Two disinfectants used extensively in PD are povidone-iodine (Betadine) and sodium hypochlorite (Amuchina, Alcavis). Sodium hypochlorite is an electrolytic chloroxidizer, obtained by partial electrolysis of hypertonic sodium chloride containing 11,000 ppm of available free chlorine. The undiluted form of sodium hypochlorite is Amuchina 50%. A diluted form of sodium hypochlorite is Amuchina 10%, ExSept Plus. The solutions are colorless and are transparent liquids. Sodium hypochlorite dissolves in cold water and is decomposed by hot water or carbon dioxide. It is a strong oxidizer, bleaching agent, and sterilizer. At the same time, it is

non-toxic and non-irritating. The use of disinfectant to decrease infection by disinfecting PD lines and transfer set will be explored in this section.

Disinfection of Peritoneal Dialysis Lines

Using Disinfectant during an Exchange

The main complication of PD is peritonitis, mostly due to line or touch contamination. Using the standard technique for continuous ambulatory PD described by Oreopoulos, the peritonitis rate was approximately 1 episode every 15 patient-months at best [1]. It was not until the concepts of 'flush before fill' using the Y-set connectology also known as the Perugia system and decreasing the number of connections by using pre-connected systems or a cycler, did the impact on infection rate became noticeable. The Y-set initially used disinfectant and 'flush before fill' to sterilize tubing between uses.

In 1983, Maiorca et al. [2] published a randomized prospective study on the use of a Y-connector with Amuchina (sodium hypochlorite) in the prevention of peritonitis. The Y-set with disinfectant was compared to a standard spike set in a randomized controlled study. Peritonitis with the standard set occurred in 17 of 30 patients which corresponded to 1 episode/11.3 patient-months. In comparison, 30 patients using the Y-set with disinfectant experienced 10 episodes of peritonitis, which corresponded to 1 episode/33 patient-months. The technique of 'flush before fill' was based on a principle introduced by Buoncristiani et al. [3]. With the Y-set design, after the spike connections were made, touch contaminated dialysate was flushed out via the Y-connection. Fresh dialysate further flushed any bacteria missed with the first flush. As subsequent patients were introduced to the Y-connector, the peritonitis rate fell from one in 27 in 1983 to one in every 40 months in 1984 compared to patients who used the standard connector, who had one episode every 14–12 months.

In a multi-center Canadian study, the Y-connector with disinfectant was compared to standard systems [4]. The peritonitis rate of 1/9.9 patient-months using the standard set decreased to 1/21.5 patient-months using the Y-set. This corresponded to a risk reduction of 61%. In the Y-set group, 15 patients had 21 episodes of peritonitis. In the standard set, 30 patients had 47 episodes of peritonitis. A Kaplan-Meier plot showed the Y-set patients had a significantly greater chance of remaining peritonitis-free compared to those using the standard connection.

The use of on-line disinfectant clearly decreased peritonitis episodes. Others have confirmed the lower peritonitis rate using on-line disinfectant with the Y-shaped disconnect–disinfectant system or O-set [5–10]. In the techniques using disinfectant to sterilize tubing in the Y-set, the disinfectant had to

be flushed out prior to the tube being used. Infections associated with PD were prevented with 'flush before fill' and the use of disinfectants. Other systems using disinfectant that did not gain popularity include the T-set evolution and O-set [9–13].

Evolution of connectology has moved away from using disinfectant instillation in the Y-set. The first description of Y-set without in-line disinfectant was made by Bazzato et al. [14] using the Double Bag System. This was followed by the disposable Y-set [15, 16]. Current technology uses two disposable bags (Ultra twin bag) which use drainage and infusion bags both secured to Y connecting tubing [17]. This system does not require any additional connection to PD bags. There is only one connection to the transfer set. Peritonitis rate was one episode per 33.9 patient-months and 1 year infection-free survival rate was 71% [18]. In this same study, in subjects using the ultra Y-set which uses only the drainage bag already attached to the Y connecting tubing, the peritonitis rate was one episode per 11.7 patient-months and 1-year infection-free survival rate was 40%. The simplicity of using twin bags and cost effectiveness in preventing peritonitis outweigh the cost of disposing two bags and tubing with each exchange.

Disinfection of Disposable Dialysis Tubing

The rate of continuous cycler PD use in the hospital setting is increasing. Using a cycler frees up the nurse's time. Instead of performing 4–8 manual exchanges per day, the nurse can put up enough dialysate for a day with one connection to initiate the cycle and one disconnection to terminate the cycle. Infection rate decreases due to fewer connect/disconnect procedures where touch contamination is possible. The patient can be disconnected for procedures and then reconnected to the same line. Despite these advantages, there is increased cost of continuous cycler PD. The costs are related to the cycler, cycler tubing sets, cycler drain line/bag and dialysate solutions. The patient must be able to disconnect and reconnect to the cycler either in between or during PD treatments as needed either in dwell or at the end of drain. Thus the concept of disinfection of disposable dialysis tubes for multiple use [19].

Multiple use of tubing sets and drain lines were performed with Pac-X/Pac-Xtra Cycler (Baxter Healthcare, McGaw Park, Ill., USA) in the hospital and home setting [19, 20] and HomeChoice Automated PD System (Baxter Healthcare, McGaw Park, Ill., USA) in the hospital setting [21]. Each set from Pac-X/Pac-Xtra cycler was used for 2–3 treatments, each of 16–24 h duration. Drain line extension set connected with the drain line of the tubing set was used for 7 days. Five-liter dialysate bags were used. Fluid was either set initially or

added as clinically indicated. Betacaps or minicaps were used to keep the tubing set sterile. Each disposable tubing set from HomeChoice Automated PD system was used for 2–7 treatments, each of 16–24 h duration. Povidone-iodine 10% was infused in the drain line.

Patients prefer to use PD supplies multiple times because of convenience and decreased set-up time. Staff prefer to use PD supplies multiple times because of cost, convenience and decreased set-up time. There was no significant increase incident of peritonitis compared to single use [19–21]. Wadhwa [21] showed that multi-use resulted in a 78% reduction in tubing sets, reducing the disposable supplies and cost, and a substantial saving in nursing time.

Disinfection of the Transfer Set during a Change

The transfer set reduces mechanical malfunction due to normal wear and tear from stress or manipulation to the chronic PD catheter. The transfer set is changed every 6–9 months to reduce infection rate. When the transfer set is separated from the chronic PD catheter, the catheter with or without the adaptor is soaked in disinfectant to reduce infection complications.

Disinfectants that are popularly used are povidone-iodine or sodium hypochlorite and will be compared for efficacy and side effects. Other disinfectants containing polyethylene glycol or alcohol will not be discussed. Cracks were observed in polyurethane catheters after exposure to polyethylene glycol or alcohol [22]. No side effects from disinfectants are associated with silicon catheters.

The use of Amuchina 50% solution versus povidone-iodine 10% solution for transfer set change in PD patients was first described by Cabralda et al. [23]. No episode of peritonitis occurred related to transfer set change using povidone-iodine or Amuchina 50%. The soaking time with Amuchina 50% was 2 min and the nursing time was 5 min compared to 10 min soaking time and 20 min nursing time for povidone-iodine. Transfer set change used 20–30 ml of Amuchina solution compared to 120 ml povidone-iodine. The procedures for using sodium hypochlorite or povidone-iodine as disinfectants during transfer set replacement are included in table 1.

Sodium hypochlorite was compared to povidone-iodine as the disinfectant used during transfer set changes to determine the impact on infection rate and peritonitis rate [24]. Two inner city PD clinics with similar patient demographics participated in this study. Clinic A used Alcavis 50 (sodium hypochlorite 50%) exclusively for transfer set change (160 procedures during 984.9 patient-months) and trained their patients to use Alcavis 50 for accidental touch

Table 1. Protocol to change the PD transfer set

Recommendations

1. Use strict aseptic technique throughout this procedure
2. Perform a solution exchange following the completion of this procedure

Gathering the supplies

1. PD Transfer Set Change Kit (10 sterile gauze, catheter or beta clamp, 30 ml soaking tray, 2 face masks with ear loop, 3 pairs of sterile gloves, 2 poly-lined towels for drape, wrap for sterile field, sterile tray)
2. Transfer set
3. Ancillary disconnect cap
4. Sodium hypochlorite 50% or povidone-iodine 10%

Getting ready

1. Wash hands with an anti-microbial scrub
2. Open the kit pouch with the label facing up to ensure the kit contents remain upright
3. Don the mask, then have the patient don his or her mask
4. Place drape under transfer set tubing making sure the catheter connection adapter is over the drape
5. Wash hands again with an anti-microbial scrub

Preparing the sterile field

1. Don one sterile glove
2. Open the wrap using the non-gloved hand
3. With the gloved hand, organize the supplies on the sterile field created by the wrap
4. With the non-gloved hand, pour approximately 30 ml sodium hypochlorite 50% into the tray or 30 ml povidone-iodine into the soaking tub and approximately 100 ml povidone-iodine into the tray
5. Don the remaining sterile glove

Scrubbing the catheter adapter connection and tubing

1. Pick up one sterile gauze by the four corners. Dip the center portion of the gauze into the sodium hypochlorite or povidone-iodine solution in the tray. Repeat with a second sterile gauze
2. Place the catheter adapter connection and tubing between the two sodium hypochlorite 50% or povidone-iodine soaked sterile gauze and scrub the catheter adapter connection and tubing for 5 min
3. Pick up a dry sterile gauze and place around the adapter connection to prevent it from touching the drape
4. Discard the gauze used for the scrub

Soaking the catheter adapter connection in the soaking tub: (for povidone-iodine only)

1. Submerge the adapter connection into the tub with povidone-iodine
2. Apply a downward and sideways pressure with the thumbs, pushing the tubing into the crimped slots of the tub
3. The adapter connection of the catheter should rest on the bottom of the tub to allow maximum coverage and soaking
4. Close the lid on the tub. Note: Lid closure is not leak-proof
5. Soak the catheter adapter connection for 5 min
6. Open the lid on the tub
7. Remove the soaked catheter adapter connection from the tub by lifting up
8. Place a dry sterile gauze around the adapter connection to prevent contact with the drape
9. Place the tub off to the side
10. Remove soiled gloves and discard

Table 1. (continued)

Soaking the open end of the catheter

1. Don the second pair of sterile gloves
2. Clamp the catheter clamp on the catheter
3. Place the second drape under catheter
4. With a sterile gauze in each hand, firmly hold each end of the transfer set junction and disconnect the transfer set from the patient catheter. Make sure the open end of the catheter does not touch the drape
5. Hold the tray with sodium hypochlorite 50% or povidone-iodine close to the open end of the catheter
6. Submerge the open end of the catheter in the container. Soak for 2 min with sodium hypochlorite or 5 min with povidone-iodine
7. Remove the soaked catheter end and place in a sterile gauze, making sure the catheter end does not touch the drape
8. Remove soiled gloves and discard

Connecting the open end catheter to the sterile transfer set

1. Open the packaging of the sterile transfer set and keep within easy reach while maintaining sterility of the set
2. Don the last pair of sterile gloves
3. Pick up the sterile transfer set, close the roller/twist clamp, and remove the tip protector
4. Lift up the open end of the catheter adapter from the gauze
5. Connect the set to the catheter adapter
6. Luer-lock firmly in place to ensure a tight connection. The double-seal locking connector does not need to be secured by taping or protective dressings
7. Open the ancillary disconnect cap packaging. Remove the tip protector on the transfer set and Luer-lock the disconnect cap into place
8. Remove the catheter clamp and the drapes. Immobilize the catheter tubing and secure the transfer set
9. The transfer set exchange procedure is completed
10. Allow 5–10 ml to drain out of the patient
11. Place a new sterile minicap

contamination at home. Clinic B used povidone-iodine for transfer set change (174 procedures during 868.6 months) and trained their patients to use povidone-iodine impregnated caps for accidental touch contamination. The protocols using Alcavis 50 and povidone-iodine for transfer set change were similar in that standard clinic procedures were used. Transfer set tip was soaked in 50 ml of Alcavis 50 solution for 1 min to treat accidental touch contamination. Whereas, subjects using povidone-iodine attached a povidone-iodine minicap to the transfer set tip for 10 min and repeated the procedure with a new cap for another 10 min, a total or 20 min. Both systems then required a flush of the system before the next fill. Total infection rate (peritonitis and exit site) was 1.7 episodes/1,000 days in clinic A compared to 2.9 episodes/1,000 days in clinic B (χ^2, $p = 0.019$). The peritonitis rate in clinic A was 0.7 episodes/1,000 days

compared to 2.2 episodes/1,000 days in clinic B (χ^2, $p < 0.001$). Exit-site infection rates were 1.0 and 0.8 episodes/1,000 days for clinics A and B, respectively (χ^2, $p = 0.092$). No adverse symptoms or reactions were reported in either group. This study showed that Alcavis 50 resulted in significantly fewer infections than the povidone-iodine group when used as a disinfectant for transfer set change and accidental touch contamination.

Disinfection of the Transfer Set Tip

After contamination of the transfer set tip, povidone-iodine impregnated in the cap should be adequate as an anti-bacterial agent. Moreover, the flush before fill further removes bacteria before the next infusion of dialysate. After a touch contamination, flushing reduces both bacterial growth and the development of bacterial biofilm, while using sodium hypochlorite at 50% concentration as the disinfectant bleach after contamination eradicates both bacteria and biofilm [25]. Sodium hypochlorite 25%, which the patient may have for exit-site care, applied to the contaminated transfer set tip for 2 min provides added anti-viral benefits.

Sodium Hypochlorite Use

The advantages for using sodium hypochlorite compared to povidone-iodine are listed in table 2. There are, however, arguments against the use of sodium hypochlorite as a disinfectant. One of the main concerns is the consequence of accidental intra-peritoneal infusion of sodium hypochlorite. The rate of accidental infusion of sodium hypochlorite ranged from one in 2,500 exchanges in the Canadian CAPD Clinical Trials Group [4] to one in 8,000 exchanges [12]. Immediate painful chemical peritonitis occurs in 25% of patients if sodium hypochlorite is accidentally infused into the peritoneal space [4, 26]. It is not clear whether accidental introduction of sodium hypochlorite into the peritoneal cavity causes any long-term damage to peritoneal membrane function. Maiorca found no reduction in peritoneal creatinine clearance or in ultrafiltration in those patients who had accidental infusion of the disinfectant into the peritoneal space [27]. Absence of sclerosing encapsulating peritonitis after sodium hypochlorite intraperitoneal infusion in animals was described by Mackow et al. [28]. Others feel that the chemical burn caused by the disinfectant has significant long-term effects on the peritoneum [29, 30]. There are no data, however, to support their views.

Table 2. Comparison between povidone-iodine and sodium hypochlorite

Povidone-iodine	Sodium hypochlorite
Frequent use causes a yellow discoloration to skin, catheter, and clothes	Bleach may damage colored clothes. There is no discoloration to skin or catheter
Soaking for 5 min with the disinfectant is required during transfer set replacement	Soaking for 2 min with the disinfectant is required during transfer set replacement
May cause skin irritation and reaction Very dry skin results from exposure to povidone-iodine	Non-irritating, non-sensitizing and does not cause skin reaction. Less dryness of the skin is observed with sodium hypochlorite exposure
Growth of *Pseudomonas* sp. was observed in an opened multi-dispensed bottle of povidone-iodine [31]	No infectious organisms have been cultured from an opened multi-dispensed bottle of sodium hypochlorite
Povidone-iodine does not kill viruses such as HIV or Hepatitis	Sodium hypochlorite kills viruses such as HIV and Hepatitis
May cause sclerosing encapsulating peritonitis [28]	Does not cause sclerosing encapsulating peritonitis
More costly	Inexpensive

Conclusion

Disinfectants are used to maintain sterility of the transfer set tip between exchanges and of the transfer set and PD catheter during a transfer set exchange. Disinfectants are no longer instilled in PD tubing since disposable tubings using the twin bags became available. Caps containing disinfectant are used with cycler tubings as well as with the transfer set tip when the patient is temporarily disconnected from the cycler. Disinfectants have a define role in maintaining the sterility of PD tubings and transfer set.

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Amuchina 10% Solution, Safe Antiseptic for Preventing Infections of Exit-Site of Tenckhoff Catheters, in the Pediatric Population of a Dialysis Program

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Abstract

Although, decreasing in incidence with the disconnection systems, the first complication is still peritonitis in patients with chronic renal failure and the second is infection of Tenckhoff catheter exit-site. All efforts made to diminish the frequency of exit-site infection lower the possibility of peritonitis. The pediatric population is well-known to have a major risk of infectious complications, and making easy and safe the care of the exit-site will prevent the peritonitis that follows. The aim of the study was to evaluate the efficacy of the Amuchina 10% solution vs. pH neutral soap in children with chronic renal failure, on preventing exit-site infection. There were 60 patients who were assigned randomly to one of two groups. One group used Amuchina 10% solution for the daily cleaning of the exit-site, and the other used pH neutral soap, with 14 months of follow-up. Before the study they have to be free of infection for at least 30 days. All were taught by the same nurse how to clean their exit-site. Groups were almost identical in years, sex, and time on dialysis. We had nine infections in the soap group and none in the Amuchina 10% solution group, with an OR: 17 ($p = 0.004$). From these nine infections, the bacteria isolated were: 4 (13%) were caused by *Pseudomona aeruginosa*, 1 (3.3%) by *Staphylococcus aureus,* coagulase-positive staphylococci in 2 (6.6%) and *Serratia marcensens* in 1 (3.3%). In conclusion, Amuchina 10% solution is effective in preventing infection on the exit-site, without any secondary topical reaction.

In Mexico, chronic renal failure (CRF) has one of the highest world prevalence rates, with more than 1,000 patients/million inhabitants, although

the number of patients treated is low. In our institution 85% of the patients are treated with peritoneal dialysis (PD), with a prevalence of 200–300 patients/ million inhabitants i.e. one of every five patients is treated. Kidney failure in children in the Mexican Social Security is approximately 8% of these patients [1].

The need of a Tenckhoff catheter installation causes in itself risk complications in patients with a poor social condition.

Peritonitis and exit-site infection remain the most important limitations to the delivery of PD. The exit-site infection is an unsolved difficulty, in which *Staphylococci* is a main problem [2–5].

A more recent problem is the appearance of *Staphylococcus aureus* isolated with a high degree of resistance to the topical antimicrobial agent mupirocin. This was documented in PD patients who have received prophylactic application of mupirocin at the peritoneal catheter exit-site [6].

It is currently believed that Amuchina is an effective antiseptic for prevention of Tenckhoff catheter exit-site infection. As an electrolytic chloroxidizer with a pH of 9.5–10.5, stable sodium hypochlorite base, absence of caustic alkalinity, fulfills the principal characteristics for a quick and powerful antiseptic action, mild on skin and other tissues.

There are few studies of Amuchina for preventing the exit-site infection; but Cabralda's studies in transfer-set change in PD showed good cost effective results [7].

Although there is still controversy over whether they are the best strategies for preventing exit-site infection, in emerging countries the best strategies are prevention, early detection and we cannot afford bacterial resistance. So Amuchina had proved good results in our poor nourished, with poor living conditions children with a very easy and safe way of spray application, but more studies had to be done.

Objective

Until now, there have been few studies published about Amuchina and the exit-site infection prevention measure on children with PD.

The aim of the study is to compare the efficacy of Amuchina against pH neutral soap on prevention of exit-site infected children with Tenckhoff catheter for cyclic continuous PD.

The incidence of Tenckhoff catheter's exit-site infection, is 1 per month in our hospital, to measure the efficacy of Amuchina, we hope to reduce this by 50% of the annual incidence.

Materials and Methods

To achieve our objective we did a randomized, prospective and longitudinal clinical assay. The research protocol was revised and approved by the Committee of Investigation of Hospital de Pediatria of Centro Medico Nacional Siglo XXI, México, D.F., México. The subjects of the study were children under 17 years of age diagnosed with CRF in the program of PD who attended outpatient care at the Department of Nephrology from January 22, 2004 to March 15, 2005. Sixty patients were assigned in two groups.

Procedures

The patients needed to be at least 3 months on the PD program and free of peritonitis or exit-site infection for at least 1 month since the last episode. In order to unify the study group, the patients with steroids, cancer or HIV positive, were excluded. The study was blind for the investigators and laboratory personnel. Patients were assigned 1:1 in two groups, with only one treatment; the Rand Corporation tables were used for randomization. After signing the agreement all patients were trained by the nurse in charge of the program on a unique cleaning technique and Amuchine application on catheter exit-site. The patients by themselves take care of their exit-site as the instructor nurse taught them.

If during the study there was a patient with an exit-site infection, defined with presence of redness and/or purulent secretion, culture was taken and treatment prescribed, without dropping the patient from the study.

Statistical Analysis

Results are expressed as median and lower and upper quartile, and percentiles. Comparison was made using the Mann-Whitney U test where appropriate. Statistical significance was taken as $p < 0.05$.

Results

Sixty patients were included, of which 30 patients went into group 1 with Amuchina, and 30 went into group 2 with pH neutral soap. In group 1, 19 patients were male (63.3%) and 11 female (36.6%) and on group 2, 11 male (36.6%) and 19 female (63.3%). Median age was 12 years on both groups, while median time on dialysis was 6 months ($Q_{25–75}$: 4–15 months) (table 1).

Nine were exit-site infected in the soap group (group 2) against no infection in the Amuchina group (group 1). This is 30% of the patients of group 2, with an OR: 17 (CI = −0.95%; p = 0.004) (table 2).

Cultures isolated from the infected exit-sites are summarized in table 3; with a surprisingly elevated 13% (4 cases) of *Pseudomonas aeruginosa*, followed by *Staphylococcus* coagulase positive. From the nine cultures of the infected exit-site only one had any isolation. Despite the fact, catheter removal was not required.

Table 1. Patients and time of dialysis

	Group 1 30 patients	Group 2 30 patients	
Sex: Male	19 (31.6%)	11 (18.4%)	
Age median (Q25–75)	12 (10–14) years	12 (8.75–14.25) years	$p > 0.05$
Dialysis median (Q25–75)	6.5 (4–15) months	6 (4–16) months	$p > 0.05$

$p > 0.05$ confirm the high group similarity.

Table 2. Exit-site infections during the study

Group 1 30 patients	Group 2 30 patients	OR
0 (0%) infections	9 (30%) infections	17 (CI 95% = 1.02–281.9) $p = 0.004$

Table 3. Etiologic spectrum of exit-site infection

Gram+ bacteria	Gram− bacteria	Others
S. coagulase + 2 (6.6%) *S. aureus* 1 (3.3%)	*Pseudomona aeruginosa* 4 (13%) *Serratia marcensens*	No isolation 1 (3.3%)

Discussion

Our study shows that Amuchina is effective in the prevention of exit-site infection during the 14 months of the study, seventeen times more than pH neutral soap. With very similar groups, in age, and time on dialysis, when is compared the Amuchina group with the soap group, the OR: 17, shows the safety of using the chloroxidizer, which is statistically significant ($p = 0.004$). There are some items to be observed, such as all children took care of their own exit-sites. Somehow it is surprising that *Pseudomonas* was our dominant strain isolated,

and in second place *Staphylococcus*, maybe because the use of mouth mask and also we can consider pH neutral soap as placebo. Anyhow, more studies, with larger population have to be done but results are hopeful for developing countries that cannot afford newer and expensive measures for preventing exit-site infection [5].

It is described that *S. aureus* is the bacteria to control, is a multifactor group that is seen in all devices that are used for treating patients. As is documented, a good and careful catheter installation, preventing antimicrobial contamination before, during and after the intervention, avoiding catheter traction, a good antiseptic can give excellent results, without getting resistant strains [8].

Finally, following the infectologist's advice for using antimicrobial drugs only when necessary.

Further studies have to be done, but we will always cope the malnourished patient, the chronic inflammation, the children, diabetic patients, etc., but the basic rules of medical devices have to be followed. Those are quality assurance, above all in developing countries, continuing education, and choice of the catheter insertion site, and hand hygiene with antiseptic techniques [3, 5, 9].

Maybe the future is in the modification of catheter material that would be antiadhesive to biofilms or at least colonization resistant [8]. Meanwhile, in our center we will continue to study the electrolytic chloroxidizer as part of many measures to avoid exit-site infections in larger population.

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Risk of Peritonitis among Disadvantaged CAPD Patients in Mexico

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Abstract

Background/Aims: Continuous ambulatory peritoneal dialysis is the first-choice treatment for ESRD in Mexico. Peritonitis is the most frequent cause of morbidity and is among the leading causes of technique failure in our country. Our objective was to compare the efficacy of the standard and double-bag disconnect systems for the prevention of peritonitis in a high-risk population with poor living standards, and high prevalence of malnutrition and diabetes rates. **Methods:** Episodes of peritonitis registered between July 1989 and June 2003 were included. Patients were divided in conventional and double-bag groups. Between July 1989 and May 1999, all patients used the conventional system. From May 1999, all incident patients were placed on a double-bag disconnect system. **Results:** Six-hundred and forty-seven patients started dialysis in the study period, 383 in the conventional group, and 264 in the double-bag. The peritonitis rate observed was 1 episode per 7.2 patient-months in the conventional group, and 1 episode per 25.1 patient-months in the double-bag system ($p < 0.001$). Cumulative peritonitis-free survival rate at 6 (50 vs. 82%), 12 (27 vs. 69%) and 24 (12 vs. 45%) months, respectively, was significantly lower in the conventional group ($p < 0.001$). Technique survival at 1 (75 vs. 85%), 2 (68 vs. 80%), and 3 years (50 vs. 80%), was worse in the conventional group ($p < 0.001$). By multivariate analysis, the only factor associated with peritonitis was the connecting system. **Conclusions:** We conclude that switching from a standard to a double-bag system using electrolytically produced sodium hypochlorite disinfectant markedly decreased the peritonitis rate, even in a high-risk population like ours.

Background

Continuous ambulatory peritoneal dialysis (CAPD) has been the first-choice treatment for ESRD in Mexico for the last 25 years. Eighty-five percent of the Mexican dialysis population are currently on this modality [1]. Peritonitis is the most frequent cause of morbidity and is among the leading causes of technique failure in our country [2, 3]. Also, it is an important barrier to long-term CAPD in developing countries [4, 5]. Attempts to decrease infection rates in CAPD have included eradication of bacteria from skin, nose, and exit-site [6–8], modification of catheter design and the use of improved disconnect systems [9]. The latter has had the largest impact [10, 11].

In a prospective controlled trial conducted in Mexican patients, the use of a double-bag system was associated with a 75% reduction in peritonitis incidence and a 20% reduction in hospitalization rates [3]. Our patients are at higher risk of peritonitis because of poor living standards, and high prevalence of malnutrition and diabetes rates [12]. Peritonitis prevention is of utmost importance in preserving the functional integrity of the peritoneal membrane and technique survival in this population, since 80% of them is on CAPD and access to hemodialysis and transplantation is very limited [1].

In the present study, we determine the incidence of peritonitis among poor, uninsured CAPD patients, and compare the efficacy of the conventional (spike) and double-bag systems for peritonitis prevention in this population. We also analyze the risk of technique failure with the use of these two systems.

Methods

This is a retrospective single-center study based on patients' records and data files. The Hospital Civil de Guadalajara is a large tertiary-care facility that offers dialysis to patients of low social strata and no medical insurance. Since 1989, we have kept an epidemiological surveillance of the episodes of peritonitis in our CAPD program. All patients who started CAPD between July 1st, 1989, and June 30th, 2003 were eligible for the study. From July 12, 1989 to May 12, 1999, both Dianeal™ (Baxter International, Inc.) and Solucion DP™ (Laboratorios Pisa, Mexico) spike systems were used (conventional group). In this period, the transfer sets were changed using povidone-iodine 10% solution. Also, a connection shield with a sponge soaked with this disinfectant was used at the transfer set's Luer-lock connector and at the spike-bag outlet port connection. From May 13, 1999, the double-bag system (BenY™, Laboratorios Pisa, Mexico) was introduced in all patients (double-bag group), and povidone-iodine was replaced by a sodium hypochlorite 50% solution (ExSept™, Alcavis International, Inc.), both at the transfer-set's Luer-lock, and for transfer-set changes. Only incident patients in both systems are included. Forty-five patients who switched from the conventional to the double-bag system, were censored at the time of change and are not included in the analysis of the double bag group. All data for the study comes from our

Table 1. Demographics and peritonitis rates in the two study groups

	Conventional	Double-bag
Patients (n)	383	264
Age (years)	42.8 ± 18.8	43.6 ± 19.0
Gender (M/F)	178/205	142/122
Diabetes mellitus (%)	40.2	38.3
Follow-up (patient-months)	5,258	2,485
Peritonitis episodes (n)	730	99
Rate (episode per patient-months)	1 per 7.2	1 per 25.1*

*$p < 0.001$.

prospective peritonitis surveillance program. Data was stored using the EPI5 and EPI6 software (Versions 5 and 6; Centers for Disease Control and Prevention, Atlanta, Ga., USA).

Peritonitis was defined by the presence of two or more of the following findings: abdominal pain, cloudy dialyzate, white cell count >100 cells/μl or dialysate positive culture. Relapses, defined as the occurrence of a new peritonitis episode within 1 month after a previous episode, were not counted. Peritonitis rates were analyzed expressing the frequency per patient-month. Additionally, the time of first peritonitis-free survival was constructed by Kaplan-Meier curves and comparisons were made with log-rank test. Loss to follow-up, death, renal transplantation, switch to hemodialysis or connecting technique, as well as recovery of kidney function, and end of study were treated as censored observations.

Switch to hemodialysis for ≥90 days and death were counted as a technique failure. Technique survival was analyzed by Kaplan-Meier curves and compared with the log-rank test. Loss to follow-up, switch of connecting technique, renal transplantation, recovery of kidney function and end of the study were treated as censoring events.

Differences between groups were assessed with t-test or χ^2 as appropriate. Peritonitis and technique failure risks were analyzed with a multivariate Cox's proportional hazards model.

A p-value of less than 0.05 was accepted as significant. All statistics were done with the SPSS (Advance Statistics, release 10.0; Statistical Package for the Social Sciences; Chicago, Ill., USA).

Results

CAPD was the initial treatment for 647 patients who started dialysis in the study period, 383 utilizing the conventional system, and 264 the double-bag system. Age, gender, and frequency of diabetes mellitus were comparable in both groups. In the conventional group, 262 patients (68%) experienced 730 episodes of peritonitis in 5,258 patient-months or 1 per 7.2 patient-months. In the double-bag group, 65 patients (25%) experienced 99 episodes of peritonitis in 2,485 patient-months or 1 per 25.1 patient-months ($p < 0.001$) (table 1).

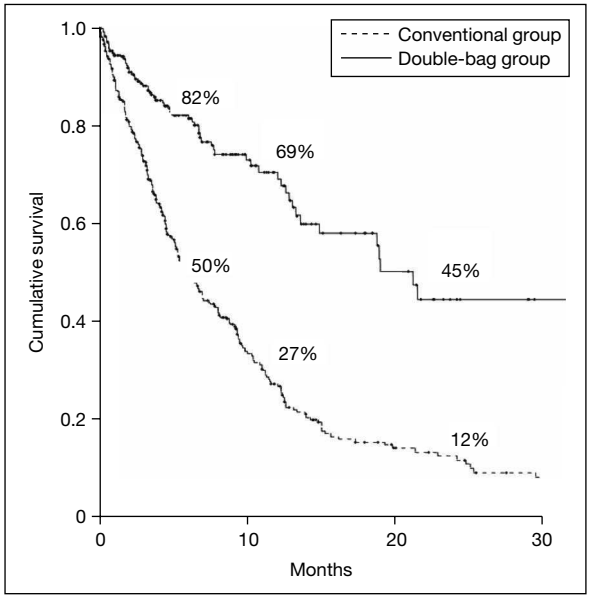

Fig. 1. Kaplan-Meier survival analysis of first peritonitis-free intervals. The double-bag group had a longer survival than the conventional system group ($p < 0.001$ by log-rank test).

Figure 1 shows the Kaplan-Meier curve of the first peritonitis-free survival time. There were significant differences between the two groups. The cumulative probability of peritonitis-free survival to the first episode of peritonitis at 6 (50 vs. 82%), 12 (27 vs. 69%) and 24 (12 vs. 45%) months, was significantly lower in the conventional than in the double-bag group ($p < 0.001$). By multivariate Cox's proportional hazard model, the use of the double-bag decreased the risk of the first episode of peritonitis in 67% ($p < 0.001$).

Technique survival at 1 (76 vs. 87%), 2 (68 vs. 80%) and 3 years (50 vs. 80%) was also significantly lower in the conventional system ($p < 0.001$) (fig. 2). By multivariate analysis the use of the double-bag reduces the risk of technique failure by 27% ($p < 0.001$). Details of organisms causing peritonitis are shown in table 2. Only 50% of dialysate cultures were positive. No culture was done in 25 cases with the double-bag system. The pattern of organisms causing peritonitis was comparable in both groups. Gram-positive organisms, predominantly of skin origin, were the most common organisms, accounting for 56% of the peritonitis episodes, followed by Gram-negative organisms, accounting for 40%. *Staphylococcus aureus* accounted for 16% of all peritonitis episodes while fungal peritonitis represented 3% of all episodes.

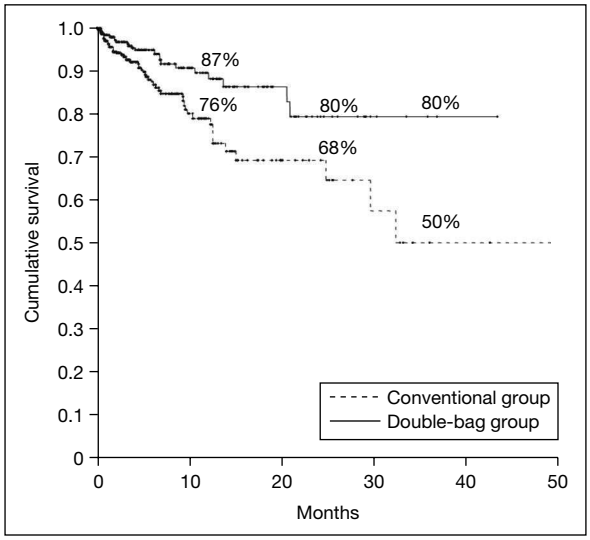

Fig. 2. Technique survival curve. The double-bag group had a longer survival than the conventional group ($p < 0.001$, by log-rank test). Death and transfer to hemodialysis are technique failures.

Table 2. Organisms isolated from peritonitis episodes in the two study groups

	Conventional total (%)	Double-bag total (%)*
Episodes	730	99
Organisms	358	37
Coagulase-neg. *Staphylococcus*	136 (38)	11 (30)
S. aureus	49 (14)	7 (19)
Enterococci	7 (2)	4 (11)
Gram-negative rod	154 (43)	14 (38)
Fungus	12 (3)	1 (3)
Negative culture	372 (51)	37 (50)

*No culture was done in 2.5 episodes.

Discussion

In Mexico, CAPD has been the first-choice treatment for the last 25 years. At present time, represents 85% of the dialysis population. Hemodialysis access is very limited, and is offered largely as a second option, mostly to patients with uncontrolled peritonitis or to those who lost their peritoneal membrane to this

complication. In most cases, they receive one or two 3-hour sessions per week and some patients are placed on a waiting list, risking death while waiting. This is especially critical among uninsured patients [1]. Therefore, preserving the integrity of the peritoneal cavity becomes crucial in our CAPD patients.

Our study shows a considerable reduction in peritonitis rate with the use of the double-bag system in combination with sodium hypochlorite 50% solution as disinfectant, when compared to the conventional system and the use of povidone-iodine 10% solution. The peritonitis rates with both systems are similar to those previously described in Mexico [3]. However, there are significant differences between the two studies. Firstly, most of the patients in the study reported by Monteon et al. [3] belonged to the Mexican Institute of Social Security (IMSS), which provides medical care only to those who have a salary. Our patients are self-employed or unemployed, lack medical insurance, and are at higher risk because of the widespread of poverty, poor environmental conditions, malnutrition and diabetes. Secondly, patients with previous abdominal surgery, abdominal hernias, and diverticulosis were excluded in the IMSS trial, while this was not the case in our study. Therefore, even in the presence of adverse conditions, the double-bag system is effective in preventing peritonitis in patients on CAPD.

Technique survival was higher than that reported previously in Mexico [2], and this was associated with the significant reduction in peritonitis incidence with the introduction of the double-bag. This finding is particularly important, since peritonitis has been reported as the most important factor for technique failure in developing nations [2, 4, 5]. Indeed, it was responsible for 69% of the cases switching to hemodialysis in a Korean CAPD population [5].

Gram-positive organisms, predominantly of skin origin, were the most common organisms, accounting for 56% of the peritonitis episodes. We did not encounter a significant reduction in the coagulase-negative *Staphylococcus* infection rate with the use of disconnect systems, as has been reported by others [3, 13–15]. However, similar findings to our study have been described [16, 17].

Although we did not address the issue of the cost of peritonitis, it has been shown by others that the higher purchase cost of disconnecting systems could be offset by the saving resulting from fewer infections and hospitalizations [3, 17, 18]. In addition, in the long-term, the reduction in the peritonitis rates will contribute to the preservation of the functional integrity of the peritoneum, because infections reduce the capacity of the peritoneal membrane for dialysis and may lead to the loss of the peritoneal cavity [19, 20]. This issue is particularly important in countries like Mexico, where the availability of hemodialysis and transplantation for the poor is severely limited, and the preservation of the peritoneum functional integrity in CAPD patients becomes a matter of life or death.

Finally, although from our study we cannot define the direct impact of the use of electrolytically produced sodium hypochlorite solution (ExSept 50%) in peritonitis rates and technique survival, its association is likely, since the efficacy and safety of this disinfectant has been previously documented in peritoneal dialysis patients [21].

Conclusion

In conclusion, switching from a standard to a double-bag disconnect system, markedly decreased the peritonitis incidence and diminished the risk of technique failure, even in a high-risk population like ours. This makes CAPD a safe therapy and a good alternative in places where hemodialysis and transplantation are not widely available.

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