Allo-Hemodialysis - Intermittent Donation of Kidney Function

Berliner DialyseSeminar

32. Berliner DialyseSeminar
06.-07.12.2019

Allo-HD - Intermittent donation of kidney function

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Disclosures

- I am an employee of the Renal Research Institute, New York, NY, a wholly owned subsidiary of Fresenius Medical Care (FMC)

- I hold stock in FMC

- I receive author royalties from UpToDate

Why would we even need to think about alternatives to current kidney replacement therapies?

Patient with ESKD, Makarere University, Kampala (2012)

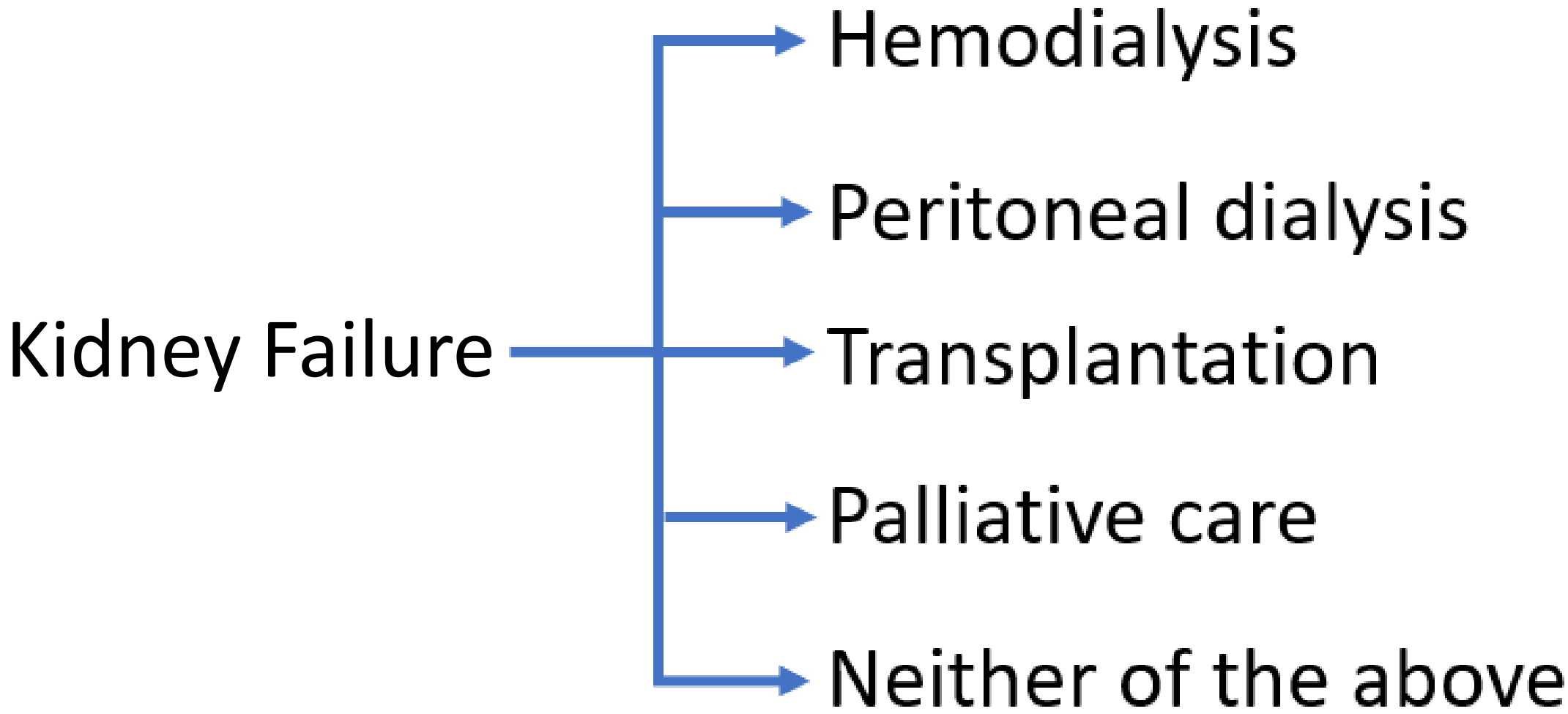
- Woman in her late 50s, single. Commenced hemodialysis about 8 weeks ago because of ESRD, 1-2 sessions a week. Last session 5 days ago.
- Shortness of breath, pitting edema, rales and bilateral pleural effusion, muscle wasting. Poor appetite. No encephalopathy. Some residual urine volume.
- Potassium slightly elevated
- Furosemide, antihypertensive medication.
- The situation is complicated by the fact that the patient ran out of funds to pay for dialysis

- **Question**: what next step would you recommend to initiate?

What next step would you recommend?

A. Increase diuretic therapy
B. Raise funds to pay for some form of renal replacement therapy
C. Follow-up in outpatient clinic later that week
D. Palliative care
E. Others

What are the Options?



Is this patient an exception?

The WHY –
the Unmet Need

THE LANCET

Worldwide access to treatment for end-stage kidney disease: a systematic review (2015)

Thaminda Liyanage, Toshiharu Ninomiya*, Vivekanand Jha, Bruce Neal, Halle Marie Patrice, Ikechi Okpechi, Ming-hui Zhao, Jicheng Lv, Amit X Garg, John Knight, Anthony Rodgers, Martin Gallagher, Sradha Kotwal, Alan Cass, Vlado Perkovic*

Discussion

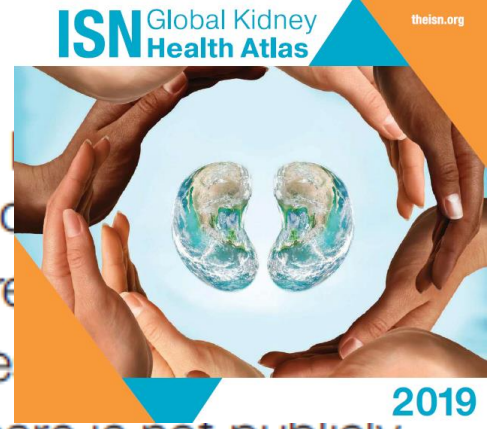
In this systematic review, we used the best available data to calculate the number of people receiving RRT in 2010, noting that about 2·618 million people received this life-sustaining treatment worldwide. Additionally, our findings suggest that, at best, only half or less of all people needing RRT worldwide had access to it in 2010, meaning at least 2·284 million people might have died prematurely because they did not have access to the treatment in 2010. Most of this burden of preventable deaths fell on low-income and middle-income countries.

The 2019 Global Kidney Health Atlas

David Harris

AM, MD (USyd), BS, FRACP

Professor of Medicine,
University of Sydney



End-stage kidney disease (ESKD) is a major
problem due to associated adverse health co
costs of treatment. People with ESKD require
intensive care that is burdensome to their life
expensive. In many countries where ESKD care is not publicly funded, people with ESKD are unable to receive treatment, resulting in poor health outcomes and often death. It is projected that in 2030, 14.5 million people will have ESKD and need treatment, yet only 5.4 million will actually receive it due to economic, social, and political factors. There are several options for ESKD treatment. Kidney replacement therapy (KRT) can be delivered through hemodialysis (HD), peritoneal dialysis (PD), or transplantation; alternatively patients can be offered non-dialytic comprehensive conservative care. Understanding the benefits and limitations of each option requires consideration of the individual patient, local context, and capacity. The high cost of HD is a key barrier for many

The 2019 Global Kidney Health Atlas

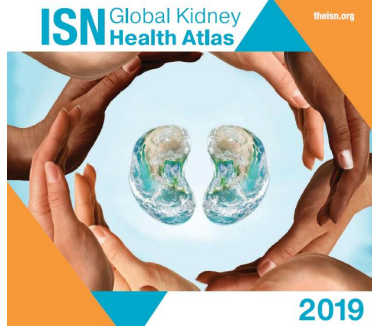
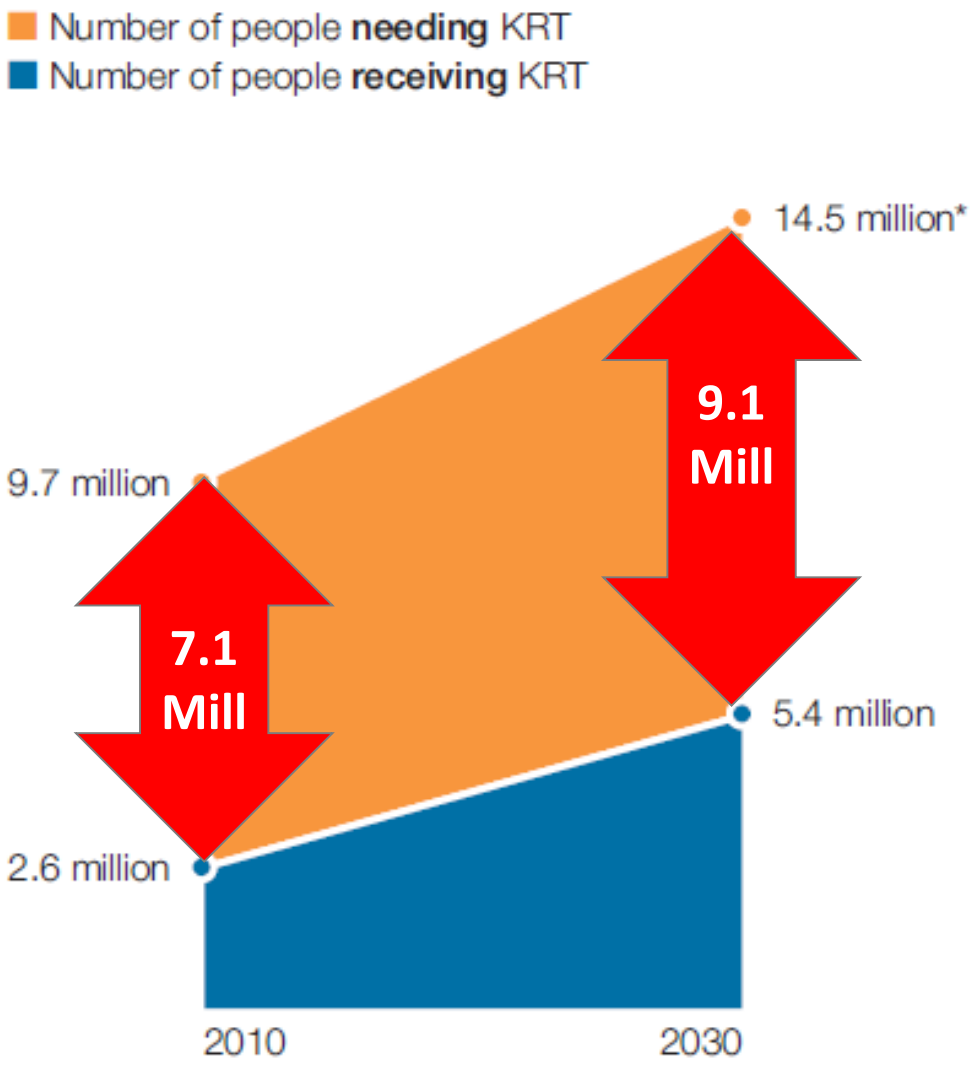


Figure 1.2 | The state of KRT need, access, and projections into the future



The annual global dialysis shortfall is expected to increase between 2010 and 2030 by two million patients.

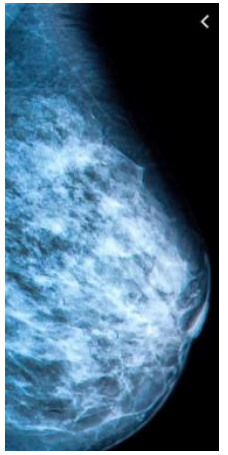
How do these numbers compare to other global causes of death?

HIV / AIDS related illnesses (2017) 940,000

Wars and genocides (pooled data 2010 to 2016) 600,000

Malaria (2017) 435,000

Breast cancer (2011) 508,000



Lung cancer (2012) 1,600,000

The 2019 Global Kidney Health Atlas

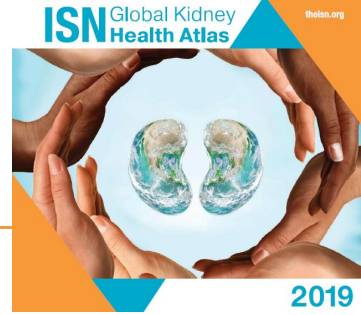
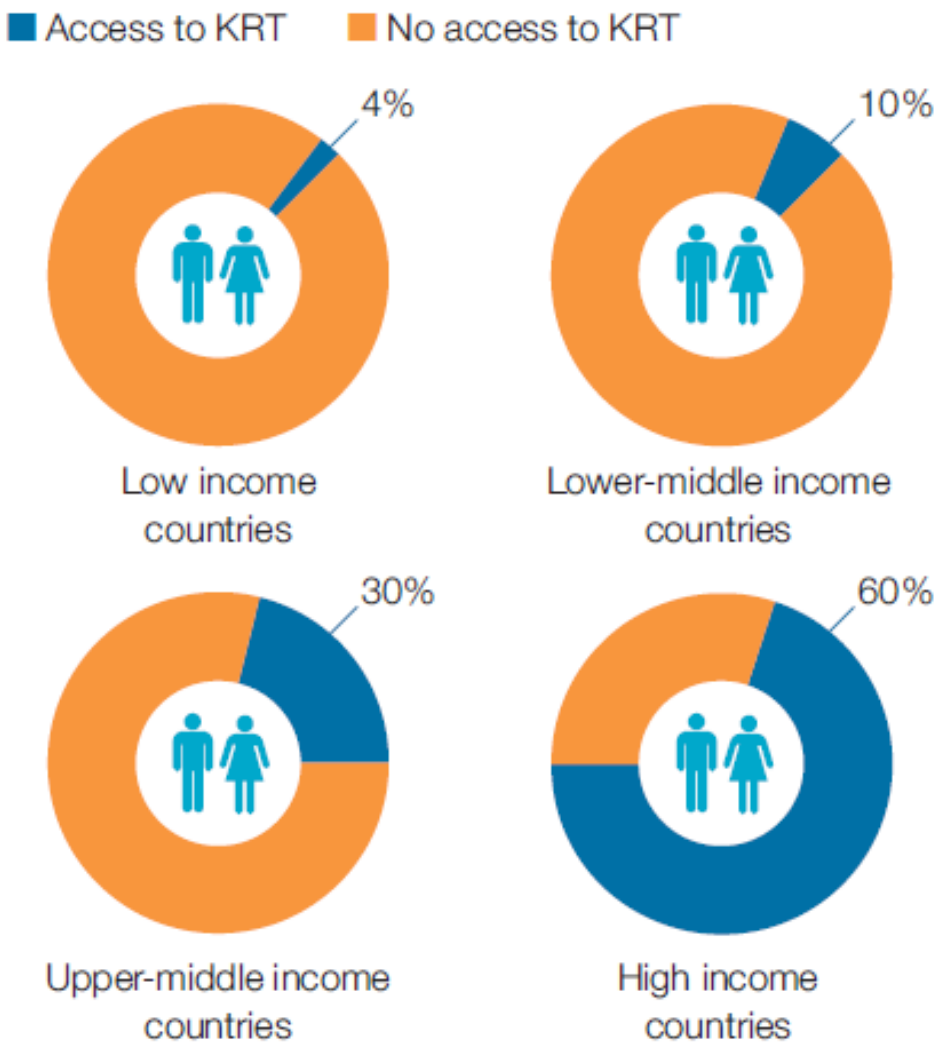
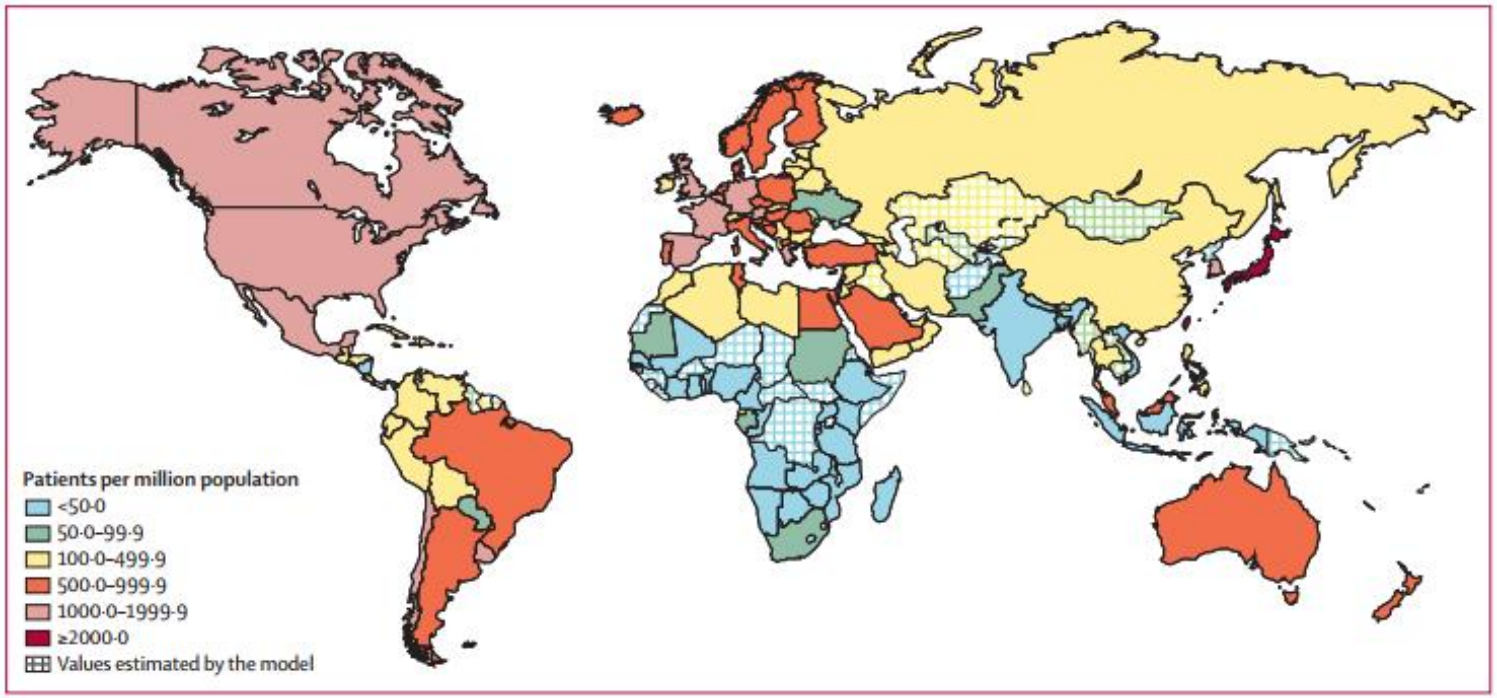


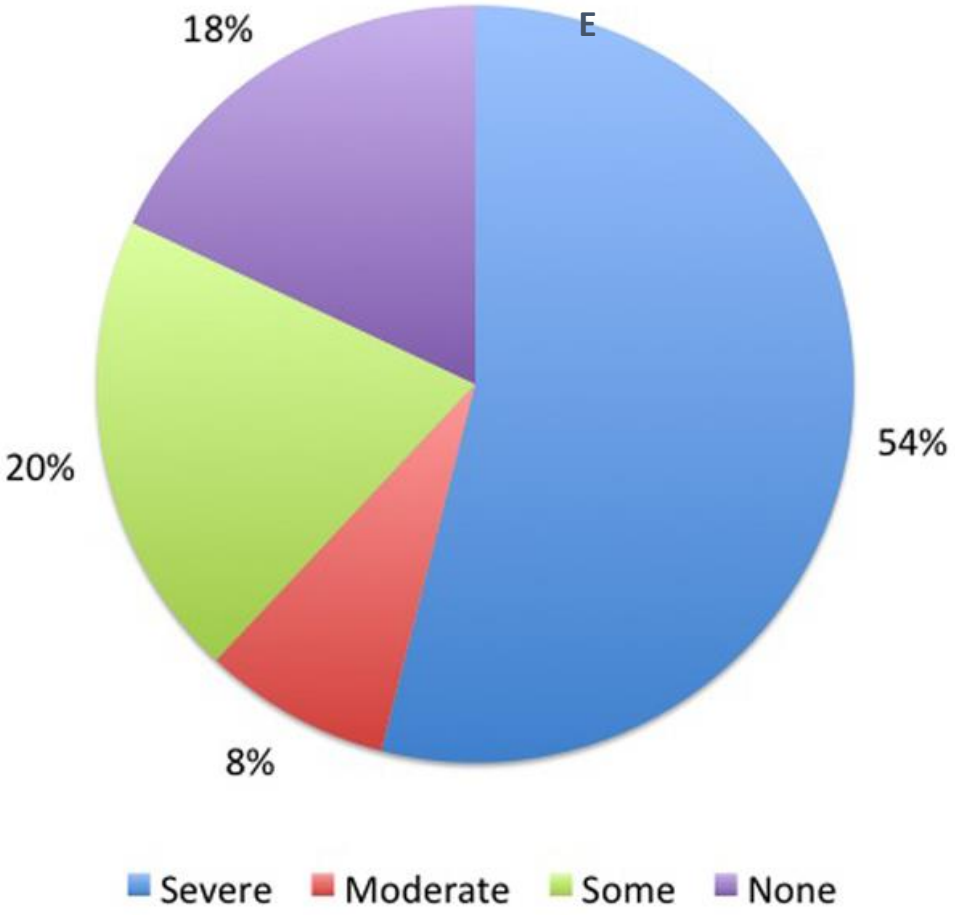
Figure 1.3 | Income-related variability in access to KRT



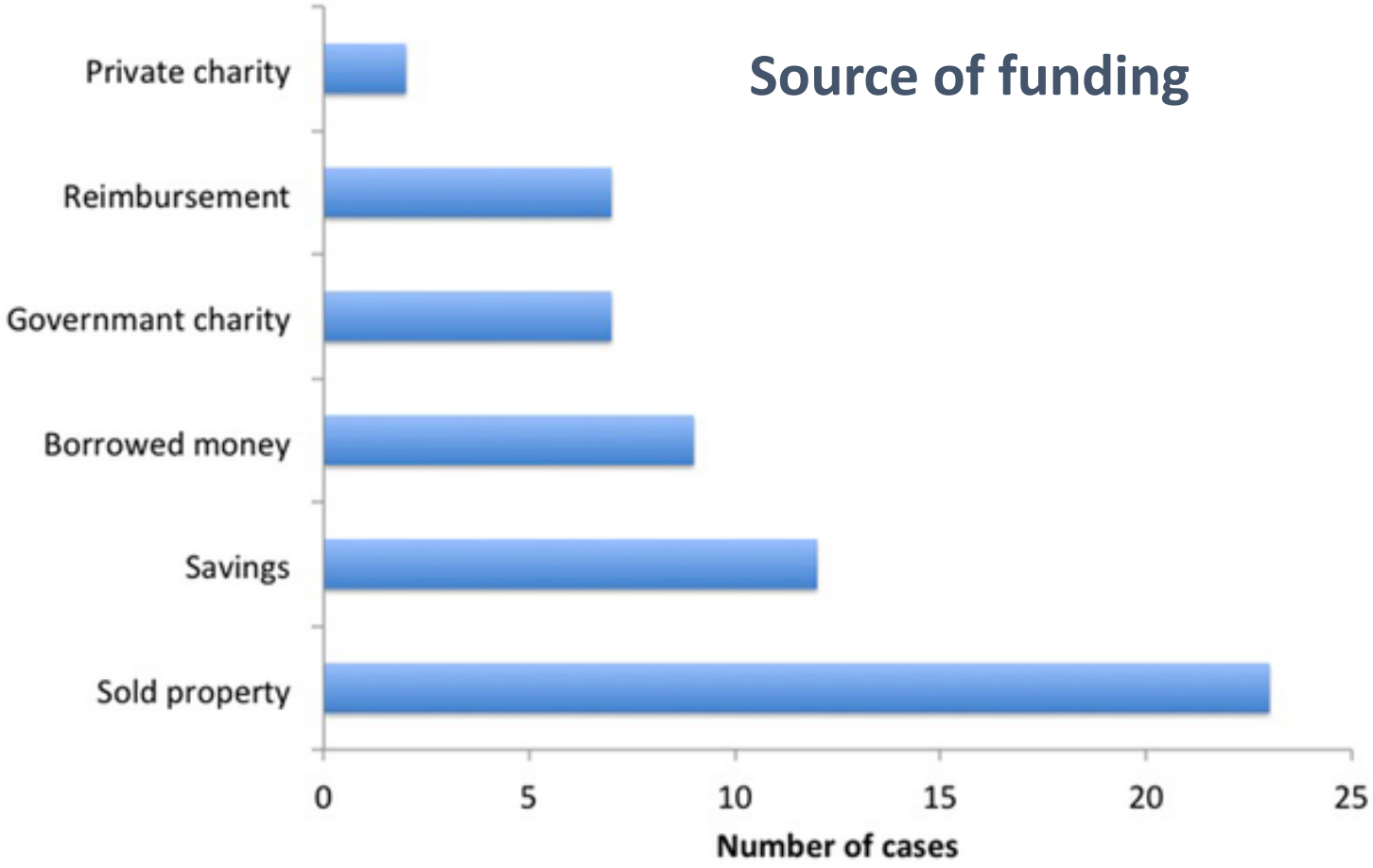
Over 90% of people with ESKD in low and lower-middle income countries are not receiving KRT.



Extent of financial crisis suffered by the families of the patients



Source of funding



Ramachandran R, Jha V (2013) Kidney Transplantation Is Associated with Catastrophic Out of Pocket Expenditure in India. PLOS ONE 8(7): e67812. https://doi.org/10.1371/journal.pone.0067812
https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0067812

PLOS ONE

The WHY – the Unmet Need

THE LANCET

Worldwide access to treatment for end-stage kidney disease: a systematic review

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[...], the number of people without access to RRT will remain substantial. These data show a pressing need to develop low-cost RRT alternatives to reduce disparities in access to the treatment, and the importance of development, implementation, and assessment of cost effective end-stage kidney disease prevention strategies.

De-constructing Hemodialysis: What is Essential?

Vascular access

Dialyzer

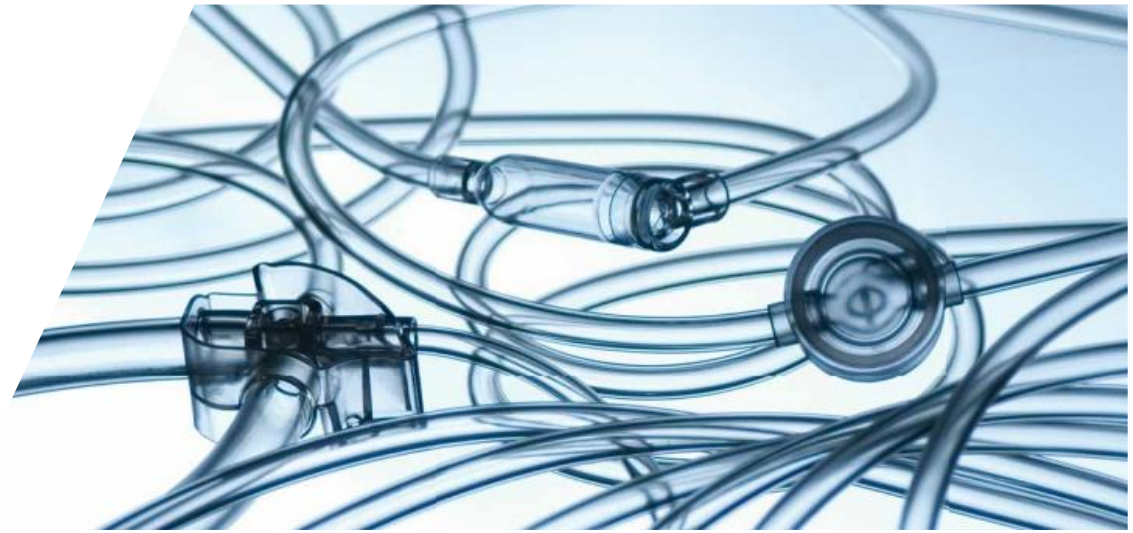
Blood lines

Dialysate

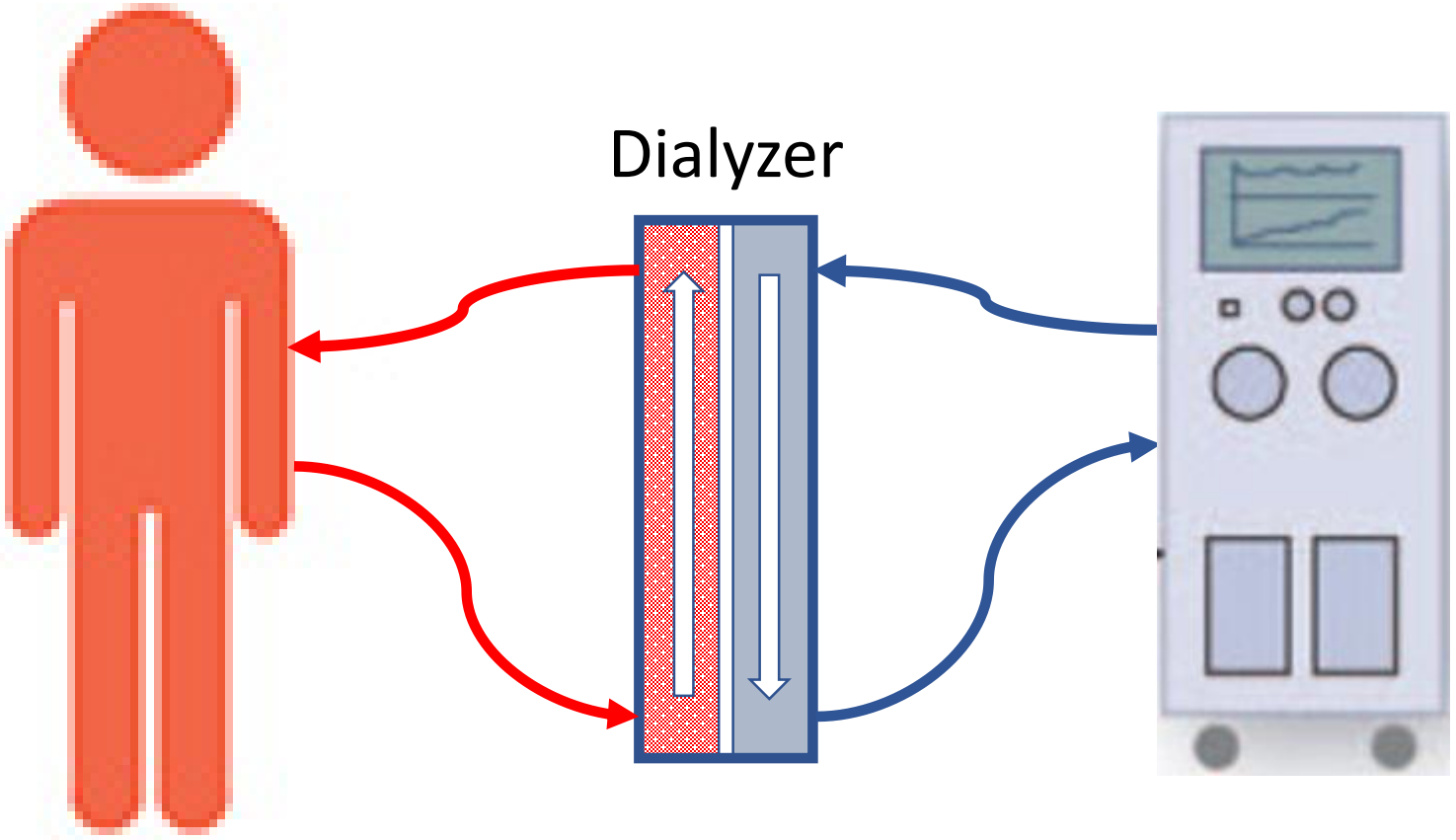
Pump(s)

Energy

Priming / rinsing fluid



Conventional In-Center Hemodialysis

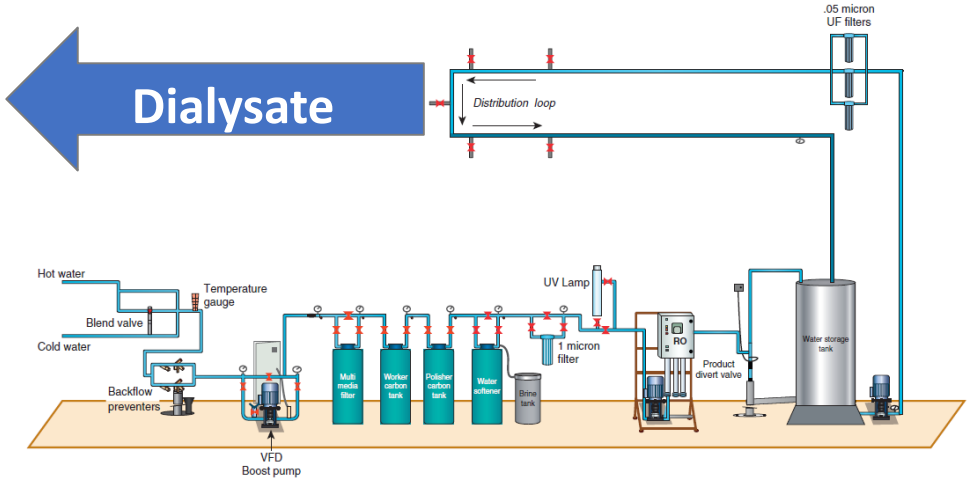


Patient

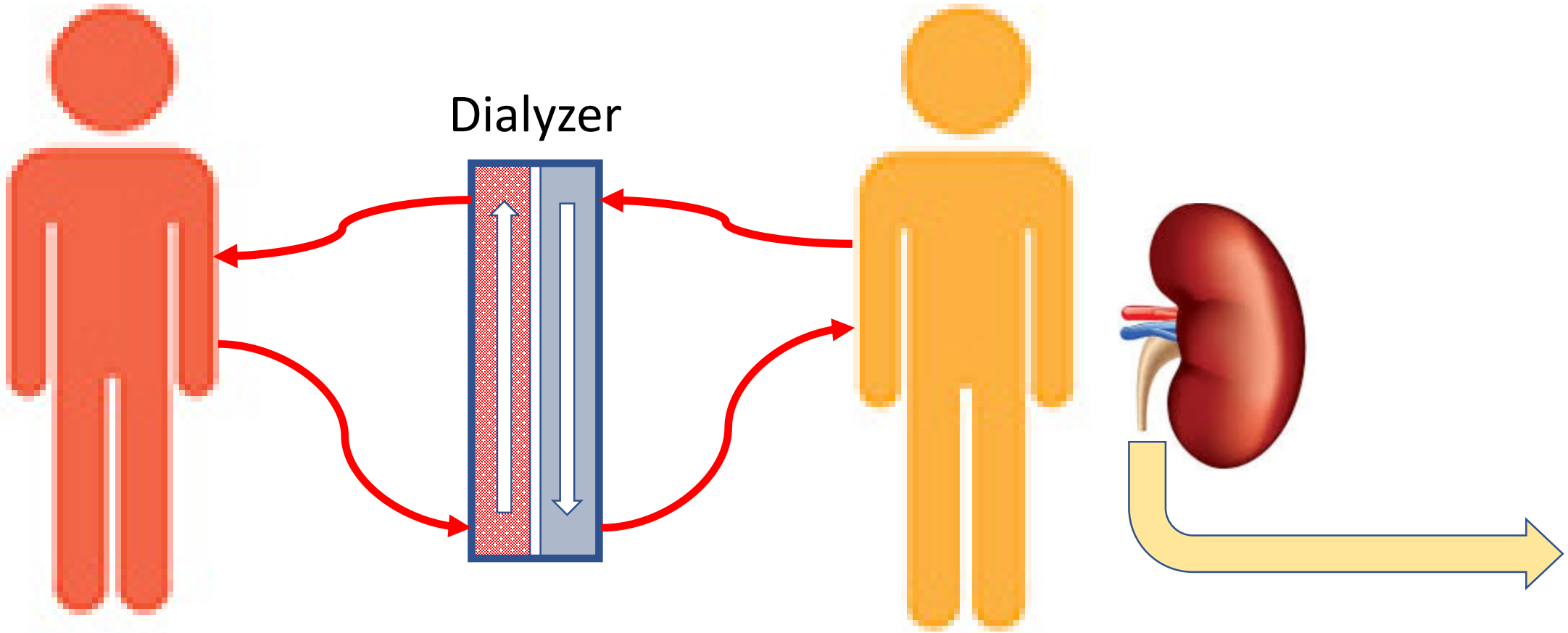
Dialyzer

Water system
(filters, softeners, RO, etc.)
200 to 500 L of water / HD

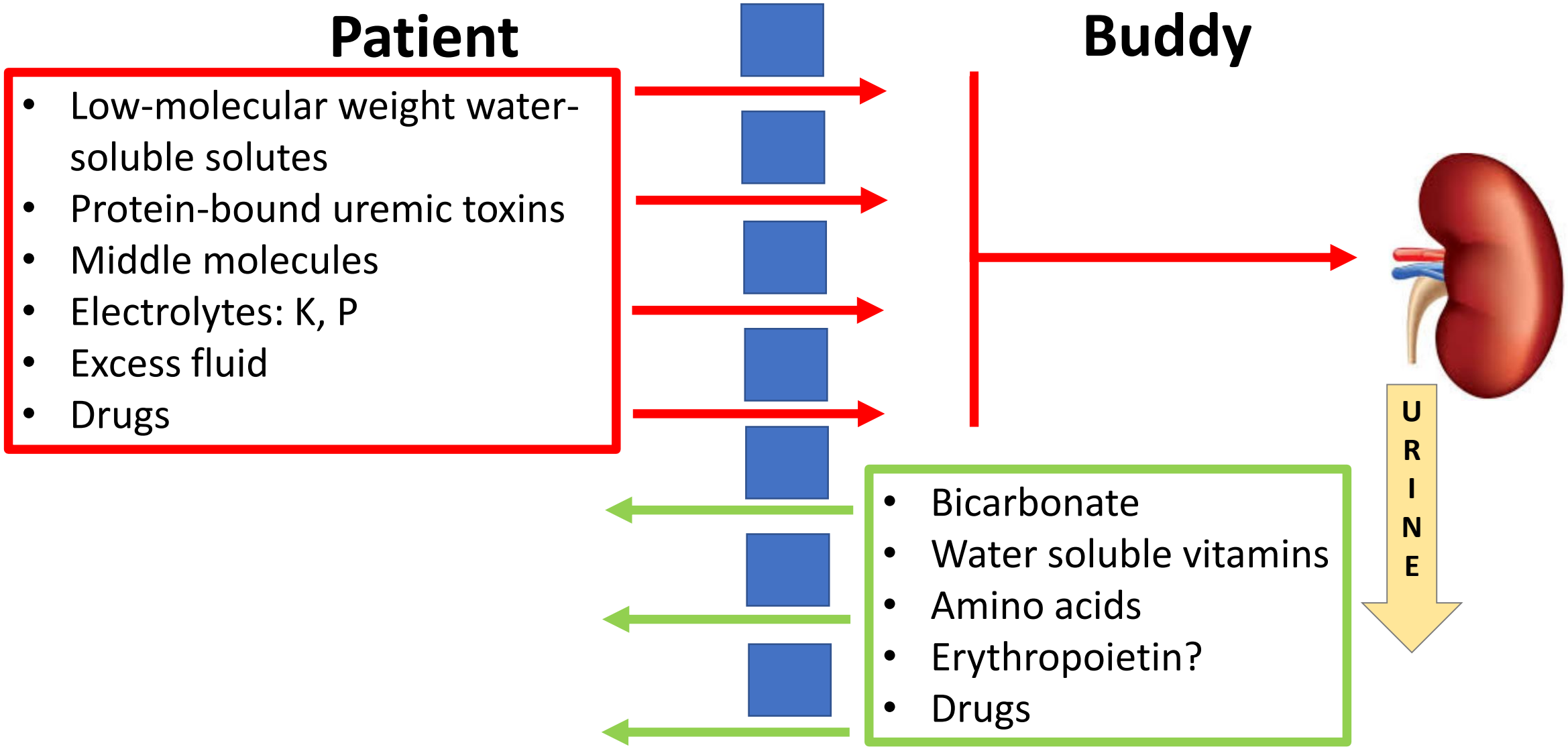
Dialysate



Alternative Hemodialysis Approach



alloHD: Like in Conventional HD, Solute and Fluid Transfer Follows Concentration and Pressure Gradients



Critical Areas to be Addressed

Medical

Ethical considerations

Technical

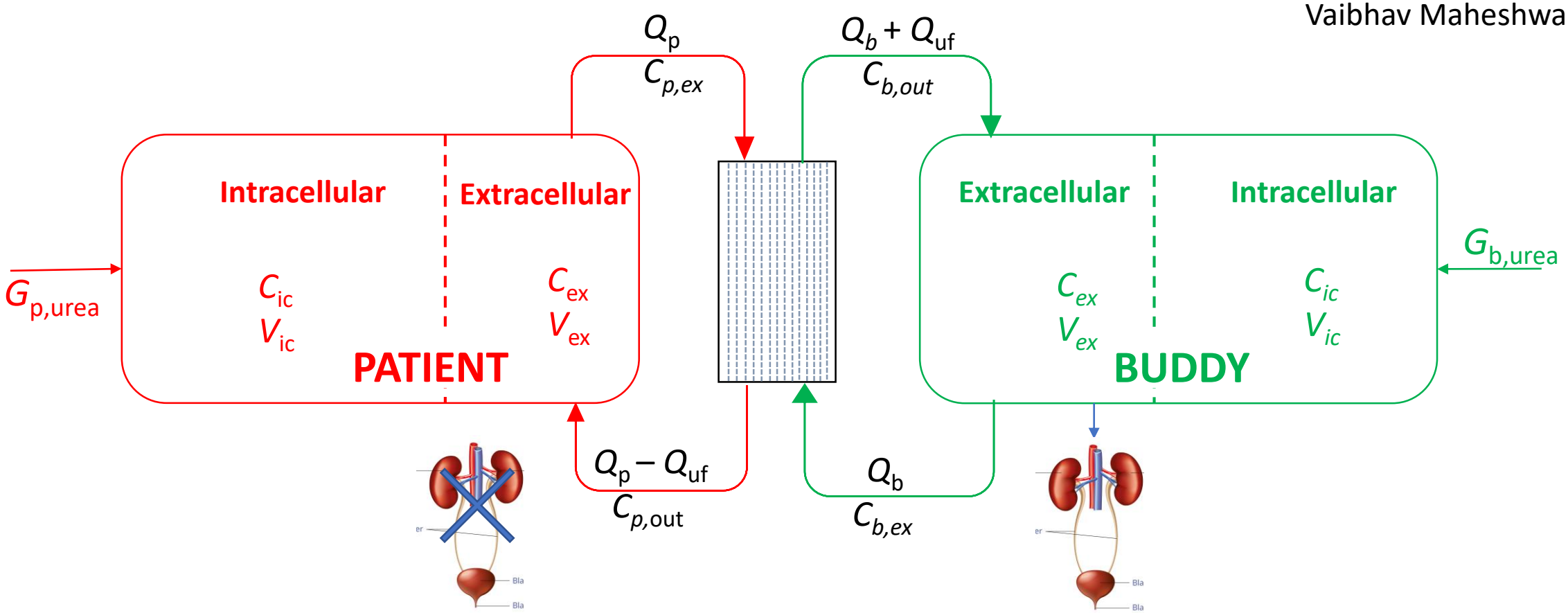
Economic & Care delivery model

Some of the Critical Medical Questions

- Adequacy and solute transfer rates
- Vascular access; blood flows
- Blood leaks: Infection due to transferred agents; transfer of antigenic material between patient and buddy
- Buddy's renal reserve
- Anticoagulation
- Membrane type: low-flux, hi-flux? Cellulose based? Symmetric / asymmetric?
- Dialyzer / blood-line re-use?
- Psychological dynamic of the patient-buddy dyad

Can alloHD provide adequate solute removal?

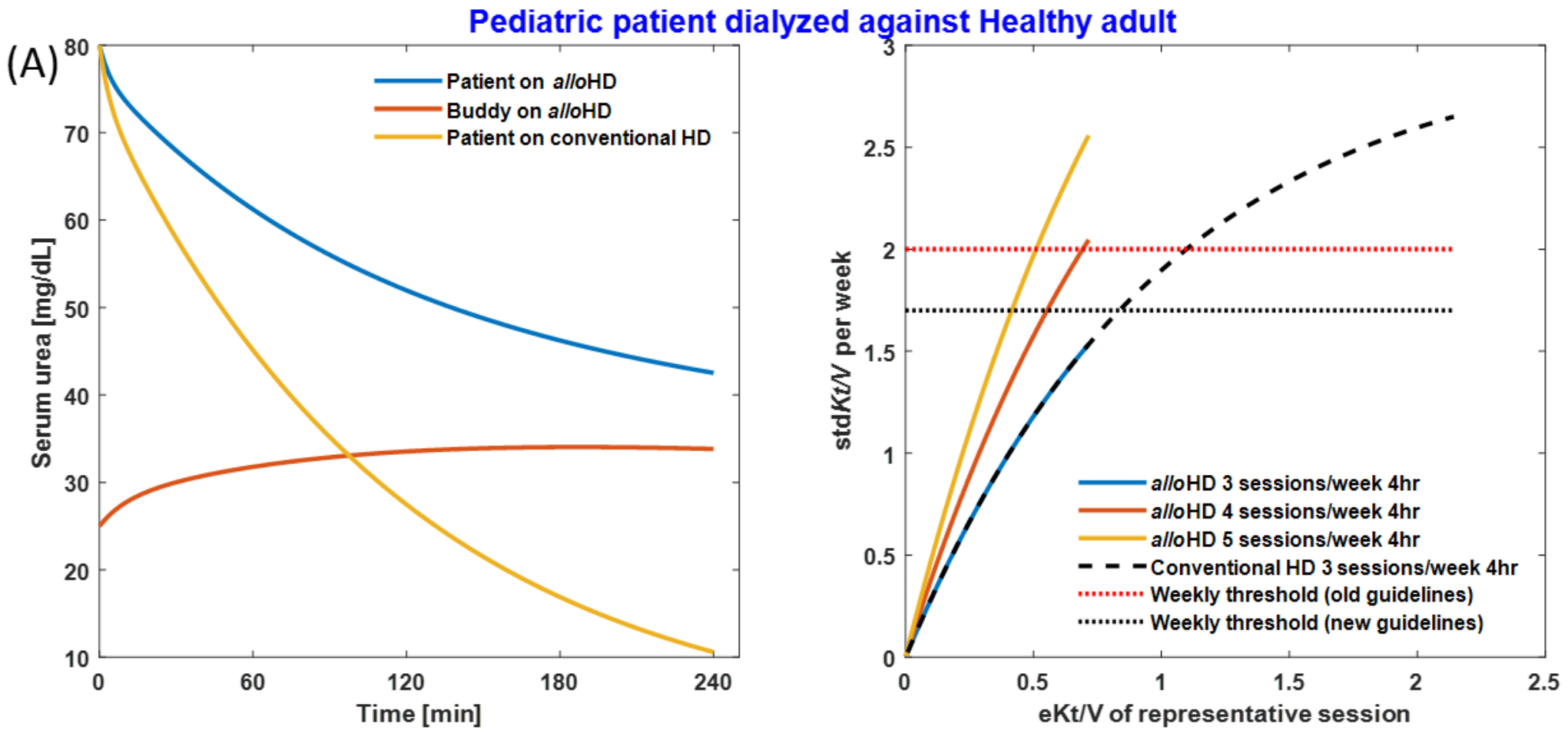
Vaibhav Maheshwari, PhD



Maheshwari V, Thijssen S, Tao X, Fuertinger D, Kappel F, Kotanko P. A novel mathematical model of protein-bound uremic toxin kinetics during hemodialysis. *Sci Rep*. 2017 Sep 4;7(1):10371

Can alloHD provide adequate solute removal?

Kotanko P, Maheshwari V, Thijssen S. ASN 2018



Can alloHD provide adequate solute removal?

Kotanko P, Maheshwari V, Thijssen S. ERA-EDTA (2019)

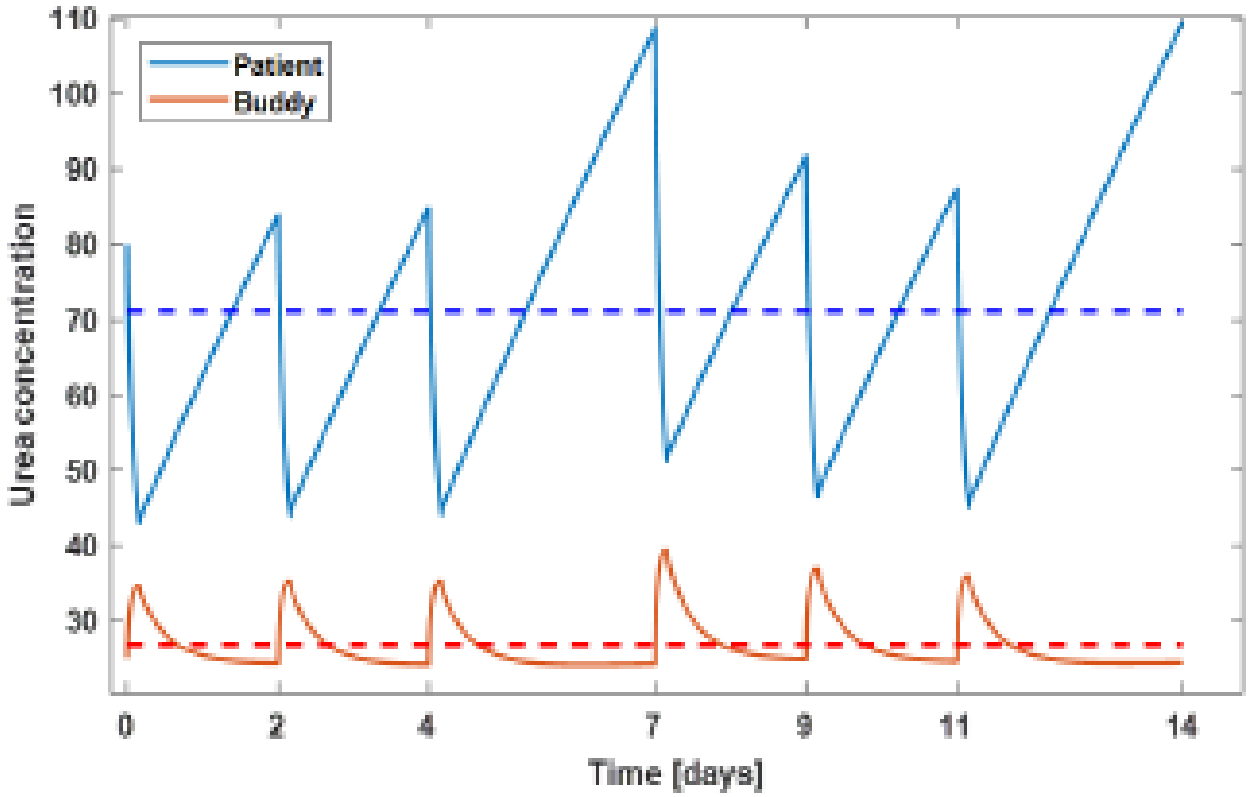


Figure 2: Urea kinetics in a pediatric patient (blue) and healthy adult buddy (red). Solid lines correspond to intra- and inter-dialytic kinetics and dashed line denote time-averaged urea concentrations.

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Ethical issues

Nicholas Steneck
Professor Emeritus of History at University of Michigan
Independent Research Integrity Consultant
Former Director, Michigan CTSA Ethics Program

Are there compelling ethical reasons against further research?

- AlloHD does raise ethical questions but in my view, none suggest that further research should not be undertaken.
- Given the magnitude of the problem (millions of individuals who do not have access to RRT), there would seem to be an ethical mandate to explore other treatment options.
- Given the fact that access to treatment clearly depends on economic status, there would also seem to be an ethical mandate to explore options that will serve developing countries.

Slide by Courtesy N. Steneck

Ethical issues

Nicholas Steneck
Professor Emeritus of History at University of Michigan
Independent Research Integrity Consultant
Former Director, Michigan CTSA Ethics Program

If alloHD offers an effective option to RRT, can it be used ethically?

- My assumption is that it could be, but final judgement will depend on the outcome of research findings.
- Presumably the most significant issue is risk to the patient and the buddy.
- If alloHD increases risk, then the equitable distribution of risk and questions about payment will have to be addressed.
- However, it is possible that alloHD might decrease risk to the patient, provide employment for the buddy, lower healthcare costs or have other unanticipated beneficial outcomes.

Slide by Courtesy N. Steneck

Would healthy subjects accept the inconveniences and risks of alloHD? Survey in Morelia, Mexico (2019)

NausLife

Renal Replacement Therapy Preferences Survey, is alloHD accepted?

ISRAEL CAMPOS, JESÚS ARELLANO, VÍCTOR GÓMEZ, JORGE QUIROZ, ALFONSO MARISCAL

Renal Replacement Therapy Preferences Survey, Morelia, Mexico (2019)

RESULTS

QUESTION 4

Do you agree with AlloHD procedure?

			Question 4	
			YES	NO
Group	Relative caregiver	**[n=33]**	87.9%	12.1%
	Non-relative caregiver	**[n=42]**	90.5%	9.5%
	Healthcare professional	**[n=50]**	64.0%	36.0%
Total			79.2%	20.8%

Science, Technology, and Societies' Choices

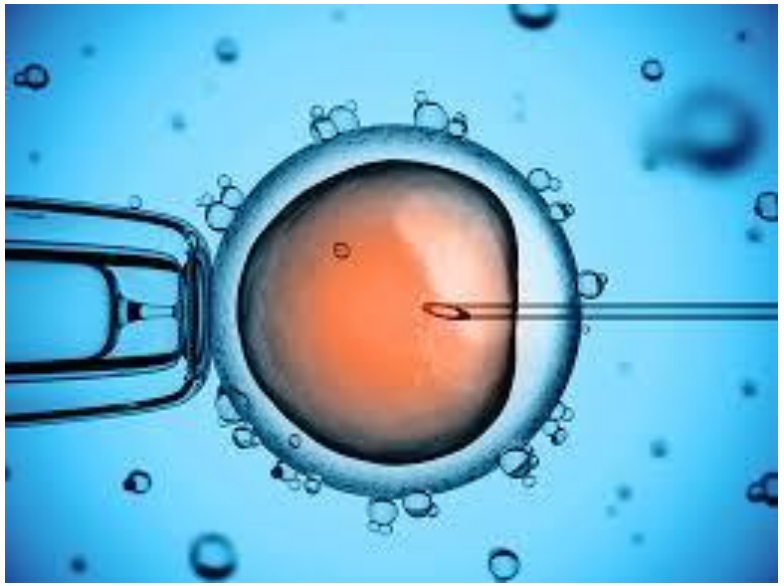
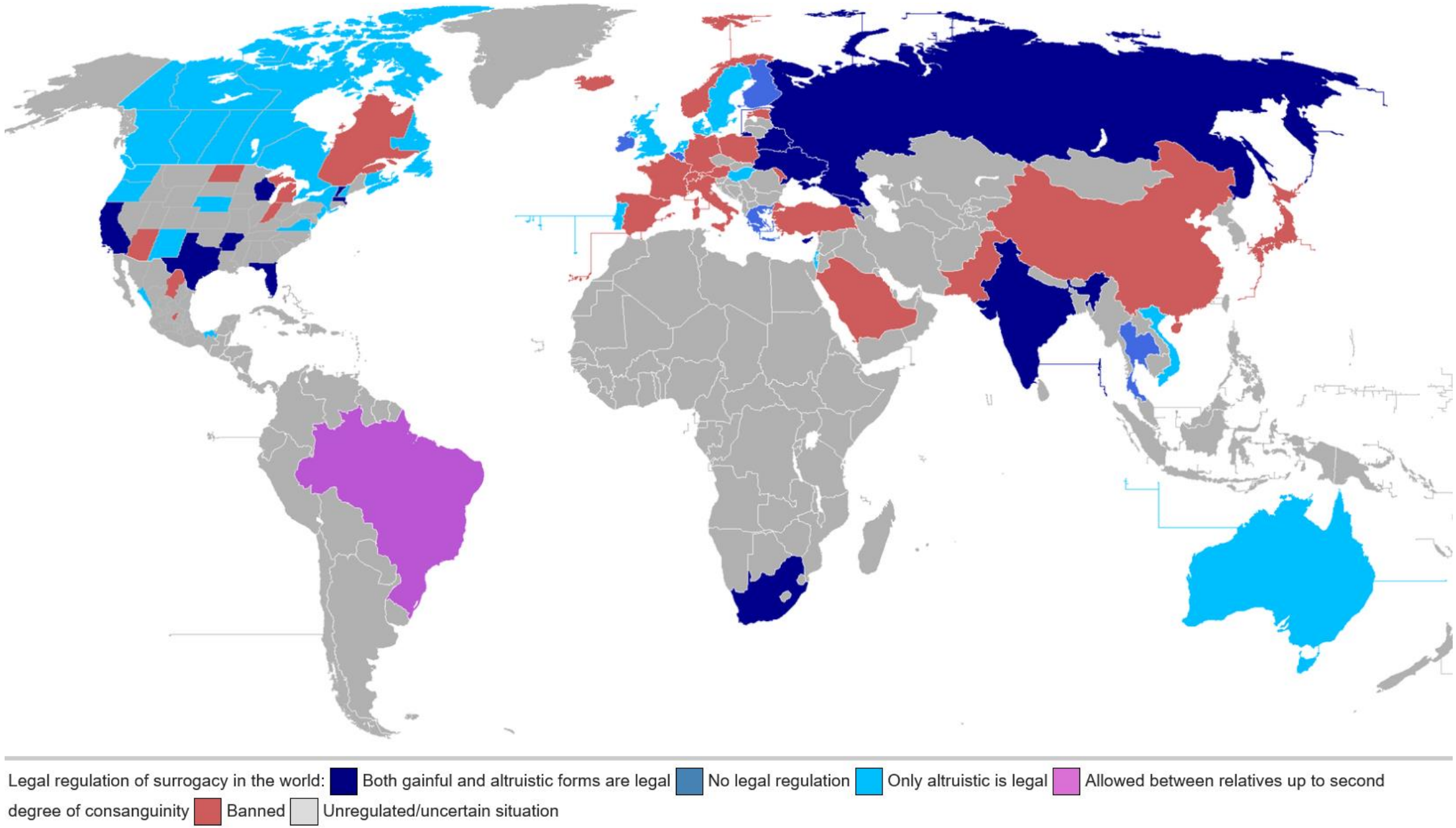


Fig. 6. Local newspaper coverage of the historical event. (Photo from the Heart of Cape Town Museum.)

January 14th, 2019

Highly Diverse Legal Situation Regarding Surrogate Mothership



Critical Areas to be Addressed

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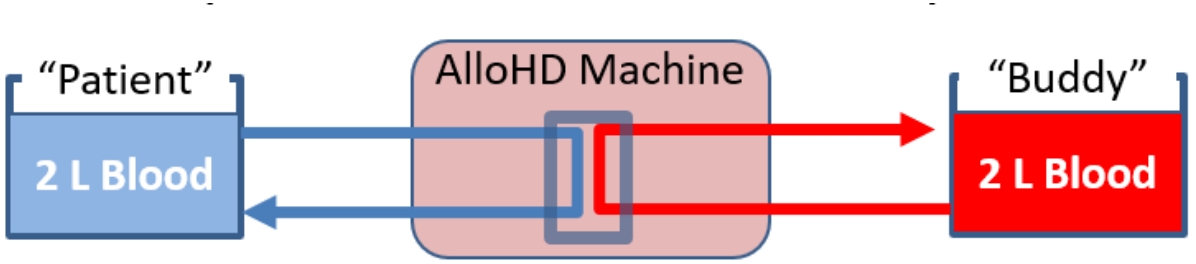
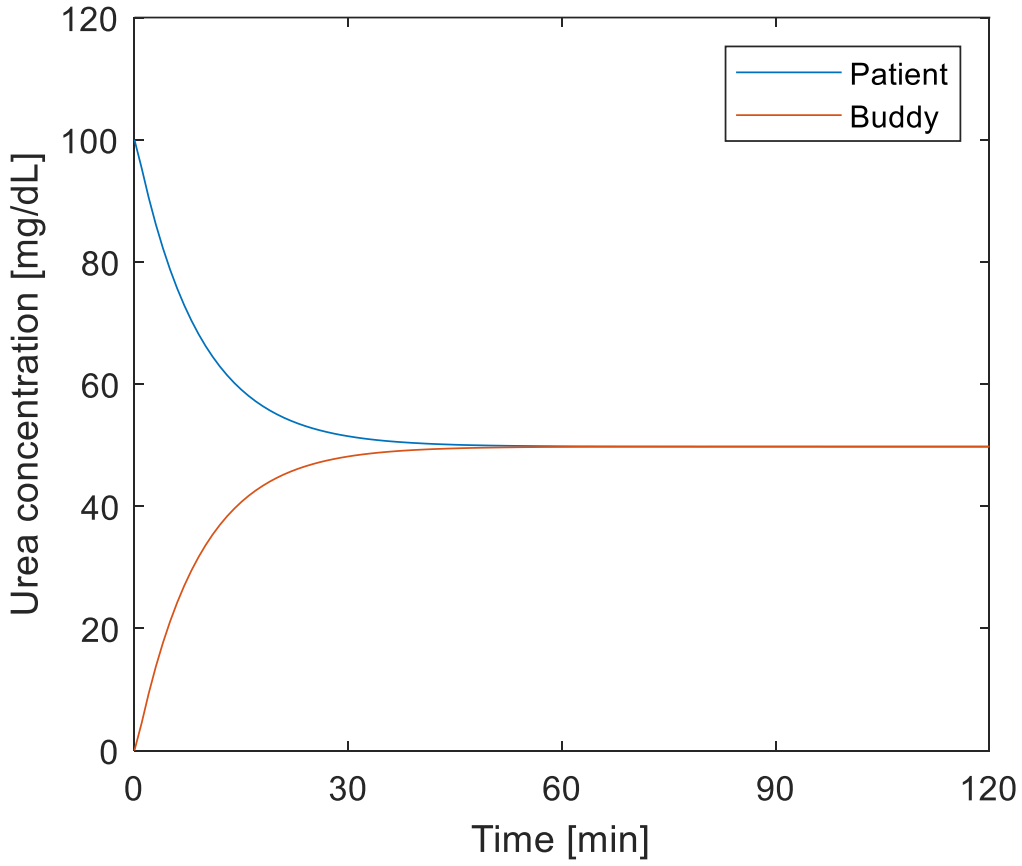
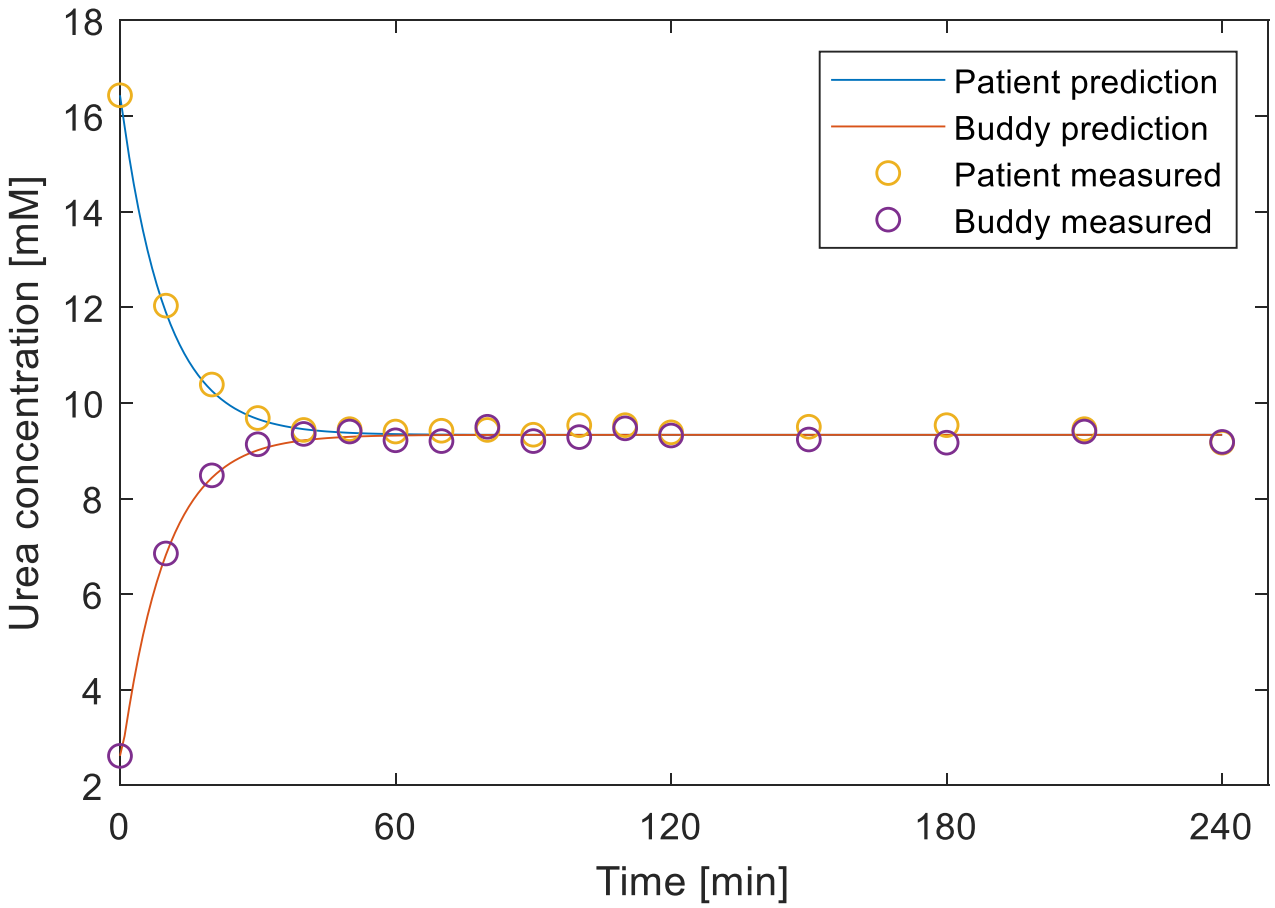
Does modeling reflect reality?



Model Predictions





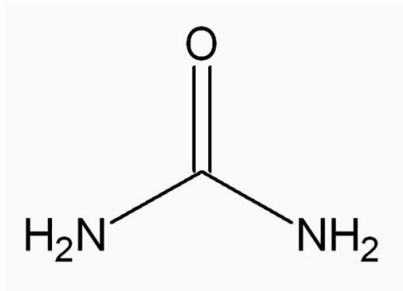
As predicted, *ex vivo* experiments show that alloHD provides clearance for all solutes tested so far

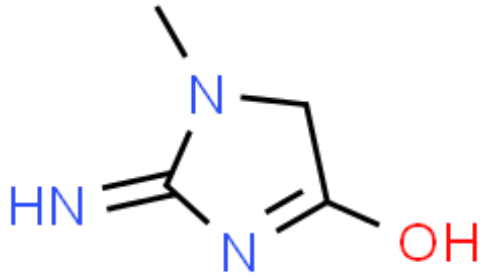
Small water-soluble molecules and electrolytes

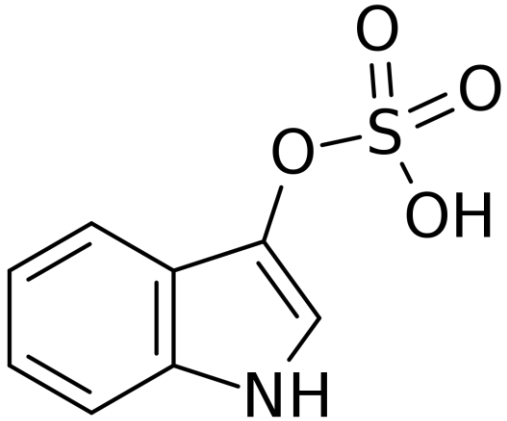
- Urea
- Creatinine
- Potassium

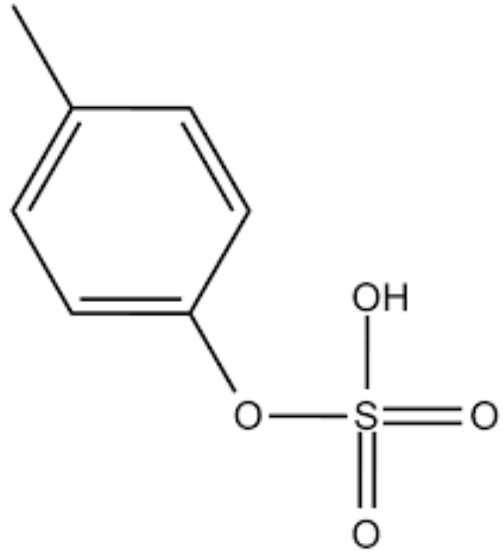
Protein-bound uremic solutes

- Indoxyl sulfate
- Para-cresol sulfate



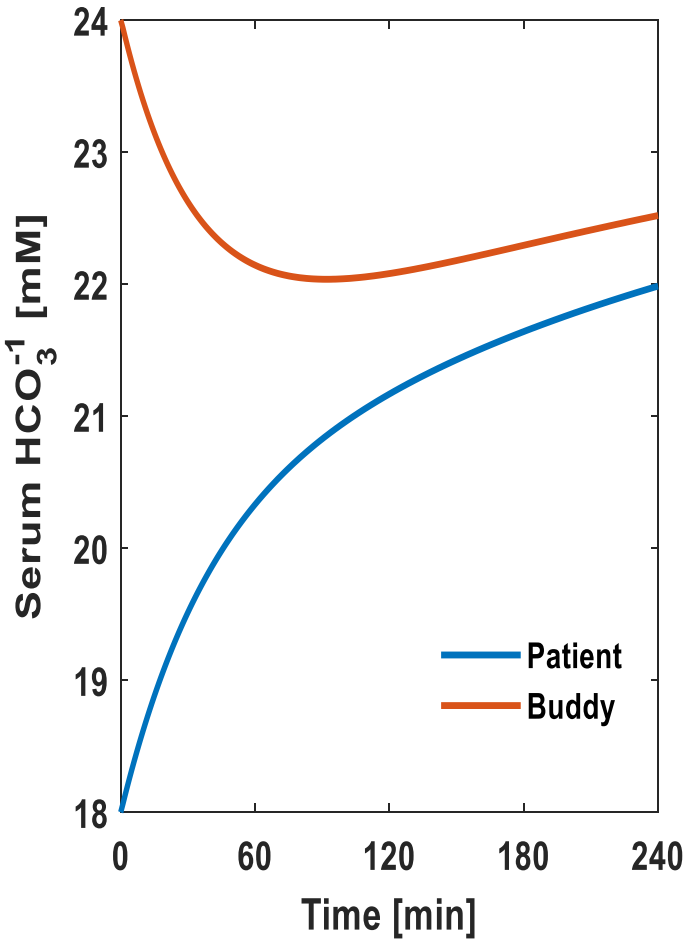


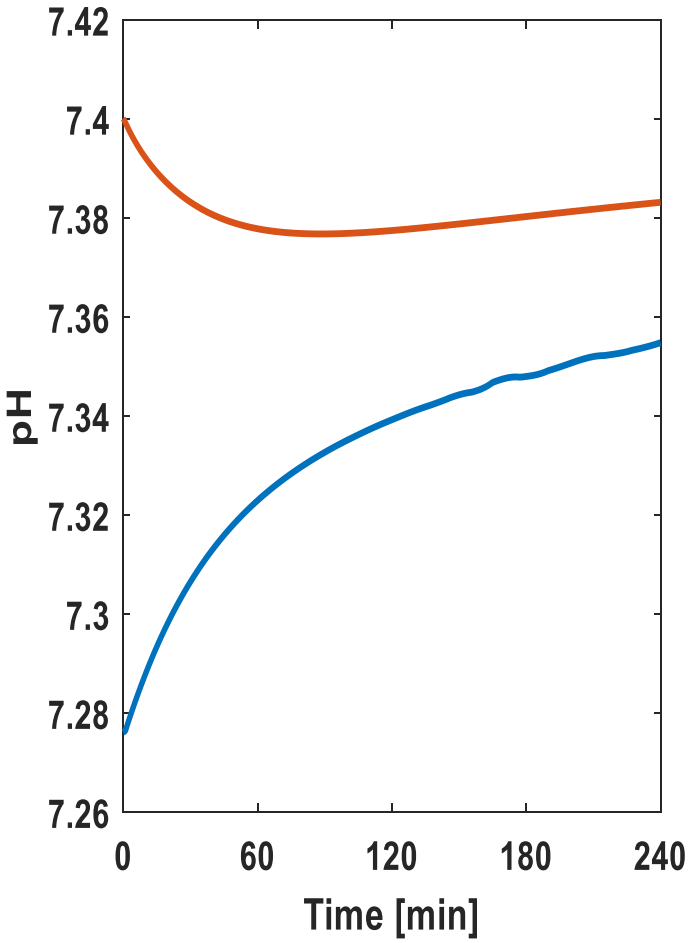


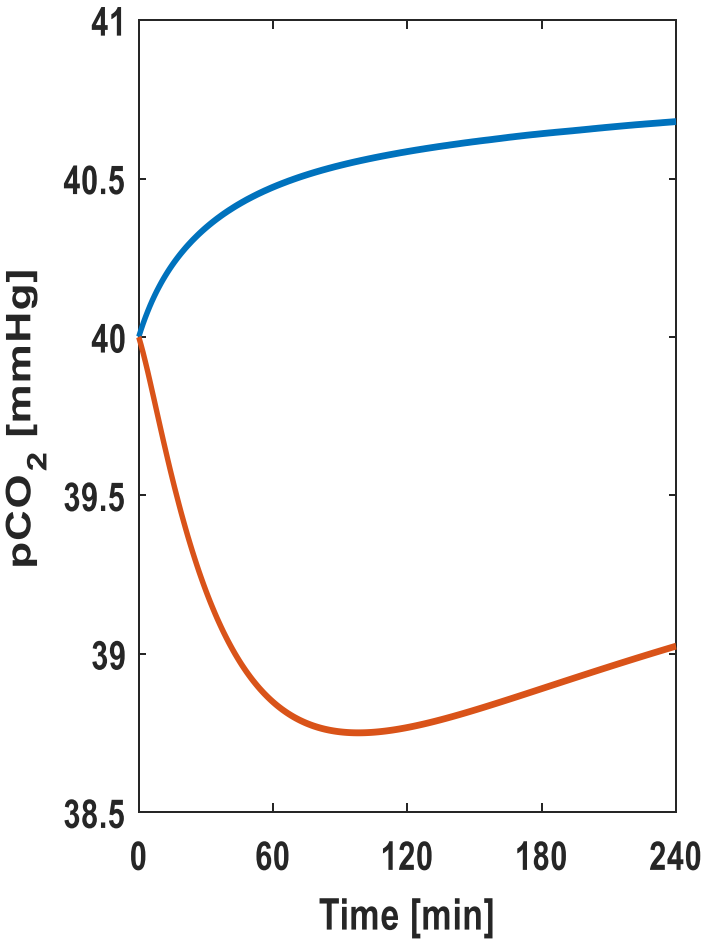


Can alloHD treat the patient's metabolic acidosis? Results from mathematical modeling indicate "yes".

V Maheshwari, A Cherif, S Thijssen, P Kotanko.







Can viruses cross the HD membranes?
Virus sizes relative to low flux membrane pore size (range 1.1 to 2.8 nm)

Virus	Minimal [nm]	Maximal [nm]	Shape
Parvovirus	20	30	icosahedrons
Picornavirus	20	30	icosahedrons
Hepatitis A	27	32	icosahedrons
Hepatitis B	42	42	icosahedrons
Hepatitis C	55	65	icosahedrons
Togavirus	60	70	polygonal
Rhabdovirus	70	190	rod-shaped (helical)
Orthomyxovirus	80	200	rod-shaped (helical)
Coronavirus	80	160	rod-shaped (helical)
Ebola	80	80	cylindrical
Retrovirus	100	120	polygonal
HIV	100	160	spherical
Dengue	105	135	icosahedrons
Paramyxovirus	150	300	rod-shaped (helical)
Herpesvirus	150	200	polygonal
Poxvirus	250	400	Ovoid/brick shaped

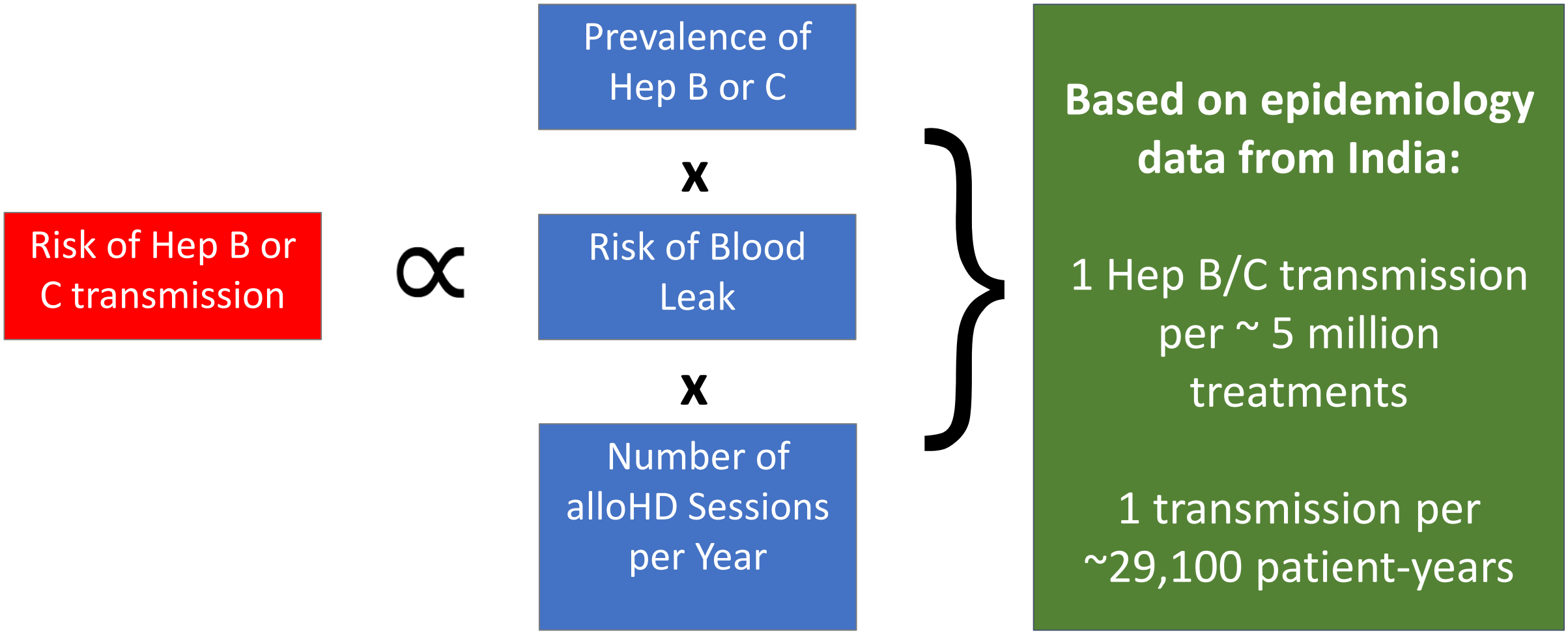
What is the Risk of Dialyzer Blood Leaks?

FDA MAUDE data base (6/2016 – 6/2019)
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.CFM

231 dialyzer blood leaks reported (external blood leaks from the dialyzer header cap and internal blood leaks combined)

This number translates into a rate of around 1.2 leaks per 1,000,000 HD sessions

Given these numbers, what are the odds for hepatitis B or C transmission in the event of a dialyzer blood leak?



Critical Areas to be Addressed

Medical

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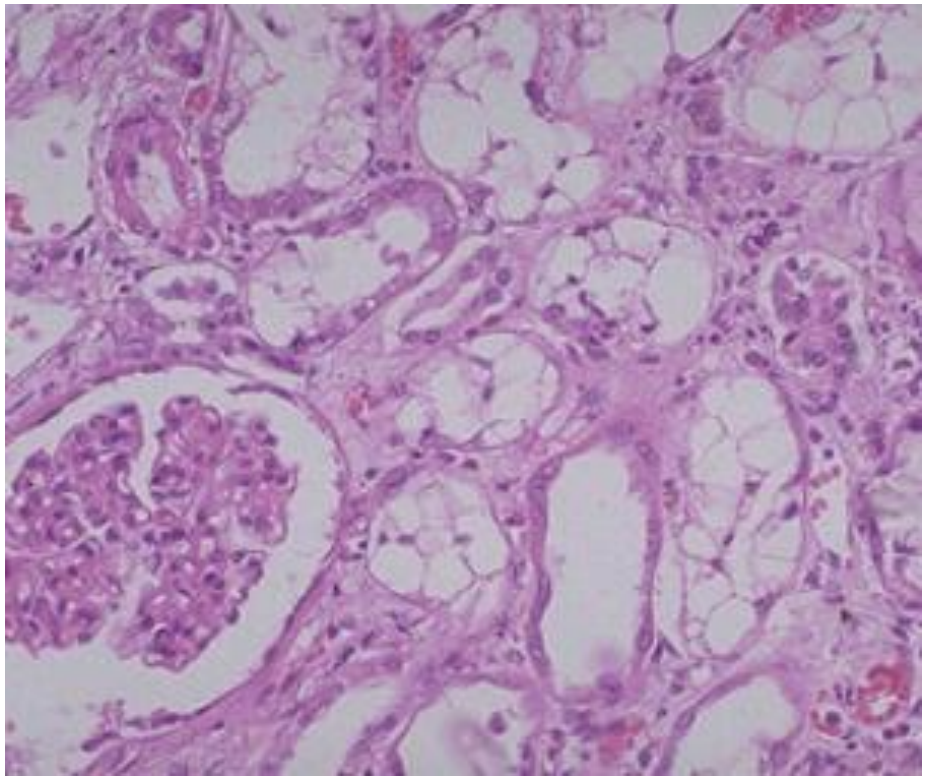
Technical

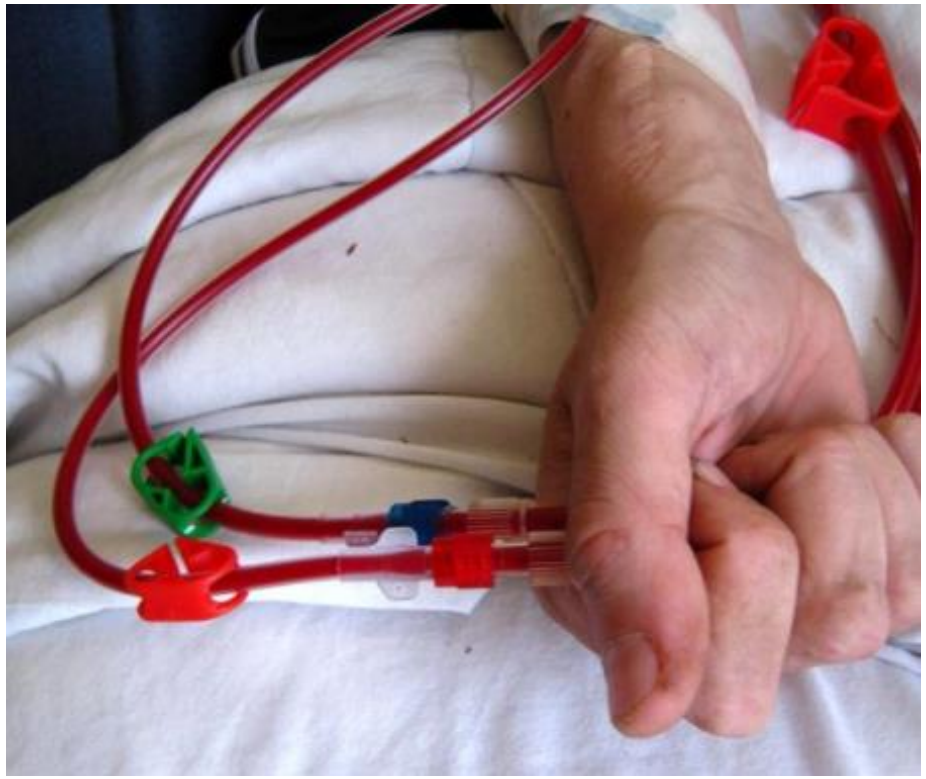
Economic & Care delivery models

alloHD Use Cases

Disasters



Acute Kidney Injury



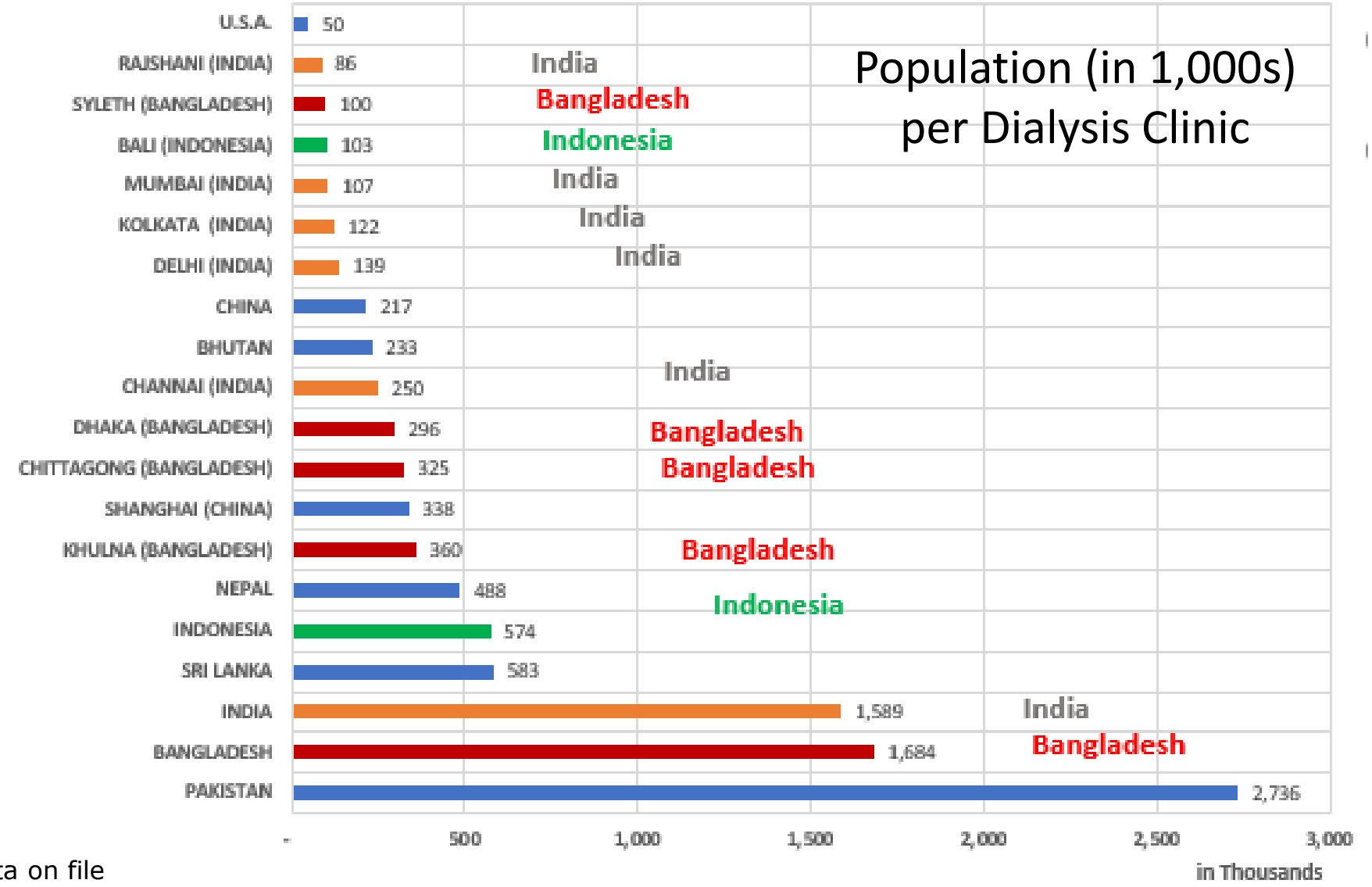
End Stage Kidney Disease

alloHD – use cases, unmet need, challenges

	Disaster		Acute kidney injury		End-stage kidney disease	
	Chronic Patient (kid/adult)	Buddy	Acute Patient (kid/adult)	Buddy	Chronic Patient (kid/adult)	Buddy
Unmet global need	100 to a few 1000 pts / year (R. Vanholder, Ghent U; pers. comm. 2/11/2018)		an estimated 1.3 to 1.7 million die annually absent dialysis (ISHD, 2018)		7+ million pts in need (GKHA 2019)	
Time horizon	Days		Days to a few weeks		Days (bridging) to years	
Vascular access	Venous/AVFG	Venous	Venous	Venous	Venous/AVFG	Venous/AVFG
Physiological adaptation of the buddy	minor		minor		electrolytes solutes, fluid hemodynamic	electrolytes solutes, fluid hemodynamic
Medical concerns	Insufficient clearance / fluid removal	Access creation; Infection	Insufficient clearance / fluid removal	Access creation; transfer of toxic agent(s); infection	Insufficient clearance / fluid removal	Intervention (access); infection; hemodynamic (AVFG)
Ethical concerns	minor		minor		major	

Venous: any venous access that allows sufficient blood flow (needs vary by patient size) e.g. central, femoral, peripheral

Need for Local Solutions: Notable Variability of Dialysis Availability Within and Between Countries



Multiple sources, data on file

Mathematical model of ESKD patient growth in a hypothetical city of 150,000 population with and without kidney replacement therapy (KRT)

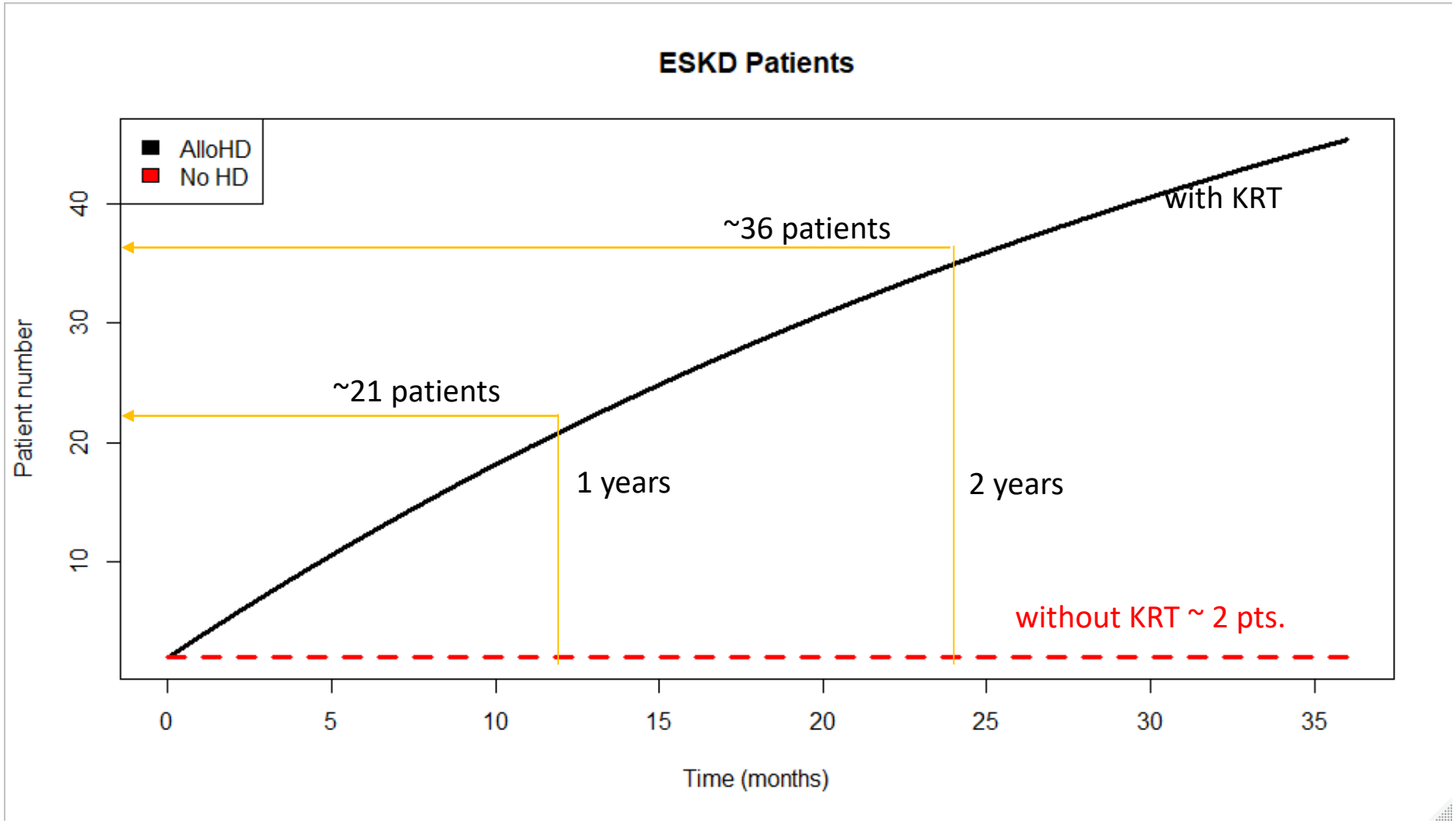
Model assumptions

Population: 150,000

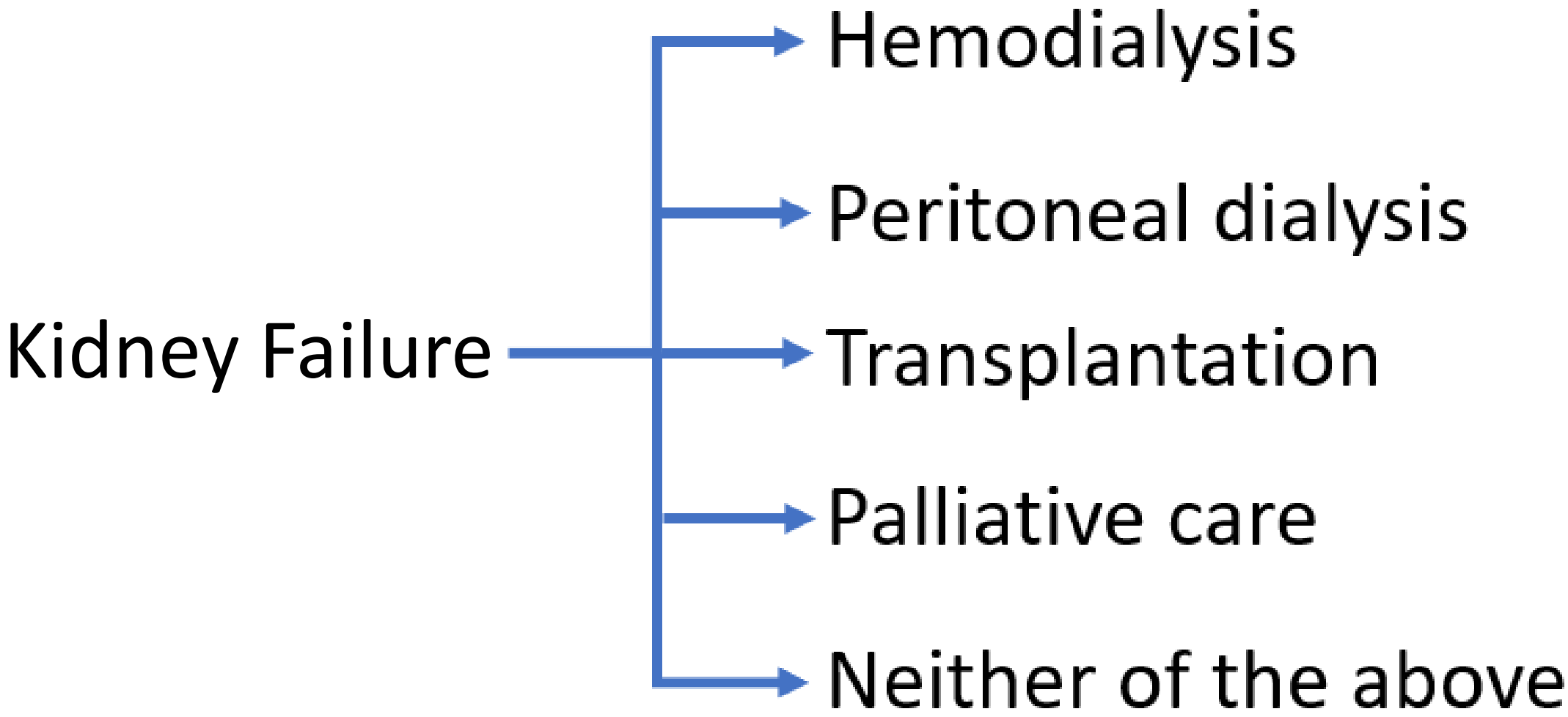
ESKD incidence: 150 per million / year

Mortality rate without KRT: 90% / month

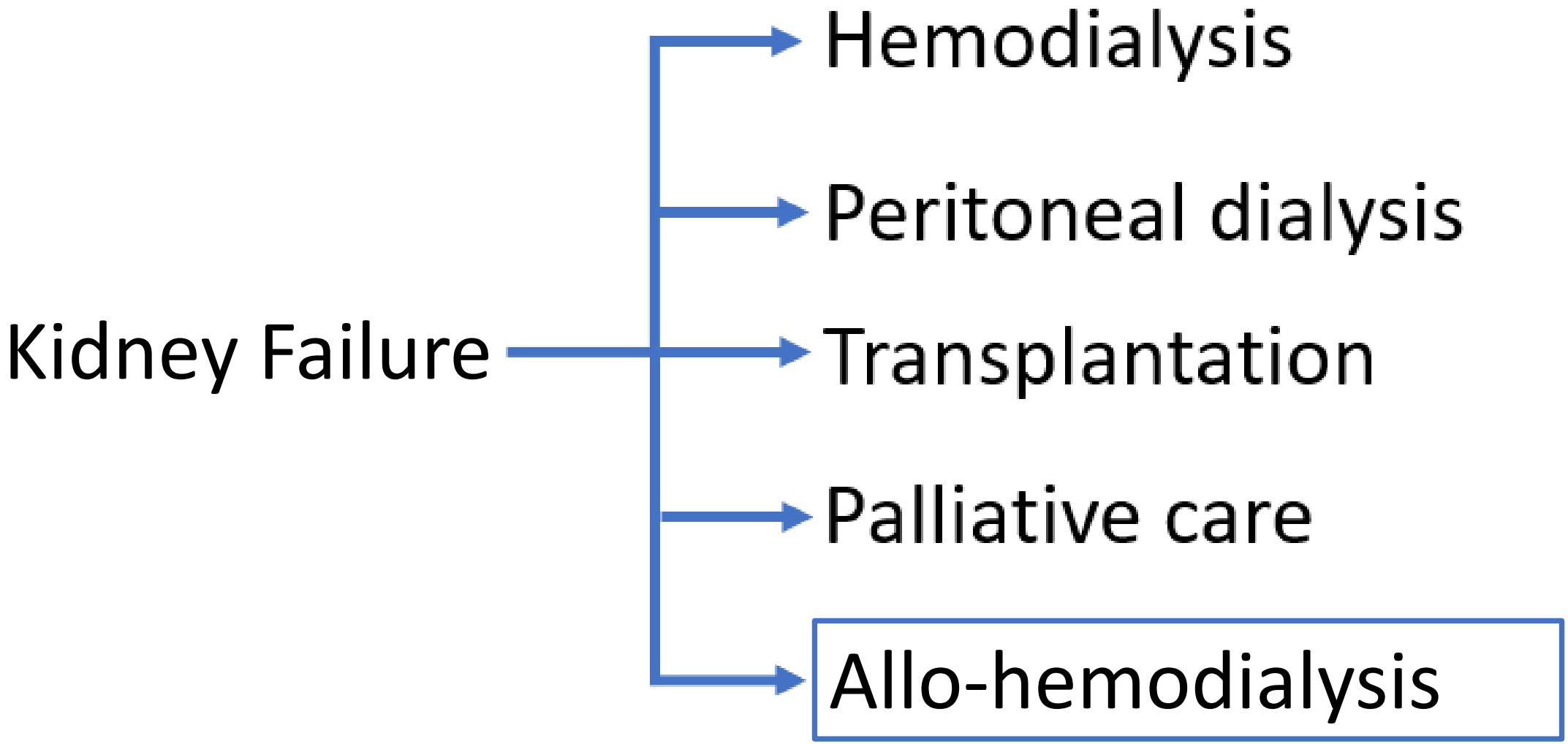
Mortality rate with alloHD: 30% / year



What are the Options?



The goal is to increase choices for patients, families, communities, and health care providers



Summary: AlloHD - Intermittent Donation of Kidney Function

- Globally, millions of patients die prematurely every year because they have no access to KRT; the number is projected to increase over the next 10 years.
- AlloHD has received an encouraging reception by nephrologists, a medical ethicist, and care givers.
- No insurmountable medical or technical problems identified
- Animal studies (pigs) will start shortly
- Strong interest in clinical studies in India and Bangladesh
- Use cases, care delivery, economic models, and societal impact warrant in-depth analysis and need to consider local circumstances
- Other use cases (e.g. severe neonatal jaundice) are being explored

The alloHD Team

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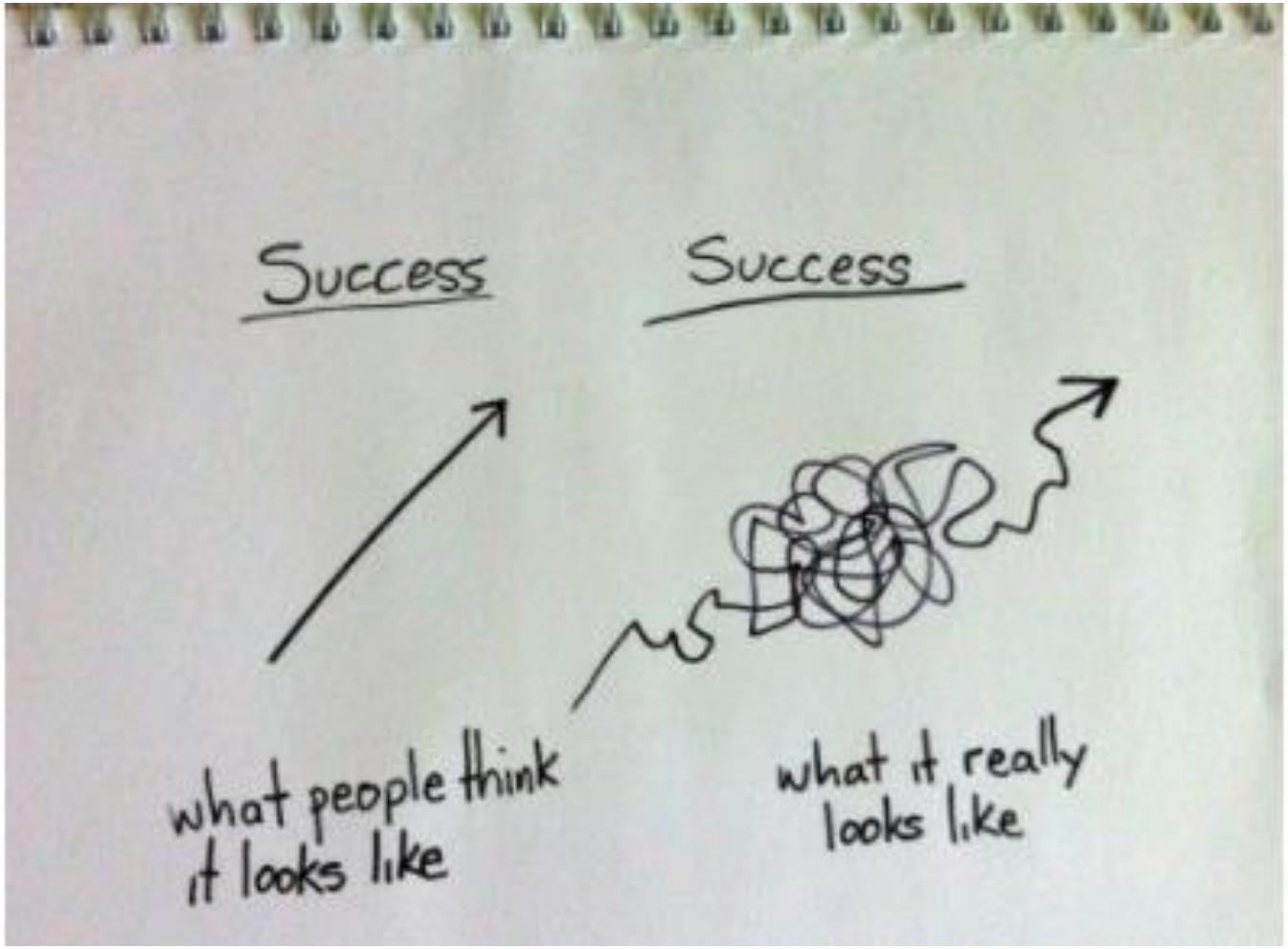
<u>Nephrology Community</u>

Over 100 nephrologists from 20+ countries provided important feedback



Herzlichen Dank für Ihre Aufmerksamkeit!

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