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Review

A New Cost-Benefit Economic Model Approach of Hemodialyzer Reuse

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Abstract: In this study, a new cost-benefit economic model for hemodialyzer reuse has been developed considering all of the direct costs (dialyzer price, disinfection fluid price, reverse osmosis water cost, personnel, and miscellaneous) as well as the number of disinfections applied to the hemodialyzer. The maximum number of disinfections/reuses for different models of hemodialyzer was estimated using statistical analysis based on the information obtained from a total of 60 adult patients on maintenance hemodialysis for approximately 4 years; from a hospital in Santiago de Cuba province, Cuba. An equal number of treatments (100) was evaluated for each hemodialyzer including 2,800 total reuses. The total cost savings for reuse/disinfection using the new economic approach is compared with the single-use modality. Obtained results by applying the proposed model indicated that the correlation between the economic advantages of the reuse/disinfection process in the total cost of the hemodialysis treatment significantly depends on the type of hemodialyzer used for the treatment, the disinfection price, the virgin hemodialyzer price, the disposal cost and its price reduction because of the number of reuses and the maximum possible reuses that could be applied to the hemodialyzer.

***Keywords*:** hemodialysis, hemodialyzer reuse, cost-benefit-analysis

1. Introduction

Hemodialyzer reuse practice has been widespread around the world for decades. Although a single use of a hemodialyzer and its reuse by chemical reprocessing are both associated with some complications. Hemodialyzer reuse has remained an integral part of the hemodialysis treatment process because of its lower cost, good overall safety record, improved membrane biocompatibility, and environmental advantages. Therefore, the economic benefits of the hemodialyzer reuse, when estimated only based on the dialyzer and its consumables are very significant and attractive [1]-[3].

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A hemodialyzer is an instrument that has been used universally to purify fluid and waste metabolites from the blood of renal failure patients [1]-[4]. A hemodialyzer is a complex system where adsorption and filtration are combined to assist periodically renal function [3]. Even though significant developments have been achieved in hemodialysis technologies, only effectiveness of around 15% is accomplished using this therapy in comparison with the renal function of a healthy kidney. Nevertheless, until now this therapy arises as to the best alternative for patients affected by chronic renal diseases.

Although both phenomena (adsorption/filtration) are present in the hemodialyzer, the predominant effect during hemodialysis treatments is the filtration using its semi-permeable membrane, where metabolic waste products of protein metabolism are eliminated by employing transport mechanisms between the blood and the dialysis fluid compartment in the hemodialyzer [1], [4]-[6].

Since the advent of Hemodialysis (HD), the number of patients with HD has been growing constantly constituting a devastating medical, social, and economic problem in health care; being more important in developing countries. As a result of economic constraints, most developing countries reduce dialysis costs by reusing hemodialyzers [1], [7]-[9]. As the resources devoted to health care do not increase at the same rate as its cost, strategies to reduce costs are highly needed. Hemodialyzer reuse has been suggested as one possible solution [1], [7]-[11].

Cost reduction strategies have been described in several studies [7], [12]-[14] and the cost difference between treatments is usually calculated on the basis of either cost of hemodialyzers or mortality and hospitalization only; meanwhile, other studies refer to disinfection cost as well to the used resources for developing this process [12]-[14]. However, the economic impact of the number of reuses in the total cost between treatments has not been evaluated yet.

The safety of the hemodialyzer reuse has been questioned over the past 20-40 years with studies that showed conflicting results [2], [6]-[11]. In early 1980, an increase in the mortality of approximately 10% was reported in freestanding facilities reprocessing hemodialyzers with peracetic acid (hydrogen peroxide and acetic acid); nevertheless, some inconsistencies were observed. Later, in the 1990 decade (up to present times) the adverse associations of peracetic acid for hemodialyzer disinfection were no longer present.

Other studies have reported that the reuse is associated with an increased incidence of pyrogenic reactions [7], [9]-[11]; however, from a historical point of view, units that reprocess the hemodialyzers manually have had more probabilities of showing pyrogenic reactions in comparison with units using automated systems [7], [9]-[11]. On the other hand, an investigation by the Centre for Disease Control (CDC) in the USA showed that many of those episodes were the result of inadequate reprocessing procedures, such as the use of lower concentrations of the disinfection agent as well as the use of water that did not meet the requirements of the Association for the Advancement of Medical Instrumentation (AAMI) [15].

Worldwide, the currently accepted guidelines for the reuse practice of hemodialyzers are those issued by the AAMI [15]. The only quantitative criterion recommended by the AAMI is that the Total Cell Volume (TCV) of the filter should not fall below 80% of its original value, assuring that the urea clearance of the hemodialyzer stands within 90-100% of its original level [16]. Conversely, this regulation is based only on an early study by Frank Gotch [17], using a small sample of cellulosic low-flux hemodialyzers, reprocessed manually using formaldehyde and operated at low blood flow rates (total inlet blood flow around 200 mL/min).

Despite all those problems, no subsequent publication has been presented about the validation of this criterion under different treatment conditions and it has been accepted by the majority of the medical community as the main criterion for acceptable hemodialyzer reuse [1], [6], [15], [16]. Considering all previous facts, hemodialyzer reprocessing is still a controversial practice that is not without risks. HD units should establish a very strict quality assurance program that includes the regular monitoring of the water quality, and at least AAMI guidelines should be followed. The impact of the reuse on mortality is still an area of concern and needs further research.

Hemodialyzer reuse has been practiced for over 40 years in HD by patients around the world. The cost, safety, and efficiency of the HD with hemodialyzer reuse have been reported in the past [12]-[14]. However, from a general point of view, there are limited studies on the evaluation of total direct cost estimations of reuse practice in developing countries and only a few equivalent studies were reported [10]-[14].

In this work, a new cost-benefit economic model for hemodialyzer reuse is proposed; statistical analysis is developed on data from an HD service in a Cuban hospital. In order to acquire the needed information, two modalities (single-use and reuse practice) were successfully simulated and were compared with each other. Interesting relationships

are found between both therapy modalities' costs. The number of reuse/disinfection arises as a fundamental parameter to be considered for the economic assessment of hemodialyzer reuse in HD.

2. Materials and methods

2.1 *Clinical data collection*

The study was performed at the HD unit of a Hospital in Santiago de Cuba province, Cuba. The data collection was conducted from 2018 to 2021. All the patients receiving either high or low flux dialysis during the studied period were informed about this study and all gave full consent for participation, thus ethical or interest conflicts were completely avoided. The study was developed using F-Series polysulfone membrane dialyzers from Fresenius Medical Care, specifically, the following hemodialyzer models were studied: F7 HPS, F8 HPS, and F10 HPS (Low Flux Dialyzers-High Performance Steam (HPS). Technical data can be found in supplementary information as Table S1.). The protocol and patient participation were approved by the Scientific Board of the Hospital.

Hemodialyzers were reused as many times as possible fluctuating between 4 and 16 reuses for low and high flux dialysis respectively. Patients with HIV, Hepatitis B, or Hepatitis C infections as well as patients with suspected sepsis or bacteremia were excluded from the study.

A total of 60 patients over 18 years old were selected for the study, 100 treatments were selected for each hemodialyzer during the study period, giving a total of 300 HD therapies (with reuse) and approximately 2,800 reuses for all the hemodialyzers. All patients were dialyzed for 4 h per dialysis session. Each hemodialyzer was reprocessed manually by trained technicians using Puristeril 340 at a concentration of 4% (v/v), from Fresenius Medical Care. The hemodialyzer was reused again for the same patient only when TCV was ≥ 80% of the original value.

2.2 *Total cell volume evaluation and exclusion criteria for reused hemodialyzers*

Hemodialyzers were discarded if any of the following rejection criteria were met:

1. TCV is less than 80% of the initial TCV (this parameter can also be referred to as "fiber bundle volume").
2. Ultrafiltration Rates (UFR) are less than 75% of the initial UFR.
3. Evidence of a pressure leakage.
4. Hemodialyzer coagulation.
5. Hemodialyzer breakout.
6. Urea Clearance values are below tabulated values in the hemodialyzers datasheet.

TCV was measured for the evaluation of the quality of each hemodialyzer and the obtained values were calculated as a percentage ratio compared to the baseline value. In this work, the TCV parameter is selected as the limiting/exclusion criterion of preference for the development of the statistical analysis of the obtained data from HD therapies with reuse to obtain the maximum possible reuses/disinfection for each studied hemodialyzer.

All patients underwent a midweek pre-dialysis blood test for routine laboratory examination; information about age, sex, type of shunt, case of End-Stage Renal Disease (ESRD), Hepatitis B, C, and HIV infections status, urea reduction ratio, dialysis dose, hematocrit, serum albumin, and co-morbidity were recorded as usually done in the service, all laboratory analyses were developed in the Clinical Laboratory Department of the hospital.

2.3 *Statistical analyses*

To estimate the maximum possible number of reuses for each evaluated hemodialyzer, statistical analyses were developed for the 300 observations/treatments after a 4 years study period. Statistical analyses as well as showed graphs and plots were performed and obtained using R® software and MATLAB®.

Of particular interest appears the one-way ANOVA test [18] used to evaluate if the number of reuses (as an average) differs among hemodialyzers. The null hypothesis for this statement is H_0: $\mu_7 = \mu_8 = \mu_{10}$; with μ_i denoting the average number of reuses of hemodialyzer number F7 HPS, F8 HPS, and F10 HPS respectively.

The ANOVA test and all conclusions derived from it are predicated on three main assumptions:

1. The residuals follow a normal distribution.

2. The variability (variance) of the residuals is constant (homoscedasticity).

3. The residuals are independent (randomness).

The Tukey procedure for multiple comparisons was used to evaluate which groups are different [19]. This technique evaluates all the pairwise comparisons while controlling the family-wise error rate. Shapiro-Wilk and Kolmogorov-Smirnov tests were used to assess the normality of the residuals [20].

Homoscedasticity (equal variance assumption) was checked using Levene's test [21]. The assumption of independence was also tested in order to evaluate if the number of reuses of a given unit in a group has no information, whatsoever on the number of reuses of another unit in the same or different group. In order to assess if the responses in each group are coming from different distributions, the Kruskal-Wallis test was used [22].

2.4 *Mass transfer process in the hemodialyzer*

In HD the mass transfer phenomenon is defined as the number of bio-molecules that are transferred from one compartment of the hemodialyzer to the other in a determined time [1], [5], [6]. In this study, the bio-molecule, urea, is handled as the target species in order to define and discuss the economic strategy. The kinetics of urea is related to the clinical evolution of the patient and determines the minimum level of dialysis dose; the kinetic model of the urea was established to serve as a method of quantifying the optimal minimal dialysis dose.

However, with the dialysis dose, it is possible to measure the diffusive transport and almost not the transport by ultra-filtration. The diffusive mechanism is in charge for the elimination of the urea. However, larger bio-molecules can be better eliminated using higher rates of ultra-filtration. Unfortunately, at the moment the dialysis dose does not give an idea about the depuration by ultra-filtration, and the medical specialists can only apply larger ultra-filtration rates, developed with the improvement of the hemodialyzer membranes, in order to achieve higher removal amounts of larger bio-molecules (Beta 2 Microglobulin, Inulin as well as inflammatory response mediators such as Il-6, Il-8, and TNF) [1], [5], [6].

Urea is transferred from the blood to the dialysis liquid (through the semi-permeable membrane) and electrolyte ions (no proteins) such as sodium, magnesium, calcium, and hydrogen carbonate, are transferred from the dialysis liquid to the blood.

The Mass Transfer (MT) direction is determined by the concentration gradient between compartments in the hemodialyzer (diffusion) as well as the pressure difference between the blood compartment and the dialysis liquid compartment (ultrafiltration). Both mass transfer phenomena can be calculated from the blood compartment and the dialysis fluid compartment according to equation 1:

$$MT = Qb \cdot (IC_u - OC_u) = DC_u \cdot Qd \tag{1}$$

Where:

MT: Mass transfer in the hemodialyzer (in mg/min)

Qb: Dialyzer blood flow (in mL/min)

IC_u: Blood concentration of bio-molecule urea at the hemodialyzer inlet (in mg/mL)

OC_u: Blood concentration of bio-molecule urea at the hemodialyzer outlet (in mg/mL)

DC_u: Dialysate concentration of bio-molecule urea (in mg/mL)

Qd: Dialysate flow (in mL/min)

The Global Mass Transfer (GMT) during the entire dialysis session can be estimated directly from the blood compartment using equation 2 and using the Watson formula for the UDV calculations [1], [5], [6].

$$GMT = UC_{pre} \cdot (UDV + \Delta V) - UC_{post} \cdot UDV \tag{2}$$

Where:

GMT: Global mass transfer in the hemodialyzer during the entire treatment (in mg)

UC_{pre}: Pre-dialysis urea concentration (in mg/mL)

UDV: Urea distribution volume (in mL) (calculated using Watson formula)

ΔV: Weight loss (water) during the dialysis (in mL)

UC_{post}: Post-dialysis urea concentration (in mg/mL)

The previous expression is valid considering the water density is equal to 1 g/mL, therefore, UDV and ΔV during the dialysis treatment can be expressed in terms of mL instead of g (as volume is measured in practice).

2.5 *Hemodialyzer clearance (K) and dialysis dose (Kt/V)*

K is usually used for the estimation of the hemodialyzer efficiency. K can be calculated from the filter blood compartment as well as the dialysate compartment, following the mass transfer principles explained in section 2.4. K, estimated from the blood compartment is usually calculated by multiplying the blood flow in the filter by the declining percentage of the bio-molecule concentration as it passes through the hemodialyzer. This approach only considers K by diffusive mechanism; however, the ultra-filtration component (FUF) must be also included for K. From a general point of view K for the bio-molecule urea can be calculated using equation 3 as follows [1], [5], [6], [23], [24]:

$$K_u = Qb \cdot \left[\frac{IC_u - OC_u}{IC_u} \right] + \left(\frac{OC_u}{IC_u} \right) \cdot FUF \tag{3}$$

Where:

K_u: Dialyzer clearance of bio-molecule urea (in mL/min)

FUF: Ultrafiltration flow (in mL/min)

FUF is usually calculated using the ultrafiltration coefficient Q_{UF} (in mL/min·mm Hg) (tabulated in the hemodialyzer technical data sheet) and the transmembrane pressure TMP (in mm Hg) using equation 4 as follows:

$$FUF = Q_{UF} \cdot TMP \tag{4}$$

High-efficiency hemodialysis techniques are based on the concept of the dialysis dose parameter. This parameter is defined as follows: Kt/V, where $Kt/V = (K_u \cdot t)/V$ (with t the duration time of the dialysis session and V the UDV in the body), developed by the US group for Non-Communicable Diseases (NCDs) [6], [25]-[27]. This research group elaborated a kinetic model for urea and was able to estimate the needed parameters for the adequate quantification of Kt/V [6], [25]-[27]. They concluded empirically that the amount of urea to be removed from the blood is the total accumulated urea and thus that Kt should be equal to V. The cleared-up volume for urea is thus equal to Kt, being the adequate dialysis dose value, producing the lowest morbidity [6], [25]-[27] and resulting in a urea clearance during HD.

In a dialysis filter, a certain Qb will pass through the filter during a time t_v (in min). From this initial Qb value, a fraction will be completely purified (clearance) and another fraction in the blood QC (in mL/min) will remain contaminated ($QC = Qb - K_u$). K_u could be also expressed in terms of the total blood volume (VF in mL) to be processed by the hemodialyzer using equation 5:

$$K_u = \left(\frac{VF}{t_v} \right) - QC \tag{5}$$

2.6 *Economic assessment of hemodialyzer reuse*

In order to describe the operational cost of an HD, an economic model has been developed considering the urea clearance of the hemodialyzer at fixed blood/dialysate flows (previously tabulated in the hemodialyzers technical data sheet). In our study, it will be defined in terms of the maximal urea clearance as $K_{u,max}$. It is possible to define an operational cost for the virgin hemodialyzer using equation 6:

$$CDF_v = K_{u,max} \cdot \frac{P_v}{K_{u,v}} \tag{6}$$

CDF_v: Operational cost of the virgin hemodialyzer (in €)

$K_{u,\,max}$: Maximum tabulated urea clearance for the virgin hemodialyzer (in mL/min)

$K_{u,\,v}$: Urea clearance of the virgin hemodialyzer during the treatment (in mL/min)

P_v: Nominal price of the virgin hemodialyzer (in €)

According to equation 6, the operational cost of the hemodialyzer can be defined as a function of its nominal price and the variations between tabulated urea clearance and real urea clearance during the treatment. From equation 6 it is possible to deduce that if the obtained clearance during the treatment matches with the maximum tabulated clearance, the operational cost of the hemodialyzer fits with its nominal price. However, if clearance values obtained during the treatment are significantly lower in comparison with the maximum tabulated value, the operational cost increases, indicating an inadequate use of the hemodialyzer according to its tabulated value.

After the first treatment, the hemodialyzer is conveniently processed for its reuse. It can be reused as many times as possible if the TCV value is higher than 80% taking as reference the virgin hemodialyzer TCV value. For the disinfection of the hemodialyzer Puristeril 340, at a concentration of 4% (v/v), is usually used. This compound has satisfactory antimicrobial properties and at the same time, it is an effective blood solvent. However, this process does not constitute a "regeneration" of the hemodialyzer, but only disinfection. Dialysis parameters (blood flow, dialysate flow, treatment time, etc.) do not change between treatments at different reuses of the hemodialyzer.

It has been demonstrated in recent publications [6], [25]-[27], that the reuse does not cause significant reductions in ultrafiltration coefficient Q_{UF} or the urea clearance in the hemodialyzer; therefore, the dialysis doses for the patients do not change between treatments, if the same initial parameters do not suffer modifications and the TCV value is higher than 80%.

As a result, it is possible to define an operational cost for the disinfected hemodialyzer using equation 7:

$$CDF_d = K_{u,\,max} \cdot \frac{P_d}{K_{u,\,d}} \tag{7}$$

Where:

CDF_d: Operational cost of the disinfected hemodialyzer (in €)

$K_{u,\,d}$: Urea clearance of the disinfected hemodialyzer (in mL/min)

P_d: Hemodialyzer disinfection price (in €)

From equation 7 it is possible to deduce that at the moment the urea clearance of the disinfected hemodialyzer is lower than the tabulated urea clearance, the operational cost of the hemodialyzer increases; and it is logical to expect a TCV below the 80% or inadequate use of the hemodialyzer during the treatment. On the other hand, the disinfection costs P_d can be defined using equation 8:

$$P_d = Vsol_d \cdot Psol_d + Vsol_{RO} \cdot Psol_{RO} + P_m + P_{tec} + P_{misc} \tag{8}$$

Where:

$Vsol_d$: Volume of the disinfection solution (in mL)

$Psol_d$: Price of the disinfection solution (in €/mL)

$Vsol_{RO}$: Volume of the reverse osmosis water used for the disinfection (in mL)

$Psol_{RO}$: Price of the reverse osmosis water used for the disinfection (in €/mL)

P_m: Price of the medicines used for the disinfection (if any) (in €)

P_{tec}: Associated personnel cost of the technicians in the disinfection process (in €)

P_{misc}: Price of any extra resource used for disinfection (miscellaneous) (in €)

Considering that the reused hemodialyzer will manage the same treatment parameters as the virgin hemodialyzer in order to achieve the same dialysis dose for the patient, it is possible to assume that $K_{u,\,max} = K_{u,\,d}$ (when it is oriented to the target bio-molecule used for the calculation of the dialysis dose, here urea). Then, replacing equation 8 in equation 7, the operational cost of the disinfected hemodialyzer is a function of the disinfection cost according to equation 9 as follows:

$$CDF_d = P_d \tag{9}$$

However, the total disinfection cost for a cycle of multiple disinfections can be defined using equation 10 as follows:

$$CDF_d = P_{d_1} + P_{d_2} + P_{d_3} + \ldots + P_{d_l} \tag{10}$$

Where:

P_{d_1}: Price of the first hemodialyzer disinfection (in €)

P_{d_l}: Price of the last hemodialyzer disinfection l (in €)

Then:

$$CDF_d = \sum_{i=1}^{l} P_{d_i} \tag{11}$$

Assuming that the disinfection cost does not change significantly between disinfections (now taking P_d as an average hemodialyzer disinfection price), it is possible to define the disinfection cost for the entire process using equation 12 as follows:

$$CDF_d = \sum_{i=1}^{l} P_{d_i} = d_l \cdot P_d \tag{12}$$

With:

d_l: Number of disinfections or disinfection cycles (dimensionless)

The ability of the hemodialyzer to give the same dialysis dose between treatments, if meanwhile, its TCV remains above 80%, provides an interesting perspective. From a clinical point of view, the hemodialyzer should have the same economic value in each reuse, because it is capable to provide the same dialysis dose if its TCV remains within range. However, a decrease in its original cost should be assessed using a depreciation of this hemodialyzer, taking as reference the possible maximum number of reuses/disinfections of the hemodialyzer (d_{max}). Therefore, it could be possible to define a depreciation in the operational cost (FD_d) for the reused hemodialyzer using equation 13:

$$FD_d = \frac{P_v}{d_{max}} \cdot d_l \tag{13}$$

Where:

FD_d: Depreciation of the hemodialyzer in each disinfection (in €)

d_{max}: Maximum number of possible reuses/disinfections of the hemodialyzer (dimensionless)

Recently, the ratio between regenerations costs and the virgin material cost for granular activated carbon management in the rum industry and electric energy industry [28], [29] has been used with reliable results as a parameter for economic assessment for the analysis of the evolution of the total cost in each regeneration compared with the conventional adsorption process [28], [29]. Applying a similar analysis for the hemodialyzer, it could be possible to use the ratio between disinfection cost and virgin hemodialyzer cost considering the depreciation of this hemodialyzer after each reuse/disinfection as a parameter for the economic assessment of the hemodialyzer disinfections:

$$0 < \left(\frac{CDF_d}{CDF_v - FD_d} \right) < 1 \qquad \text{Economically feasible}$$

$$\left(\frac{CDF_d}{CDF_v - FD_d}\right) = 1 \qquad \text{Breakout}$$

$$\left(\frac{CDF_d}{CDF_v - FD_d}\right) > 1 \qquad \text{Economically not feasible}$$

Combining equations 7, 12 and 13 and assuming that ($K_{u,max} = K_v$) is possible to obtain:

$$\frac{CDF_d}{CDF_v - FD_d} = \frac{d_l \cdot P_d}{P_v - \left(\frac{P_v}{d_{max}} \cdot d_l\right)} \tag{14}$$

Working on equation 14 the expression adopts the form shown in equation 15:

$$\frac{CDF_d}{CDF_v - FD_d} = \frac{d_l \cdot d_{max} \cdot P_d}{P_v \cdot \left(d_{max} - d_l\right)} \tag{15}$$

According to the proposed model (equation 15), it is possible to notice that an excessive increase in the desired reuses of the hemodialyzer could cause an increase in the ratio $\left(\frac{CDF_d}{CDF_v - FD_d}\right)$ after the first disinfections cycle, making the reuse of the hemodialyzer economically not feasible.

On the other hand, if the price of the virgin hemodialyzer increases (buying a more expensive hemodialyzer) in comparison with the disinfection price, the ratio $\left(\frac{CDF_d}{CDF_v - FD_d}\right)$ could remain in the economically feasible range for more disinfection cycles. Nevertheless, a lower disinfection price should be maintained in order to achieve economically feasible disinfection.

According to the proposed model, economically feasible reuse of the hemodialyzer depends on several factors such as the disinfection price, the cost of a virgin hemodialyzer, the number of reuses, and the maximum possible reuses that could be applied to the hemodialyzer. Nevertheless, the number of economically feasible disinfections could be assessed by solving the inequality presented in expression 16 for d_l.

$$\frac{d_l \cdot d_{max} \cdot P_d}{P_v \cdot \left(d_{max} - d_l\right)} < 1 \tag{16}$$

Then solving the expression 16 for d_l yields:

$$d_l < \frac{P_v \cdot d_{max}}{P_v + \left(P_d \cdot d_{max}\right)} \tag{17}$$

When the disinfection cost increases, the reuse/disinfection of the hemodialyzer is not economically feasible anymore. Therefore, in order to develop economically reasonable disinfections cycles, the condition shown in equation 17 must be fulfilled.

From equation 15, it is possible to observe that the number of disinfection cycles (d_l) given to the hemodialyzer must be lower than the maximum possible disinfections that could be applied to the filter (d_{max}), for $d_l \rightarrow d_{max}$, it is possible to write:

$$\lim_{d_l \to d_{max}} \frac{d_l \cdot d_{max} \cdot P_d}{P_v \cdot (d_{max} - d_l)} \to \infty \tag{18}$$

According to equation 18 when the number of reuses/disinfections approaches the maximum number of possible disinfections, the ratio $\left(\frac{CDF_d}{CDF_v - FD_d}\right)$ tends to the infinite; this constitutes an expected result because according to equation 13 when the maximum number of possible disinfections matches with the number of disinfections given to the hemodialyzer, the hemodialyzer depreciation maximizes ($FD_d = P_v$). Therefore, according to the proposed model, the number of disinfections given to the hemodialyzer should be always lower than the maximum number of disinfections that could be applied to the hemodialyzer considering its physical and mechanical characteristics ($d_l < d_{max}$).

During each disinfection cycle, the permeability of the hemodialyzer for specific molecules will be reduced, decreasing also its performance in the system. Internal modifications in the hemodialyzer structure due to the dialysis process will produce changes in its original capacities imposing a limited number of reuses/disinfections. Therefore, after a determined number of disinfection cycles the hemodialyzer should be removed from the system and replaced with a new one.

The ratio $\left(\frac{CDF_d}{CDF_v - FD_d}\right)$ could then be an effective alternative to evaluate the possible number of economically feasible disinfections that could be applied to the hemodialyzer before its complete exhaustion. Variations in the ratio $\left(\frac{CDF_d}{CDF_v - FD_d}\right)$ could be simulated and evaluated by using different values of disinfection costs, virgin hemodialyzer price, the number of applied disinfections, and the maximum possible disinfections that could be applied to the hemodialyzer. This maximum number of possible disinfections is estimated using statistical analysis on collected data from studied patients under maintenance hemodialysis.

The total cost of the d_l dialysis treatment TC_d (in €) for a patient under maintenance hemodialysis developing a disinfection/reuse of the same hemodialyzer in each treatment could be assessed using equation 19:

$$TC_d = P_v - \left(\frac{P_v}{d_{max}} \cdot d_l\right) + d_l \cdot P_d \tag{19}$$

For $d_l > 0$.

Afterwards, the total cost of the whole hemodialysis therapy developing a disinfection/reuse of the same hemodialyzer in each treatment (TCH) could be assessed using equation 20:

$$TCH = P_v + P_s + \sum_{i=1}^{d_l} TC_d \tag{20}$$

Where:

P_s: Disposal cost of the hemodialyzer after finishing the treatment (in €)

Disposal costs are estimated usually regarding the energy consumption used for the incineration of each dialyzer after its extensive use and the type of waste produced by the dialysis process (mainly hazardous waste); however, several studies have already estimated these costs [30]-[33]. Ranging between 2.7-21 USD (2.5-19.5 €) depending on the waste management policy.

Doing similar reasoning, the total cost of a medical service (TC_v) that replaces the hemodialyzer after each treatment could be assessed using equation 21 as follows:

$$TC_v = \left(P_{v_1} + P_{s_1}\right) + \left(P_{v_2} + P_{s_2}\right) + \left(P_{v_3} + P_{s_3}\right) + \ldots + \left(P_{v_l} + P_{s_l}\right) \tag{21}$$

Where:

P_{v_1}: Nominal price of the virgin hemodialyzer at the first use (in €)

P_{s_1}: Nominal disposal price of the hemodialyzer at the first use (in €)

P_{v_l}: Nominal price of the virgin hemodialyzer at its last l use (in €)

P_{s_l}: Nominal disposal price of the hemodialyzer at its last l use (in €)

Working on equation 21 and assuming that the hemodialyzer price and the disposal price does not change significantly between treatments equation 21 can be rewritten as:

$$TC_v = \sum_{j=1}^{l}\left(P_{v_j} + P_{s_j}\right) = v_l \cdot \left(P_v + P_s\right) \tag{22}$$

Where:

v_l: Number of treatments using virgin hemodialyzers (dimensionless)

Until now the approach of the economic model has been developed using K_u as the main parameter for the evaluation of the Kt/V. However, if the general expression (equation 3) is used for all the main bio-molecules involved in the HD process the model is still applicable and instead of K_u an overall hemodialyzer clearance constant $K_{(urea\ +\ creatinine\ +\ ...\ +\ bio\text{-}molecule_n)}$ should be used. Nevertheless, in order to carry out this strategy, a kinetic model of each of those extra bio-molecules should be included in the model and developed and related to the patient clinical evolution.

The strategy of a medical service that reuses hemodialyzers as a common practice could be assessed in comparison with the strategy of a medical service that changes the hemodialyzer in each treatment; this comparison could be a useful tool in order to evaluate the economic advantage of the disinfection/reuse of the hemodialyzer in the time.

3. Results and discussion

3.1 *Statistical analysis for F7 HPS, F8 HPS, and F10 HPS hemodialyzers*

Some exploratory statistical analysis was carried out to identify patterns in the data of these three hemodialyzers. The construction of a notched boxplot for the reuses of each hemodialyzer as well as the 95 % confidence intervals for the average number of reuses obtained with each hemodialyzer is depicted in Figures 1 (a) and (b).

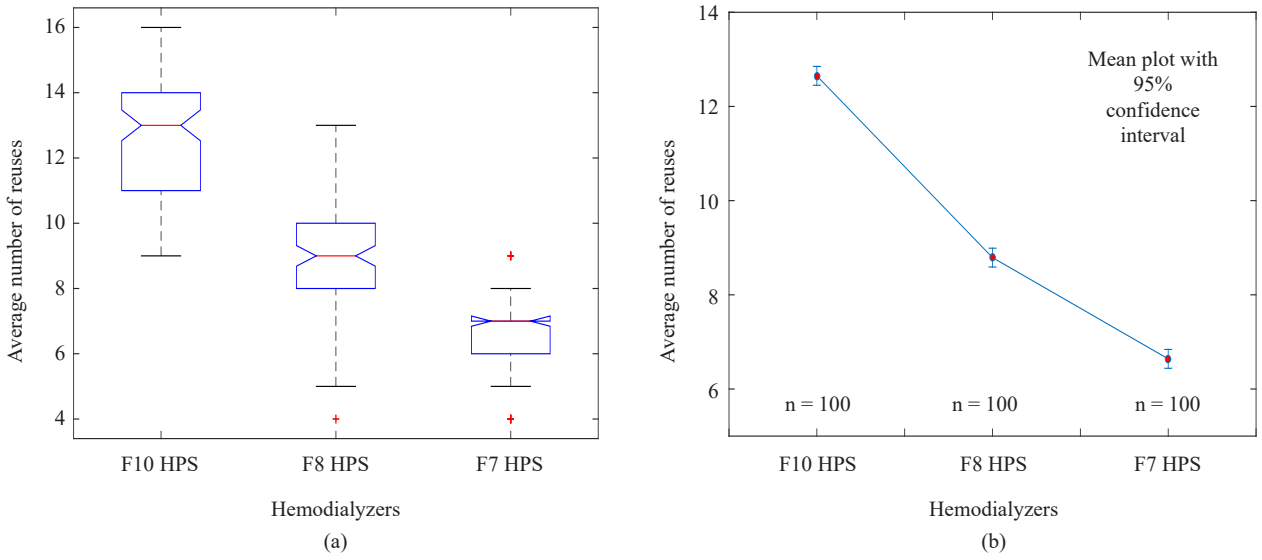

Figure 1. Notched boxplot for the reuses of each hemodialyzer (a) and 95% confidence intervals for the average number of reuses for F7 HPS, F8 HPS, and F10 HPS hemodialyzers (b)

From Figure 1 (a) it is clear that the hemodialyzer F7 HPS seems to have the lowest reusability with a median of around 6.64, followed by F8 HPS (8.79) and F10 HPS leading to the largest reusability with a median value around 12.65 for the latter. A similar pattern can be seen in Figure 1 (b); the lowest average value of reuses is obtained for F7 HPS followed by F8 HPS and F10 HPS, the last showing the best performance. Another interesting aspect is the distribution of reuses in each studied group. Figure 2 shows the probability density plots for the number of reuses of each studied hemodialyzer.

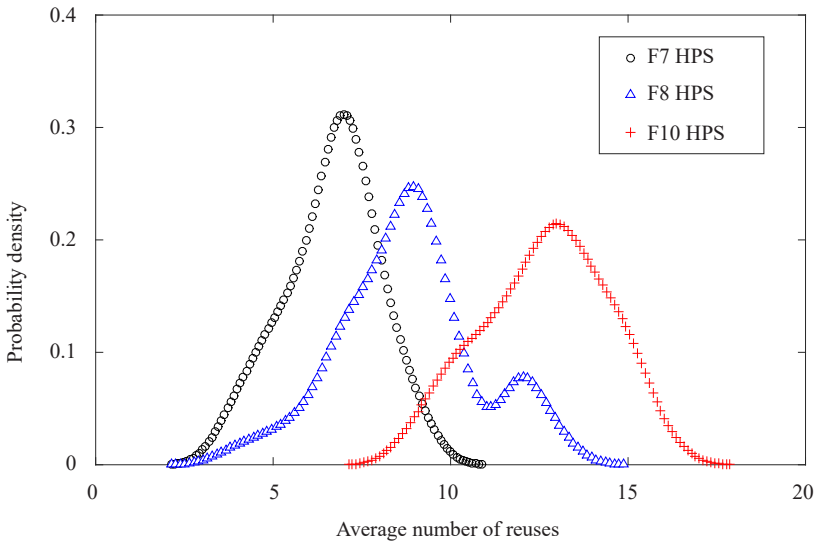

Figure 2. Probability density plots for the number of reuses of F7 HPS, F8 HPS and F10 HPS hemodialyzers

Figure 2 shows very interesting patterns. A similar trend is obtained again, with hemodialyzer F10 HPS having a larger probability density for high numbers of reuses, hemodialyzer F7 HPS having a probability of zero for reuse values larger than 10, and hemodialyzer F8 HPS lying in between.

The density plot for the F8 HPS hemodialyzer seems to have two local modes (maxima) in clear contrast with F10 HPS and F7 HPS hemodialyzers which show a unimodal distribution indicating that the number of reuses does not follow a normal distribution in any of the given groups.

The One-Way ANOVA test is used to assess if the average number of reuses differs among hemodialyzers. Table 1 depicts the results of the fitted model.

Table 1. One-Way ANOVA parameters for F7 HPS, F8 HPS, and F10 HPS hemodialyzers

Source	Df	SS	Mean square	F-ratio	P-value
Between-groups	2	1854.7	927.4	327.7	$2 \cdot 10^{-16}$
Within-groups	297	840.4	2.8		

If the average number of reuses was the same for each hemodialyzer, i.e., the null hypothesis (see section 2.3) is true, then the F-ratio should be closer to one. The statistical treatment of the data (see ANOVA test parameters in Supplementary material) produced a value for the F-ratio (see equation S9) of about 300 meaning that the null hypothesis can be rejected as confirmed by the P-value which is virtually zero. It can be concluded that the three

selected hemodialyzers have a different average number of reuses.

Actually, the previous analysis raises the question of which groups are different. The Tukey procedure for multiple comparisons between means was applied (see Tukey procedure for multiple comparisons in Supplementary material); this technique evaluates all the pairwise comparisons while controlling the family-wise error rate. Table 2 depicts the results for Tukey multiple comparisons of means with a 95% family-wise confidence level.

Table 2. Tukey parameters for multiple comparisons between means

Source	Diff	lower	Upper	p adj
F7 HPS-F10 HPS	-6.01	-6.57	-5.45	0
F8 HPS-F10 HPS	-3.86	-4.42	-3.30	0
F8 HPS-F7 HPS	2.15	1.59	2.71	0

Since p adj < 0.05 the following conclusions can be formulated:

• Hemodialyzer F10 HPS produces between 5.45 and 6.57 more reuses than hemodialyzer F7 HPS.

• Hemodialyzer F10 HPS produces between 3.30 and 4.42 more reuses than hemodialyzer F8 HPS.

• Hemodialyzer F8 HPS produces between 1.59 and 2.71 more reuses than hemodialyzers F7 HPS.

The pairwise comparison demonstrates that the difference in the average number of reuses between hemodialyzers F10 HPS-F7 HPS, F10 HPS-F8 HPS, and F8 HPS-F7 HPS is statistically different.

In order to assess the normality of the residuals, the following histogram was created.

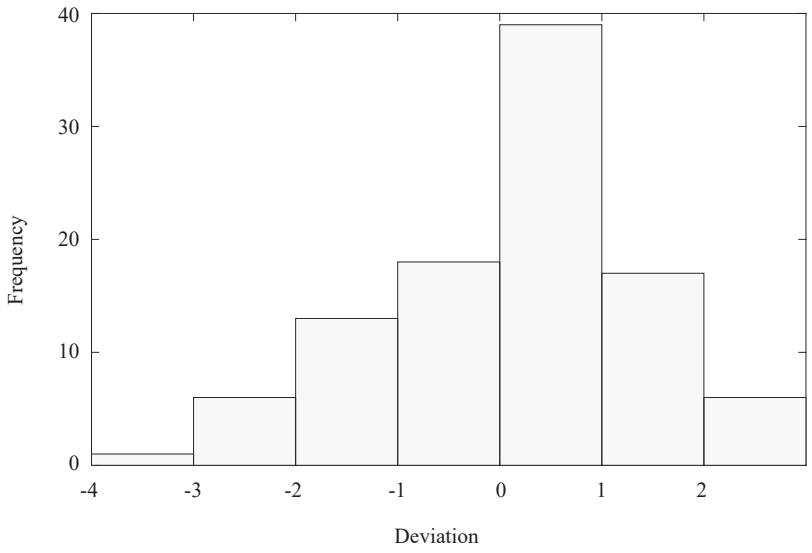

Figure 3. Histogram of the residuals for F7 HPS, F8 HPS, and F10 HPS hemodialyzers

According to Figure 3, the distribution of residuals does not seem to be symmetric and reflects no normal distribution.

Both the Shapiro-Wilks (see equation S14 and Shapiro-Wilks test parameters in Supplementary material) and Kolmogorov-Smirnov (see equation S16 and Kolmogorov-Smirnov test parameters in Supplementary material) tests confirmed this observation showing W-value = 0.97 and P-value = $2 \cdot 10^{-5}$ for Shapiro-Wilks normality test as well as

D-value = 0.56 and P-value = $2 \cdot 10^{-16}$ for one-sample Kolmogorov-Smirnov test.

Homoscedasticity was checked using Levene's test (see Levene's test in Supplementary material). A summary of the results is depicted in Table 3.

Table 3. Levene's test for homogeneity of variance

Source	Df	SS	Mean square	F-ratio	P-value
Between-groups	2	14.81	7.4	5.73	$4 \cdot 10^{-3}$
Within-groups	297	383.9	1.29		

Clearly, the assumption of homoscedasticity is violated as well (P-value < 0.05). Finally, it will be appropriate to test the assumption of independence; in order to check that indeed the number of reuses of a given hemodialyzer in a group of the same type of hemodialyzer has no information whatsoever about the number of reuses of another hemodialyzer in the same or different group of hemodialyzer types.

The validity of this assumption is difficult to assess and it is typically guaranteed by the design of the study. Figure 4 seems to indicate that independence of the residuals is indeed achieved since data are spread fairly evenly both horizontally and vertically.

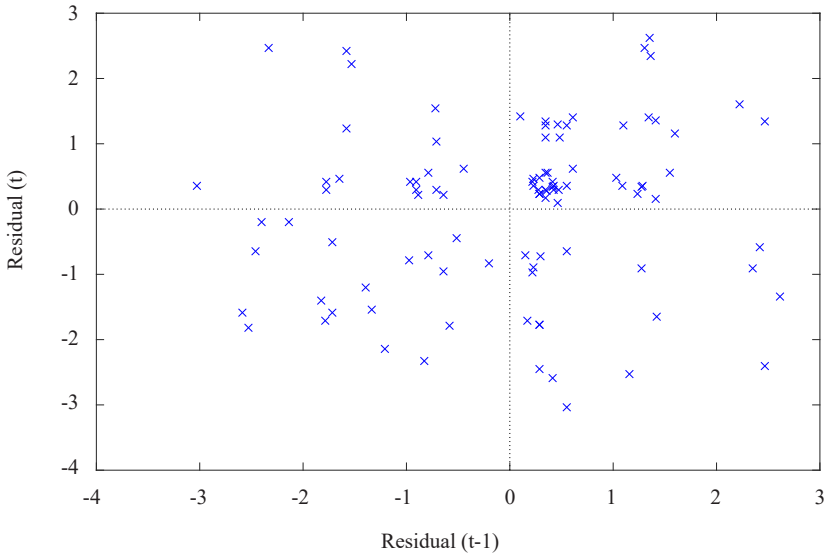

Figure 4. Plot of the residuals vs lagged residuals for F7 HPS, F8 HPS, and F10 HPS hemodialyzers

According to obtained results (Figure 3 and 4, Table 3), so far two of the three assumptions for the ANOVA test were violated; namely, the normality and homoscedasticity assumptions.

The study has a relatively large number of experimental data, 300 observations were used to fit the model. As a consequence, lack of normality should not be of great concern. On the other hand, the study is also balanced, i.e., each group of hemodialyzers has exactly 100 observations. Balanced designs are more robust to the departure of homoscedasticity. In any case, as a sensitivity analysis, a nonparametric technique was also used to assess if the responses from each group of hemodialyzers are different [34].

The Kruskal-Wallis test (see Kruskal-Wallis test parameters in Supplementary material) assesses if the responses

in each group of hemodialyzers are coming from different distributions, giving the following results: Kruskal-Wallis statistic H = 207.7, $df_{(between)}$ = 2 and P-value < $2 \cdot 10^{-16}$, confirming that each group of hemodialyzers is different ($p < 0.05$) and in line with the parametric model (see equation S18). To evaluate all the pairwise comparisons controlling the family-wise error rate, the Kruskal-Wallis test was applied again with the Holm-Bonferroni correction (see equation S19) obtaining $H_{(Corrected)}$ = 207.7 and P-$value_{(Corrected)}$ = 0 (see equation S20). Table 4 depicts a summary of obtained results.

Table 4. Kruskal-Wallis test between all hemodialyzer groups corrected with Holm-Bonferroni

Dialyzers	Mean	Std	Minimum	Maximum
F10 HPS	12.65	1.75	9	16
F8 HPS	8.79	1.95	4	13
F7 HPS	6.64	1.27	4	9

In conclusion, the nonparametric analysis fully supports the conclusions obtained with the parametric ANOVA test.

3.2 *Economic assessment simulation*

According to the increment of the number of disinfections (d_l), the ratio $\left(\frac{CDF_d}{CDF_v - FD_d}\right)$ changes as a function of the maximum possible number of reuses for each hemodialyzer (d_{max}), the disinfection price (P_d), and the cost of a virgin hemodialyzer (P_v). The maximum possible number of reuses for each hemodialyzer was calculated using statistical analysis (see section 3.1).

The cost of the dialysis water (RO water) was estimated as a function of the electric energy consumption needed to produce the volume of water used for the disinfection of each hemodialyzer. One of the water pumps recommended in the market for reverse osmosis applications is the Altamira pump, model ALPERES. This pump uses 2 kW of power in order to achieve a water flow of 96 L/min; the approximated amount of RO water used for the manual disinfection of one hemodialyzer is approximately 45 L.

Taking into account the best possible performance of the reverse osmosis unit used in the hospital (15 L/min of dialysis water), the Cuban price for energy consumption as well as the actual exchange rate between the Cuban peso and the Euro (€) (1 Cuban peso = 0.036 €) the cost of the RO water used for the disinfection of one hemodialyzer is around 0.00144 ≈ 0.0015 € (or thus 0.000032 €/L). On the other hand, the disinfection cost of one hemodialyzer by reprocessing was estimated at approximately 0.1 €/dialyzer (personnel cost of technicians).

The disinfection agent (Puristeril 340) is diluted to a concentration of 4% (v/v) for the disinfection process, the priming volume for each hemodialyzer is approximately 96 mL, 113 mL, and 132 mL for F7 HPS, F8 HPS, and F10 HPS hemodialyzer respectively; taking into account the transmission line, the total volume to be filled with Puristeril 340 (4% (v/v)) for the disinfection will be approximately 196 mL, 210 mL, and 250 mL for each hemodialyzer respectively.

The original container commercialized by Fresenius has a volume of 6 L with an approximated price of 21 €; therefore, the approximated cost is 3.5 €/L. As a result, the approximated price of 1 L of diluted Puristeril 340 at a concentration of 4% (v/v) will be the sum of the price of 40 mL of Puristeril 340 (pure) and 960 mL of RO water.

Then the price of the diluted solution is around 0.14 €/L (in this case considering the low price of 960 mL of dialysis water, only the disinfection agent price has been taken into account). Therefore, the prices for disinfecting one hemodialyzer (including the transmission lines), are approximately 0.027 €, 0.029 €, and 0.035 € for F7 HPS, F8 HPS, and F10 HPS hemodialyzer respectively, considering the priming volume for each hemodialyzer.

The price of one low permeable/high efficient hemodialyzer from Fresenius Medical Care in 2021, according to their sales price list, was approximately 1 € per polysulfone hemodialyzer for F7 HPS, F8 HPS, and F10 HPS.

Considering the packaging and shipment costs, the price was estimated at approximately 5 €/hemodialyzer. However, this estimation should be properly calculated by each medical center considering their specific characteristics.

In order to simulate the effects of the costs of the dialyzers disposal in the economic model, a disposal price for each filter has been fixed at 3 €. Nevertheless; this price should be estimated by each medical center considering its own characteristics as well as its waste management policy.

In order to develop a simulation of the economic model proposed, additional costs related to medicines or miscellaneous used in the disinfection process have not been considered; however, all those parameters can be estimated in each reprocessing unit according to its particularities.

Using previous information, the approximated disinfection price of each hemodialyzer can be estimated using equation 8. Figure 5 depicts the economic impact of the disinfection cycles based on the simulation of the proposed model for the three analyzed hemodialyzers.

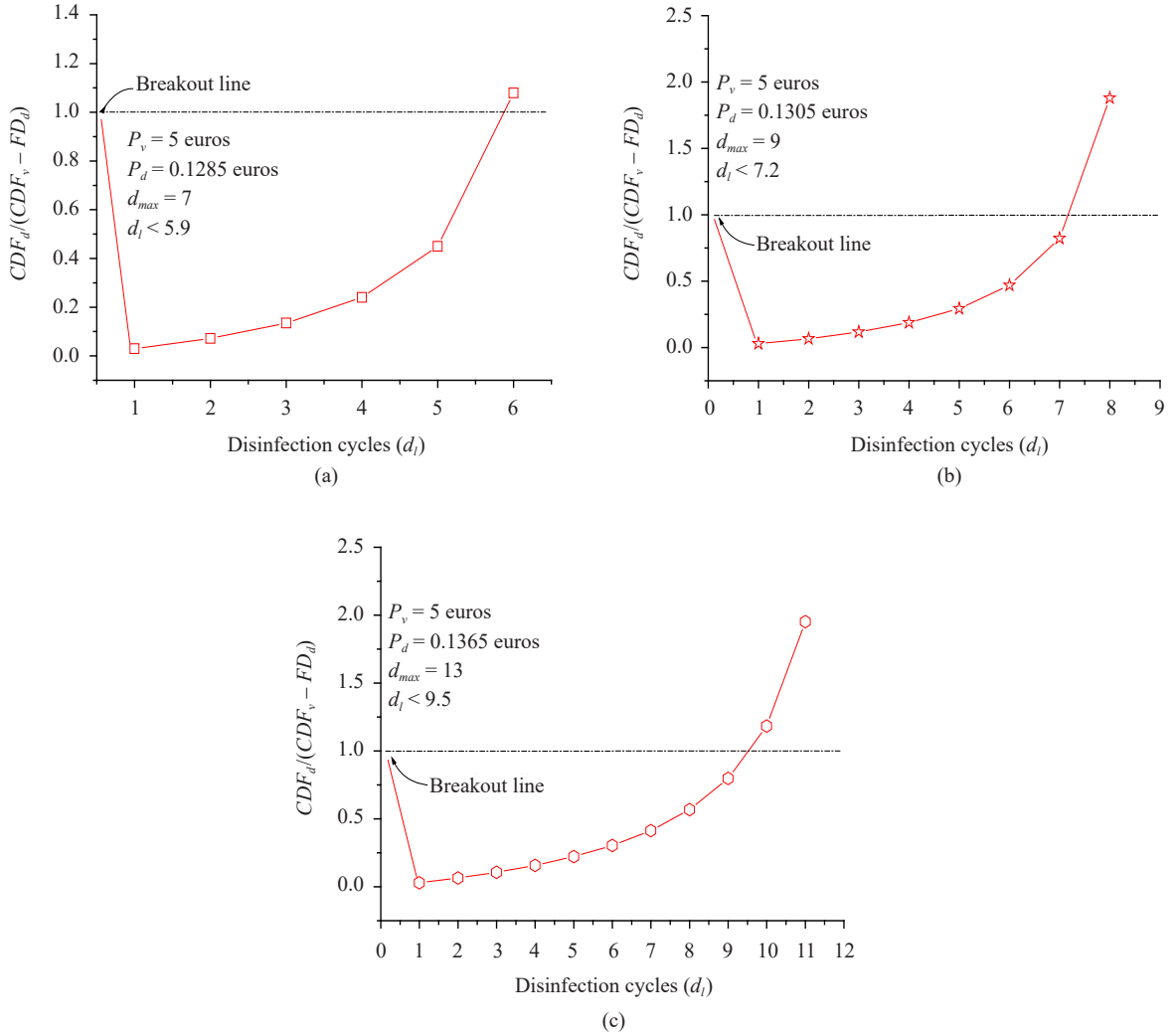

Figure 5. The economic impact of the disinfection cycles based on the simulation of the proposed model for F7 HPS (a), F8 HPS (b), and F10 HPS (c) hemodialyzer

In Figure 5 (a), for the F7 HPS hemodialyzer, it is possible to observe that after the sixth reuse the disinfection of the hemodialyzer is not economically feasible anymore $\left(\frac{CDF_d}{CDF_v - FD_v} > 1\right)$. The calculated number of economically

feasible reuses/disinfections according to equation 17 is $d_l < 5.9$, indicating that reusing the hemodialyzer more than 5 times causes economic losses. However, in this particular case considering that obtained value of d_l for economically feasible disinfections is very close to 6, it could be possible to apply a sixth disinfection/reuse.

In Figure 5 (b), the economically feasible region for the F8 HPS hemodialyzer is displayed at $d_l < 7.2$. Therefore, when using F8 HPS hemodialyzers the number of reuses/disinfections should be lower than or equal to 7 considering a disinfection price of 0.1305 € and a maximum of reuses $d_{max} = 9$.

Considering that F8 HPS polysulfone hemodialyzer is slightly superior to F7 HPS hemodialyzer when permeability and surface area are considered, better performance with respect to the F7 HPS hemodialyzer could be expected. However, according to the proposed model, this hemodialyzer could be reused/disinfected only one or two times more in comparison with the F7 HPS hemodialyzer in order to sustain an economically feasible disinfection process. The behavior of the F10 HPS hemodialyzer is presented in Figure 5 (c), with a maximum number of reuses $d_{max} = 13$.

According to Figure 5 (c), the number of economically feasible reuses/disinfections for this hemodialyzer is $d_l < 9.5$, therefore, the number of economically feasible reuses/disinfections when using F10 HPS hemodialyzers should be lower than or equal to 9. All previous estimations could change considering the characteristics of the medical service where maintenance hemodialysis treatments are developed.

Table 5 depicts a comparison between both proposed models (equations 19 and 21) evaluating the economic impact of a medical center that reuses the hemodialyzer and another one that uses virgin F10 HPS dialyzer in each treatment, for a determined number of treatments. According to Table 5, it is possible to observe that after the first treatment the total cost of the reused/disinfected hemodialyzer (TC_d) decreases with each reuse/disinfection of the hemodialyzer. On the contrary, the cost of each treatment using a virgin hemodialyzer increases with the number of needed treatments for the patient.

Therefore, after 10 treatments the total cost of the therapy using virgin hemodialyzer in each treatment arises up to 80 €. However, the total cost of the therapy reusing/disinfecting the hemodialyzer after each treatment is around 42 €. After nine disinfections the ratio $\left(\frac{CDF_d}{CDF_v - FD_d}\right)$ is higher than 1, making the reuse/disinfection of the hemodialyzer not economically feasible anymore; therefore, after the nine disinfections (10 treatments), the medical service that reuses the hemodialyzer should purchase a virgin hemodialyzer.

Table 5. Comparison between TC_v, TC_d, and TCH for 10 treatments using F10 HPS dialyzer

v_l	d_l	$FD_{(d)}$	CDF_d	$\left(\frac{CDF_d}{CDF_v - FD_d}\right)$	TC_d	TCH	TC_v
1	0	0.00	0.00	0.00	-	5.00	8
2	1	0.38	0.14	0.03	4.75	9.75	16
3	2	0.77	0.27	0.06	4.51	14.26	24
4	3	1.15	0.41	0.11	4.25	18.51	32
5	4	1.54	0.55	0.16	4.01	22.52	40
6	5	1.92	0.68	0.22	3.76	26.28	48
7	6	2.31	0.82	0.31	3.51	29.79	56
8	7	2.69	0.95	0.41	3.26	33.05	64
9	8	3.08	1.09	0.57	3.01	36.06	72
10	9	3.46	1.23	0.79	2.77	38.83	80
Total					33.83	41.83	80

P_v: 5 €, d_{amx}: 13, P_d: 0.1365 €, P_s: 3 €

According to the data shown in Table 5, the disinfection strategy is always economically feasible in comparison with the strategy that uses a virgin hemodialyzer for each treatment; however, the number of economically feasible reuses/disinfections that could be applied to the hemodialyzer should be better assessed using equation 17.

Looking at Table 5, after 10 hemodialysis treatments a medical service that reuses the F10 HPS hemodialyzer saves approximately 48% of the total cost of the treatment only using one hemodialyzer in comparison with medical services that do not apply the reuse. On the other hand, a medical service that applies virgin F10 HPS hemodialyzers in each treatment requires the use of 10 hemodialyzers in order to achieve the desired number of hemodialysis therapies.

Using an estimate of 60 patients under maintenance hemodialysis, with a minimum of three hemodialysis therapies per week, using F10 HPS hemodialyzers; on a yearly basis, a medical center that uses virgin hemodialyzers in each treatment will need to use approximately 8,640 hemodialyzers to fulfill the minimum required number of treatments for the patients with an approximate total cost of 69,120 €. On the other hand; a medical center that applies the reuse/disinfection strategy will need approximately 900 hemodialyzers for the same period with an approximated cost of 37,647 € using only the 10% of the number of hemodialyzers needed in a medical service that does not apply the reuse/disinfection strategy.

4. Conclusions

According to the obtained model (equation 15), the number of economically feasible reuses for each hemodialyzer depends directly on the number of applied disinfections, the disinfection price, the price of a virgin hemodialyzer, and the maximum number of possible reuses/disinfections of the hemodialyzer.

It has been demonstrated that the number of economic feasible disinfections, must always be lower than the maximum number of possible reuses/disinfections of the hemodialyzer and dependent on the hemodialyzer type: for F7 HPS, F8 HPS, and F10 HPS, the number of optimal disinfections is 6, 7, and 9 respectively.

The proposed model has been obtained considering the dialysis dose concept. Therefore, the urea clearance arises as the target variable to be evaluated from a clinical point of view in order to assess the efficiency of the hemodialyzer in the hemodialysis treatment as well as its influence on possible relative variations of the original filter price with modifications on tabulated urea clearance values.

According to the developed statistical analysis, it has been demonstrated that the hemodialyzers have a different average number of reuses/disinfections (F10 HPS ≈ 13, F8 HPS ≈ 9, and F7 HPS ≈ 7); demonstrating that the F10 HPS hemodialyzer shows the best performance within the studied series.

From the comparison using the proposed economic tool between both modalities, the reuse/disinfection practice will be always economically feasible in comparison with a non-reuse/disinfection policy; however, the number of economically feasible reuses/disinfections of used hemodialyzers could be better assessed using the proposed mathematical tool.

Additionally, a full regeneration of the hemodialyzer, in order to recover the membrane characteristics after reaching 80% of TCV, has to be studied with proper methods. In theory, the performance of the hemodialyzer should be significantly better applying a disinfection-regeneration process in comparison with disinfection only; arising the use of ultrasonic waves is a very interesting alternative for physical regeneration. However, this hypothesis still should be tested as well as the economic implications of this process and its feasibility. Therefore, the regeneration of the hemodialyzer will be the subject of the next research.

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Conflict of interest

All authors declare that there is no conflict of interest.

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