투석막 재사용

아주대학교 의과대학 내과학교실

김 도 헌

혈액 투석에 관련된 여러 가지 논점 중에서 투석막 재사용의 유용성은 학술적, 윤리적, 법률적인 차원에서 상당히 민감한 문제점들을 내포하고 있다. Shaldon이 1964년 투석막과 튜브를 heparin으로 채운 뒤 며칠 후 다시 사용한 것이 투석막 재사용의 시작이다. 몇 년 후 Pollard와 Scribner가 Kill 투석막 재사용에 관한 논문을 발표하였으며 그 이후 hollow fiber 투석막의 사용, 투석막 재사용의 기술적인 개발, 재사용의 자동화, 그리고 적절한 소독액 개발 등으로 인하여 투석막 재사용은 상당히 보편화 되었다. 특히 미국에서는 약 80% 이상의 투석실에서 투석막을 재사용하고 있다. 반면에 유럽에서는 약 10%, 호주에서는 약 20%의 환자에서 재사용되고 있으며, 일본에서는 투석막 재사용이 불법으로 규정되어 있다.

투석막 재사용은 물론 경제적인 측면에서 시작되었고 강조되고 있지만, 의학적인 차원에서도 장, 단점이 있다. 즉, 일차 사용 반응(first use reaction)의 감소, 생체 적합성(biocompatibility) 향상, 그리고 의료 보험 체계가 열악한 우리나라 여건상 고효율, 고유량 투석막을 사용할 수 있는 것이 장점이다. 또한 생체 의학 폐기물 감소는 환경 차원에서 이점이 있다. 그러나 아직 해결되지 않은 여러 가지 단점도 있다. 즉 간헐적으로 보고된 내독소 혈증, 패혈증, 불충분한 투석량, 소독액에 장기적으로 노출됨으로 인한 문제점, 그리고 특히 법정 문제로까지 확대되었던 사망률 증가 등은 투석막 재사용으로 초래될 수 있는 문제들이다. 투석막 제조 회사는 일회 사용만 가능(for single use only)하다는 라벨을 표기하기 때문에 이에 따른 여러 가지 법적인 책임 문제가 대두된다.

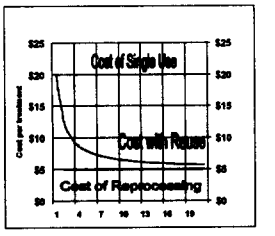
성공적인 재사용 프로그램을 운영하기 위한 필수적인 조건으로 세심한 질 관리 체제를 성립해야 한다. 특히 수질 관리에 특별한 노력을 요한다. 현재 시행되고 있는 국내 수질 관리 차원에서 투석막 재사용 프로그램을 광범위하게 시작하기에는 여러 가지 미흡한 점이 있는 것이 사실이다. 국내 여러 가지 여건들을 감안할 때 투석 환자들의 의견 수렴 및 교육, 관련 보건 당국자들의 견해 수렴, 그리고 특히, 국내에서는 투석막 재사용에 관련된 임상연구 결과가 전무한 상태이므로 긍정적인 충분한 임상결과가 발표된 후 활성화되어야 할 것이다.

History of reuse

1964 Shaldon et al
reuse of refrigerated - coil dialyzer
1967 Pollard et al
Kill dialyzer - rinse, clean, disinfect
1980 automated reprocessing technique
1983 a composite reimbursement system
for each dialysis in U.S.A.

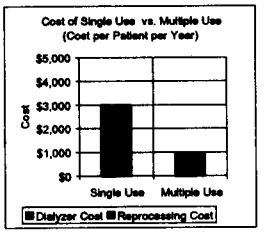
Reuse Cost Reduction Curve

So although the amount of additional cost savings per use decreases with each additional use, ...



Reuse Reduces Dialyzer Costs

Assuming a dialyzer price of $20, costs of reprocessing of $5, and 15 uses, the cost savings for one patient are $2,050 every year with reuse.



Mortality risk of re-used high-flux dialyzers compares favourably with single use low-flux dialyzers.

Held et al
Am. J. Kid. Dis. 1994

Relative risk of mortality by membrane and model[a]

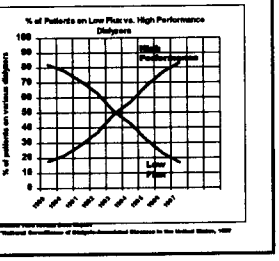
Membrane	Model: Unadjusted[b] for Kt/V	Adjusted[b] for Kt/V	Stratified by region[c]
Cellulose	1.00(ref)	1.00(ref)	1.00(ref)
Modified cellulose	0.72[d] (0.59-0.89)	0.74[d] (0.60-0.92)	0.80[f] (0.63-1.01)
Synthetic	0.72[d] (0.59-0.88)	0.75[d] (0.61-0.73)	0.80[e] (0.64-0.99)

[a] Numbers in parenthesis represent range of 95% of confidence interval
[b] After adjustment for all other risk factors and co-morbid conditions
[c] After adjustment for all other risk factor and co-morbid conditions as well as Kt/V
[d] p<0.002 [e] p=0.045 [f] p=0.062

Hakim et al. Kidney Int 50:566, 1996

Reuse Makes High Flux Affordable

In the USA, the use of Low Flux dialyzers has decreased from 80% to 20% while High Flux and High Efficiency dialyzers has increased.



Reuse Makes High Flux Affordable

From 1989 - 1997, in the USA, the use of High Flux dialyzers increased from 10% to 46%. This is possible in part, because of dialyzer reuse.

Multiple Use is Better for the Environment

- Approx. 75,000,000 dialyzers are used around the world every year.
- At approx. 300 g per dialyzer, this represents approx. 22,000,000 kg of medical waste per year.
- Dialyzer reprocessing could eliminate over 15,000,000 kg per year!

U.S.A. reuse data 1997

- Centres 82%
- Reuse average median 15 (1-65)
  maximum median 30 (1-179)
- Systems
  - Automated 62%
  - Manual 34%
  - Both 5%
- Germicide
  - Renalin (per-acetic acid) 56%
  - Formaldehyde 34%
  - Glutaraldehyde (diacide) 7%
  - Heat 3%

Tokars
Centre for Disease Control, 1997

Trend in dialyzer reuse practice by ownership

	No Reuse-Facility Ownership		
Year	Hospital	Freestanding For-Profit	Freestanding Not-For-Profit
1989	62.0	13.7	23.7
1990	59.2	13.2	22.3
1991	58.0	12.3	19.1
1992	55.5	12.7	19.9
1993	55.4	12.6	20.0
1994	52.8	12.2	20.3
1995	49.8	11.2	18.0
1996	47.7	9.2	12.8

Note. Time trends in the practice of dialyzer reuse by facility ownership. Data from CDC annual survey.

Agodoa et al. AJKD 32:S88, 1998

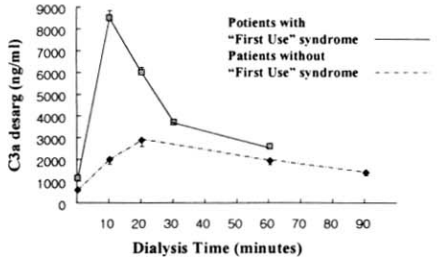
Advantages and disadvantages of dialyzer reuse

Advantages	Disadvantages
Reduction of first use reactions	Environmental and possible intravenous exposure to disinfectants
Improved biocompatibility	Anti-N antibodies with formaldehyde
Decreased treatment cost	Risk of pyrogenic reactions and septicemia
Allows use of more expensive (high flux) dialyzers	Decreased dialyzer efficacy with time
Reduced exposure to plasticizers and LAL-reactive material in new dialyzers	?Increased mortality with certain disinfectants

The issue of biocompatability clinical outcomes morbidity and mortality

No prospective randomised trials to date.
Serveral retrospective trials

• Hospitalization ↓ x 3	Chanard 1982
• Mortality ↓ 13% ($p<0.001$)	Hornberger 1993
• Infection related admission ↓ x 2	Hornberger 1993
• Mortality ↓ 25%	USRDS 1996
• Carpal tunnel syndrome RR 0.64	Koda 1997
• Mortality RR 0.613	Koda 1997
• Infection ↓ 30%	Levin 1991
• β_2 microglobulin ↓ rate of rise over 18/12	Hakim 1997
• Infection and atherogenesis ↓	USRDS 1999
• Nutrition better (CRP ↓ Alb ↑)	Hakim 1998



Complement activation during hemodialysis with new cuprophane-membrane dialyzers in patients with and without the first-use syndrome Each data point is the mean ± S.E.M. for all patients in that group

Hakim et al. N Engl J. Med 311:878 1984

Percent incidence of selected findings reported in three studies of dialysis with new and reprocessed cellulosic hemodialysis membranes

	Bok et al			Kant et al			Robson et al		
Finding	ND	RD	P	ND	RD	P	ND	RD	P
No. of treatments	161	235		3.232	3.892		4.933	21.659	
Hypotension	39	25	NR	26	16	0.001	34	29	0.0001
Cramps	28	27	NR	19	19	NR	19	15	0.0001
Nausea/vomiting	30	27	NR	11	3	0.001	14	12	0.0002
Headache	25	25	NR	NR	NR		4.1	3.4	0.02
Chest pain	29	21	0.013	2.5	1.6	0.01	4.9	1.7	0.0001
Back pain	34	24	0.0003	NR	NR		3.6	0.6	0.0001
Itching	35	34	NS	NR	NR		3.3	2.4	0.0001
Agitation/restlessness	31	23	NS	NR	NR		0.85	0.8	NS
Dyspnea	26	23	NS	0.37	0	0.001	0.64	0.23	0.0001
Fever	NR	NR		0.77	0.23	0.01	0.32	0.19	NS
Tremors	NR	NR		NR	NR		0.24	0.08	0.005
Chills	NR	NR		0.50	0.36	NS	0.54	0.21	0.0001
Sweating	NR	NR		0.40	0	0.001	0.62	0.72	NS

Abbreviations:ND, treatments with new dialyzers; RD, treatments with reprocessed dialyzers; NS , not significant; NR not reported.

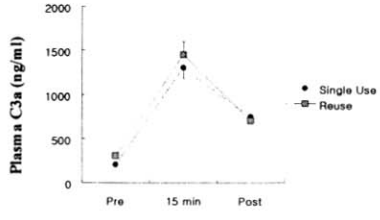
Shusterman et al. AJDK 14:81, 1989

Hospitalization rate in patients treated with single-use and reprocessed dialyzers

	Single-Use dialyzers	Reprocessed dialyzers
All hospitalizations	1.32	0.96
Dialysis-related hospitalizations	0.89	0.48*
Dialysis-unrelated hospitalizations	0.43	0.48

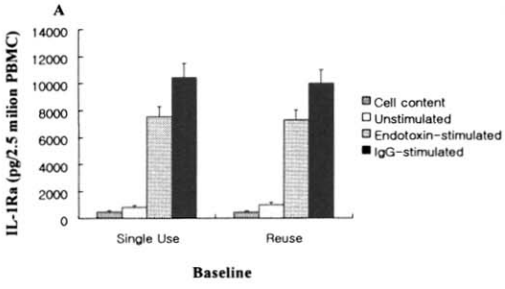
Data expressed as days per patient-month.
*p< 0.05 compared with single-use dialyzers

Shusterman et al. AJDK 14:81, 1989



Plasma activated C3 (C3a) levels in patients dialyzed with new (single use) or reprocessed (reuse) cellulose dialyzers. Compared with predialysis levels, there was a significant increase in plasma C3a levels at 15 min after the start of dialysis (p=0.0001), which persisted until the end of dialysis (p=0.0001). However, there were no significant differences between patient groups at any of the three time point (p=0.79). Data are from the first dialysis session in the last week of the 12-wk study

Pereira et al. JASN 7:861, 1996



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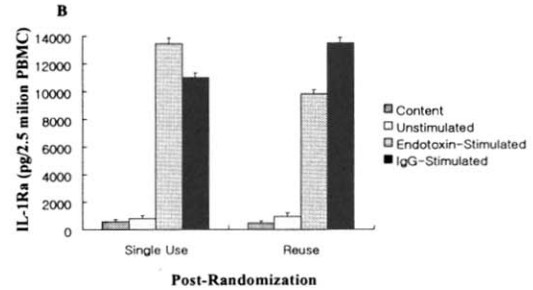
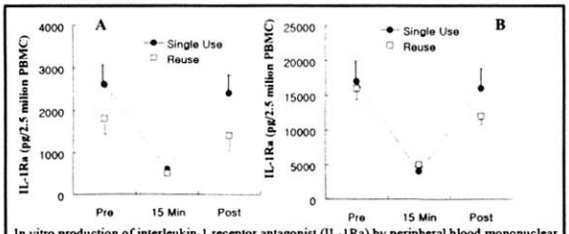
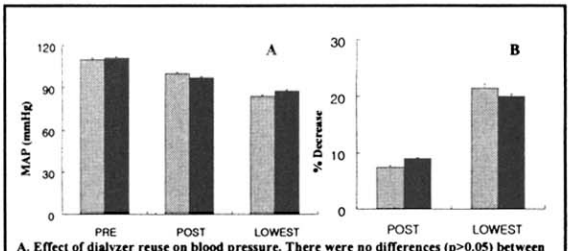


Pereira et al. JASN 7:861, 1996

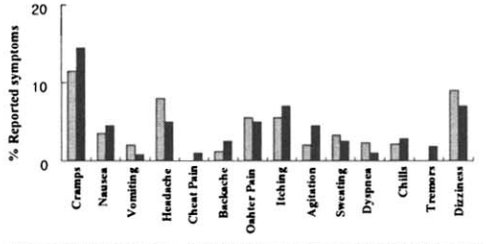


In vitro production of interleukin-1 receptor antagonist (IL-1Ra) by peripheral blood mononuclear cells (PBMC) in patients dialyzed with new (single use) or reprocessed (reuse) cellulose dialyzers. Before randomization (A), there were no significant differences between patients assigned to reuse or single use of dialyzers with respect to cell content (p=0.39), unstimulated (p=0.99), endotoxin stimulated (p=0.86), or IgG-stimulated PBMC (p=0.60). After 12 wk of follow-up in the assigned arm of the study (B), there were no significant differences between groups with respect to cell content (p=0.40), unstimulated (p=0.40), endotoxin-stimulatd (p=0.18), or IgG-stimulated PBMC (p=0.49). All data are the mean of three consecutive IL-1Ra measurements in the week before random assignment or in the week at the end of the 12-wk study.



A. Effect of dialyzer reuse on blood pressure. There were no differences (p>0.05) between the predialysis (Pre) mean BP (MAP), postdialysis(post) MAP or lowest MAP during the dialysis sessions associated with first use (▨) and reuse (■). B. Decrease in BP during first use and reuse. Postdialysis (post) mean BP (MAP) and nadirs in MAP during the dialysis sessions (Lowest) were represented as percent reduction from the predialysis values. There were no differences (p>0.05) between first use (▨) and reuse (■) for both of these variables.

Cheung et al. Am J Nephrol 11:397, 1991



Effect of dialyzer reuse on individual types of symptoms. The frequency of occurrence of each type of symptom during first use (▨) and reuse (■) was similar(p>0.05 between the two groups by X^2 analysis)

Cheung et al. Am J Nephrol 11:397, 1991

Percent reductions of serum urea, creatinine, β^2M, RBP following up to 20 uses of polysulfone membranes after automated reprocessing with peroxyacetic acid

	Percent reduction			
Compound	1st Use (n=26)	2nd Use (n=26)	10th Use (n=23)	20th Use (n=13)
Urea	69.9± 1.1	70.0 ± 1.1	68.0 ± 1.2	66.3 ± 2.4
Creatinine	63.9 ± 1.3	64.2 ± 1.0	63.0 ± 1.4	64.9 ± 2.7
β^2M	71.8 ± 1.1	72.7 ± 1.3	66.8 ± 1.5*	66.8 ± 2.2*
RBP	18.6 ± 2.1	15.3 ± 2.6	16.0 ± 2.9	11.2 ± 2.4*

*** p<0.05 compared with first use by paired t test.**

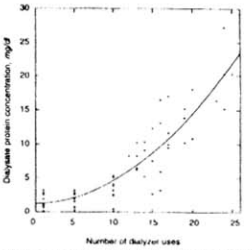
Kerr et al. AJKD 19:433, 1992

Dialyzer reuse and dialysis dose

	Dialysis Dose (Kt/V)			
Reuse Status	< 1.0	1.0-1.2	1.2-1.4	> 1.4
No	857(25.02)	1,035(30.22)	861(25.14)	672(19.62)
Yes	1,857(18.48)	2,925(29.11)	2,803(27.89)	2,464(24.52)
Total no. of units	2,714(20.14)	3,960(29.39)	3,564(26.45)	3,136(23.27)

Note. The association between dialyzer reuse and the delivered dialysis dose (Kt/V) in incident incenter hemodialysis patients, 1993. Data expressed as no. of units (%). Data from the USRD DMMS waves 1, 3, and 4.

Agodoa et al. AJKD 32:S88, 1998



Relation between dialysate protein concentration and the number of bleach processed dialyzer uses ($y=1.23 + 0.01\,x + 0.03\,x^2$, N=63, r= 0.904, p<0.001).

Kaplan et al. Kidney Int 47:573, 1995

↑ Sepsis

2 cluster reports of mycobacterium chelonei
4/5 patients had graft infection
2 died
2.5% renalin, 2% formalin
a cluster of pseudomonas sepsis

Incidence of PR in hemodialysis patients with filtered or unfiltered dialysis fluids by treatment modality

Type of treatment	No. of treatment	No. of PR	PR/1.000 treatment	P Values
Conventional				
Filtered	2,474	1	0.4	1.000
Unfiltered	13,123	7	0.5	
High efficiency				
Filtered	19,245	6	0.3	0.066
Unfiltered	11,345	9	0.8	
High flux				
Filtered	6,288	2	0.3	0.134
Unfiltered	2,409	3	1.2	
Total				
Filtered	28,007	9	0.3	0.046
Unfiltered	26,877	19	0.7	

Pegues et. J. Am. Soc. Nephrol. 3:1002, 1992

Clinical and laboratory characteristics during the 3-month random assignment to reuse or single use of dialyzers in patients who completed the study[a](I)

Characteristic	Single Use(N=17)	Reuse(N=20)	P[b]
During the 12-Wk study			
Hospital admission days	1 ± 1	1 ± 0	0.32
Episodes of access malfuntion			0.12
0 (%)	71	65	
1(%)	29	15	
>1(%)	0	20	
Number of blood transfusions			0.53
0(%)	76	75	
1 to 2	18	15	
>2	6	10	

Pereira et al. JASN 7:861, 1996

Clinical and laboratory characteristics during the 3-month random assignment to reuse or single use of dialyzers in patients who completed the study[a](II)

Characteristic	Single Use(N=17)	Reuse(N=20)	P[b]
Number of reuses/dialyzer	0	7 ± 1	
Chills	0	0	
Rigors	0	0	
Fever	0	0	
Episodes of symptomatic hypotension	8± 2	11 ± 3	0.75
Volume of saline infused	1642 ± 434	2183 ± 525	0.48
Urea reduction ratio (%)	65 ± 2	63 ± 2	0.36
At the completion of the 12-Wk study			
Hematocrit(%)	31 ± 1	32 ± 1	0.56
White blood cell count (X1000/mm^3)	7.1 ± 0.6	7.4 ± 0.4	0.96

Pereira et al. JASN 7:861, 1996

Clinical and laboratory characteristics during the 3-month random assignment to reuse or single use of dialyzers in patients who completed the study[a](III)

Characteristic	Single Use(N=17)	Reuse(N=20)	P[b]
Serum calcium (mg/dL)	9.4 ± 0.2	9.1 ± 0.2	0.19
Serum phosphorous (mg/dL)	6.5 ± 0.5	5.8 ± 0.4	0.08
Serum cholesterol (mg/dL)	166 ± 8	176 ± 7	0.45
Serum triglycerides (mg/dL)	155 ± 20	154 ± 18	0.87
Serum total protein (g/dL)	6.7 ± 0.2	6.6 ± 0.1	0.83
Serum albumin (g/dL)	3.6 ± 0.1	3.7 ± 0.1	0.60

[a] Data for continuous variables are presented as mean(SE), and for discrete vaiables as percentage.
[b] Wilcoxon's test for continuous variables, chi-squared/Fisher's test for discrete variables, and Mantel-Haenzel test for ordinal variable

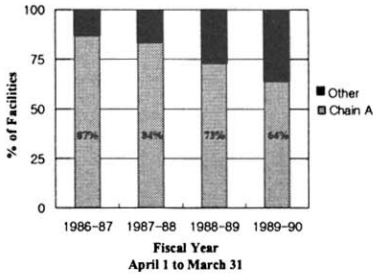
Pereira et al. JASN 7:861, 1996

Relative mortality risks for dialyzer germicides and reprocessing techniques(I)

Germicide	Reprocessing Technique	Reference	Patient Model+ N	Patient Model+ RR
Formalin	**Manual**	**Nonreuse**	**20,301**	**1.06**
Formalin	**Automated**	**Nonreuse**	**5,822**	**1.03**
Glutaraldehyde	**Any**	**Nonreuse**	**2,970**	**1.16**
PAM	**Manual**	**Nonreuse**	**7,741**	**1.15**
PAM	**Automated**	**Nonreuse**	**11,744**	**1.11**

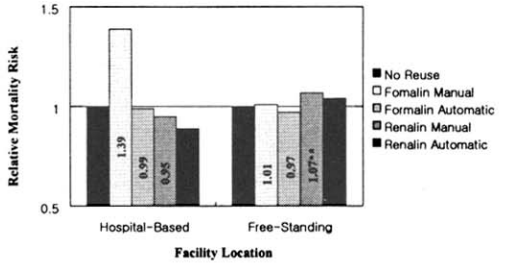
+ Relative risk from patient Cox proportional hazards regression (n=66,097)

Held et al. AJKD 23:692, 1994



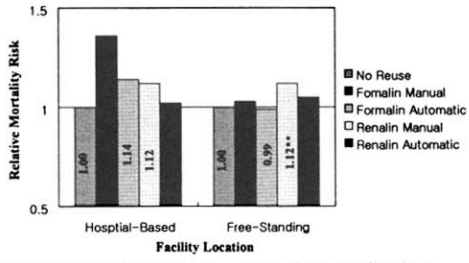
Distribution of manual renalin reuse facilities

Luehmann et al. Dialysis & Transplantation 23:248, 1994



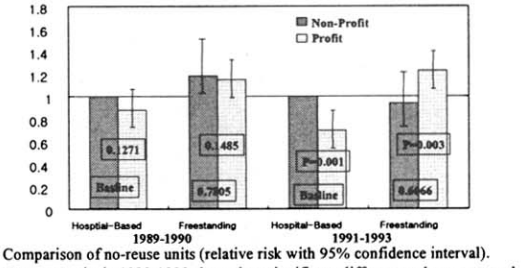
Low-flux dialyzers reused with formalin or Renalin facility location vs. relative mortality risk, complete model.
***=p<0.05; **=p<0.01**

Luehmann et al. Dialysis & Transplantation 23:248, 1994



All dialyzers reused with formalin or Renalin: facility locations vs. relative mortality risk, complete model.
***=p<0.05; **=p<0.01**

Luehmann et al. Dialysis & Transplantation 23:248, 1994

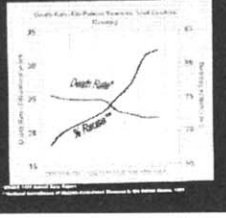


Comparison of no-reuse units (relative risk with 95% confidence interval). No-reuse units in 1989-1990 showed no significant difference when compared with hospital-based, nonprofit units. The pattern of mortality risk in for-profit units in 1991-1993 was similar to that of 1989-1990, but was highly significant

Collins et al. JASN 9:2108, 1998

Reuse Does Not Increase Mortality

From 1989 - 1997, mortality in the USA decreased from 26% to 22%, while reuse increased from 68% to 82% of dialysis centers.



Reuse Does Not Increase Mortality

"There is no conclusive evidence to substantiate the notion that either morbidity or mortality associated with single use or reuse is different."

National Kidney Foundation Report on Dialyzer Reuse, AJKD 1997

Patient's concerns

- Failure to provide adequate treatment
- Failure of sterility
- Risk of infusion of the sterilant
- Inadequate training of re-use technicians
- Asthetic apperance of the dialyser
- Receiving the wrong dialyser

Water quality

- Reverse osmosis and accessories
- Maintenance policies and procedures
- AAMI standards
  - bacterial contamination ≤ 200 CFU/ml
  - endotoxin level ≤ 5 EU/ml (1 ng/ml)
  - should be monitored monthly

Most Dialyzers are Reuseable

Most manufacturers have validated their dialyzers for multiple use and have received approval from the FDA

But they still label them "For single use only" outside the U.S.A.!

Conclusion

Economical and enviromentally favorable

Allows high efficiency dialysis

Allows high flux dialysis

More biocompatible?

Mortality ?

Quality control program essential

Further studies required