Renal Replacement Therapy

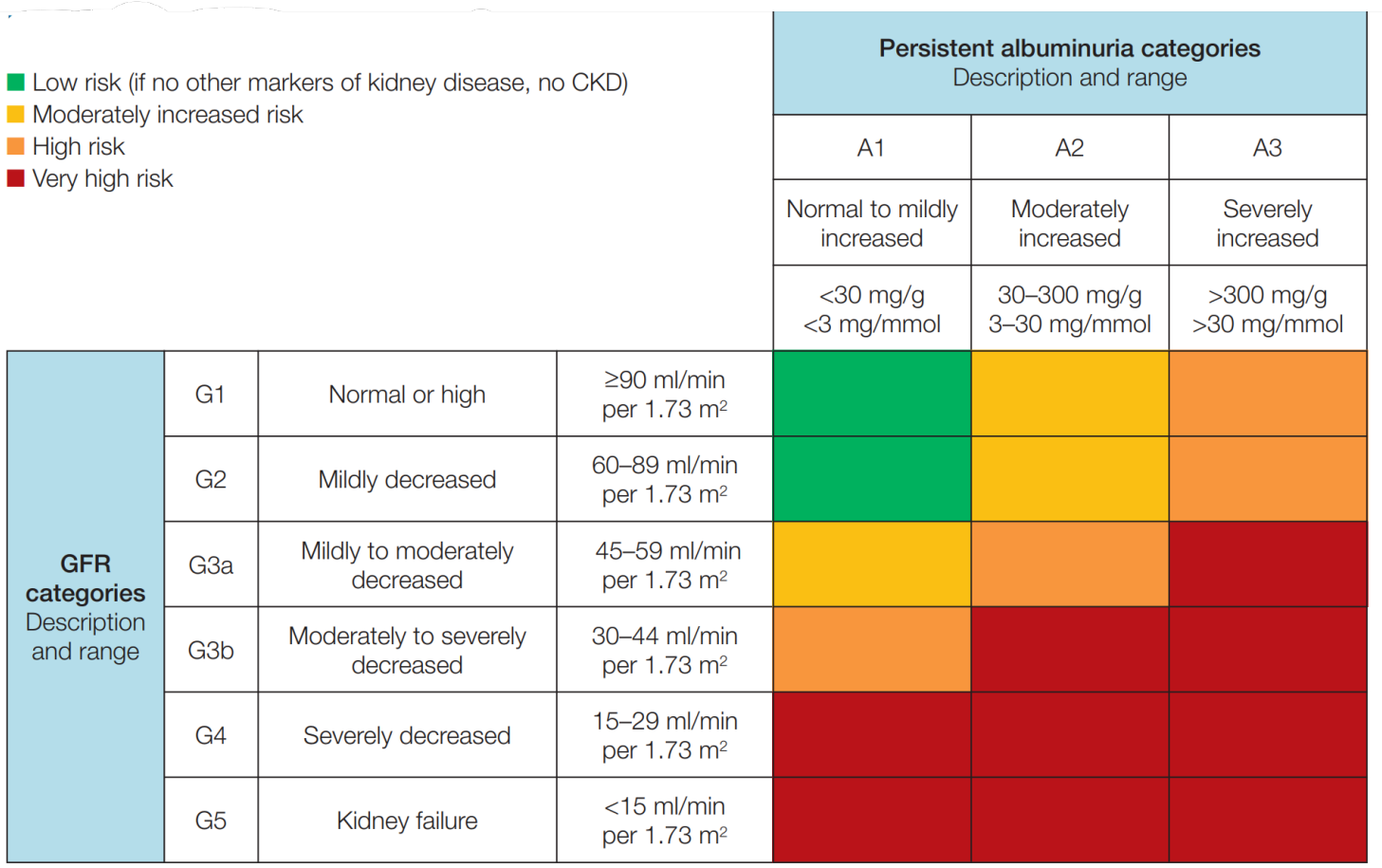
Short timeline

- 1923 – First human PD
- 1924 – First human HD
- 1933 – First (**unsuccessful**) cadaveric kidney transplant
- 1946 – PD used to treat AKI
- 1948 – HD used to treat AKI in the Korean war
- 1954 – First successful monozygotic twin transplant (Nobel prize in 1990)
- 1960 - First long-term HD patients (Seattle, USA)

Kidney functions

- Remove excess salt, water, and acid.
- Remove or regulate other electrolytes (e.g. K^+, Ca^{2+}, Mg^{2+}, PO_4).
- Remove waste products of metabolism (Ur and Cr are measured routinely, but there are many others).
- Make erythropoietin.
- 1α-hydroxylate (and therefore activate) vitamin D

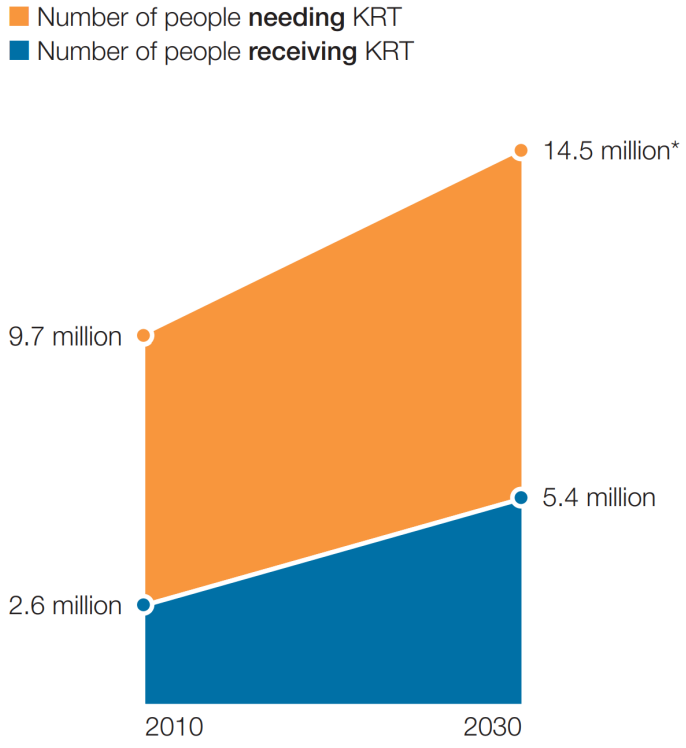
KDIGO CKD Classification

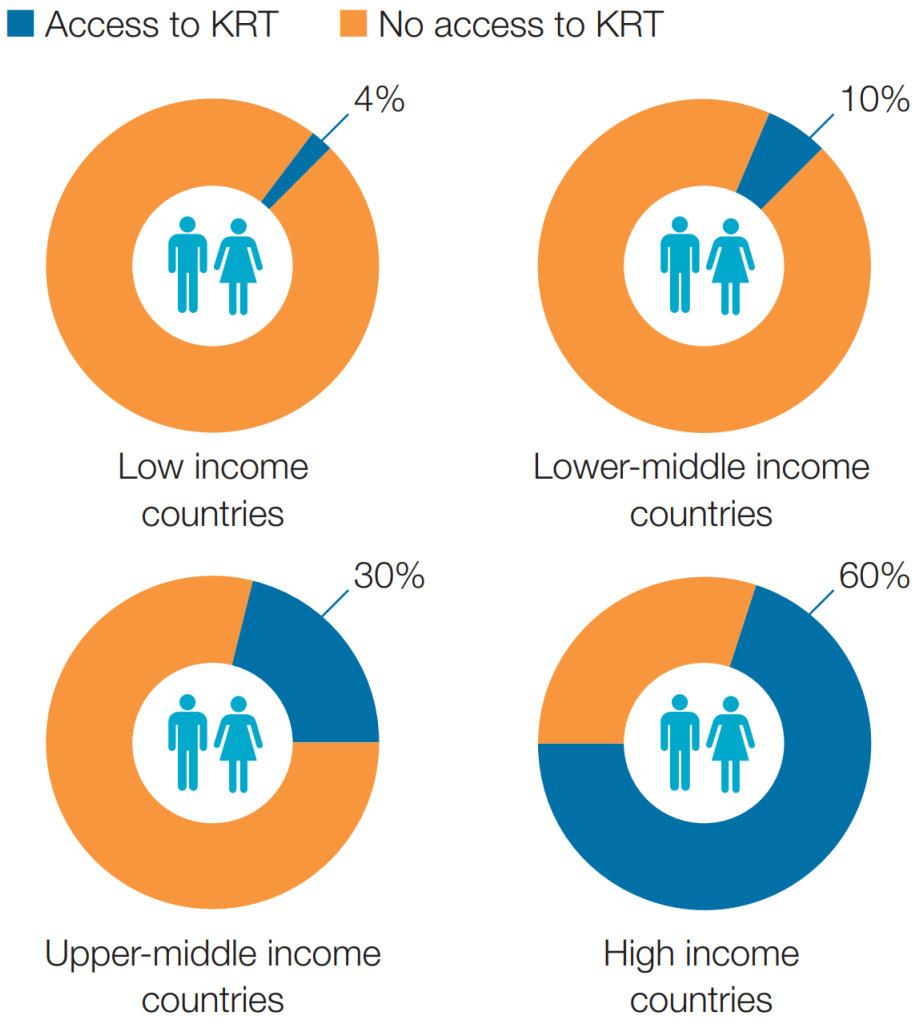


- Low risk (if no other markers of kidney disease, no CKD)
- Moderately increased risk
- High risk
- Very high risk

				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories Description and range	G1	Normal or high	≥90 ml/min per 1.73 m^2			
	G2	Mildly decreased	60–89 ml/min per 1.73 m^2			
	G3a	Mildly to moderately decreased	45–59 ml/min per 1.73 m^2			
	G3b	Moderately to severely decreased	30–44 ml/min per 1.73 m^2			
	G4	Severely decreased	15–29 ml/min per 1.73 m^2			
	G5	Kidney failure	<15 ml/min per 1.73 m^2			

The state of RRT need and access





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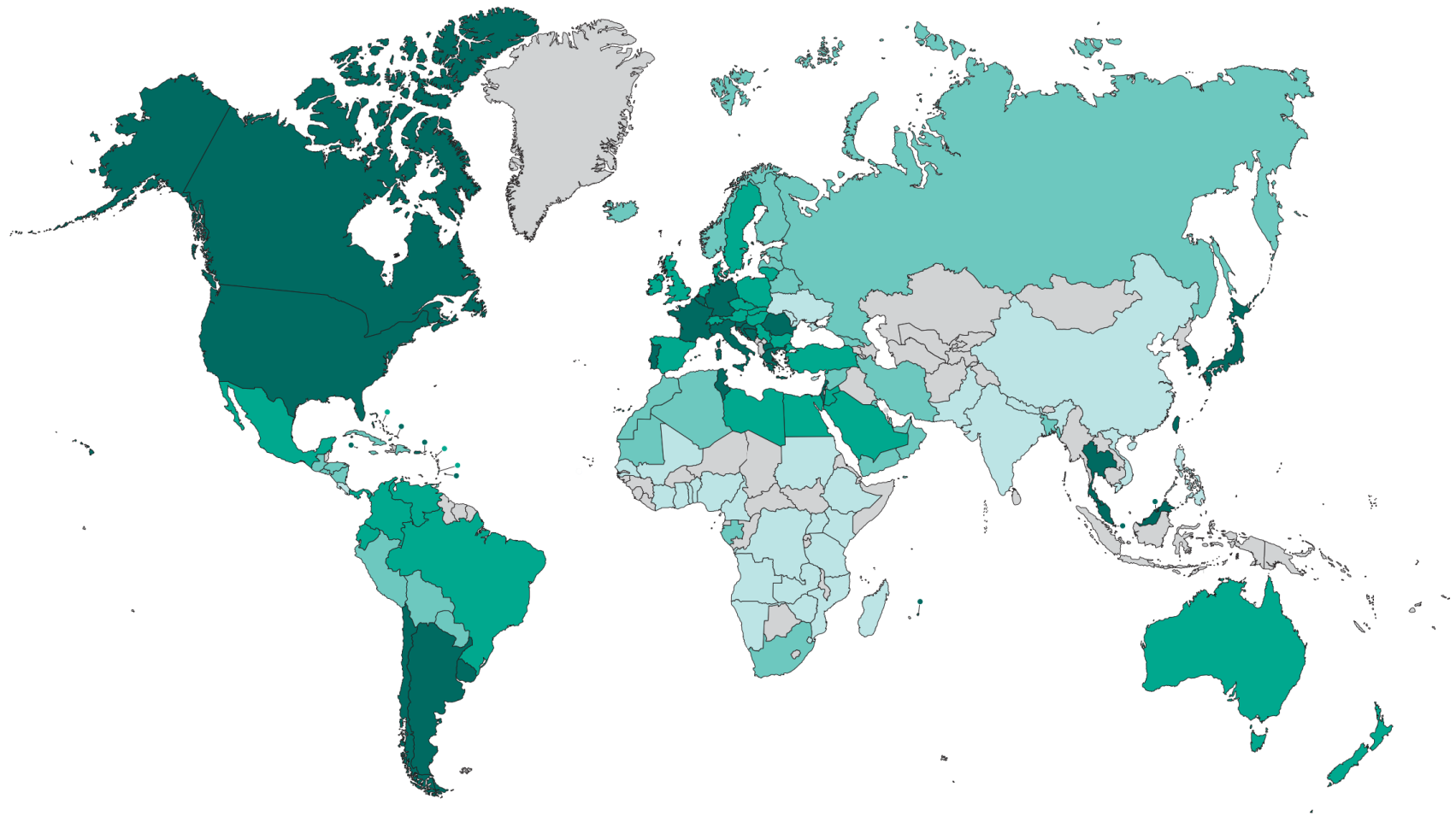
3 main types of RRT

1. Hemodialysis
2. Peritoneal dialysis
3. Renal transplant

Global prevalence of chronic HD

Rate per million population (pmp), age ≥ 18 years



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Urgent Indications for RRT in AKI

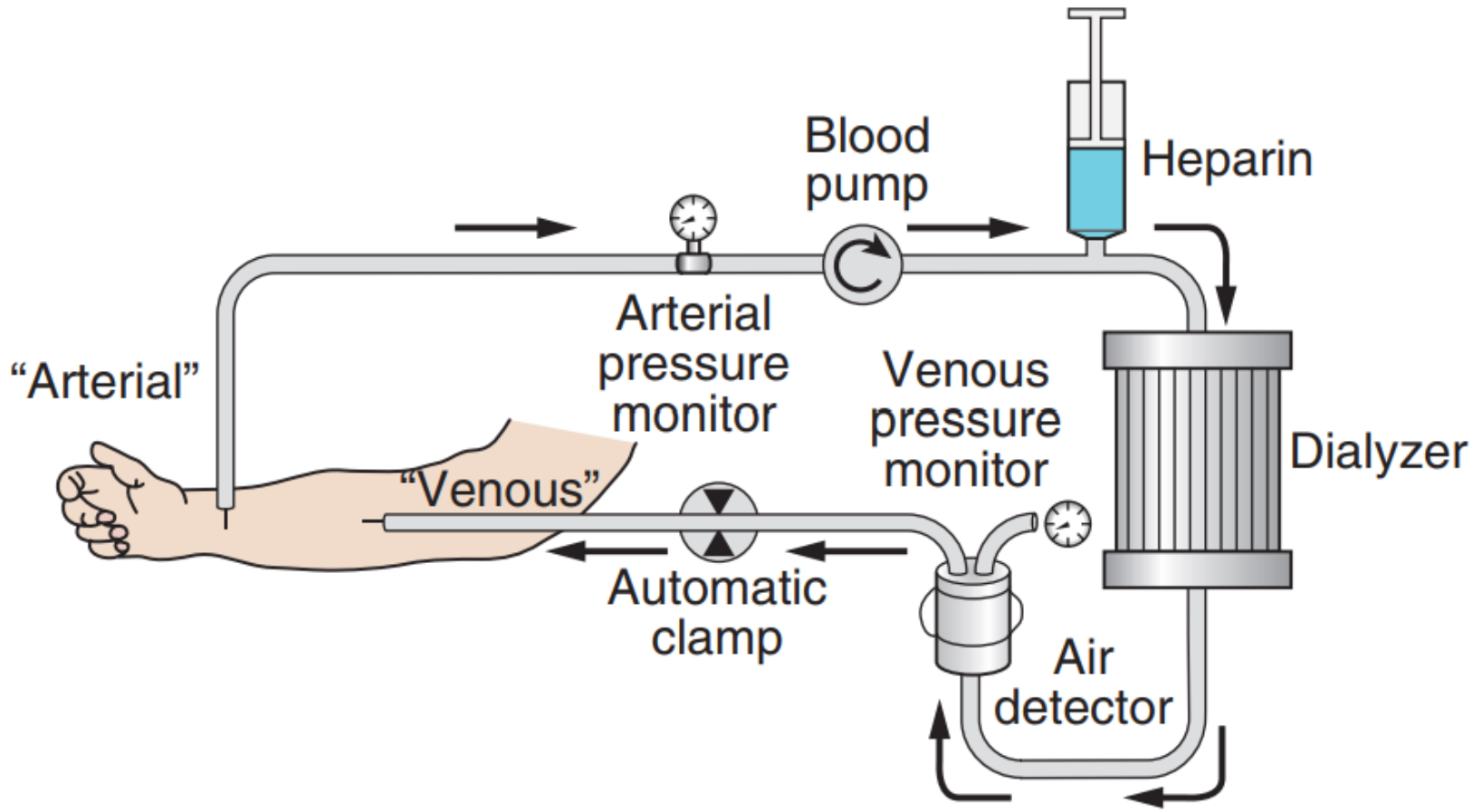
- Refractory fluid overload
- Severe hyperkalemia (plasma potassium concentration >6.5 mEq/L) or rapidly rising potassium levels
- Signs of uremia, such as pericarditis, encephalopathy, or an otherwise unexplained decline in mental status
- Severe metabolic acidosis (pH <7.1)
- Certain alcohol and drug intoxications

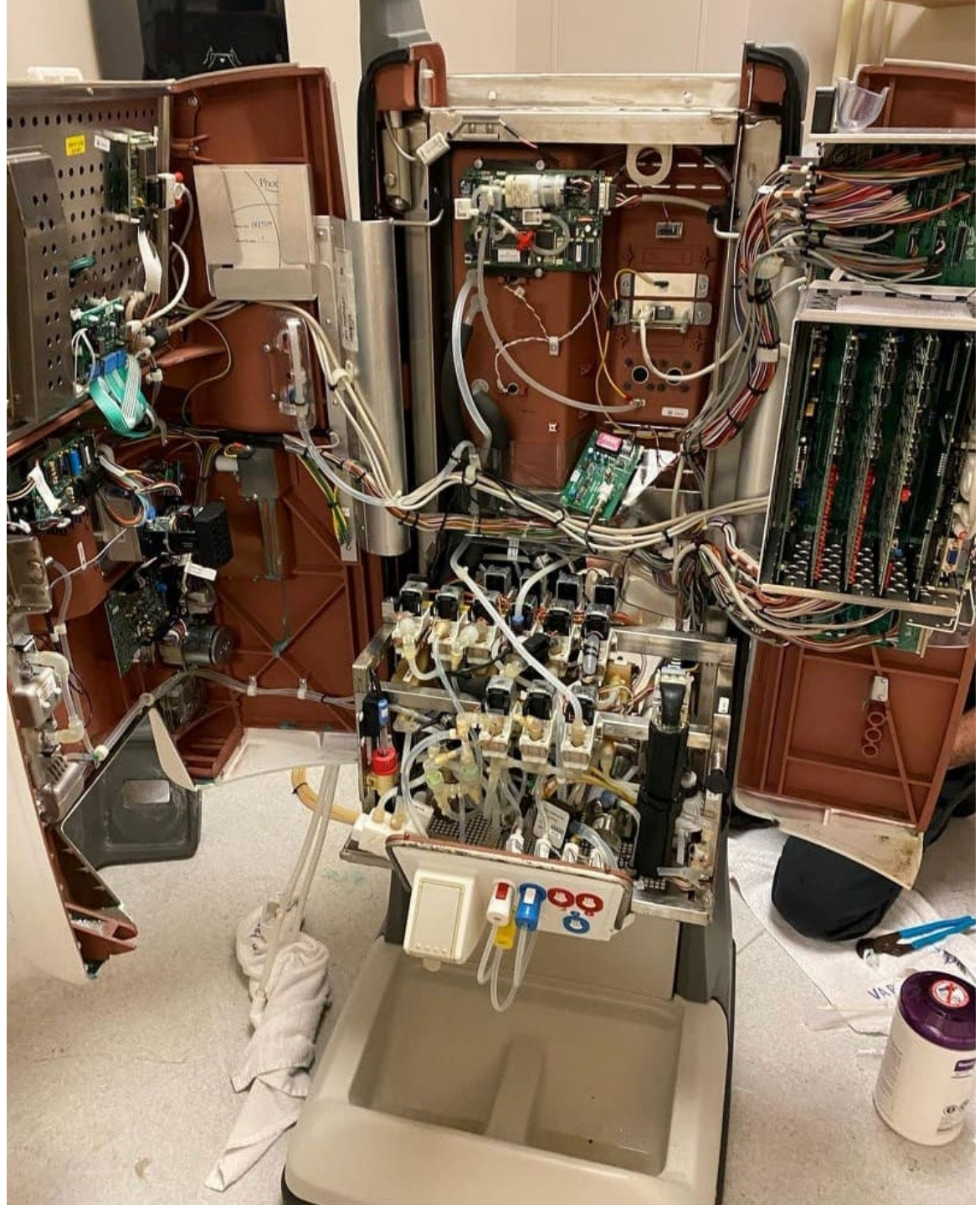
Hemodialysis

- During dialysis, blood is exposed to dialysate (with physiological concentrations of electrolytes) across a semi-permeable membrane
- Small molecules such as Urea, Creatinine and electrolytes pass through pores in the membrane. Large molecules such as albumin, IgG and blood cells do not.
- Concentration differences across the membrane allow molecules to diffuse down a gradient. This allows waste products to be removed and desirable molecules or ions (e.g. $HCO3–$) to be replaced.

What is required for hemodialysis?

- Dialysis membrane: a biocompatible membrane with adequate surface area/permeability for solute clearance and ultrafiltration
- Dialysate: of sufficient purity and containing the required concentration of electrolytes.
- Vascular access: large volumes of blood are removed from a patient, exposed to a dialysis membrane, and then returned. Options are:
  - AV fistulas – optimal form of vascular access
  - PTFE graft – second best
  - Tunneled, cuffed central venous catheter
  - Temporary central venous catheter – for immediate use.
- Anticoagulation: prevents blood clotting in extracorporeal circuit


Blood pump
Heparin
Arterial pressure monitor
"Arterial"
Venous pressure monitor
Dialyzer
"Venous"
Automatic clamp
Air detector



Dialysate

- A solution of ultrapure water, Na^+ (132 – 150mmol/L), K^+ (usually 1.0 – 3.0mmol/L), Ca^{2+} (1.0 – 1.25mmol/L), Mg^{2+}, Cl^-, dextrose, and buffer
- Ultrapure water is generated in a treatment plant
- HD machines either mix dialysate concentrate, buffer, and water for the individual patient or this is done centrally before distribution around several machines.

Dialysers and membranes

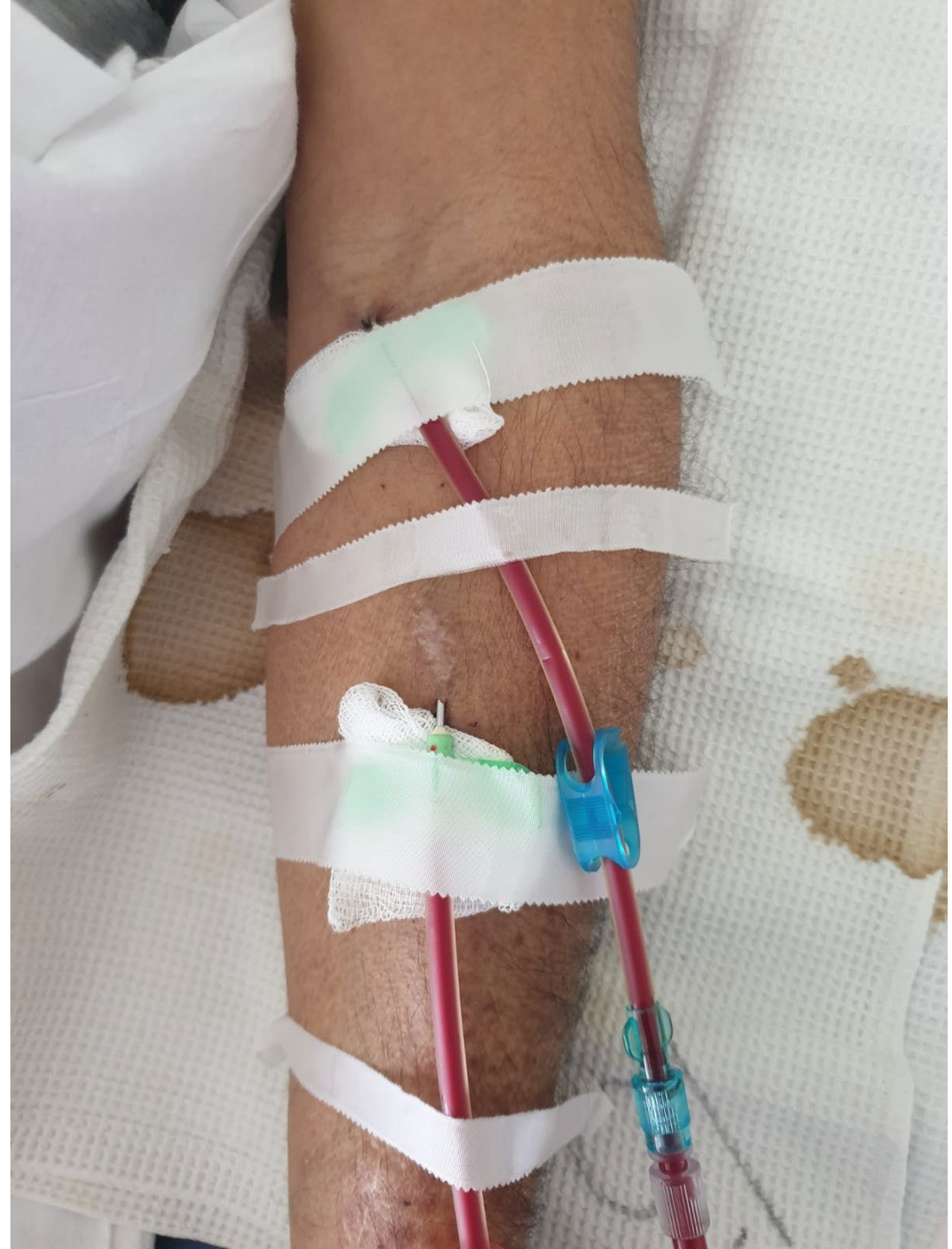
- *Cellulose membranes (e.g. Cuprophan®)*
  - The original membrane and least biocompatible
  - Largely superseded by synthetic membranes
- *Modified cellulose (e.g. Hemophan®)*
  - More biocompatible.
- *Synthetic membranes (e.g. Polysulfone®, polyamide, polyacrylnitrile)*
  - More recently developed.
  - Most biocompatible.
  - More permeable than cellulose membranes:
    - Solute clearance similar to cellulose membranes.

Anticoagulation

- Unfractionated heparin
  - Mixture of glycosaminoglycans between 3 and 30 kDa.
  - Highly negatively charged.
  - Indirect thrombin inhibitor.
  - Narrow therapeutic window and highly variable dose response.
  - Metabolized in the liver and by vascular endothelial heparinases.
  - No single dosing protocol but usually single bolus 1,000 – 2,000 IU, followed by infusion of 1,000 – 1,500IU/h.
  - Adjust if weight <50kg or >90kg
  - Monitor using activated clotting time (ACT) at the bedside.
  - Short half-life and fully reversible with protamine.
- Low molecular weight heparin
  - Smaller molecules, typically 4 – 5kDa.
  - Different preparations have variable lengths, weights, and charges (enoxaparin least ‘ heparin-like ’ , tinzaparin most).
  - Primarily work through inhibiting factor Xa.
  - Predominantly renally clearly, therefore increased half-life in ESRD.
  - Tinzaparin, commonly used at doses of 2,500IU or 3,500IU, is considered safe and effective. Enoxaparin (e.g. 10–40mg) is used in many centres.
  - Monitor using anti-Xa activity, aiming <0.4IU/mL (historically slow turnaround in results, but now usually available in 90–120mins.

Dialysis vascular access

- Very important for HD therapy.
- AV fistula
  - Requires surgical anastomosis of an artery and a vein (under LA or GA)
    - at the wrist (radiocephalic)
    - elbow (brachiocephalic, brachiobasilic).
  - Maturation for 6–8 weeks (minimum) is required prior to needling
- Polytetrafluoroethylene (PTFE) graft
  - A synthetic graft is interposed between an artery and a vein
  - Useable within days, but thrombosis and infection (usually necessitating removal) are problematic.
  - Half-life shorter than an AVF



Fistula care: what every doctor and patient should know

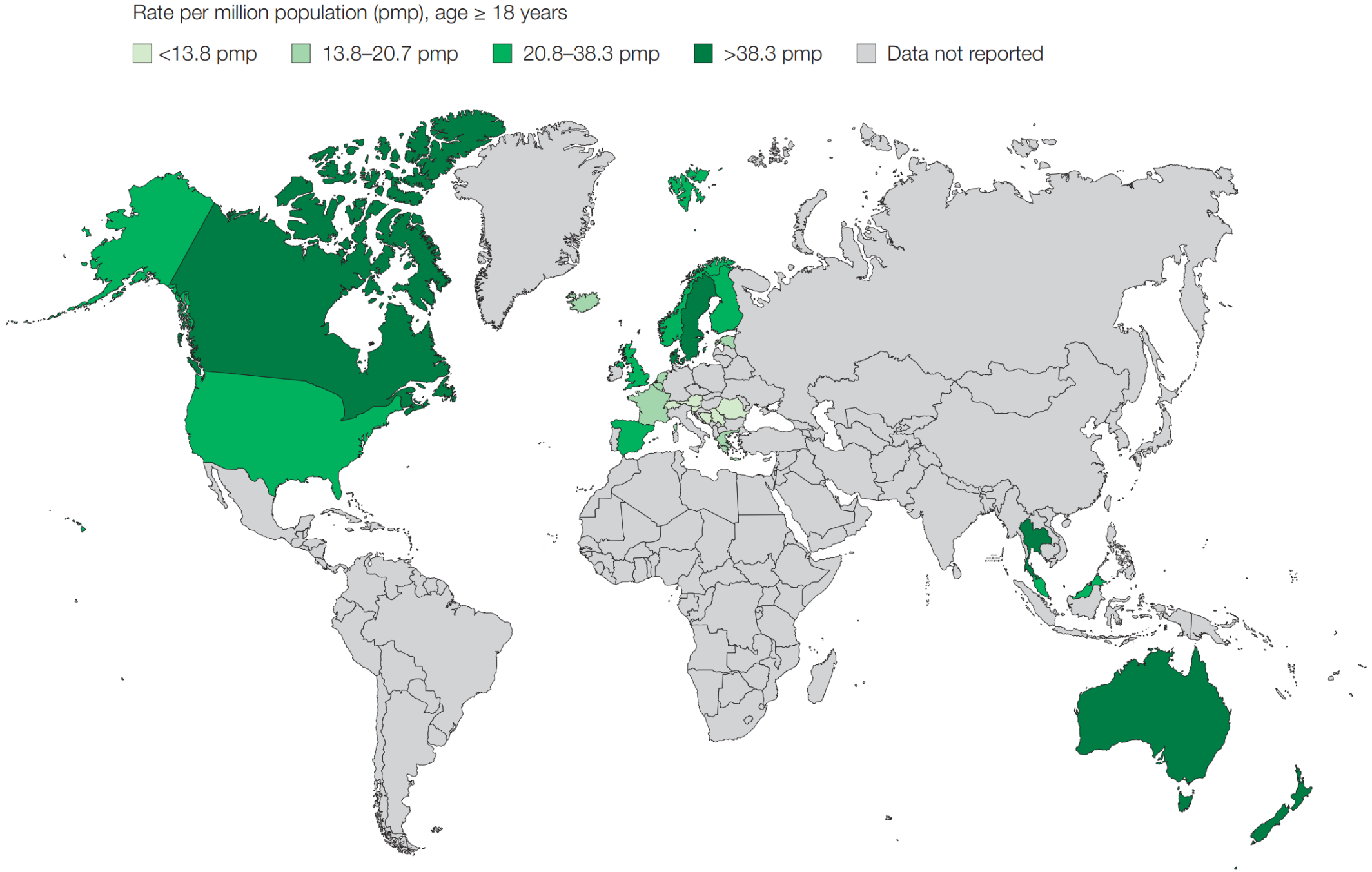
- Dialysis access is extremely precious
- Arm veins should be preserved in pre-dialysis patients (no IV cannulae between elbow and wrist).
- Needling should only be carried out by a trained operator (usually a dialysis nurse, ideally the patient).
- ***Never*** put a tourniquet or BP cuff on a fistula arm.
- Do not use a fistula to take blood.
- Hypotension (and volume depletion) → ↑ thrombosis risk
- ↑ Hct (too much ESA) predisposes to thrombosis. Keep within recommended guidelines and at the lower end of these, if at risk.
- A clotted fistula or graft requires immediate attention (time to declotting is a major determinant of success).

Management of dialysis patients on non-renal wards

- Many dialysis patients are oligo-anuric, so DO NOT routinely administer IV fluids (unless the patient is hemodynamically compromised—if so, use small boluses, assess volume status regularly and call for expert help).
- DO NOT give K+ supplementation. Discuss with renal team if being considered.
- DO NOT place a urinary catheter unless there is a clear urological indication. Oligo-anuria is virtually universal in this patient group!
- If the patient is clinically overloaded inform the renal team immediately, as the patient may require urgent dialysis
- When considering any new medication, check whether the drug is safe in ESRD and if a dose adjustment is required.
- Does the patient have an AVF? NEVER insert an IV cannula into a fistula arm. The back of the hand on the non-fistula arm is the best site
- If patient has a dialysis central venous catheter (CVC), it should not be used for anything else but HD

HD complications

- Acute
  - Cramps
  - Nausea and vomiting
  - Headache
  - Hemolysis
  - Clotting of extracorporeal circuit
  - Air embolism
  - Disequilibrium
    - Caused by high blood urea levels being reduced too rapidly. Usually occurs during first dialysis session.
  - Blood leak
- Chronic
  - Cardiovascular disease
    - 20x more likely to die due to CV disease compared to general population
  - Vascular calcification
  - Malnutrition
  - Aluminium toxicity
  - Amyloidosis



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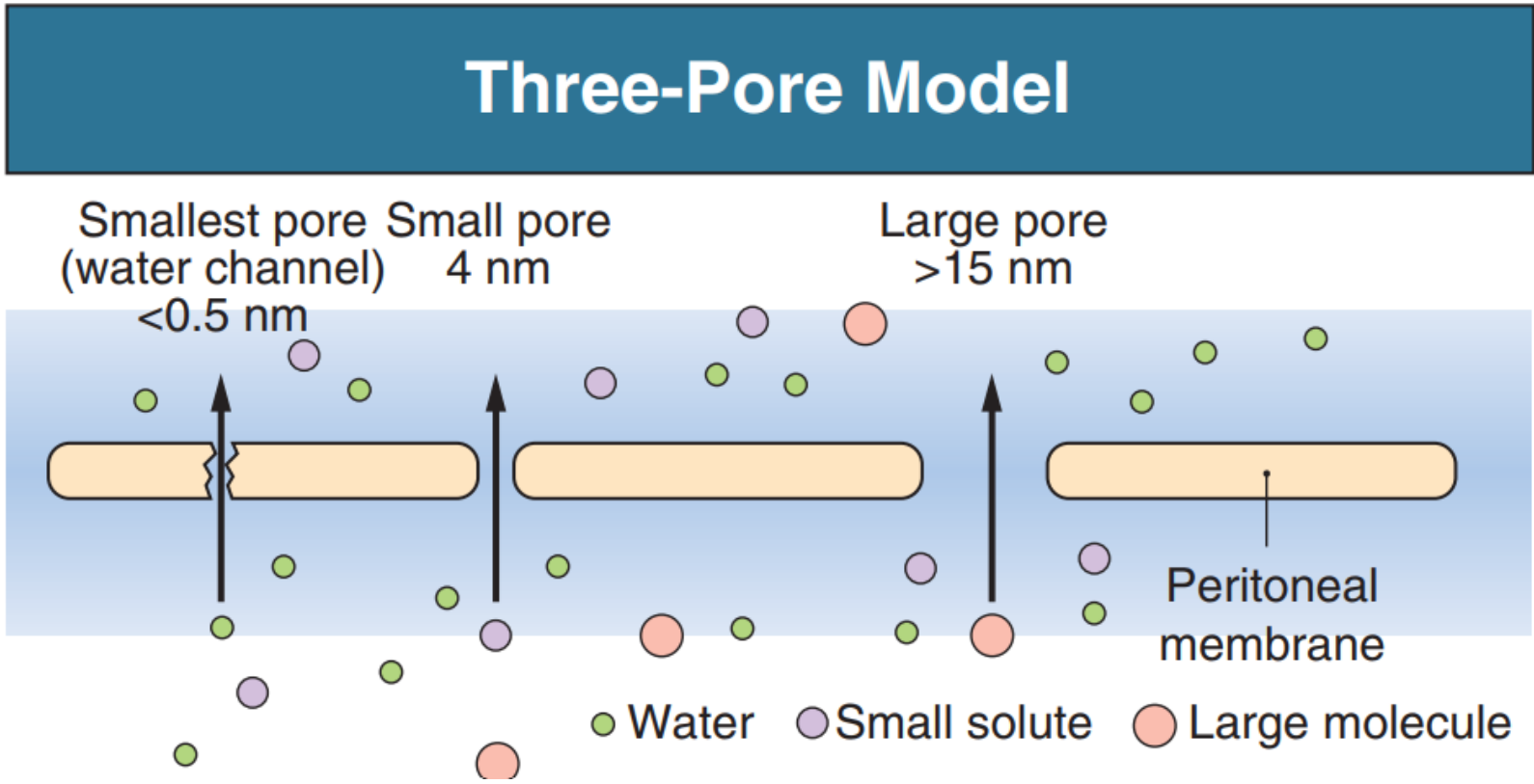
Advantages of PD

- Preservation of residual renal function.
- No need for vascular access
- Mobility (e.g. easy to transport dialysis to holiday destinations).
- Patient engagement in treatment.
- Home-based therapy — maintains patient independence.
- Less expensive than HD.
- Less risk of transmission of blood-borne viruses

Peritoneum dialysis mechanism

- The semi-permeable dialysis membrane of the peritoneum comprises the capillary endothelium, supporting matrix, and peritoneal mesothelium.
  Fluid and solutes move between the fluid-filled peritoneum and blood via, what is termed, the ‘ three-pore model ’ of PD
  - *Large pores (20 – 40nm)*: allow macromolecules, such as proteins, to be filtered between compartments (effectively via venular or lymphatic absorption).
  - *Small pores (4 – 6nm)*: responsible for the transport of small solutes, such as sodium, potassium, urea, and creatinine.
  - *Ultrasmall pores (<0.8nm)*: transport water alone (shown to be aquaporin 1)

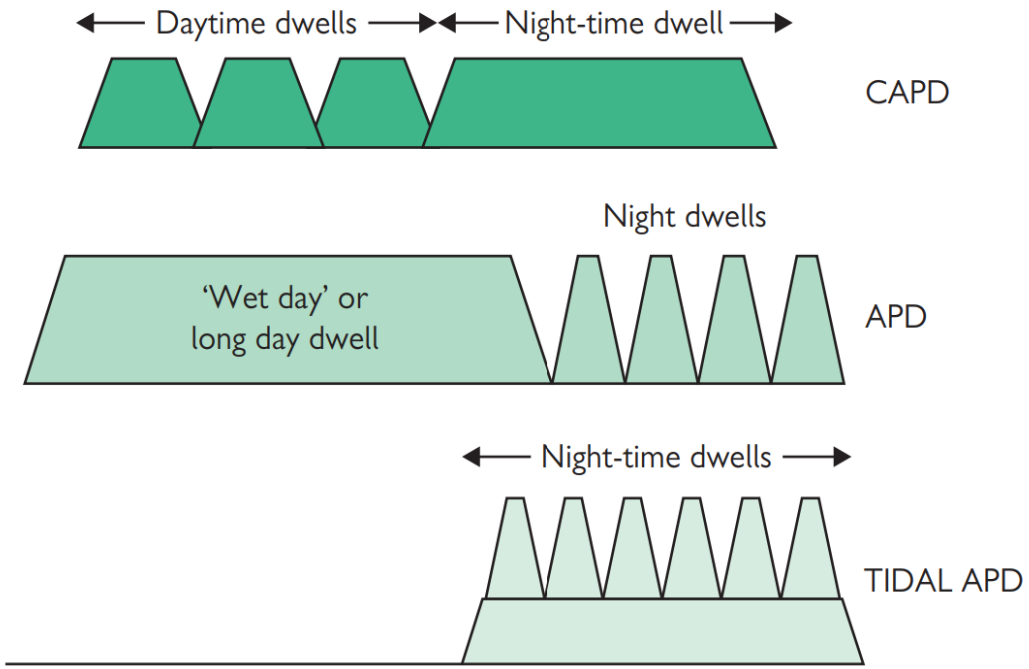


Contraindications to PD

- *Absolute*
  - Patient or caregiver unable to train adequately in the technique.
  - Inguinal, umbilical, or diaphragmatic hernias (esp. pleuroperitoneal leak).
  - Ileostomy or colostomy.
  - Abdominal wall infections or intra-abdominal sepsis, e.g. active diverticular disease
- *Relative*
  - Abdominal surgeries (adhesions). The more extensive the surgery, the more likely PD will be unsuccessful.
  - Morbid obesity (inadequate clearance).
  - Huge polycystic kidneys (insufficient intraperitoneal space).
  - Severe gastroparesis (worsening vomiting).
  - Severe lung disease (diaphragmatic splinting).

Types of PD

- *Continuous ambulatory PD*
- *Automated PD*
- *Tidal APD*
- *Assisted APD*



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Complications to PD

- Peritonitis
- Catheter exit site infection
- Drainage problems of the catheters
- Peritoneal leaks
- Sclerosing encapsulating peritonitis
  - SEP is a feared complication of long-term PD therapy, with a poor prognosis.
  - It is extremely rare before 3 years and has an incidence around 5% at 5 years.

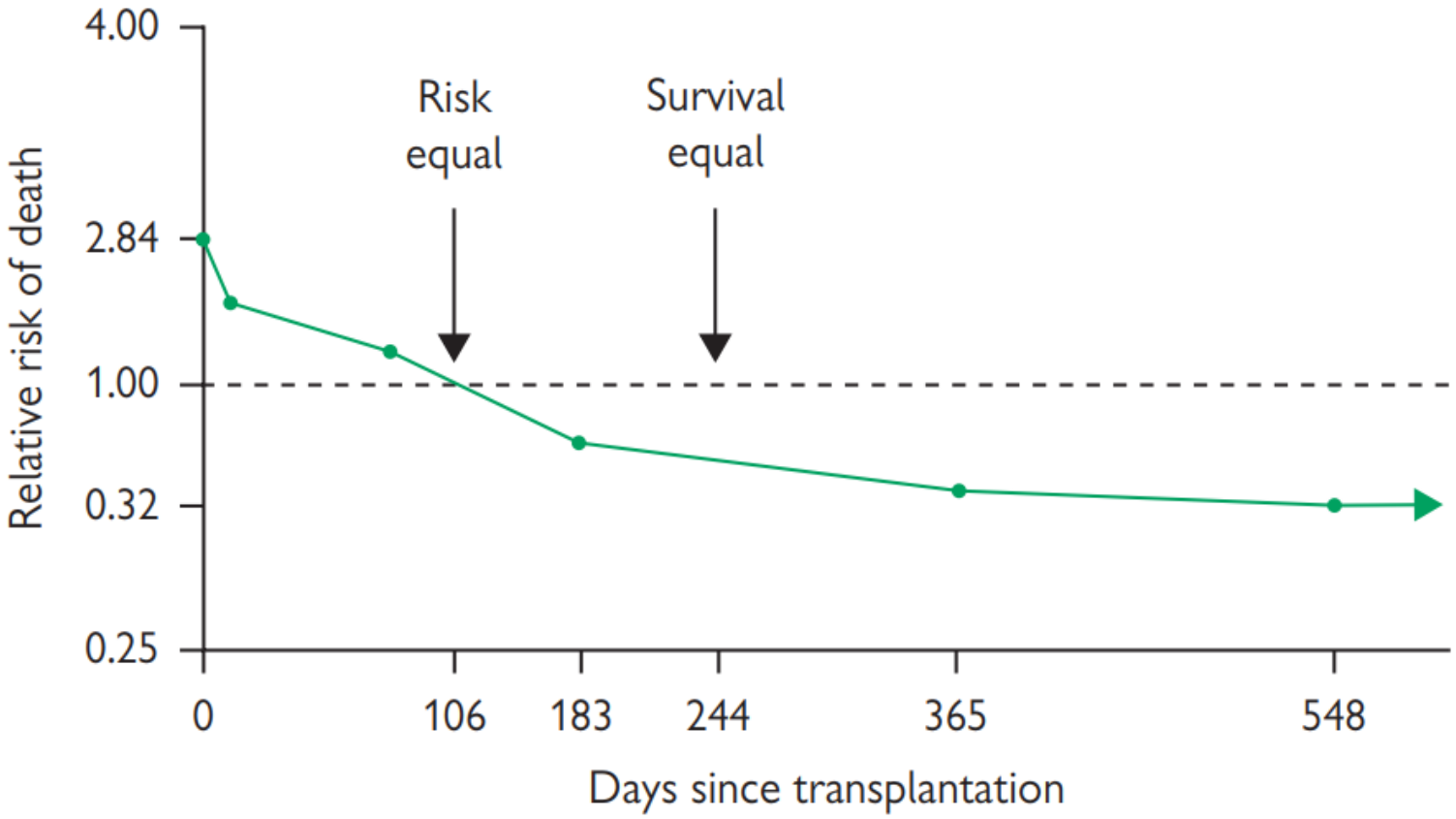
PD vs HD

	Peritoneal Dialysis	Hemodialysis
Rate	Slow	Fast
Location	Home	Hospital (usually)
Ultrafiltration	Osmotic pressure via dextrose dialysate	Hydrostatic pressure
Solute removal	Concentration gradient and convection	
Membrane	Peritoneum	Semi-permeable artificial membrane
Method	Indwelling catheter in peritoneal cavity	Line from vessel to artificial kidney
Preferred when	Residual renal function Success depends on presence of residual renal function Hemodynamic instability	Comorbidities, no renal function History of abdominal surgery

Renal transplant. Benefits of transplantation

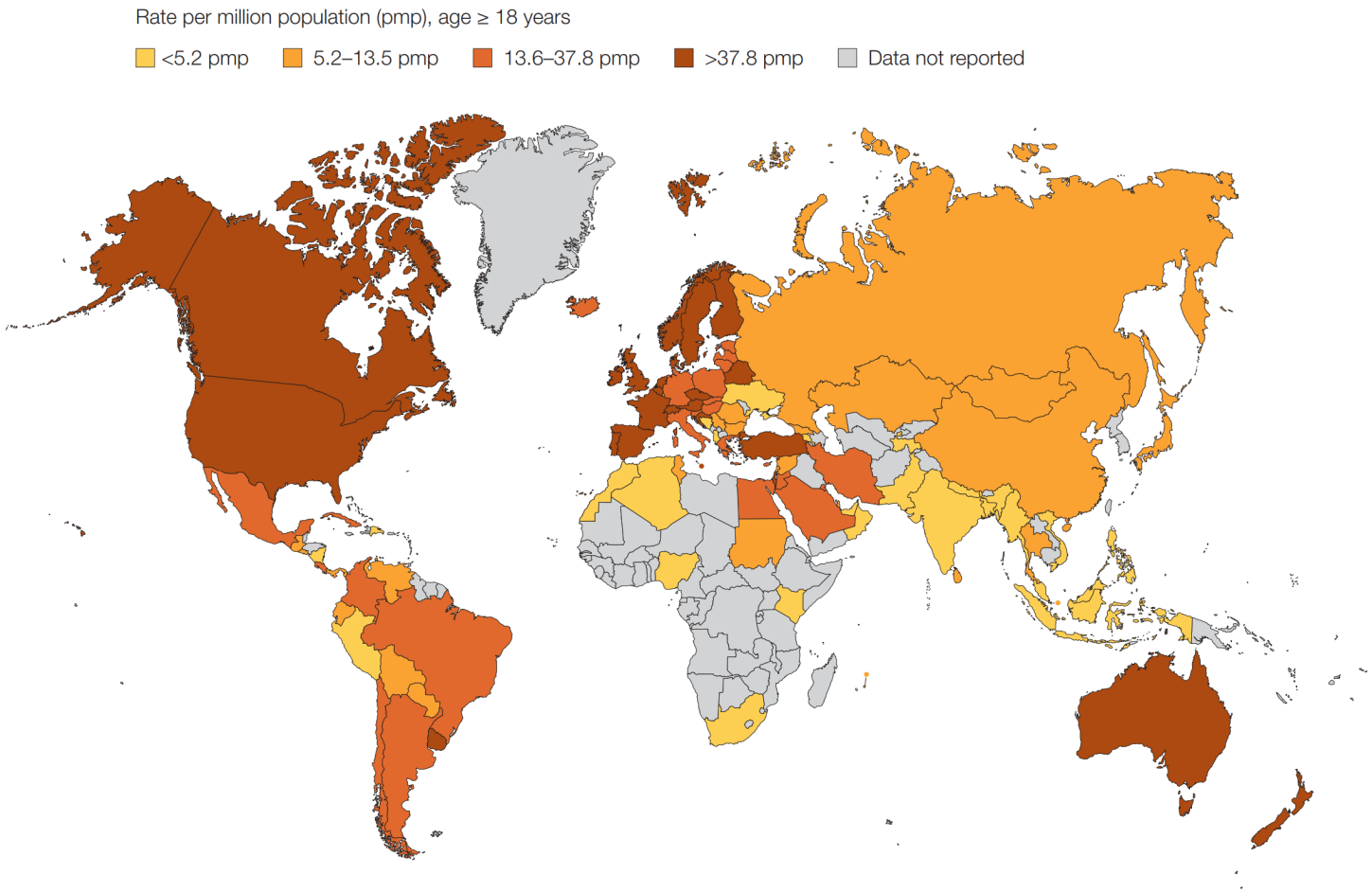
- Improved patient survival.
- Improved quality of life.
- More complete and physiological correction of the uremic milieu, including complications, such as anemia and CKD-MBD.
- Improved sexual function and fertility, including the potential for successful pregnancy in
- Better for the health economics: transplantation is less expensive than dialysis (after the first year)

Survival rate in Kidney transplantation



- The number of patients listed for transplantation globally has plateaued in recent years after an extended period of relentless growth. Demand continues to outstrip the supply of organs
- This inevitably leads to longer waiting times for deceased donor transplantation
- This disparity has encouraged the use of organs from more marginal donors, e.g. donation after cardiac death (DCD) and elderly donors with acknowledged comorbidity.

Global incidence of kidney transplantion



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Typical recipient work-up

- *Immunological*
  - Blood group.
  - HLA type.
  - HLA antibody screen.
- *Virology*
  - HIV.
  - Hepatitis B.
  - Hepatitis C.
  - Epstein – Barr virus (EBV).
  - Cytomegalovirus (CMV).
  - Varicella zoster virus (VZV).
  - Toxoplasma.
  - Syphilis.
  - HTLV 1 and 2 (only for Caribbean/Japanese or HIV +ve)
- *Hematology*
  - FBC, platelet count, PT/INR/APTT.
  - Thrombophilia screen (if previous thrombotic event, relevant FH, SLE, or recurrent miscarriages).
  - Serum and urine protein electrophoresis and immunofixation (age >60 years)
- Imaging
  - Chest Xray
  - ECG
  - Ultrasound
  - Doppler

Compatibility: matching donor to recipient

- Blood group.
- Tissue type (HLA).
- Anti-HLA antibodies (particularly donor-specific antibody, DSA).
- Donor characteristics.
  - Donation after brain death
  - Donation after cardiac death
- Recipient characteristics.
  - Time on the waiting list, with priority to those that have waited the longest.
  - Age: priority to those younger than 18.
  - HLA mismatch, with priority to a zero-antigen mismatch.
  - HLA antibodies, with priority to those with a high PRA or calculated RF.
  - Medical priority, e.g. a patient has limited options for sustainable dialysis access.

Donor characteristics

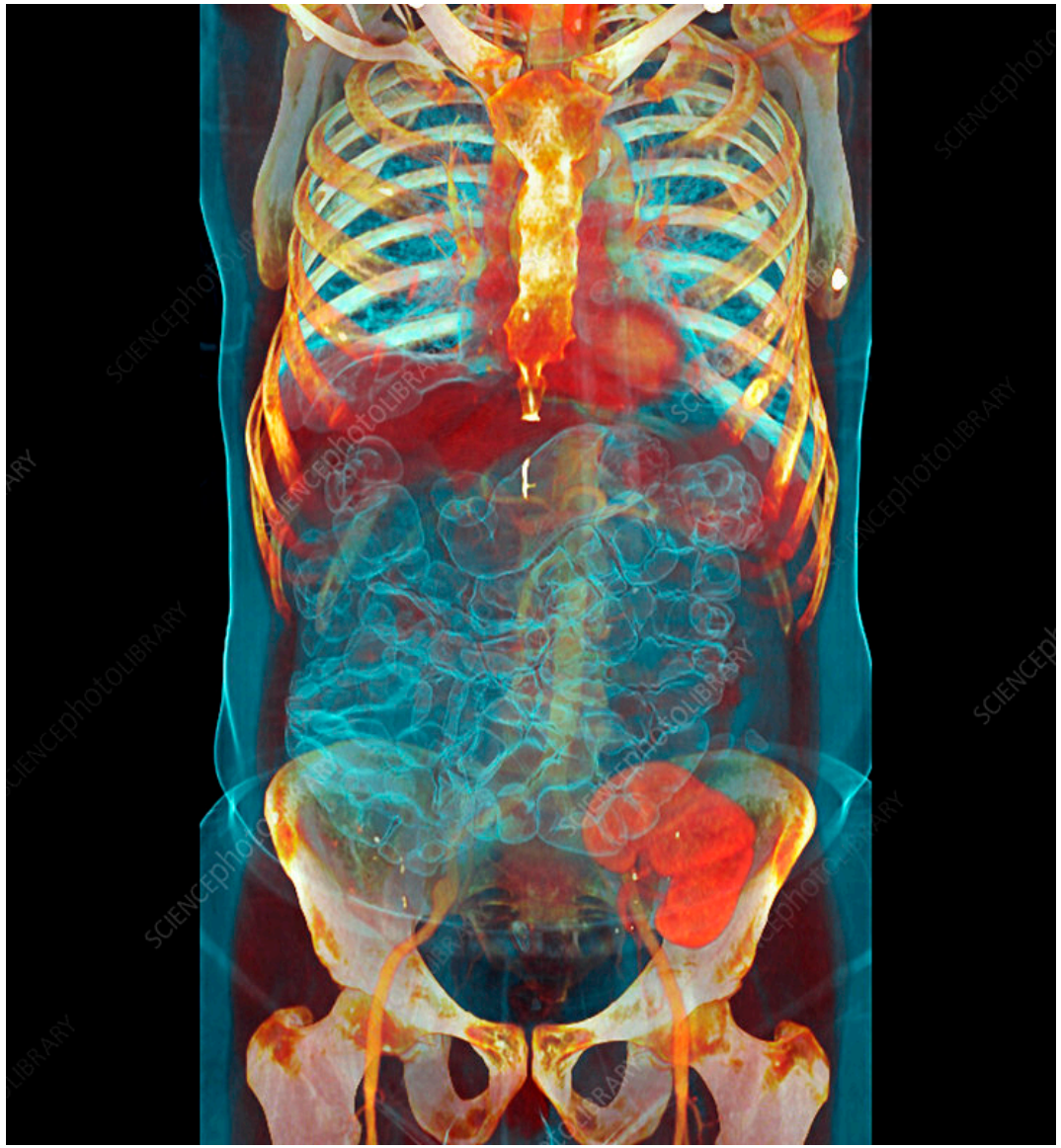
- Living donor
- Donation after brain death
- Donation after cardiac death:
  - Maastricht classification (modified)
    - Uncontrolled (organ retrieval cannot be planned)
      - Category I: dead on arrival in hospital.
      - Category II: unsuccessful resuscitation.
      - Category V: unexplained cardiac arrest in hospital.
    - Controlled (allow organ retrieval to be planned, warm ischemic time to be minimized and organ outcomes optimized)
      - Category III: expected cardiac arrest.
      - Category IV: cardiac arrest in brainstem-dead donor.

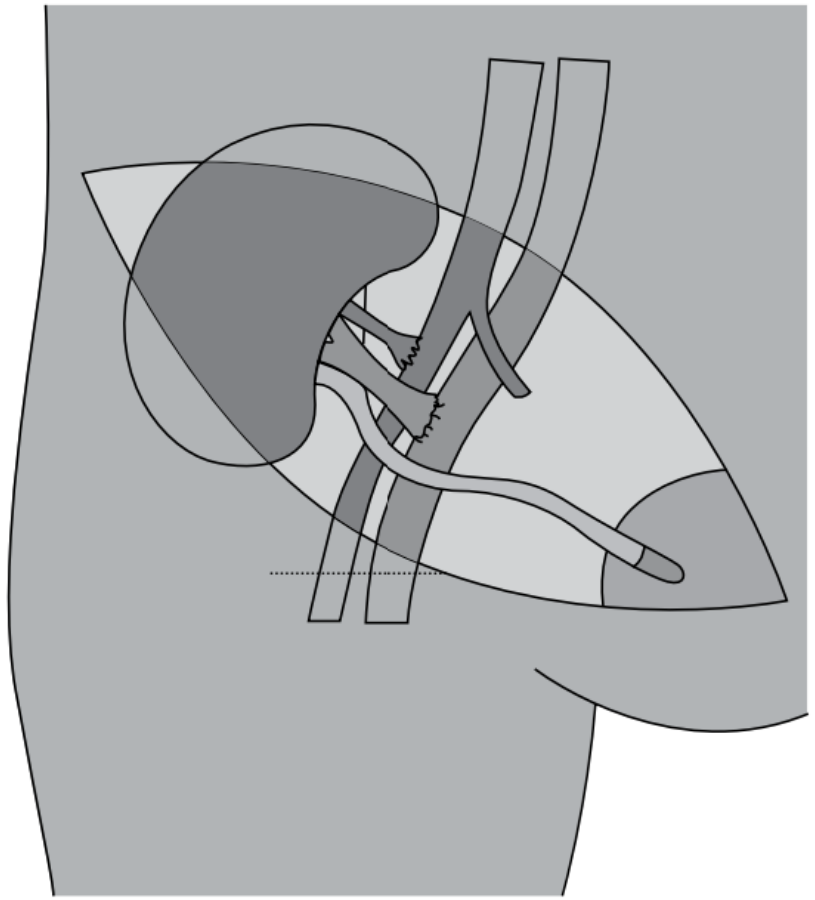
Live donor transplantation. Advantages.

- Better graft and patient survival than deceased donor transplantation—regardless of genetic relationship and HLA mismatch.
- Pre-emptive transplants (i.e. pre-dialysis) have the best outcome of all.
  - Time on dialysis is associated with poorer transplant outcomes
- Live donor transplantation is elective surgery and easier to organize.
- Laparoscopic donor techniques have helped acceptability.
- Closer HLA matching *may* be possible.
- Live donor transplantation expands the overall donor pool — leaving deceased donor kidneys for those with no other options.
- There is minimal ischemic damage to graft (↓ DGF).
- Less potent immunosuppression (possibly).
- Psychological benefits (better compliance, sense of well-being, etc.)

Live donor transplantation. Disadvantages.

- Perioperative donor mortality is ~1 in 3,000 (causes: occult cardiac disease, venous thromboembolism).
- Major complications occur in 2% (intraoperative bleeding, wound problems, DVT).
- Minor complications occur in 20%.
- Stress to donor (and family).
- Later development of donor ↑ BP, proteinuria, or CKD (mean donor GFR after 25 years is ~70% of that prior to donor nephrectomy).
- Difficult to guarantee ‘ freely given ’ consent — has the donor been coerced? Potential donors should be assessed in isolation from recipients and allowed to withdraw (without explanation) at any stage





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Recipient operation

- The kidney is carefully examined ‘ on the bench ’ , paying particular attention to the arterial anatomy (accessory arteries cannot be sacrificed, as there is no collateral supply). Small veins may be more expendable, as there is some overlap in venous drainage. Vascular reconstruction may be necessary prior to implantation.
- The left renal vein is longer, making it easier to implant.
- Graft implantation is heterotopic, usually into the right iliac fossa (the right iliac vessels are generally more accessible), although some surgeons favour placing a right donor kidney on the left side and vice versa (as kidney orientation is easier). If a previous transplant remains *in situ*, the contralateral side will be favoured.
- An implantation biopsy may be taken (esp. if the donor is considered marginal) to help predict graft function in the post-operative period.
- The operation is largely extra-/retroperitoneal.
- **Note: the native kidneys are not removed.**

Immunosuppression. Induction.

- Higher initial doses of agents that will subsequently be used for maintenance, e.g. pulsed IV and high-dose oral corticosteroids and ciclosporin or tacrolimus, with higher early target therapeutic levels.
- Antibody induction with a ‘ biological ’ agent; this will be with either a *depleting* or *non-depleting* antibody.
- Depleting antibodies: ATG, OKT3, alemtuzumab.
- Non-depleting antibodies: basiliximab.
- Antibody induction is used for >80% of transplants. In broad terms, depleting antibodies are favoured in the USA, whilst non-depleting antibodies are more widely used in the UK and Europe.
- While the evidence that antibody induction reduces acute rejection is good (depleting antibody > non-depleting antibody), the effects on long-term graft outcome are less clear.
- Other potential advantages (depleting antibody > non-depleting antibody): lower baseline maintenance immune suppression (esp. steroids), allows gradual introduction of CNI to assist recovery from DGF, facilitates higher immunological risk transplants
- Potential disadvantages (depleting antibody >> non-depleting antibody): higher infection rates, greater long-term risk of malignancy

Immunosuppression. Maintenance.

- Maintenance immune suppression is given for the lifetime of the graft to prevent rejection. These agents are administered orally, and regimens usually involve several agents.
- Standard ‘triple therapy’ consists of a
  - calcineurin inhibitor - ciclosporin, tacrolimus
  - an antimetabolite - Mycophenolic acid, azathioprine, sirolimus
  - corticosteroids.

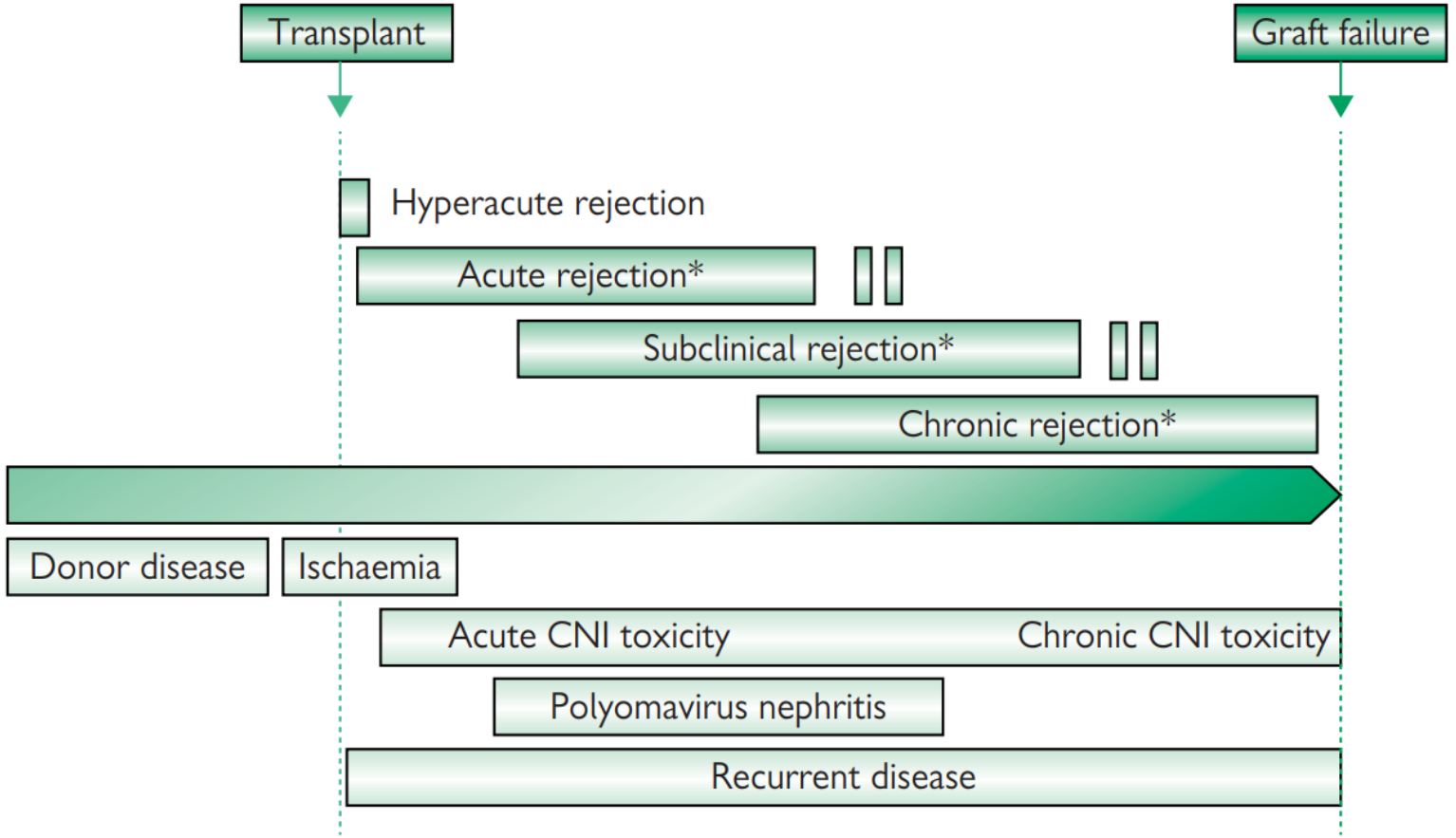
Transplant complications. Acute.

- Bleeding
- Wound infection
- Vascular thrombosis/occlusion
- Urinary leak
- Lymphocele
- Early obstruction

Transplant complications. Chronic

- Renal artery stenosis
- Ureteric stenosis
- Bladder dysfunction

Graft dysfunction



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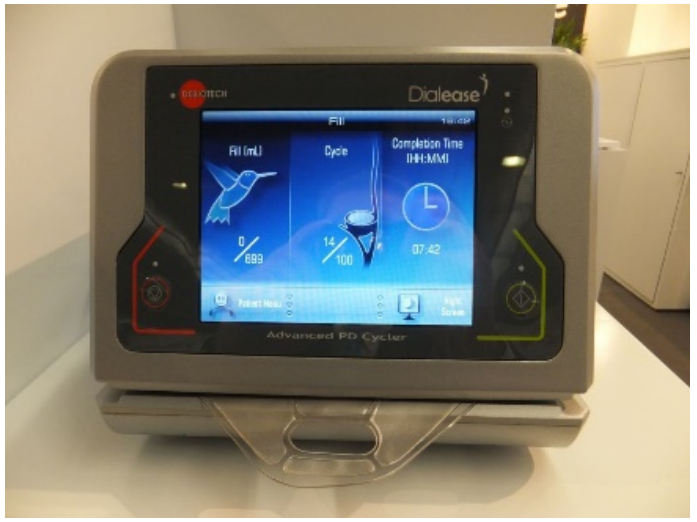
Post-transplant infections

- *1–6 months*
  - Viral infections (often reactivation of latent disease): CMV, HSV, VZV, EBV, BK virus.
  - TB.
  - Opportunistic infections: *Listeria*, *Aspergillus*, pneumocystis pneumonia.
- *Beyond 6 months*
  - Conventional community-acquired pathogens.
  - Chronic viral infection: BK nephropathy, EBV-driven PTLD.

Kidney-pancreas transplantation

- Treatment of choice for diabetic patients with ESRD
- Benefits:
  - Pancreas transplantation corrects the glycemic state (HbA1c falls to normal), leading to improved quality of life (freedom from both insulin and dialysis).
  - Prevention of progression of diabetic complications.
  - Comparable survival to live donor kidney transplant alone

Future of RRT



1. **Enhanced dialysis**
2. **Portable and/or wearable kidneys**
3. **Biohybrid and or implantable kidneys**
4. **Regenerated kidneys**
5. **3D printed kidneys**