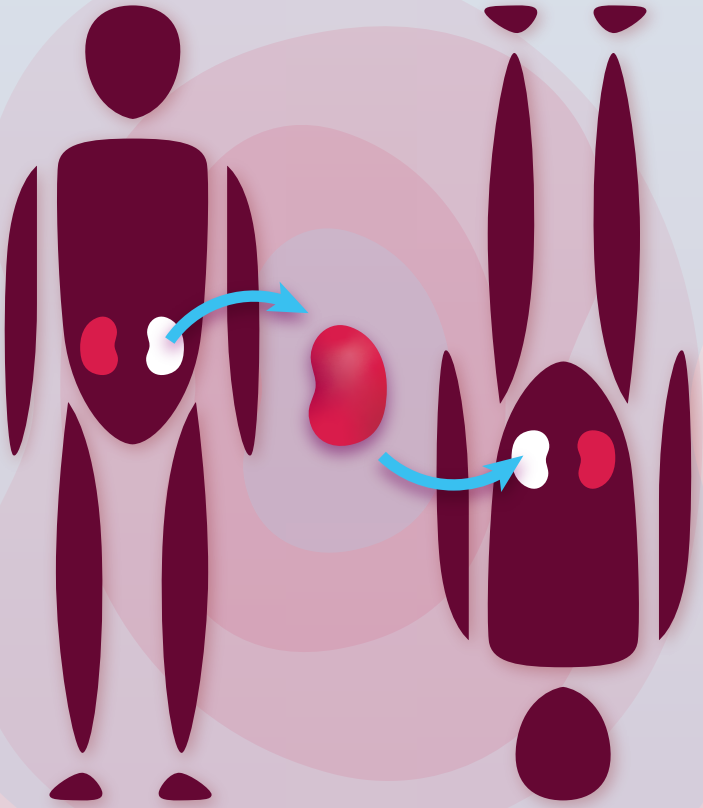
EDTNA/ERCA
Caring Together

KIDNEY TRANSPLANTATION

A guide to clinical practice



Editor: Naceur Chouayet

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Kidney Transplantation

A guide to clinical practice

Editor

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Chapter 1

The history of kidney transplantation

Learning objectives

- To emphasize the significant historical phase of kidney transplantation.
- To outline the historical development of kidney transplantation across continents.
- To highlight the contribution of art in illustrating the success of kidney transplantation.

Introduction

Kidney transplantation is one of the most significant advancements in modern medicine, offering patients with end-stage kidney disease (ESKD) a renewed chance at life. The history of kidney transplantation is rich with milestones that have shaped current medical practices. Understanding this history provides nephrology nurses with essential knowledge of the evolution of transplantation, the challenges encountered, and the breakthroughs achieved over time.

Early Attempts and Experimental Transplants

The concept of organ transplantation dates back centuries, with early experimental kidney transplants performed in animals. In 1902, Emerich Ullmann successfully transplanted a kidney between two dogs. Around the same time, Alexis Carrel developed pioneering vascular suturing techniques that would later become fundamental in kidney transplantation. Carrel's contributions earned him the Nobel Prize in Physiology of Medicine in 1912.[1]

The First Successful Human Kidney Transplants

The first human kidney transplants were performed in the 1930s and 1940s but were largely unsuccessful due to immune rejection. The breakthrough came in 1954 when Dr Joseph Murray performed the first successful human kidney transplant between identical twins, Richard and Ronald Herrick, at Brigham Hospital in Boston. Since the twins were genetically identical, the issue of immune rejection was avoided, marking a turning point in transplantation history.[2-3]

The Development of Immunosuppression

The success of kidney transplantation depended on overcoming immune rejection. The introduction of immunosuppressive drugs in the 1960s, such as azathioprine, significantly improved transplant survival rates. The discovery of ciclosporin in the late 1970s revolutionised the field, leading to higher long-term success rates. Today, a combination of immunosuppressive therapies, including tacrolimus and mycophenolate mofetil, has further enhanced graft survival.[4-5]

Challenges in Early Kidney Transplantation

Despite early successes, kidney transplantation faced numerous challenges:

- **Immune Rejection:** The lack of effective immunosuppressive therapies resulted in high rates of transplant failure.
- **Surgical Limitations:** Early surgical techniques were not well refined, leading to complications in vascular anastomosis and graft survival.
- **Ethical Concerns**: The use of living donors, particularly in cases without informed consent, raised significant ethical issues.
- **Limited Organ Availability:** Kidney donation programmes were underdeveloped, leading to a scarcity of available kidneys.[6]

Milestones in Kidney Transplantation by Continent

Europe

Europe has played a pivotal role in the development of kidney transplantation. In 1952, Jean Hamburger performed the first human kidney transplant in France, using a mother as a donor for her son. The UK saw its first successful kidney transplant in 1960 at the Royal Infirmary of Edinburgh. Europe also pioneered organ-sharing networks, with organizations like Eurotransplant facilitating cross-border organ allocation.[7]

North America

The first successful kidney transplant in North America was performed in 1954 by Dr Joseph Murray. The establishment of the United Network for Organ Sharing (UNOS) in 1984 significantly improved the organisation and distribution of deceased donor organs across the United States. Advances in immunosuppressive therapy have further solidified North America's leadership in transplantation research and practice.[8]

Asia

Asia has made significant contributions to kidney transplantation, particularly in living-donor transplants. Japan, due to cultural restrictions on deceased kidney donation, developed highly advanced techniques for living-donor transplantation. India performed its first successful kidney transplant in 1971, while China has rapidly expanded its transplantation programme in recent decades.[6]

Africa

The first kidney transplant in Africa was performed in South Africa in 1966. Since then, South Africa has remained a leader in transplantation on the continent. Egypt has also emerged as a regional centre for kidney transplantation, focusing primarily on living-donor programmes. However, many African nations continue to face challenges in access to transplantation services due to limited healthcare infrastructure.[6]

South America

South America has an established history of kidney transplantation, with the first successful procedure taking place in Argentina in 1957. Brazil has since developed one of the world's most advanced public kidney transplant programmes, supported by robust legislation promoting deceased kidney donation. Other countries, including Colombia and Chile, have also expanded their transplantation programmes in recent years.[6]

Advancements in Surgical Techniques

Kidney transplantation surgery has evolved significantly over time. Key advancements include:

- **Minimally Invasive Techniques:** Laparoscopic donor nephrectomy has replaced open surgery, reducing recovery time for living donors.
- **Robotic-Assisted Surgery:** The use of robotics has improved precision and reduced complications.
- **Improved Kidney Preservation:** Machine perfusion technology has enhanced the viability of donor kidneys, extending preservation times and improving transplant outcomes.[8]

Post-Transplant Challenges and Long-Term Management

While kidney transplantation is lifesaving, patients face ongoing challenges:

- Chronic Rejection
- Infections
- Cardiovascular Disease
- Medication Side Effects
- Recurrent Kidney Disease.[5,10]

Renaissance Art and Anatomical Studies

The Renaissance era (14th–17th century) witnessed a surge in anatomical exploration, with artists like Leonardo da Vinci and Andreas Vesalius creating highly detailed anatomical drawings. These works contributed to an understanding of the human body, including the kidneys' structure and function, paving the way for later surgical advancements.[6]

The miracle of the leg is known as the first pictorial representation of a transplant in history (figure 1). The miracle was performed by Cosmas and Damian, two brothers who dedicated themselves to healing the sick, and who are now celebrated as the patron saints of physicians, surgeons and pharmacists.



Figure 1: The miracle of the saints Cosmas and Damian in which they transplanted the leg of black man onto a white recipient in medieval Rome [1515]. Collection Wüttembergisches Landesmuseum, Stuttgart, Germany.

20th Century Artistic Depictions of Kidney Transplantation

In 1996, artist Joel Babb was commissioned to create a painting depicting the first successful human kidney transplant, performed by Dr. Joseph E. Murray on December 23, 1954 (figure 2). This artwork captures the historic moment at Peter Bent Brigham Hospital in Boston, where Dr. Murray and his team transplanted a kidney from Ronald Herrick into his identical twin brother, Richard Herrick. The painting serves as a visual tribute to this groundbreaking medical achievement.[11]

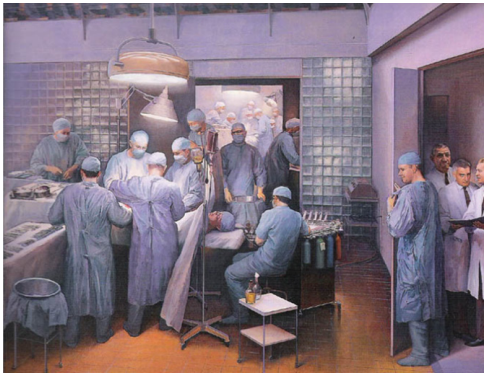


Figure 2: Joel Babb, The First Successful Kidney Transplantation, 1996. Oil on canvas, 70 × 88. The Harvard Medical Library in the Francis A. Countway Library of Medicine, Boston, Massachusetts.

The Role of Nephrology Nurses in Kidney Transplantation

Nephrology nurses play a crucial role in the kidney transplant process by:

- Educating patients and families
- Assisting in pre-transplant evaluations and post-transplant care
- Monitoring immunosuppressive therapy
- Providing psychological support
- Participating in research and policy development.[6]

Conclusion

The history of kidney transplantation reflects the remarkable progress made in medical science and patient care. As nephrology nurses, understanding this history enhances clinical practice and improves patient outcomes. By being informed about advancements in transplantation, nurses contribute to the continued success of kidney transplants worldwide.

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Chapter 2

What next in Kidney Care – Devices as Bridges towards Transplantation, and the Roadmap towards an Implantable Artificial Kidney

Learning objectives

- The lack of human-donated transplantable organs is a big problem.
- Moreover, transplantation is not really a cure, and the need for immune suppression to counter transplant rejection has severe side effects.
- In the future, xenotransplantation, using genetically modified animal kidneys (e.g. from genetically modified pigs), may become clinically available. Although this looks a promising route to generate many more transplantable organs, it does not solve the immune suppression problem.
- Dialysis preferably should be a bridge to transplantation. But not all patients are eligible for transplantation, some have an immune system that will reject any transplanted organ. This is the reason why this chapter was added to the book, to describe innovative *technology-based* kidney replacement alternatives that are in the innovation funnel.
- It is important to understand and apply Technology Readiness Levels (TRLs) when writing or reading research articles and press releases, especially when it regards medical topics where patients are craving for a better therapy.

Introduction

Current Kidney Replacement Therapy (KRT) modalities include kidney transplantation from a human donor (preferred treatment if the patient is eligible for transplantation and a matching donor kidney is available) as well as peritoneal dialysis (PD) and haemodialysis (HD).

Regarding transplantation, there is a persistent lack of donor kidneys (both from living and deceased donors). However, March 2024 saw a big breakthrough in xenotransplantation: A kidney from a genetically modified pig was successfully transplanted into a patient who could return home a few weeks after surgery.[1] Sadly, 2 months later this patient died.[2]

In April 2024, another patient received an electro-mechanical left ventricular assist device (LVAD) plus a genetically modified pig kidney that (due to complications from low perfusion episodes) was explanted in June, and the patient died July 7th, 2024.[3-4] At the time of writing this chapter, for both these patients, the aetiology or cause of death had not been published, but another patient had survived for 10 weeks with a genetically modified pig kidney.[5] Xenotransplants are true breakthroughs and xenotransplantation is clearly opening promising new perspectives. Therefore, it is good news that the FDA approved 2 more trials with xenotransplantation.[6] Yet, such xenotransplants logically will require stronger immune suppression than allotransplants from a human donor. Lab-cultivated, 3D-bioprinted, and other fully biology-based replacement kidneys are also being worked upon, but these seem much further away on the timeline.[7]

Unfortunately, not all patients are suitable for transplantation, and thus other forms of KRT (and innovations thereof) will remain essential in the foreseeable future.[7] This chapter will add some information about such alternative technological and/or techno/bio hybrid forms of KRT that are being worked upon, while leaving the description of the exciting perspectives regarding transplantation of fully biology-based kidneys to the other chapters of this book.

PD and HD will remain important KRT modalities for those who cannot receive a transplant, but in their present forms they are expensive and strongly dependent on infrastructure for water and electricity (especially HD) as well as on transportation and logistics (both HD and PD), which severely hampers their uptake in low-income countries. It is highly plausible that decreasing those dependencies can go hand in hand with decreasing treatment costs and increasing mobility, which could result in serving a larger proportion of patients in need of KRT at the places they live and work.[8]

A transplant clearly offers the highest degree of freedom. For those who *cannot* receive a transplant, highly compact mobile dialysis modalities with far less infrastructural restrictions, or even (partly) implantable fully artificial kidneys offering functionality *beyond* the definitions of present HD or PD might offer an alternative. Chip technology looks a very promising candidate to achieve such miniaturized KRT-devices.[8-9]

Present kidney replacement therapies and main trends towards increased mobility

Figure 1 graphically summarizes the main presently available KRTs, as well as various innovative KRT-approaches that are in the innovation funnel.

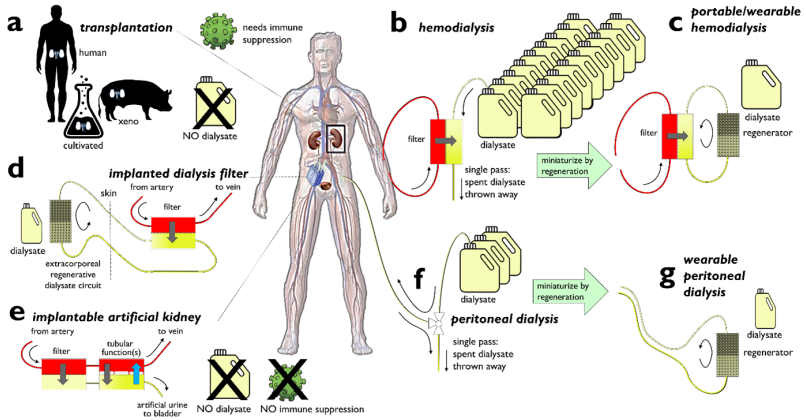


Figure 1: Graphical summary of the main forms of present & future-projected KRTs, reproduced with minor edit from.[9]

Jerrycan symbols depict the relative amount of water consumption by the various modalities.

a) Transplantation of human kidneys is the present "first choice" therapy, but there is a structural shortage of donor kidneys, for which xenotransplantation or lab-cultivated kidneys may become solutions. However, not all patients are suited for a transplant, and to prevent rejection patients must take immune-suppressive drugs, which unfortunately increases the risks of cancer and infections.
b) HD (in a single-pass embodiment) is the most widely applied form of KRT, but it is costly and not very mobile.
c) Regenerating dialysate in a closed loop can improve HD mobility, but still requires an extracorporeal blood circuit.
d) Implanting the HD filter would eliminate the need for an extracorporeal blood circuit. Only an extracorporeal dialysate circuit would then be needed to perform HD.
e) Adding a bioreactor to an implantable haemofiltration filter could (partly) replace tubular functions. This method goes beyond the definition of HD and forms an autonomous implantable artificial kidney, which would not require immune suppression.
f) PD (here shown in its' simplest form) does not require an extracorporeal blood circuit but requires quite some dialysate volume. The dialysate is instilled into the peritoneum, remains there for a few hours, and is then drained.
g) PD mobility can be significantly improved by regenerating the dialysate in a closed loop, preferably in continuous flow mode.

Targeted levels of device mobility

Air travel has the strictest rules for baggage size and weight. Typically, the most desirable baggage category is 'carry-on' because it is much less likely to get damaged or lost during handling, which is crucial for travellers. The International Air Transport Association (IATA) states that "*As a general guide, carry-on baggage should have maximum length of 22 in (56 cm), width of 18 in (45 cm) and depth of 10 in (25 cm). These dimensions include wheels, handles, side pockets, etc.*".[10] For this chapter, we particularly looked for HD devices/prototypes that at least meet this IATA recommendation, while regarding *PD* devices (typically less bulky already) we specifically looked for *wearable* systems nearing the market. Implantable (parts of) KRTs should fit to around the dimensions of a regular kidney. There are no such devices as products yet, but we scanned the PUBMED database for R&D projects working towards this.[8]

Wearable peritoneal dialysis

At the time of writing this chapter, three innovative wearable PD systems were in human clinical trials, but not yet on the market (see figure 2). This book chapter will inevitably become outdated, but the not-for-profit organization Home Dialysis Central also actively maintains a website with home PD devices: https://homedialysis.org/home-dialysis-basics/machines-and-supplies/peritoneal-dialysis-machines.



Figure 2: Three types of wearable PD machines currently in human clinical trials, reproduced from.[9]

a) Automated Wearable Ambulant Kidney (AWAK), rapidly cycling sorbent-based regenerated dialysate.
b) Re-engineered AWAK, rebranded to VIVANCE
c) Weakid PD device from Nanodialysis (using rapid cycling of regenerated dialysate), with (1) mobile unit with sorbents; (2) dialysate reservoir for night treatment; (3) wireless interface to mobile phone; (4) sterile connection set to patient catheter; (5) cassette with sorbents, with device opened up; (6) reusable control unit in front part of the device.
d) Weakid mobile unit in use.
e) Peritocare wearable PD from IMEN (single-pass, no dialysate regeneration).
f) Peritocare in mobile use.

The Singaporean AWAK PD system (fig 2a) was already included in a 2018 AJKD 'perspective' article.[11] It is a sorbent-based dialysate-

regenerating tidal-flow PD device using a single lumen catheter with a tidal-flow rate of 2 L/h and a fixed dialysate glucose concentration and can be carried in a shoulder strap bag for which in-human preliminary safety trial results were published.[12-13] Since then, the product has been re-engineered (see fig 2b) and in October 2024 rebranded to VIVANCE (website https://vivance.com/).

The Dutch Weakid PD system (fig 2c-d) is intended for nocturnal use, where a mobile console with a clicked-in sorbent cartridge is supported by an externally connected dialysate reservoir. The mobile console with clicked-in cartridge can be used stand-alone during the day for additional clearance (optional). A first in-human clinical trial on 12 patients is currently ongoing (manufacturer website https://www.nanodialysis.nl/).

In contrast to the above-mentioned sorbent-based dialysate-regenerating PD systems, the Malaysian Peritocare PD system is a wearable *single-pass* PD system. A first in-human clinical trial on 11 patients was completed in March 2022.[14] The project is still ongoing, led by prof. Azrul Azlan Hamzah, Director of Institute of Microengineering and Nanoelectronics (IMEN), University Kebangsaan Malaysia.[15]

An interesting additional pathway to increase PD mobility is local dialysate preparation.[16] There is even an initiative ongoing towards achieving this by using solar power.[17]

Portable/wearable haemodialysis and beyond

The international standard IEC 60601-2-16 contains requirements for the safety and essential performance of HD devices, and defines HD as follows: "*Process whereby concentrations of water-soluble substances in a patient's blood and an excess of fluid of a patient are corrected by bidirectional diffusive transport and ultrafiltration across a semi-permeable membrane separating the blood from the dialysis fluid*".[18]

Figure 3 shows simplified diagrams and photos of typical stages of miniaturization regarding HD (fig. 3a–e) as well as a techno/bio hybrid Implantable Artificial Kidney (IAK, fig. 3f) going beyond HD, plus two different approaches to make silicon nanoporous membranes (fig. 3g,h) that form key enabling technologies for such partly (fig. 3e) or fully (fig. 3h) implantable devices.

It is important to note that the IEC definition does not demand an extracorporeal blood circuit. This is why the principle shown in figure 3e falls within the IEC definition of HD.

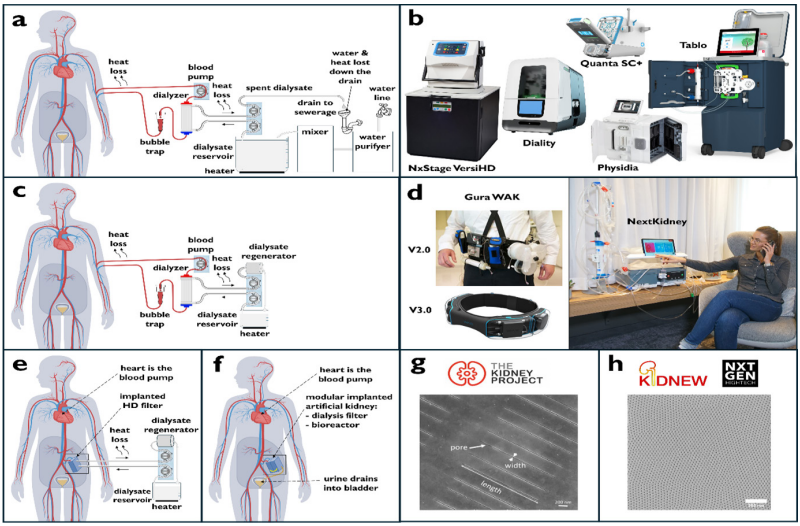


Figure 3: Strongly simplified diagrams to illustrate progressive miniaturization of HD devices (a – e) and a techno/bio hybrid implantable artificial kidney beyond the definition of HD (f – h), reproduced from.[9]

a) Single-pass HD block diagram.
b) Some examples of existing transportable single-pass HD devices (non-exhaustive, photos from websites manufacturers). No commercial single-pass HD devices were found that match IATA carry-on baggage guidelines.
c) Dialysate regenerating HD block diagram.
d) Some examples of dialysate regenerating HD devices that reached human clinical trials (non-exhaustive) and fit IATA carry-on requirements for air travel.
e) Partly implantable HD principle. The natural heart forms the blood pump and an extracorporeal dialysate regenerating device can be connected to dialyze.
f) Fully implantable techno/bio hybrid artificial kidney principle, with a nanoporous (e.g. silicon wafer-based) filter, and a bioreactor. Also here, the natural heart forms the blood pump.
g) Silicon nanoporous membrane of 'the Kidney Project' with patterned slit pores.[19]
h) Silicon nanoporous membrane pore patterning technology as applied by IMEC in the 'KIDNEW' and 'NXTGEN HighTech' projects (note: about double magnification, compare the 200nm wide scale bars in g and h).[20]

Presently commercially available transportable HD devices use the '*single-pass*' principle: Once the dialysate has passed through the dialyzer, it is discarded into a drain connected to the sewerage (hence the term 'spent dialysate'). Consumption of water and electricity (for heating the water) are therefore large.[21] Figures 3a & 3b show a strongly simplified typical block diagram and some photos of transportable single-pass HD devices on the market. The pictured examples are not exhaustive and this book chapter will inevitably get outdated, but the not-for-profit organization Home Dialysis Central also maintains a website with home HD devices which is periodically updated: https://homedialysis.org/home-dialysis-basics/machines-and-supplies/hemodialysis-machines.

Dialysate regenerating HD devices circulate a much smaller volume of dialysate through a closed loop, in which the dialysate is regenerated. This provides more degrees of freedom for miniaturization into a portable (IATA-compatible) or even wearable format. Considerably less water (10 to 20-fold) and electricity are consumed (less water to heat). Figures 3c & d show a simplified block diagram and two examples that have reached the stage of in-human clinical trials: The wearable HD device (also referred to as WAK) from Dr. Gura[11,22] and the portable HD device (also referred to as Neokidney) from NextKidney, which meets IATA carry-on baggage criteria.[23] During ASN Kidney Week 2024, first-in-human trial results of this device were presented.[24]

The IEC definition of HD also covers partly implantable HD (fig. 3e). Implanting the HD filter renders the extracorporeal *blood* circuit superfluous. The blood stays in the body, and continuously loops through the implanted HD filter, so that only an extracorporeal dialysate circuit is needed (e.g. by a compact dialysate regeneration device). When unused, the transcutaneous dialysate catheters (which are already known technology from PD) are simply connected to each other.

Consequently, making needles and vascular cannulation of the bloodstream obsolete is a giant leap forward. But ultimately, one would like to get rid of *all* extracorporeal connections. This may be achieved by a fully implantable artificial kidney, containing two modules: a nanoporous silicon (or other material) wafer-based filter (likewise as in fig. 3e), and an *additional bioreactor* (containing cultured tubular cells). The bioreactor would reclaim water, maintain

homeostasis and help to actively expel uremic toxins, via a urine outlet to the bladder (fig 3f).[25]

It must be highlighted that the concepts depicted within the figures 3e and 3f were first defined by David Humes and persistently matured by the research group around William Fissel (Vanderbilt Medical School) and Shuvo Roy (University of California San Francisco), also known as 'The Kidney Project'.[11,26-27] The 'Kidney Project' has already demonstrated basic feasibility of the bioreactor concept and also created a well-defined animal model to test and compare silicon-wafer-based nanoporous filters.[28-29] In addition to this USA-located project, two EU-located synergetic consortia, called KIDNEW and NXTGEN HighTech, recently also started working towards these goals, combining their chip-based nanofilters with add-on modular on-chip integrated electronics for sensing, control, actuation and data storage as well as wireless powering and bidirectional data communication.[8-9]

Both sides of the Atlantic thus work separately on creating a partly implantable HD system (fig. 3e), eventually followed by a techno/bio hybrid IAK (fig. 3f). The stepwise modular approach applied by both projects resembles the Apollo project, a classic example of how to decrease risks while making meaningful steps towards an ambitious and complex target. The underlying silicon wafer-based filter manufacturing technologies of the USA-located and EU-located consortia are, however, fundamentally different. The 'kidney project' uses slit-shaped pores (fig 3g) where the width of the slit-pores is tuned by process parameters, but the minimum distance between the individual slit-pores is dictated by technical limitations of the applied lithographic waferstepper generation. Within the European KIDNEW & NXTGEN HighTech projects, IMEC achieves a high pore density by applying *molecular self-assembly* (fig 3h) which is fully independent of lithographic waferstepper generation and simplifies large-scale manufacturing.[20]

Using the gut as a 'third kidney' to create more room for KRT engineering trade-offs

A new and interesting "add-on" oral sorbent approach may be used to delay the onset of KRT, and – once KRT is started – to support the therapy.

The small intestine is mostly impermeable to high-weight molecules but freely permeable to small and charged ions like Na^+, K^+, $Phos^{2-}$, H^+ and (from urea hydrolysis) $NH4^+$.[30] In ESKD patients ≥ 50% of daily generated urea passes from the blood into the small bowel, where bacteria decompose it into bicarbonate and NH_4^+, which are then – after return to the blood – resynthesized to urea in the liver. Removing the above listed 5 components via the gut could simplify KRT-miniaturization engineering trade-offs. A daily 30g oral dose of monovalent-selective cation-exchanger zirconium cyclosilicate (ZS, efficiently binding K^+ & $NH4^+$) can normalize K^+ in ESKD patients and decrease the BUN-level by 20-25% (through removal of NH_4^+).[31-34] A daily 10g dose can prevent significant hyperkaelemia during inter-dialytic periods.[35] Combination with inorganic H^+-loaded cation exchangers and OH^--loaded anion exchangers increases binding for Na^+, K^+, $Phos^{2-}$, H^+ and NH_4^+.[36-37] Animal studies of this oral sorbent are ongoing. Adding a hydrophobic gas-permeable coating to the *cation*-exchanging sorbent particles further increases NH_3 removal.[38-39]

Using the gut as a 'third kidney' opens new perspectives. In the very long run, this approach might help simplify dialysate regeneration to applying a low-cost activated carbon block for removal of remaining organic toxins (many protein-bound) which to a great extent cause the actual uraemia symptoms.[35,40-42] Easily suspended, fine-powdered, and tasteless oral sorbent might also become a "kidney support" modality during earlier CKD-stages, before uraemia requires KRT.

Understanding research communications: the Technology Readiness Level (TRL) concept

As this book chapter will inevitably become outdated regarding specific projects or devices, we here also (briefly) explain the concept of Technology Readiness Level (TRL). Within the fields of military, aerospace and chips industry the TRL-concept is well-known, but far less so in medical technology. It is a useful tool to communicate the progression of new technologies into daily life. Fundamental breakthroughs in medical technologies undoubtedly deserve exciting media coverage, but it would be good if science journalists would consequently add a TRL-indicator and explain what it means. Hence in Table 1, we present a TRL-scale reproduced from.[8]

Table 1: Applied Technology Readiness Level (TRL) scales, used by the European Union (EU) and NATO Medical Staff.

TRL	Horizon Europe NCP Portal TRL Self-Assessment Tool.[43]	NATO TRL-Scale for Medical Devices.[44]
1	**Basic principles observed**	**Basic Principles Observed & Reported in Context of a Military Capability Shortfall** Lowest level of technology readiness. **TRL 1 Decision Criterion:** Scientific literature reviews and initial Market Surveys are initiated and assessed. Potential scientific application to defined problems is articulated.
2	**Technology concept formulated**	**Technology Concept and/or Application Formulated** Invention begins. Intense intellectual focus on the problem with generation of scientific "Paper Studies" that review and generate research ideas, hypothesis, and experimental designs for addressing the related scientific issues. **TRL 2 Decision Criterion:** Hypothesis(es) generated. Research plans and/or protocols are developed, peer reviewed, and approved.
3	**Experimental proof of concept** Initial proof of concept demonstrated with a limited number of in vitro & in vivo trials including the expected device characteristics.	**Analytical & Experimental Critical Function and/or Characteristic Proof of Concept** Active research and development is initiated. Basic research, data collection, and analysis begin in order to test hypothesis, explore alternative concepts, and identify and evaluate component technologies. Initial tests of design concept, and evaluation of candidate(s). **TRL 3 Decision Criterion:** Study endpoints defined. Animal models (if any) are proposed. Design verification, critical component specifications and tests (if a system component, or necessary for device Test & Evaluation) developed.
4	**Technology validated in lab** Proof of concept and safety of the device is demonstrated in vitro, ex vivo or in vivo conditions (non-GMP, Good Manufacturing Practice). System components integrated and tested regarding preliminary efficiency and reliability.	**Component and/or Breadboard Validation in Laboratory/Field Environment** Basic technology components are integrated to establish that they will work together. Non-GLP laboratory research to refine hypothesis and identify relevant parametric data required for technological assessment in a rigorous (worst case) experimental design. Exploratory study of candidate device(s)/systems (e.g., initial specification of device, system, and sub-systems). Candidate devices/systems are evaluated in laboratory and/or animal models to identify and assess potential safety problems, adverse events, and side effects. Procedures and methods to be used during nonclinical and clinical studies in evaluating candidate devices/systems are identified. **TRL 4 Decision Criterion:** Proof-of-concept demonstrated for candidate devices/systems and laboratory/animal models defined. Initial device master record completed.

TRL	Horizon Europe NCP Portal TRL Self-Assessment Tool.[43]	NATO TRL-Scale for Medical Devices.[44]
5	**Technology *validated* in relevant environment (industrially relevant environment in the case of key enabling technologies)** Pre-clinical studies including GLP animal safety & toxicity. GMP manufacturing process and quality controls identified. Classification of the device by appropriated regulatory body established. Accreditation when appropriate initiated.	**Component and/or Breadboard Validation in a Relevant (Operating) Environment** Fidelity of sub-system (breadboard) representation increases significantly. Further development of selected candidate technologies. Devices compared to existing modalities and indication for use and equivalency demonstrated in model systems. Examples include devices tested through simulation in tissue or organ models, or animal models if required. All component suppliers/vendors are identified and qualified. Vendors for critical components audited for GMP compliance. Component tests, component drawings, and device master record verified. Product development Plan drafted. **TRL 5 Decision Criterion:** Regulatory authorities have reviewed submissions of required data to determine if clinical trials may proceed.
6	**Technology *demonstrated* in relevant environment (industrially relevant environment in the case of key enabling technologies)** Medical device prototype demonstrated in operational environment. Clinical testing and safety demonstrated. Required accreditation in progress.	**System/Sub-System Model or Prototype Demonstration in a Realistic (Operating) Environment or Context** Representative model or prototype system, which is well beyond the representation tested for TRL 5, is tested in a more realistic laboratory or simulated operational environment. Represents a major step up in a technology's demonstrated readiness. First phase clinical trials conducted to demonstrate the safety of the candidate device in a small number of humans under carefully controlled and intensely monitored clinical conditions. Validation of the master plan for critical components and final device assembly. Production technology demonstrated through production-scale GMP plant qualifications. **TRL 6 Decision Criterion:** Data from first phase trials meet national clinical safety requirements and support proceeding to next phase of clinical studies.

TRL	Horizon Europe NCP Portal TRL Self-Assessment Tool.[43]	NATO TRL-Scale for Medical Devices.[44]
7	**System prototype demonstration in operational environment** Medical device final product design is validated. Final prototypes intended for commercialization use produced and tested. When applicable, accreditation completed.	**System Prototype Demonstration in an Operational Environment or Context (e.g., Exercise)** Prototype near or at planned operational system level. Represents a major step up from TRL 6, requiring the demonstration of an actual system prototype in an operational environment, such as in a relevant platform or in a system-of-systems. Second phase clinical effectiveness and safety trials are conducted with a fully integrated device prototype in an operational environment. Continuation of closely controlled studies of effectiveness and determination of short term adverse events and risks associated with the candidate product. Functional testing of candidate devices is completed and confirmed, resulting in final selection of prototype device. Regulatory agencies have approved continued development and testing. **TRL 7 Decision Criterion:** Second Phase clinical effectiveness and safety trials are completed. Final product design is validated, and final prototypes and/or initial commercial scale devices are produced. Data is collected, presented, and discussed with regulatory agencies. Agencies support continued development. Clinical endpoints and test plans agreed to by regulatory agencies. Next Phase clinical study plan is approved.
8	**System complete & qualified** Manufacturing process validated. Pre-market application submitted and approved for medical device. Device demonstrated in real life conditions, support structure in place for technical problems.	**Actual System Completed and Qualified through Test and Demonstration** Technology has been proven to work in its final form and under expected conditions. Implementation of expanded controlled and uncontrolled Phase 3 trials to gather information relative to the safety and effectiveness of the device. Trials are conducted to evaluate the overall risk-benefit of using the device, and to provide an adequate basis for product labeling. Process validation completed and followed by lot consistency/reproducibility studies. **TRL 8 Decision Criterion:** Approval of the device by national or international regulatory authorities.

TRL	Horizon Europe NCP Portal TRL Self-Assessment Tool.[43]	NATO TRL-Scale for Medical Devices.[44]
9	**Actual system proven in operational environment (competitive manufacturing in the case of key enabling technologies; or in space)** Medical device ready to be acquired by clients & end users.	**Actual System Operationally Proven through Successful Mission Operations** Application of the technology in its final form and under mission conditions. Post-Marketing studies (clinical or non-clinical) may be required by national or international regulatory authorities. **TRL 9 Decision Criterion:** None – continue (Post Marketing) surveillance.

Concluding remarks

Within the present state of the art, transplantation from a human donor is by far the best form of KRT that mankind presently has. Xenotransplantation recently has made remarkable steps forward, but it would be highly unlikely to expect that xenotransplantation would require less immune suppression compared to human transplantation.

For the group of patients that cannot be transplanted better forms of KRT are needed than the presently at hand PD and HD modalities, possibly enhanced by oral sorbents. We summarized the main developments that are presently being worked upon and provided links to websites that are actively maintained to offer overviews of new devices for home dialysis.

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Chapter 3

Immunosuppression medications

Learning objectives

- To explain the rationale behind the current immunosuppression strategy in kidney transplantation.
- To describe the mechanism of actions of the most common immunosuppressants.
- To identify and apply appropriate administration and common doses of immunosuppressive drugs in the clinical setting.
- To recognise and manage expected side effects and troubleshooting.

Introduction

In the 1950s, during the early days of kidney transplantation, graft survival rates were dismal due to frequent rejection episodes, largely because effective immunosuppressive agents were unavailable. At that time, steroids were the cornerstone of immunosuppressive therapy, despite their significant side effects, including weight gain, diabetes, and osteoporosis.

In the early 1960s, the development of azathioprine added another important tool to the immunosuppressive armamentarium.[1] Azathioprine works by inhibiting the proliferation of immune cells, which helps to prevent the rejection of the transplanted kidney. When used in combination with corticosteroids, this combination significantly improved transplant outcomes.

Nonetheless, a game-changer in transplant immunosuppression arrived in 1983 with the introduction of *cyclosporine*, an immunosuppressant belonging to the class of calcineurin inhibitors (CNI) that specifically inhibits T-cell activation (a key component of the immune response).[2] Cyclosporine drastically improved kidney transplant survival rates, and its introduction is often considered one of the major milestones in organ transplantation. It allowed transplant physicians to use lower doses of corticosteroids, thereby reducing some of the negative side effects that the first transplant patients experienced. Cyclosporine is still used today, even though its role has been largely replaced in most developed countries by a newer version of CNI, tacrolimus.

At the same time, the development of polyclonal antibodies (e.g., anti-thymocyte globulins, ATG) and monoclonal antibodies (e.g., basiliximab) laid the foundation for induction therapy, a more aggressive form of immunosuppression used at the time of transplantation to help prevent early rejection.[3] In the 1990s, the introduction of the anti-proliferative agent mycophenolate and mTOR inhibitors, such as everolimus and sirolimus, offered new alternatives to azathioprine, which had been the standard immunosuppressant since the 1960s.[4,5] In recent years, the most important novelty in immunosuppression is constituted by the introduction of the so-called inhibitors of co-stimulation, that prevents T cells activation in an early phase.[6]

1. Pathophysiology of rejection

Alloreactivity refers to the activation of the immune system in response to an alloantigen, which is an antigen derived from another individual of the same species and that is recognized as foreign. Proteins that are identical between individuals, for example albumin or collagen, do not generate an alloimmune response since the immune system does not recognize them as foreign. Conversely, proteins that vary among individuals, meaning that they are polymorphic, can trigger an alloimmune response. This is the case of the HLA (Human Leukocyte Antigens) proteins, the most polymorphic systems present in the human species. Apart from HLA-identical siblings, almost 100.0% of recipient-donor pairs present at least 1 HLA incompatibility. These polymorphic antigens are recognized as foreign by the immune system, prompting activation of recipient T cells and initiating the process of graft rejection.[7]

The activation of T cells starts with the presentation of the antigen by another cell, usually a dendritic cell, which can be of either donor's or recipient's origin. Crucially, the dendritic cell must deliver a co-stimulatory signal to trigger T cell activation. Upon recognizing the antigen, T cells activate calcineurin, a cytoplasmic enzyme that induces nuclear transcription of inflammatory and replication genes. Subsequently, T cells stimulate their own replication by secreting interleukin-2 (IL-2), a cytokine that signals for cell proliferation. This proliferation is driven by the activation of intracellular pathways, including mTOR (Mammalian Target of Rapamycin), and the synthesis of nucleotides required for rapid T cell expansion.[8]

All these steps in T cell activation are precisely the points where current immunosuppressive drugs intervene to block the immune response at different stages. Early activation of T cells is prevented by Calcineurin inhibitors (CNI), i.e. cyclosporine or tacrolimus, or co-stimulatory inhibitors. T cell self-activation signal to replicate is blocked by IL-2 receptor antagonists, such as Basiliximab. Proliferation of activated T cells is blocked by either mTOR inhibitors, such as everolimus or sirolimus, or nucleotide synthesis inhibitors, such as mycophenolate or azathioprine. Inflammatory and replication genes activation is blocked by steroids, while broad T cell depletion can be achieved by using polyclonal anti-thymocyte antibodies (Figure 1).

Nowadays, kidney transplant recipients usually receive a combination of calcineurin inhibitors, antimetabolites, and steroids which are used at high dose in the early post-transplant period and slowly tapered afterwards. In developed countries, the most common immunosuppressive strategy consists in the CNI tacrolimus, associated with either the antiproliferative mycophenolate or with a mTOR inhibitor as a valid alternative. The treatment schedule depends on the nature of the surgery, the risk of graft rejection and recipients' characteristics, among other factors. The aim is to maintain an effective balance between suppressing the immune system to prevent graft rejection and avoiding excessive doses, which can increase the risk of infections and other complications.

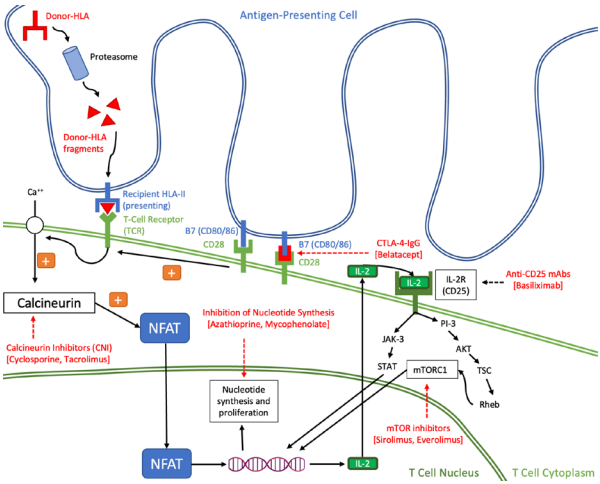


Figure 1: Pathway of T cell activation upon presentation of a donor HLA antigen and action of common immunosuppressants.

Upon alloantigen presentation and costimulatory signalling (B7/CD28 interaction) by dendritic cells, T cells activate calcineurin, a cytoplasmic enzyme that transduces the signal into the nucleus via Nuclear Factor of Activated T Cells (NFAT). This critical initial step can be inhibited by calcineurin inhibitors (CNI) such as cyclosporine or tacrolimus, or by co-stimulation blockers like Belatacept. Once activated, NFAT triggers inflammatory and replication gene expression, leading to the proliferation of alloreactive T cells under the stimulus of IL-2, which can be blocked by the monoclonal antibody Basiliximab. Downstream signalling for T-cell replication depends on the mTOR pathway, which can be inhibited by mTOR inhibitors such as Everolimus or Sirolimus. Finally, DNA replication is essential for T-cell proliferation and can be interfered with by nucleotide synthesis inhibitors, such as Azathioprine and Mycophenolate.

2. Types of immunosuppression (ISS)

The purpose of immunosuppression is to prevent the immune system from rejecting the kidney graft while still maintaining the body's ability to fight off serious infections and minimizing side effects. However, achieving this delicate balance with a single drug has not been possible to date.

Current approaches typically involve a combination of drugs that target different points in the immune response, specifically T cell activation upon antigen presentation. The combination of different drugs allows each one to be administered at a reduced dosage, thereby preventing excessive side effects. Immunosuppressive drugs can be classified based on the time at which they are used, as either induction or maintenance.

2.1. ISS for induction

Transplant guidelines recommend induction therapy for all patients undergoing kidney transplantation, as it has been shown to reduce the incidence of early rejection.[9] Induction must start before the transplant procedure, usually in the operating theatre, and is based on a steroid pulse (250-1000mg), combined with either anti-IL2 receptor basiliximab or polyclonal anti-thymocyte globulins (ATG). The choice between basiliximab and ATG is generally determined by the immunological risk. ATG is used in high-risk cases, such as patients with previous transplants, those with pre-formed antibodies,

or when the kidney has experienced significant ischemic injury.[10] On the other hand, basiliximab is preferred in most low-risk scenarios due to its more targeted action with fewer side effects.[11]

Anti-thymocyte Globulins (ATG)

Mechanism of action: Anti-thymocyte globulins (ATG) are antibodies against human lymphocytes generated in rabbits (rATG) or horses (equine ATG) immunized with human thymocytes (thymus-derived lymphocytes). ATG causes unspecific lysis of recipient's lymphocytes, with the aim of causing a transient lymphopenia.[12]

Storage: ATG should be stored refrigerated at a temperature between 2°C and 8°C (36°F to 46°F) and should not be frozen, as freezing can damage the medication and reduce its efficacy. It should be kept in a dark place, away from direct light, since some formulations may be light-sensitive, and should always be stored in its original packaging.

Administration: ATG should be administered through a central venous catheter. Before administration, it is recommended to pre-medicate the patient with the corresponding dose of corticosteroids and a first-line analgesic to minimize adverse reactions. The dilution of ATG varies based on the manufacturer's recommendations but is typically prepared in saline solution at a concentration of 1 to 5 mg/mL. This prepared medication will be connected to the infusion set at its distal end. A 0.2-micron filter will be required for the set connection to the central venous catheter as it serves as an additional barrier to prevent infections, but most importantly, it prevents the passage of large particles produced by protein aggregation that can occur with this type of medication, thereby avoiding the risk of immunological reactions or embolism. The infusion generally should last between 4 or 6 hours, according to the manufacturer's instructions. It is a common precaution that the rate during the first dose should be at least 6 hours to carefully monitor the occurrence of cytokine release syndrome (CRS).

Dosage: The dose of polyclonal anti-thymocyte globulins (ATG), such as Thymoglobulin (Sanofi), is typically adjusted based on the patient's body weight (in kg) and is administered over several days, with the first dose usually given in the operating room during the transplant procedure. For example, the FDA-approved dose of Thymoglobulin for induction in kidney transplantation is 1.5 mg/kg

per day for 4-7 days. However, the exact dosage and duration may vary depending on the specific commercial brand being used, as well as local protocols and individual patient factors.

Side effects: Cytokine release syndrome (CRS) can be observed, especially when infusion rate is fast and can manifest mildly with fever, chills, hypotension, headache and nausea. Moderate to severe CRS can progress to hemodynamic instability and respiratory distress. As soon as after receiving the first dose, patients can experience leukopenia and low platelets counts. The profound immunosuppression induced by ATG leads to an increased risk of bacterial and viral infections, which can occur even months after its administration. In the long-term, the use of Thymoglobulin in combination with multiple immunosuppressive agents has been linked to an increased incidence of malignancies, including lymphoproliferative disorders (LPD), other lymphomas, and solid tumours.

Troubleshooting: Mild cases of CRS can be managed by temporarily halting the administration or slowing down the infusion rate. In the induction phase, steroids are usually administered before ATG to reduce the possibility of CRS. Other preventive or treatment measures for CRS include antihistamine such as dexchlorpheniramine (5mg) and antipyretic drugs such as paracetamol (1g). Moderate to severe CRS can be life-threatening and must lead to prompt suspension of drug administration, treatment with high-dose steroids (up to 1g), anti-IL6 antibodies (tocilizumab 8mg/Kg), apart from the management of hypotension with intravenous fluids and vasopressors and respiratory support.

When administering ATG, it is crucial to ensure that the complete dose has been infused. One must also ensure that any remaining dose in the infusion set is administered at the end of the infusion. To achieve this, it is recommended to infuse an additional 20 mL of clean saline solution after the medication, maintaining the same infusion rate. It is important to monitor for the appearance of symptoms even after the administration is complete. To reduce the risk of anaphylactoid reactions in patients who have previously received ATG, such as those with a prior kidney transplant, the ATG formulation can be switched between rabbit and horse. Additionally, ATG can be used to treat moderate to severe cases of cellular rejection.

IL-2 receptor antibodies (Basiliximab):

Mechanism of Action: Basiliximab is a chimeric monoclonal antibody that binds to the alpha chain (CD25) of the IL-2 receptor on activated T-cells, inhibiting T-cell activation and their proliferation. Compared to ATG, basiliximab targets directly proliferating T cells and does not cause lymphopenia.[11]

Storage: Basiliximab should be stored in the refrigerator at 2°C to 8°C (36°F to 46°F) and should not be frozen, as freezing can damage its protein structure, potentially rendering it ineffective. It should be kept away from direct light, as it is light-sensitive and may degrade with prolonged exposure. To maintain its stability, it should always be stored in its original packaging.

Administration: Basiliximab should be diluted in an appropriate intravenous solution, typically 0.9% sodium chloride or 5% dextrose in water, following the manufacturer's guidelines. For a 20 mg dose, the medication is usually diluted in 100 mL of saline solution for infusion. It must be administered intravenously through a catheter inserted into either a central or peripheral vein under appropriate clinical supervision. The infusion should be given over a 30-minute period to ensure safe administration and minimize adverse reactions.

Dosage: The total dose is 40 mg administered over two days, 20mg on Day 0 and Day 4. The dose on Day 0 must be administered in the operating theatre.

Side Effects: Hypersensitivity/anaphylactoid reactions are uncommon. The incidence of infectious and neoplastic diseases in the long term were not different from that in the placebo group in pivotal clinical trials. Reported adverse effects include hypotension, tachycardia, cardiac failure, dyspnoea, wheezing, bronchospasm, pulmonary oedema, respiratory failure, urticaria, rash, pruritus, and/or sneezing.

Troubleshooting: In comparison with ATG, basiliximab is used only for induction and not for treating rejection. Since it is a medication that can be administered through a peripheral catheter, it is important to monitor the venous access before, during, and after administration to prevent extravasation.

2.2. ISS for maintenance

Maintenance immunosuppression is a lifelong treatment for all kidney transplant recipients. Low compliance is the most common cause of chronic graft rejection, leading to poor graft survival.[7] Patients must be aware of this risk and educated before discharged. Immunosuppressants for maintenance are commonly combined to ensure maximum efficacy to prevent rejection and to minimize side effects as much as possible.

Calcineurin Inhibitors (CNI)

Tacrolimus (Prograf, Advagraf, Envarsus)

- **Mechanism of action:** Tacrolimus inhibits calcineurin, a cytoplasmic enzyme responsible for early activation of T cells upon alloantigen recognition and co-stimulation signal by dendritic cells. Since this is the first step of the alloimmune response, inhibiting calcineurin represents the most important step to prevent rejection.
- **Administration:** Original tacrolimus formulations were based on twice daily oral administration (e.g. Prograf, Astellas). Most recent formulations (e.g. Advagraf, Astellas; Envarsus, Chiesi) are based on once-daily oral administration. Tacrolimus absorption is heavily influenced by food intake and gastrointestinal motility, so it must be taken on an empty stomach (at least 1 hour before the meal).
- **Dosage:** The starting dose is 0.1-0.2 mg/kg, divided into two doses for the twice-daily formulation (Prograf, Astellas). For once-daily formulations, the usual starting dose is 0.1 mg/kg for Advagraf (Astellas) and 0.07 mg/kg for Envarsus (Chiesi). Two to three days after the first dose, checking blood trough levels is recommended to adjust the dose to the target range. During the first two weeks after transplantation, tacrolimus trough levels should be monitored two to three times per week. Thereafter, trough levels should be checked at every patient visit. Target trough levels typically range between 4 and 8 ng/mL, but adjustments may be made based on the patient's immunological risk and time from transplant.
- **Side effects:** Apart from the increased incidence of infectious and neoplastic complications common to many

immunosuppressants, tacrolimus-specific side effects include diabetes, hypertriglyceridemia, hypercholesterolemia, gastrointestinal disturbances (e.g., nausea, diarrhoea), hypertension, electrolyte imbalances (e.g., hypomagnesemia, hyperkalaemia), alopecia, and neurological disturbances such as tremor, headache, insomnia, confusion, and, in severe cases, seizures. Tremor is a frequent side effect, especially in the first months after kidney transplantation, and can be debilitating, particularly in frail or elderly patients. It can be managed using some beta-blockers, such as propranolol, and it may indicate high trough levels. Counterintuitively, tacrolimus can also be nephrotoxic. It is a common clinical observation that elevated tacrolimus trough levels are linked to a decline in kidney function. However, this effect is typically transient, with kidney function recovering once trough levels normalize. In contrast, long-term nephrotoxicity remains a significant concern, requiring continuous lifelong dose adjustments to keep trough levels within the therapeutic range. This balance is crucial to prevent rejection (associated with low trough levels) while minimizing nephrotoxicity (associated with high trough levels).[13]

- **Troubleshooting:** If a dose is missed, it is important to consider the patient's fasting status. If they are still fasting, the missed dose should be taken as soon as possible. However, if the patient has already eaten, the healthcare provider should determine the appropriate waiting time before taking the forgotten dose. In any case, the dose should not be doubled or altered. It is generally best to take the missed dose as soon as possible, if it is not too close to the next scheduled dose. Tacrolimus is metabolized in the liver by the CYP3A4 enzyme, whose baseline activity varies significantly among individuals. As a result, the same dose of tacrolimus can lead to low trough levels in fast metabolizers or high trough levels in slow metabolizers, depending on genetic background. Additionally, CYP3A4 activity can be inhibited or induced by various drugs and certain foods, necessitating caution. Healthcare providers should advise patients to avoid specific foods, such as grapefruit, and adjust dosages while monitoring trough levels whenever a patient is prescribed a medication that interacts with CYP3A4. A list of common drugs affecting CYP3A4 is provided in Table 1.

Table 1: List of most common drugs that can alter tacrolimus trough levels by either inhibiting or inducing the enzyme responsible for its metabolism (CYP3A4).

Drug Class	Example of drugs	Effect on CYP3A4	Effect on Tacrolimus trough levels
Macrolide antibiotics	Azithromycin Clarithromycin Erythromycin	Inhibitor	Increase tacrolimus trough levels , leading to higher incidence of side effects.
Azole antifungals	Fluconazole Voriconazole Ketoconazole Itraconazole	Inhibitor	
Calcium channel blocker	Verapamil Diltiazem	Inhibitor	
HIV protease inhibitor	Ritonavir Cobicistat	Inhibitor	
Miscellaneous	Amiodarone	Inhibitor	
Rifamycins	Rifampicin	Inducer	Decrease tacrolimus trough levels, leading to higher likelihood of rejection.
Antiepileptics	Carbamazepine Phenytoin Phenobarbital Oxcarbazepine	Inducer	
HIV non-nucleoside reverse transcriptase inhibitors	Efavirenz	Inducer	
Herbal supplements	St. John's Wort	Inducer	

Cyclosporine (Neoral, Sandimmune)

- **Mechanism of action:** Like tacrolimus, cyclosporine inhibits calcineurin, thereby blocking early T-cell activation upon recognition of donor antigens. The significance of this pathway is underscored by the substantial improvement in kidney graft survival following the introduction of cyclosporine in 1983.[2] Since then, calcineurin inhibitors (CNI) have remained the cornerstone of maintenance immunosuppressive therapy. However, cyclosporine is now rarely used, as the newer CNI, tacrolimus, is preferred worldwide due to its superior efficacy and more favourable side effect profile.

- **Administration:** Cyclosporine is available in twice-daily oral formulations and must be taken consistently in relation to meals, as its absorption is significantly affected by food intake and gastrointestinal motility. The first commercial formulation, Sandimmune (Novartis), is oil-based and depends on bile for absorption, leading to unpredictable pharmacokinetics. In contrast, the newer formulation, Neoral (Novartis), is a microemulsion that does not rely on bile for absorption, resulting in more predictable trough levels and improved bioavailability.
- **Dosage:** cyclosporine is usually administered at a starting dose of 10 to 15 mg/kg divided in two doses. This high dose is usually tapered down in the first two weeks after transplant to a final target of 2 - 6 mg/kg, with trough levels typically being between 150 and 250 ng/ml early post-transplant, tapering progressively down to 50-150 ng/ml at the end of the first year.
- **Side effects:** The side effect profile of cyclosporine closely resembles that of tacrolimus. However, cyclosporine is more strongly associated with hypertension, hypertriglyceridemia, hypercholesterolemia and nephrotoxicity, raising concerns about long-term graft survival. In contrast, it has a lower risk of new-onset diabetes and fewer neurological side effects, such as tremors, confusion, or seizures. In clinical practice, patients may be switched from tacrolimus to cyclosporine in cases of uncontrolled diabetes or neurological disturbances, especially in elderly patients when these adverse effects cannot be managed otherwise. Cyclosporine-specific side effects include hirsutism, which is particularly common in women, and gingival hyperplasia, which can lead to dental complications and requires good oral hygiene to minimize severity. Despite these side effects, cyclosporine remains a viable alternative even today for select patients who experience intolerable adverse effects from tacrolimus.
- **Troubleshooting:** Cyclosporine is metabolized in the liver by the CYP3A4 enzyme, like tacrolimus, making it susceptible to drug and food interactions that should be carefully managed (Table 1).

Antiproliferative Agents

Mycophenolate

- **Mechanism of Action:** Mycophenolate inhibits the enzyme inosine monophosphate dehydrogenase, which is essential for purine synthesis. Since purine synthesis is crucial for DNA replication, blocking this pathway effectively halts the proliferation of alloreactive T and B cells. Due to its immunosuppressive properties, mycophenolate is commonly used in combination with calcineurin inhibitors (CNIs) as part of maintenance therapy in transplantation.[4]
- **Administration:** Mycophenolate is available in two formulations: the first developed was mycophenolate mofetil (MMF, e.g., CellCept, Roche), followed by the enteric-coated mycophenolate sodium (MPA, e.g., Myfortic, Novartis). MMF is a prodrug that is converted into the active compound, mycophenolic acid, upon absorption. In contrast, the enteric-coated formulation delivers mycophenolic acid directly to the small intestine, bypassing the stomach, which improves gastrointestinal tolerability. MPA is available only in tablet form, while MMF is available in tablets, oral suspension, and intravenous formulations.
- **Dosage:** The initial dose for both is typically twice daily, with 1000 mg of MMF (2000 mg/day) and 720 mg of MPA (1440 mg/day). Over time, this dose is often reduced for maintenance therapy, typically to 500 mg twice daily (1000 mg/day) for MMF and 360 mg twice daily (720 mg/day) for MPA, depending on the patient's immunological risk and drug tolerance. In cases of poor drug tolerance, further dose reductions to 250 mg or 180 mg twice daily for MMF or MPA, respectively, may be considered. Mycophenolate should ideally be taken on an empty stomach, as food may interfere with its absorption. MPA is less affected by food due to its enteric-coated formulation but taking it on an empty stomach is still recommended for optimal absorption. If taken with food, both formulations should be taken consistently the same way to maintain stable drug levels and minimize fluctuations.
- **Side effects:** The most common side effects of mycophenolate include gastrointestinal disturbances such as nausea, vomiting, diarrhoea, abdominal pain, and flatulence, as well as

haematological abnormalities, including leukopenia, anaemia, and thrombocytopenia. The enteric-coated formulation offers improved gastrointestinal tolerance, reducing the incidence of these side effects. Additionally, mycophenolate is teratogenic and is therefore contraindicated during pregnancy.

- **Troubleshooting:** In patients with low kidney function, excretion of mycophenolic acid metabolites is impaired, leading to increased incidence of side effects. It is common clinical practice to reduce MPA/MMF dose in this setting.

Azathioprine

- **Mechanism of Action:** Azathioprine is a purine analogue that inhibits DNA synthesis, which suppresses the proliferation of T-cells and B-cells. After its administration azathioprine is converted in the body to its active form, 6-mercaptopurine. It inhibits purine synthesis, which is essential for DNA production, thus limiting immune cells proliferation.
- **Administration:** Its use is not common since the introduction of mycophenolate due to the latter's more favourable side effects profile. It can still be used in certain patients in association with CNI when mycophenolates's side effects are intolerable and patients cannot be switched to mTOR inhibitors. It is usually administered orally in tablet form, but an intravenous formulation also exists.
- **Dosage:** The typical starting dose for adults is 1 to 2 mg/kg of body weight per day, divided into one or two doses. It can be taken with or without food, although taking it with food can help reduce gastrointestinal effects such as nausea. To monitor the patient's response to the drug, regular blood tests are necessary, including liver function and blood cell counts, since azathioprine can affect bone marrow and liver function. Intravenous azathioprine is used in more acute settings, when patients are unable to take oral medications or in certain hospital situations.
- **Side Effects:** The most common and dreadful azathioprine-specific side effect is leukopenia, followed by low platelet count and gastrointestinal problems, such as nausea and anorexia. Liver toxicity is also a rare event but should be monitored.

Alike mycophenolate, azathioprine is teratogenic and must be avoided in pregnancy.

- **Troubleshooting:** The risk of leukopenia is increased in patients with genetic defects in thiopurine S-methyltransferase (TPMT), an enzyme involved in the metabolism of azathioprine. Individuals with low to absent TPMT activity are particularly vulnerable to severe, potentially fatal neutropenia when exposed to azathioprine. Additionally, xanthine oxidase inhibitors, such as allopurinol, should be avoided as they also interfere with azathioprine metabolism, further increasing the risk of toxicity.

mTOR Inhibitors

- **Mechanism of Action:** Sirolimus and Everolimus inhibits the mTOR pathway, which is important for cell cycle progression and T-cell activation. They prevent T-cell proliferation in response to IL-2.[14]
- **Administration:** Both drugs are typically used in combination with a calcineurin inhibitor, such as tacrolimus. Sirolimus is administered once daily, whereas everolimus requires twice-daily dosing. Both are taken orally and can be administered with or without food.
- **Dosage:** Sirolimus is initiated post-transplant at a daily dose of 1-2 mg, while everolimus is started at 1-1.5 mg twice daily. Dosages are adjusted to achieve target trough levels of 3-5 ng/ml.
- **Side Effects:** Metabolic side effects of mTOR inhibitors include hypertriglyceridemia, hypercholesterolemia, and diabetes, increasing cardiovascular risk. Delayed wound healing is a concern, particularly in obese patients or those who have undergone complex surgeries. Post-surgical lymphocele is another frequent complication in patients receiving mTOR inhibitors. Common gastrointestinal side effects include nausea, abdominal pain, and mouth ulcers. Although rare, severe complications such as non-infectious pneumonitis and thrombotic microangiopathy require prompt recognition to allow timely drug discontinuation.
- **Troubleshooting:** In patients with a functioning graft whose immunosuppression regimen includes mTOR inhibitors, these

medications may be temporarily discontinued before complex surgeries to promote wound healing. During this period, mTOR inhibitors can be replaced with mycophenolate and reintroduced once the surgical scar has fully healed.

Corticosteroids

- **Mechanism of Action:** Corticosteroids (CS) work by suppressing the overall immune response through multiple mechanisms, including inhibition of cytokine production and T-cell activation. Prednisone is a corticosteroid that, once converted into its active form (prednisolone) in the liver, binds to glucocorticoid receptors in immune cells. This complex moves into the cell nucleus, where it alters gene expression, leading to a decrease in the production of pro-inflammatory and proliferation cytokines, reducing inflammation and replication of alloreactive T cells.
- **Administration:** Corticosteroids (CS) are administered either orally, as prednisone or methylprednisolone, or intravenously, as methylprednisolone. They are used in both the induction and maintenance phases of immunosuppressive therapy. Additionally, steroid pulses are employed for the treatment of rejection.
- **Dosage:** At induction, corticosteroids (CS) are administered as an intravenous pulse (250-1.000 mg) in the operating theatre. In the initial post-transplant days, patients typically receive intravenous methylprednisolone at 0.5 mg/kg until they can tolerate oral medication. Thereafter, the dosage is gradually tapered according to institutional protocols. Tapering generally continues until reaching a maintenance dose of 2.5-5 mg of prednisone daily by the second- or third-month post-transplant. Complete CS withdrawal may then be implemented gradually. In patients with very low immunological risk, however, steroid withdrawal can be achieved as early as the first week after transplantation.
- **Side Effects:** Beyond an increased risk of infections, CS have a broad range of side effects. They can cause fluid retention and increased appetite, often leading to weight gain. Metabolic complications include diabetes, hypercholesterolemia, and hypertriglyceridemia, increasing cardiovascular risk. In

children, chronic CS therapy can result in growth suppression. Neuropsychiatric effects range from mood swings, irritability, and insomnia to more severe conditions such as anxiety, depression, or euphoria. Long-term corticosteroid use is also associated with osteoporosis, Cushing's syndrome, hypertension, cataracts, and glaucoma. Avascular necrosis of the femoral head, though rare, is a severe and potentially debilitating complication. Additionally, prolonged use can cause muscle weakness or atrophy, particularly in the lower limbs, increasing the risk of frailty. Corticosteroids also induce skin changes, including easy bruising (purpura), acne, folliculitis, hirsutism, and red striae (stretch marks), particularly on the abdomen and thighs. Wound healing may also be impaired due to skin thinning and reduced collagen synthesis.

- **Troubleshooting:** Chronic prednisone therapy suppresses adrenal gland function, reducing natural cortisol production. Abrupt discontinuation can lead to withdrawal symptoms, making gradual tapering essential to prevent adrenal crisis.

Other Agents

Belatacept

- **Mechanism of Action:** Belatacept interferes with T-cell activation by preventing the co-stimulatory signal required for T-cell activation. This results in T cell anergy and absence of response to the alloantigen presented by the dendritic cell.[6]
- **Administration:** Belatacept serves as an alternative to calcineurin inhibitors (CNIs) and is typically used in patients with contraindications to CNIs. Belatacept is administered via intravenous infusion and can be administered either through a peripheral vein or a central venous catheter. The infusion is given over 30 minutes and should be performed in a clinical setting. Premedication like antihistamines or corticosteroids may be given to reduce the risk of infusion-related reactions. Belatacept must be stored in a refrigerator at 2°C to 8°C (36°F to 46°F), and any unused product should be discarded.
- **Dosage:** Belatacept is initiated before transplantation at a dose of 10 mg/kg and administered again on days 5, 14, and 28, as well as at the end of the second- and third-months post-

transplant, maintaining the same dosage. Starting from the fourth month, the dose is reduced to 6 mg/kg and can be administered monthly, with a flexibility of ±3 days to accommodate the patient's schedule. Belatacept can also be used to convert a patient previously receiving a calcineurin inhibitor (CNI). The recommended conversion schedule involves administering a 6 mg/kg dose every two weeks for the first eight weeks, followed by monthly administration. CNI tapering until suspension is usually performed during the first month of conversion.

- **Side Effects:** as all immunosuppressants, belatacept increases risk of infection and malignancies. Other side effects include infusion-related reactions (fever, chills, nausea), anaemia, thrombocytopenia, elevated liver enzymes, gastrointestinal issues, fatigue, skin reactions and headaches. The most serious side effect is post-transplant lymphoproliferative disorder (PTLD).
- **Troubleshooting:** Belatacept is contraindicated in EBV-negative patients due to the increased risk of post-transplant lymphoproliferative disorder (PTLD).

Rituximab

- **Mechanism of Action:** Rituximab is an anti-CD20 antibody targeting B cells and is used in various clinical contexts, including desensitization for ABO-incompatible kidney transplantation, treatment of antibody-mediated rejection, and the treatment or prevention of recurrent glomerulopathies in the graft, such as focal and segmental glomerulosclerosis.
- **Storage:** Rituximab should be stored in a refrigerator at a temperature between 2ºC and 8ºC (36ºF to 46ºF) and must not be frozen. It should be protected from light and kept from shaking, as agitation can potentially damage the medication. This treatment is typically prepared by pharmacy professionals in a hospital setting before administration, following the manufacturer's guidelines. The preparation process includes reconstitution, handling, and preparing the infusion to ensure safe and effective delivery to the patient.
- **Administration:** Rituximab is administered through an intravenous infusion. Prior to the first infusion, any previous

hypersensitivity to Rituximab or other similar medications should be assessed, as well as for conditions that could affect the treatment (e.g. infection or liver issues). To minimize the risk or infusion reactions, antihistamines, acetaminophen, and sometimes corticosteroids, are usually administered 30 minutes before the administration. The infusion rate of rituximab should be specified by the pharmacy according to the dose administered. The recommended initial infusion rate is 50 mg/h, and after the first 30 minutes, it can be increased in increments of 50 mg/h every 30 minutes, up to a maximum of 400 mg/h. For subsequent infusions, if the first one has been well tolerated, the infusion rate can start at a rate of 100 mg/h, scaling up every 30 minutes. Monitoring before, during and after the administration is crucial to observe any possible reaction.

- **Dosage:** Rituximab is typically administered as part of a treatment regimen designed to eliminate antibodies, such as those targeting ABO or HLA antigens, which includes plasma exchange and intravenous immunoglobulins. In this context, Rituximab is given at both the beginning and the end of the treatment cycle at a dose of 0.5-1 g or 375 mg/m^2 body surface area.[15]
- **Side effects:** Infusion reactions are common and may be even life-threatening, especially during the first dose, and may manifest with bronchospasm, fever, nausea, hypotension and angioedema. Monitoring before, during and after the administration is crucial to detect any of these. In the medium- to long-term, Rituximab can develop hypogammaglobulinemia due to B cell depletion, increasing the incidence of infectious disease, including common bacterial, viral and fungal infections, as well as rare infectious such as progressive multifocal leukoencephalopathy (PML) caused by the JC virus. Interstitial lung disease or pneumonitis is a rare but severe side effect. Other common side effects include bone marrow suppression, hypotension/hypertension, arrhythmias and alopecia.
- **Troubleshooting:** To prevent infusion reactions, Rituximab is usually administered following prophylaxis with an intravenous antihistamine (e.g. Dexchlorpheniramine 5mg), paracetamol (0.5-1g) and, sometimes, a corticosteroid as mentioned in the administration section.

3. Standard treatment plans

All immunosuppressive regimens consist of an induction phase, followed by a maintenance phase, which patients must adhere to for the entire lifespan of the graft to prevent rejection and ensure long-term transplant success. A schematic representation of a common immunosuppressive regimen for low-risk kidney transplant recipients is depicted in Figure 2.[16]

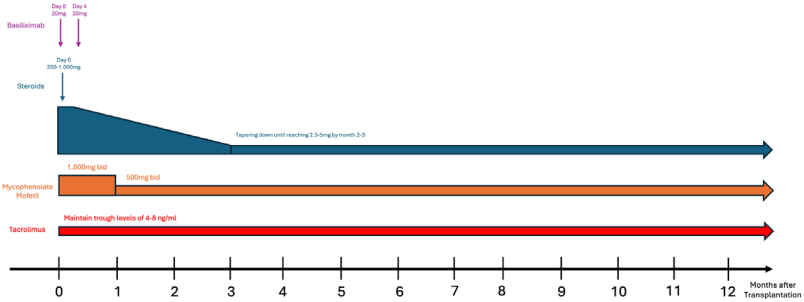


Figure 2: Classical immunosuppressive regimen for low-immunological risk kidney transplant recipients, consisting of induction with basiliximab and maintenance therapy with tacrolimus, mycophenolate, and steroids.

The induction phase begins in the operating theatre before graft reperfusion and typically includes Basiliximab or Anti-Thymocyte Globulin (ATG), accompanied by a steroid pulse.

- Basiliximab is preferred for low-risk kidney transplant recipients, such as first-time transplant patients with a low risk of rejection.
- ATG is reserved for medium- to high-risk recipients, including those at high risk of rejection or cases where the graft has experienced significant ischemia-reperfusion injury, which increases the risk of rejection.
- Steroid pulse therapy (250-1.000 mg) is administered first in the operating theatre before ATG or Basiliximab.

Maintenance therapy typically consists of a three-drug regimen, including i) a calcineurin inhibitor (CNI), ideally tacrolimus, combined with ii) either mycophenolate or an mTOR inhibitor, and iii) a steroid.

- Tacrolimus can be initiated pre-transplant or delayed post-transplant in cases where the graft is highly susceptible to CNI-induced nephrotoxicity, such as following severe ischemia-reperfusion injury.

- Mycophenolate can be started before or after surgery and administered intravenously if oral intake is not tolerated.
- mTOR inhibitors (e.g., everolimus, sirolimus) are typically initiated on postoperative days 0-1.17
- The steroid pulse at induction (250-1000 mg) is administered intraoperatively before ATG or Basiliximab. Some guidelines recommend early steroid withdrawal with rapid tapering within the first week post-transplant, but this is commonly performed only in very low-risk recipients. In most patients, steroids are gradually reduced to a maintenance dose of 2.5-5 mg by the second- or third-month post-transplant. Further tapering and potential withdrawal should be approached cautiously based on the patient's immunological risk.

Treatment for rejection

Mild cases of cellular rejection, caused by alloreactive T cells infiltrating the graft, are treated with steroid pulses (250-1.000 mg) administered once daily for three days. Moderate to severe cases require additional treatment with anti-thymocyte globulin (ATG), such as Thymoglobulin at 1.5 mg/kg for 3-5 days, alongside steroid pulses.

Antibody-mediated rejection (ABMR) is managed by eliminating donor-specific antibodies through a regimen of plasma exchanges alternating with intravenous immunoglobulins (IVIG). A typical course consists of 5-6 plasma exchanges, with IVIG administration (200–300 mg/kg) every 2-3 sessions. Rituximab (0.5-1 g) is administered at both the beginning and end of the treatment cycle to prevent the development of newly formed donor-specific antibodies. Additionally, in ABMR, three steroid pulses (250–1,000 mg) are usually administered at the beginning of the cycle to reduce graft inflammation.

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Chapter 4

Complications of kidney Transplantation

Learning objectives

The healthcare professionals should be:

- aware of kidney transplant complications
- able to identify and recognize symptoms and signs of kidney transplant complications
- able to establish early diagnose in order to provide suitable treatment and prompt intervention.

Introduction

Kidney transplantation is the most cost-effective therapy for end-stage kidney disease (EKSRD). Observed improvements in mortality and morbidity have been attributed to patient selection, surgical technique, perioperative management, and immunosuppressive regimens. Early graft failure is most often due to acute rejection, technical problems, and nonviable kidneys, while chronic failure can stem from user death with a functioning graft and chronic kidney disease (CKD). Currently, 4.8% of post-transplant patients have resumed dialysis.

Complications may be grouped into surgical, infectious, immunological, and metabolic categories. Surgical complications occur with a frequency between 2% and 30%, have the greatest influence on early graft outcome, and include haemorrhage, urine leakage, vascular complications, and wound infections. Infectious complications appear in 20-65% of transplant recipients and represent the most common cause of morbidity and mortality. Immunological complications represent the main cause of late graft loss (acute and chronic rejection) and include recurrence of the original glomerulonephritis in the donated grafts. Metabolic complications encompass post-transplant diabetes mellitus, hypertension, hyperlipidaemia, gout, and bone disease.[1]

1. Overview of Complications

Kidney transplantation is considered the most cost-effective therapy for ESRD. Despite the 5-year survival rate for patients with a functioning kidney transplant being markedly better than that for

individuals on dialysis (85.5% versus 35.8%), a significant number of kidney transplant recipients experience complications. These can be classified as pathological or surgical and include graft-endangering issues such as vascular complications accounting for 3-15% of cases, and urologic complications like ureteral obstruction (3.0%), urinary leak (2.9%), bladder outlet obstruction (1.1%), and obstructive ureteral calculi (0.3%). Although these have traditionally been managed with open surgical procedures, advances in equipment have enabled more patients to be treated with less invasive techniques.[2]

Successful kidney transplantation relies on immunosuppression and an optimal surgical course with few complications. Studies reporting postoperative complications are often heterogeneous and lack systematic reporting. Evaluations of short-term and long-term complications indicate that within 30 days, 60% of patients experience at least one complication, with increasing age, previous transplantation, and low body mass index identified as factors increasing the risk of severe complications,[1] no associations have been found for long-term complications. Graft survival at two years is approximately 90%, but 30% of patients have lost the graft or died within five years. Early graft failure is mainly due to acute rejection, technical problems, or a nonviable kidney, whereas chronic failure may result from non-kidney-related death with a functional graft or CKD. Currently, 4.8% of post-transplant patients have returned to dialysis.[3]

2. Surgical Complications

The common surgical complications that occur after kidney transplantation include wound haematomas, wound infections, and ureteral injury, arterial injury, venous thrombosis, incisional hernia, arterial stenosis, vesicourethral occlusion, and lymphocele.[1] The incidence of surgical complications varies from 2.4% to 12.2%. Several factors affect the development of surgical complications: multiple vessels in the graft, right donor kidney, recipient BMI greater than 30, presence of atherosclerosis in the recipient, the experience of the surgeon, and deceased-donor transplantation. Obesity and deceased donor transplantation are found to be the most significant risk factors. Open wounds are treated with temporary negative pressure vacuum devices, and the majority of minor complications are treated conservatively, with only 4% requiring operative interventions.[2] Untreated arterial stenosis leads to deterioration of

the graft function, kidney dysfunction, and resistant hypertension that can contribute to graft loss. Most of these surgical complications respond well to endovascular interventions and successful treatment requires prompt diagnosis and early intervention.

2.1. Bleeding

Kidney transplantation is the preferred treatment for ESRD; however, the procedure is arthritogenic and associated with specific complications that may influence patient and graft survival.[4] Complications require an immediate and accurate diagnosis to provide prompt and effective treatment. Bleeding is the most common complication in the immediate postoperative course of kidney transplantation, and delayed bleeding is a catastrophic complication that can recur and necessitates aggressive intervention.[5]

2.2. Infection

Immunosuppression is generally of longer duration in kidney transplantation than in other types of organ transplants, and greater immunosuppression in the early phase after transplantation provides substantial benefit to the patient. However, the reduced host defences and the side effects of the agents used also predispose the patient to potentially serious infections. Kidney transplantation is accompanied by a high incidence of infections. These include infections by various bacteria, fungi, and viruses, many of which are part of the recipient's normal commensals and would not typically be pathogenic in individuals with an intact immune system.[6] Infectious complications such as urinary tract infections and tuberculosis are extremely common in the posttransplant period.[7]

2.3. Urinary Leak

Urine leak is among the most common early urologic complications of kidney transplantation, with reported incidence rates between 1.2% and 8.9%.[2] Such leaks can result from devitalization of the distal ureter or technical errors incurred during the transplantation procedure. Although the routine use of ureteral stents remains controversial, several studies have associated prophylactic stenting with reduced rates of urinary leakage. Initial management typically entails placement of a Foley catheter and percutaneous nephrostomy tube, followed by an antegrade ureteropyelogram to

localize and assess the severity of the leak. Large urinomas may be drained percutaneously. Definitive treatment has traditionally involved open surgical reimplantation with excision of devitalized ureter. Several small series have examined primary endourologic management, reporting success rates ranging from 36% to 87%, with a mean follow-up of 35 months). Contraindications to an endourologic approach include extensive contrast extravasation and inability to place a ureteral stent. Treatment involves simultaneous maximal decompression with nephrostomy, ureteral stent, and Foley catheter. After leakage has resolved, the nephrostomy tube and Foley catheter are removed, whereas the stent is maintained for 4 to 6 weeks. Close follow-up is necessary to detect stricture formation and silent obstruction.

2.4. Haematoma Formation

Haematoma formation remains a significant concern following kidney transplantation, attributable to the extensive tissue dissection and manipulation of blood vessels intrinsic to such procedures. Postoperative bleeding typically arises from small, sub-cutaneous vessels and is generally self-limiting. However, the ensuing haematoma may contribute to wound breakdown and predispose to secondary infection. More ominous is the prospect of haemorrhage arising in a deeper location, particularly within the confines of the transplant recess. Blood loss may then be considerably more severe and also potentially temper the flow of blood reaching the graft. Delayed bleeding, several days after kidney transplantation, is a catastrophic complication which may recur and necessitates aggressive intervention.[5]

Subcapsular haematomas, albeit rare in the transplant setting, may provide a further impetus to deteriorating graft function. The underlying mechanism of kidney compression, with a consequent reduction in blood flow, has mediators in common with recipient renovascular hypertension. Severity worsens as extrinsic pressure increases and transmission into the capillary bed, both glomerular and peritubular, becomes compromised. An initial drop in flow leads to the expected decrease in glomerular filtration rate and subsequent impairment of urine output. Nevertheless, the perfusion pressure within the kidney is also reduced, and this, by hindering kidney hydrostatic filtration pressure, will ultimately influence urine flow

even if the artery itself remains patent. A kidney Ultrasound (US) was performed on the patient to evaluate fluctuating kidney function and aid in the differential diagnosis of increased serum creatinine levels.[8]

The typical presentation in terms of resistive index is difficult to define. Where compressive impairment of blood flow is severe, an elevated resistive index is generally expected and may be associated with diastolic flow reversal in the intra-kidney arteries. Sub-capsular haemorrhage remains a surgical emergency and early reliable diagnosis therefore essential. Following confirmation by US, an effective course of action consists of urgent decompression and evacuation of the haematoma, bleeding site ligation and wound closure with or without packing.

3. Immediate Post-Transplant Complications

With over 90,000 kidney transplantations performed annually and a 15-year survival rate of approximately 40%, kidney transplantation is the preferred treatment for many with ESRD. This is made possible by significant progress in immunosuppressive medications and the resolution of surgical complications.[1] A successful kidney transplantation relies on immunosuppression to prevent rejection and an optimal surgical course with few complications. Short-term complications can delay optimal function of the new kidney or result in serious graft compromise. Immediate post-transplant complications encountered during the first month can be broadly sorted into vascular, urologic, and wound complications.[3]

3.1. Acute Rejection

Kidney transplantation has become the method of choice for treating nephrology disorders, although acute graft loss still occurs. In a 37-year retrospective study of 2,250 patients, 36% experienced acute graft loss during the first month after transplantation. Of these patients, 50% were men and 50% women. Graft rejection was most frequent during the first week, with 53 patients responding well to medical treatment, but 33 requiring nephrectomies. The onset of acute rejection during the initial weeks has a significant impact on the physical, mental, and economic well-being of the patient. Published studies highlight renal vein thrombosis as a potential cause of early graft failure and transplant rejection.[9]

3.2. Delayed Graft Function

Delayed graft function (DGF) refers to an acute kidney injury within the first week post-transplantation, characterized by the recipient's need for dialysis thereafter. This complication affects approximately 25% of deceased-donor and 4% of living-donor kidney transplant recipients. DGF arises from multifactorial causes, chiefly ischemia-reperfusion injury, and significantly elevates the risk of acute rejection and graft loss.[10]

DGF due to ischaemia-reperfusion injury emerges from the interplay of donor, recipient, and transplant procedure factors. Graft function typically improves within one to four weeks; however, DGF may persist for several months in some cases. The incidence of DGF declined during the 1990s, concomitant with advances in donor management and immunosuppression. However, the current trend toward greater use of marginal or extended-criteria donors, along with an increasing recipient burden of diabetes and hypertension, has led to an increase in DGF incidence.[10,11]

The severity and duration of DGF exert a significant influence on graft survival. The impact of DGF on graft survival at one year depends on the donor type and enrichment for acute rejection episodes during DGF, remaining substantial regardless of acute rejection occurrence.[12]

Strategies to prevent or minimise DGF include selection of suitable donors without hypotension, good oxygenation, and avoiding nephrotoxins to the donor; limiting cold ischaemia; and reducing warm ischaemia during implantation. Although the choice of preservation solution appears not to greatly influence DGF incidence, the use of in situ pump perfusion of kidneys is associated with a reduced incidence of DGF in kidneys from extended-criteria donors. Other approaches aimed at minimising ischaemic injury –such as remote ischaemic preconditioning and anti-inflammatory monoclonal antibodies– remain experimental. No treatment is available to accelerate recovery from DGF, and once it has developed, careful haemodynamic and fluid management, together with minimisation of nephrotoxic agents, offers the best prospect of the graft regaining function.[13]

3.3. Thrombosis

Arterial and venous kidney graft thromboses are infrequent but catastrophic complications of kidney transplantation. Such events frequently culminate in graft loss despite attempts at revascularization. Vigilant monitoring using Doppler US during the early post-transplantation period is critical, particularly in the setting of DGF. Early detection permits the performance of urgent thrombectomy and re-anastomosis, thus increasing the chances of graft salvage and enabling open surgical exploration when thrombosis is detected. However, unnecessary exploration should be avoided if no evidence of thrombosis exists.

Several risk factors for vascular thrombosis have been identified. Donor age below 6 years or above 60 years, recipient age below 5-6 years, perioperative hemodynamic instability, peritoneal dialysis, diabetic nephropathy, history of thrombosis, deceased-donor grafts, and prolonged cold ischemia time are strongly correlated with the occurrence of thrombosis. Multiple renal arteries and use of the right kidney constitute additional, albeit less severe, risk factors; the latter often relate to difficulties in vessel handling and technical aspects of anastomosis. Although many of these factors are not amenable to modification, some protective measures have demonstrated efficacy. In particular, aggressive fluid management before and during the operative period in paediatric patients and the administration of anticoagulation in recipients with a known thrombophilic state may substantially reduce the incidence of thrombotic events.[14]

Efforts to predict patients at risk for venous thrombosis primordially rely on thorough assessment of clinical history, laboratory parameters, and meticulous evaluation of both donor and graft characteristics. Even with extensive vigilance, thrombosis cannot always be prevented; successful thrombectomy does not guarantee graft recovery and rarely maintains function beyond the early post-operative period. Nonetheless, endoluminal thrombo-aspiration has been reported as a potentially beneficial therapeutic modality when diagnosis occurs sufficiently early. Because renal vein thrombosis represents a surgical complication highly correlated with graft loss, establishing effective prophylactic protocols remains imperative. Strategies including low-dose aspirin and low-molecular-weight heparin have been explored in select clinical contexts to mitigate the risk of acquisition during the early post-transplant phase.[15]

4. Long-Term Complications

Long-term complications after kidney transplantation include chronic rejection, graft loss, cardiovascular disease (CVD), and diabetes mellitus. Chronic rejection remains the primary cause of late graft loss despite advances in immunosuppressant drugs. CVD constitutes about 30% of mortality among post-transplant patients, by far the leading cause of death in transplant recipients, generally caused by atherosclerosis. CKD is an independent risk factor for atherosclerotic coronary artery disease, with incidence increasing progressively in parallel with GFR decline from the early stages of CKD. Diabetes mellitus, resulting from pre-transplant conditions or chronic use of glucocorticoids or calcineurin inhibitors, is the second leading cause of graft loss and a significant CVD risk factor.[1,16]

4.1. Chronic Rejection

Chronic rejection, also known as chronic allograft nephropathy, represents a progressive deterioration in allograft function and remains the principal cause of late transplant failure.[17] It may manifest at any stage post-transplantation but typically develops months or years after surgery, following an initial period of stable graft function. A multifactorial process, chronic rejection is considered the end stage consequence of several immunological and non-immunological insults. The prevalence of chronic rejection corresponds with the overall longevity of the transplant; the majority of surviving kidney allografts, although adequate in function, will eventually develop histological features consistent with chronic rejection.[17,18]

4.2. Graft Loss

Kidney graft survival has improved dramatically since the advent of calcineurin inhibitor-based immunosuppression in the 1980s. Despite these advances, 5-year graft loss remains approximately 13% across all types of transplantation. There are several causes of graft loss that can be broadly categorized into early and late events. Early failures are associated with technical or surgical complications, hyperacute rejection, arterial or venous thrombosis, or primary non-function. Late failures are most commonly caused by chronic rejection, medication non-adherence, or recurrence of the original disease.[1]

Surgical complications are associated with graft survival, but rarely cause complete graft loss, and a multidisciplinary team involving urologists is recommended for management. Graft thrombosis is one of the earliest causes of complete graft loss, exceeding 80% prior to calcineurin inhibitor immunosuppression. It is now responsible for 6-12% of graft failures within the first 30 days and remains the leading cause of early graft loss. Late vascular thrombosis occurs in 0.5% of cases. Hyperacute rejection has become rare with current antibody screening techniques, but antibody-mediated rejection –acute, active, or chronic– continues to be a major cause of graft loss. The introduction of potent maintenance immunosuppression has shifted emphasis away from acute rejection toward long-term graft attrition.[1,19]

4.3. Cardiovascular Disease

CVD stands out among long-term complications of kidney transplantation. Its presence significantly raises the hazard ratio for graft failure, underscoring a serious threat to patient survival. Notably, this does not appear to be related to long-term immunosuppressant toxicity but rather the direct effects of established risk factors prior to transplantation.[20]

Kidney transplant recipients have a marked increase in the rate of cardio- and erebro-vascular disease compared with the general population. Due to the perioperative and long-term risk of cardiovascular complications, estimated as high as 42%, CVD at some point after kidney transplantation has a greater mortality than any other complication.[21,22] Non-renally related pre-transplantation hypertension, diabetes mellitus, smoking, pre-existing coronary artery disease, and chronic rejection contribute far more than the nephrotoxic effect of immunosuppressive drugs, which, at current doses, is negligible.[23]

Numerous other risk factors make the transplant patient more susceptible to CVD than the general population, including pre-existing obesity, hyperlipidaemia, and homocysteinaemia. Diabetes mellitus, either pre-existing or new onset post-transplantation (NODAT), has a profound influence on cardiovascular system morbidity and mortality and is the major cause of death with a functioning graft.[24,25]

4.4. Diabetes Mellitus

Diabetes mellitus represents a significant long-term complication following kidney transplantation, with a reported incidence ranging from 20 to 50% among recipients. Although rare, recurrence of primary diabetic nephropathy is possible in the transplanted organ. Kidney transplantation remains the preferred treatment option to augment life expectancy in diabetic patients with ESKF.[26] Kidney allograft transplantation enhances overall survival when compared to chronic dialysis therapy but remains a common and serious complication in the diabetic population. Post-transplant diabetes mellitus (PTDM) associates with increased mortality, primarily through aggravated CVD risk. The incidence of PTDM appears to be rising, especially in recipients of recent transplants. Various factors increase the risk of developing diabetes after transplantation, including HCV infection, immunosuppressive therapy, and metabolic syndrome.[27] To minimize the detrimental effect of diabetes on comorbid conditions following transplantation, newer protocols and medications devoid of diabetogenic properties are currently under development.

5. Immunosuppressive Therapy and Its Complications

Immunosuppressive therapy with calcineurin inhibitors, such as cyclosporine and tacrolimus, is the mainstay of post-transplant immune suppression in most centres. It has been estimated that 90% of kidney recipients receive one of these agents as part of their outpatient maintenance immunosuppression regimen. However, both calcineurin inhibitors are nephrotoxic and can cause kidney damage either acutely or chronically. Dyslipidaemia is a recognized risk factor for CVD, which is the main cause of death after kidney transplantation. Calcineurin inhibitors have been implicated in the development of dyslipidaemia after solid organ transplantation. The newer immunosuppressive agents include the inhibitors of the mammalian target of rapamycin (mTOR), sirolimus and everolimus, and the anti-lymphocyte antibodies. In addition to the calcineurin inhibitors, many centres use other groups of immunosuppressive therapy, which include corticosteroids, azathioprine, mycophenolate mofetil and some of the anti-lymphoid antibodies. The balance of immune suppression is always a trade-off between adequate tertiary immune suppression and the side effects of the drugs and general immune impairment.[28]

5.1. Infection Risk

Infections remain a common posttransplant complication. Greater experience and newer immunosuppressive drugs have resulted in a more complex infectious disease environment in kidney transplant recipients. Infection risk after kidney transplantation depends on the net state of immunosuppression, exposures, and prophylaxis. The net state of immunosuppression is the sum of all factors that predispose to infection and include immunosuppressive drug dosage, neutropenia, disruption of mucocutaneous barriers, lymphocyte dysfunction, and infections such as cytomegalovirus (CMV) and Epstein-Barr virus (EBV), which further impair host defence. Exposure to particular pathogens reflects the community, hospital, and transplantation-related environments, personal contact including the donor/recipient, and geographic location. Approximately 20-30% of kidney transplant recipients experience an infection during the initial 3 years after transplantation, with the rate being slightly higher (30-45%) in patients receiving an allograft from a deceased donor. Infection risk varies over time; infections that occur in the early posttransplant period should be considered separately from those occurring later.[29,30]

5.2. Malignancy

Malignancy remains a major challenge for kidney transplant recipients, with higher incidence than in the general population. Malignancy after kidney transplantation has been reported in many studies, including a 40-year single-centre experience in Korea and the outcome of 400 patients at a single centre. Patients with ESRD are generally at increased risk of cancer –particularly those who were previously on dialysis. Cancer risk among patients with ESRD is further increased once the patients undergo kidney transplantation. The development of malignancy following solid organ transplantation remains a major challenge for the survival of patients and grafts.[31]

Malignancy remains a common complication after kidney transplantation, and it is an important cause of death among recipients. A study evaluated the risk factors related to the outcomes of graft loss and death with a functioning graft. Data were collected from 266 cases of malignancy at a single centre in Iran. Analyses of the data indicated that nephrologists could use the risk factors to predict the likelihood of the two outcomes. When graft loss is found

to be the more likely outcome, a reduction of immunosuppressive medications may reduce the incidence of graft loss.[32]

Kidney transplantation improves quality of life and lifespan for patients with ESRD. However, patients undergoing kidney transplantation face several risks, including graft loss and complications such as CVD, infections, and malignancies. The use of immunosuppressive agents has markedly reduced the risk of graft rejection, but the patients now face an increased likelihood of experiencing transplant-related complications such as malignancies, which are expected to become the leading cause of death among transplant recipients in the foreseeable future.[33]

Despite increasing awareness of the issue, few studies have specifically examined malignancy after living kidney transplantation. Although large studies investigating the incidence and risk factors of malignancy in living kidney transplantation exist, the results in the main focus on deceased transplantation. They are therefore unable to accurately reflect the experience with living donors, leaving a gap in the literature for this particular patient cohort.

5.3. Nephrotoxicity

Nephrotoxicity is a major limitation to the use of calcineurin inhibitors (CNI) and remains a leading cause of late allograft failure. CNI target calcineurin, which dephosphorylates nuclear factor of activated T cells and facilitates the inflammatory response. In T-cells, this results in a lack of cytokine expression and immunosuppression. Tubular and glomerular cells also use this pathway, and their calcineurin signalling pathways are impaired by CNI use, leading to altered signalling and cellular stress. Acutely, CNI cause vasoconstriction of afferent renal arterioles, resulting in reduced glomerular filtration rate (GFR) and ischemic injury.1 Chronic CNI toxicity is characterized histologically by a reduction in the density of peritubular capillaries associated with tubular atrophy, interstitial fibrosis, and glomerulosclerosis. Both acute and chronic injuries share common mechanisms, including activation of the renin–angiotensin system, endothelin-1, transforming growth factor-β1, and fibrogenic cytokines.

Nephrotoxicity of mammalian target of rapamycin (mTOR) inhibitors differs from that of CNI and primarily occurs in patients with pre-existing kidney damage in the form of acute tubular necrosis or in the presence of a renal vein thrombosis or bilateral nephrectomy. Acute

tubular necrosis tends to be exacerbated by the introduction of mTOR inhibitors. mTOR inhibitors are associated with the development of proteinuria that ranges from asymptomatic proteinuria to nephrotic syndrome. The mechanism by which this occurs is currently unclear and requires further work. Unlike CNI, mTOR inhibitors have the ability to enhance graft survival by permitting recovery from tubular cell damage and limiting glomerular cell proliferation.[16]

6. Psychosocial Complications

With the increase in lifespan after transplantation, the incidence of psychosocial and psychiatric problems has risen. Management of psychosocial complications requires an interdisciplinary approach involving psychologists and psychiatrists.[34] Although kidney transplantation is the preferred therapy for ESRD, it is associated with psychiatric morbidity, concerns about medication compliance, fears of transplant rejection, and suboptimal quality of life.[35] Patients with immunosuppressive medication regimens frequently demonstrate traumatic stress symptoms and may exhibit post-transplant substance abuse. Careful evaluation and implementation of strategies to improve emotional well-being constitute essential components of the post-transplant paradigm.

6.1. Depression

Kidney transplantation is now an accepted treatment for patients with ESRD. The procedure corrects many of the physiological and metabolic abnormalities associated with ESRD and anti-rejection therapy has evolved to a state at which long-term graft function with a relatively low incidence of rejection is possible. The ability of a transplant patient to undertake full social functioning is pivotal. However, transplant recipients experience psychological distress possibly leading to depression that affects their ability to respond to stressful events. They are at high risk of developing psychiatric disorders (depression, anxiety, and adjustment disorders) that can adversely affect graft and patient survival. Depression is a serious illness with a profound negative impact on quality of life and is a major factor affecting compliance with treatment. Up to 41% of dialysis patients report some form of depressive symptom and the condition is often undiagnosed because symptoms may be masked by other features of chronic illness. Most studies conclude that the prevalence of depression is as high as 20-30% in the dialysis population compared

with 5-10% of the general population. In addition, there have been reports of a high prevalence of non-compliance to medication in post-transplanted patients. This association has also been extended to the kidney transplant setting where the presence of depression may increase the risk of non-compliance, leading to poor outcome.[36]

6.2. Anxiety

Any medical or surgical procedure can generate considerable subjective and objective anxiety. Anxiety is an unpleasant state of inner turmoil, often accompanied by nervous behaviour such as pacing back and forth, somatic complaints, and rumination. It is subjective feelings of dread over anticipated events and is more clearly distinguished from fear which is the emotional response to a real or perceived immediate threat. Anxiety can also be a psychological and physiological state characterised by cognitive, somatic, emotional, and behavioural components.[37] Kidney transplantation in patients affected by ESRD is accepted as the best therapeutic option to restore normal kidney function and to improve life expectancy. Along with improvement in physical health, mental health also improves.[38] However, very few studies have mentioned and elaborated on the nature of anxiety in these patients.

6.3. Social Isolation

Social isolation and the associated reduction in social participation constitute important complications among recipients of kidney transplantation.[39] Changes in social participation during the first year after transplantation have been described in a prospective study, which investigated the impact of clinical factors, health status, transplantation-related symptoms, and psychological characteristics on social integration. The results showed an increase in participation in obligatory activities and diversity of leisure engagement between the early and late intervals of observation, although the pre-ESRD level was not fully regained and remained below that observed in the general population. At the early interval, a majority of employed recipients were still on sick leave, but many returned to work by the later measurement point. No significant associations were found with type of donation, comorbidity, or kidney function. Clinical factors were predominantly linked to improvements in societal participation. While health-status-related variables and the psychological attribute of self-efficacy appeared to influence recovery of social participation,

their effects were overshadowed by the stronger influence of clinical predictors in multivariate analysis.[40] The psychological burden of isolation may also be aggravated by the need for transplant recipients to shield themselves during the COVID-19 pandemic and by the chronic and recurrent character of organ failure, which exposes them to multiple hospital admissions and ongoing treatment.[41]

7. Monitoring and Management of Complications

Successful kidney transplantation is the optimal treatment for ESRD, dramatically enhancing the recipient's quality of life as well as length and quality of survival. Despite recent advances in surgical techniques and immunosuppressive therapy, kidney transplantation is associated with a wide range of potentially serious complications that occasionally necessitate early graft nephrectomy or patient death. They may occur at any stage in the patient's history but are more frequent during the first 3 months after transplantation, calling for careful monitoring to make an earlier diagnosis and treatment.[2]

Doppler US plays a fundamental part in this scenario, serving as the first-line imaging method used for graft assessment, due to its non-invasiveness, repeatability, cost-effectiveness, and excellent accuracy in differentiating most post-transplant complications. Magnetic resonance imaging (MRI) and computed tomography (CT) are employed on a selective basis, the former because of the requirement for patient collaboration and the popularity of Doppler US, which usually provides sufficient information; the latter because of its relatively high invasiveness and irradiation dose; both are effective in providing a more confident diagnosis when Doppler US is equivocal or in the presence of atypical clinical and laboratory findings.[42]

7.1. Regular Follow-Up

Regular follow-up of patients after kidney transplantation is essential. The clinical history must not go farther back than the last dialysis session prior to transplantation, and must include: the date of the transplant and the characteristics of the donor and recipient; the type of dialysis; the immunosuppressive protocol; the clinical evolution; the history of rejections; the surgical complications; the analytical controls; and the current therapy; all of this is to be recorded on a specific sheet for follow-up of transplanted patients. Although

ESRD is a leading cause of premature mortality, and the death rate for patients on dialysis remains many times higher than that of the general population, kidney transplant reduces this mortality by 68%; however, patients still face numerous posttransplant complications, including cardiovascular, metabolic, oncologic, and infectious problems. CVD remains a primary concern, since transplant is the most effective intervention to lower CVD risk, but CVD death still accounts for 30% of overall mortality; the most important CVD risk factors include diabetes, prior CVD, long dialysis vintage, left ventricular hypertrophy, age over 60 years, smoking, hypertension, and dyslipidaemia.[16]

7.2. Laboratory Tests

Numerous laboratory procedures assist in the early detection of complications. Urinalysis, for example, can detect haematuria, proteinuria, or gas bubbles related to urologic complications. A drop in haemoglobin and haematocrit values, with normal white blood cell counts, supports the suspicion of bleeding. The presence of neutrophilic leucocytosis is useful for the diagnosis of infection. A reduction in platelet counts could indicate a side effect from immunosuppressive therapy. US, with Doppler evaluation, represents the first imaging modality for routine post-operative monitoring of kidney transplants.[43,44]

7.3. Patient Education

Patient education following kidney transplantation is crucial in reducing complications and in the achievement of long-term graft survival. Comprehensive pretransplant counselling gives the individual a better understanding of the operation and the complications that may occur during or after transplantation. Postoperative instruction continues the education process with emphasis on meticulous adherence to treatment regimens, early identification of complications and reinforcement of the principles of adjunctive therapy. The information is presented to the patient as early in the process as possible so that he or she has adequate time to assimilate and interact with the health care team regarding concerns or questions. The kidney recipient is required to understand his or her medical condition and to recognise the signs and symptoms that may indicate a complication or an adverse reaction to a drug. Patients are expected to participate in the management of their regimen at a level suitable to their education

and capability. To reinforce the education process, the transplant nurse initiates all pre- and post-transplant teaching while transplant medical personnel at the specialists' centre assume follow-up care. The emphasis on education regarding complications extends to family members who contribute to the well-being and support of the recipient.[45]

8. Future Directions in Kidney Transplantation

The current shortage of donor organs results in a longer dialysis period for many patients awaiting transplantation. Sensitization to human leukocyte antigen (HLA) represents another challenge, both by decreasing access to transplantation and by reducing graft survival owing to the risk of chronic and acute antibody-mediated rejection. Desensitization protocols, including the use of the immunoglobulin G-degrading enzyme of Streptococcus pyogenes (IdeS), are under investigation –small pilot studies show promise, and several clinical trials are ongoing. The efficacy of clazakizumab in transplantation also remains the focus of recent research.[46,47] A shortage of experienced professionals to guide the diagnostic process could further limit accurate assessment of post-transplantation complications.

8.1. Advancements in immunosuppressive therapy

Kidney transplantation remains the best therapeutic option for patients with ESRD, offering improved survival and quality of life compared to dialysis. However, a well-functioning graft requires lifelong immunosuppressive therapy to prevent rejection. The first breakthrough in reducing acute rejection rates came with the clinical introduction of cyclosporine in the early 1980s. Striking advances in immunotherapy followed, and a host of new immunosuppressive agents have been clinically introduced since, yet prevention of rejection remains the major challenge after transplantation.

Adverse events after kidney transplantation represent a major cause of late graft loss or patient death. As patients are monitored closely and followed up rigorously, adverse events can be detected and managed earlier in transplanted patients. Multiple concomitant drugs with overlapping toxicities further complicate adverse event management. In addition to immunosuppressants and chemoprophylaxis agents, a myriad of drugs is used to treat underlying disease and medical conditions resulting from ESRD. Toxicities from these drugs translate into an increased risk of graft loss and mortality.

Despite its limitations, cyclosporine has become the standard for immunosuppression in the post-transplant period. It is often supplemented by azathioprine and steroids. Toxicity may be diminished by reducing the dosage administered. The degree of immunosuppression must still be sufficient to prevent rejection. The need for newer agents has been acknowledged for some time, but the ability to monitor immunosuppressive drugs still provides mild encouragement to clinicians to continue with current regimens. Considerable worldwide effort continues to develop monitoring assays for immunosuppressive medications.[44,48]

8.2. Improved Graft Preservation Techniques

One of the major challenges in kidney transplantation is graft preservation. Advances in the field of organ preservation have increased the number of kidneys available for transplantation and improved graft function.3 Historically, harvested organs were preserved through simple immersion in iced solutions, a method that limited preservation times to roughly 6 hours.[1] The introduction of kidneys from non-heart-beating donors further challenged the field by increasing cold ischemic periods; however, multiple preservation methods, such as the use of various perfusion solutions, have helped maintain graft viability. Organ preservation techniques have evolved significantly, moving from static cold storage to hypothermic machine perfusion.

8.3. Innovative Surgical Techniques

Despite advances in endourological treatment options, open surgery continues to play a substantial role in the management of post transplantation complications. Factors such as elevated body mass index, anatomical challenges including multiple kidney arteries, and vascular complications often necessitate an open surgical approach. Haematoma formation secondary to biopsy, arterial injuries involving polar arteries, and venous thrombosis are typically addressed surgically. Chronic problems like incisional hernia frequently require mesh repair. The prevalence of vascular complications underscores the importance of open surgery to preserve graft function. In particular, kidney arterial stenosis, the most common vascular complication, affects 3% to 23% of transplant recipients within the first year; it is associated with end-to-end anastomosis and cadaveric grafts and can lead to graft deterioration if left untreated. Therefore, surgical

expertise remains critical in complex cases unamenable to minimally invasive techniques.[2]

Conclusion

Kidney transplantation is regarded as the most cost-effective therapy for ESRD, improving survival and quality of life for recipients. Despite this advantage, a significant number of kidney transplant recipients suffer urologic complications among the most common post-operative issues. These complications include ureteral obstruction, urinary leak, bladder outlet obstruction, and obstructive ureteral calculi. Vesicoureteral reflux and urinary fistulae have also been reported. A study of paediatric recipients identified cases of obstruction and/or urinary extravasation, reflux, and graft loss among the observed complications.[2] Traditionally, these complications were managed with open surgical procedures. Advances in equipment have allowed for less invasive endourological techniques, which are now increasingly employed in managing kidney transplant complications. Epidural spinal cord stimulation (ESCS) delivered in 30-second bouts reduced blood pressure that patients adjusted to in recurrent bouts. Prolonged bouts of ESCS have family-wide changes in autonomic control with activation of different phytocomponents needed for blood pressure regulation.[1] Prolonged bouts to lower or increase blood pressure are achievable by stimulating at different spinal sites for activation of distinct circuits supplying appropriate sympathetic efferent. The system can be programmed to deliver continuous stimulation for rapid onset of an acute hypotensive response.

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Chapter 5

Nutrition Needs for Kidney Transplant Recipients

Learning objectives

- To Gain knowledge and understanding of food-drug interaction and impact to nutritional status.
- To understand the nutrition management challenges and strategies in kidney transplant recipients.

Introduction

Organ transplantation is a vital, life-saving procedure for people living with end-stage kidney disease, providing the opportunity for enhanced quality of life and significantly extended survival.[1] However, successful transplantation goes beyond the surgical procedure; it encompasses comprehensive post-transplant care, including meticulous attention to nutrition management. Nutrition is pivotal in the pre-transplant preparation, perioperative period, and long-term post-transplant outcomes for recipients.[2,3]

The management of nutrition in organ transplantation presents unique challenges due to the interplay of various factors, such as underlying organ dysfunction, immunosuppressive medications, and metabolic changes post-transplantation.[4,5] These challenges necessitate tailored nutrition interventions to optimize recipient health and mitigate the risk of complications.

This chapter explores the strategies and challenges associated with nutrition management in kidney transplantation. It will delve into the complexities of nutritional support pre- and post-transplant, examine the impact of immunosuppressive medications on dietary requirements, and discuss emerging trends and future directions in this critical aspect of transplant care.

Through a comprehensive literature review, this chapter will highlight the importance of nutrition in maximizing transplant outcomes while addressing the barriers and hurdles faced in implementing effective nutrition management strategies. By understanding the intricacies of nutrition management in kidney transplantation, healthcare providers can better support transplant recipients in their journey towards improved health and well-being.

Nutrition and its challenges in kidney transplantation

Nutrition plays a vital role in improving the outcomes of organ transplantation by supporting healing, preventing complications, and enhancing long-term health.[6] Adequate nutrient intake after transplantation is essential for tissue repair and strengthening the immune system, which helps prevent infections and other complications. Controlling the side effects of immunosuppressive drugs is essential for maintaining graft function.[7]

Post-transplant recipients face several nutritional challenges that require careful management to optimize recovery and long-term health. Firstly, reduction in lean body mass is a common finding, often resulting from anorexia, dialysis-related nutrient losses, and increased catabolism. Secondly, as pre-transplant restrictions, electrolyte and mineral imbalances may need reassessment post-transplant, particularly during organ rejection or medication adjustments. Thirdly, elevated cholesterol levels accelerate the progression of cardiovascular and kidney diseases, posing a major risk to the longevity of both the patient and the graft. Even more concerning, metabolic syndrome and new-onset diabetes after transplantation (NODAT) further exacerbate these risks.[8,9] Table 1 shows nutrition consideration in specific posttransplant complications.[10]

Table 1: Nutrition considerations for specific post-transplant complications

Complications	Nutrition considerations	Suggested therapy
Rejection	Rejection rates are reduced in malnourished recipients. Anti-rejection medications have many nutritional side effects. Corticosteroids increase protein catabolic rate and effects are dose dependent. Protein catabolism increases during rejection treatment. If muromonab-CD3 is used to treat rejection, nausea, vomiting, diarrhoea, and headache may prevent adequate dietary intake.	Provide 1.5 to 2 g protein/kg/day. Monitor dietary intake for adequacy. Regular monitoring and prompt management of drug-related side effects.

Complications	Nutrition considerations	Suggested therapy
Infection	KTRs on immunosuppressive therapy face a heightened risk of infections. Malnutrition also increases rate of infection. Antimicrobial agents may cause gastrointestinal upset and affect dietary intake or cause diarrhoea.	Provide adequate protein and other nutrients necessary to fight infection. Monitor dietary intake for adequacy.
Wound healing	Severely malnourished or obese recipients are at increased risk of wound complications.	Provide adequate protein, vitamins A and C, iron, copper, and manganese for to wound healing. Achieve euglycaemia to aid wound healing.
Kidney insufficiency	If kidney replacement therapy is required, 5 to 10 g amino acids may be lost in dialysate. During hemofiltration, 300 g glucose can be absorbed over 24 hours from glucose-rich replacement fluids. 43% to 45% of glucose is absorbed from dialysate with continuous haemodialysis.	Fluid and electrolyte restrictions may be required when kidney function is impaired and kidney replacement therapy is not utilized. Electrolytes must be monitored closely and restricted or supplemented as needed. Consider losses and additional calories from kidney replacement therapies.
Hyperglycaemia	Hyperglycaemia is common due to metabolic stress, insulin resistance caused by corticosteroids, and inhibition of islet cell function and insulin release by cyclosporine and tacrolimus. Infection rates are higher in people with diabetic than in those without diabetes.	Limit glucose and treat with hypoglycaemic agents.

Complications	Nutrition considerations	Suggested therapy
Surgical complications	Vascular complications, postoperative bleeding, or complications requiring further surgery will delay oral intake. Severe pancreatitis or ileus may be indications for total parenteral nutrition. Oedema and ascites may respond to sodium restriction. Intestinal complications (diarrhoea, ulcers, etc) may require that the route of feeding or type of food be altered.	Provide oral diet if possible. Enteral feeding is preferred over parenteral nutrition when oral intake is prohibited or inadequate.

Immunosuppressive therapy changes to nutritional status

Nutritional status significantly influences post-transplantation outcomes, with various factors contributing to changes in overall or nutrient-specific status.[11] Medication in kidney transplant recipients (KTRs) affects body weight, macronutrient metabolism, and vitamins and minerals.[12] Malnutrition weakens immune function, increasing complications and graft rejection risks.[3]

Weight gain is common in KTRs, often leading to being overweight or obesity, sometimes alongside sarcopenia. This combination markedly elevates metabolic and cardiovascular risk, which may result in graft failure and reduces survival rates. Contributors include chronic illnesses, steroid use, sedentary behaviour, and poor dietary habits, all of which contribute to muscle loss.[13]

Vitamin deficiencies are also prevalent. Vitamin B12 deficiency correlates with low dietary intake and mycophenolate mofetil use,[14] while immunosuppressive therapy disrupts vitamin B6 metabolism.[15] Prednisone and mycophenolate correlate with vitamin D deficiency, particularly at higher doses, and tacrolimus increases vitamin D deficiency risk.[16]

Mineral imbalances are also notable. Hypophosphatemia which is, common post-transplant, leads to bone issues like osteomalacia and osteodystrophy.[17] Hypomagnesemia frequently occurs, especially during the early transplantation phase, often due to tacrolimus.[18] Serum potassium fluctuations necessitate low-potassium diets for hyperkalaemia management.[13]

Immunosuppressive therapy accelerate metabolic syndrome progression.[7] Post-transplant diabetes mellitus can be reversed through medication adjustments, proper diet, and weight management.[19,20] Lipid disorders may arise due to the use of immunosuppressive drugs, including steroids, calcineurin inhibitors, and mTOR inhibitors, which contribute to lipid disorders,[21,22] while arterial hypertension, a common post-transplant issue, increases cardiovascular disease risks.[23]

Table 2 highlights the side effects of common immunosuppressants like corticosteroids, cyclosporine, azathioprine, tacrolimus, mycophenolate mofetil (MMF), and sirolimus. These include hypertension, glucose intolerance, hyperlipidaemia, and gastrointestinal disturbances.[7] Recognizing these effects is essential for effective medication management and risk reduction in KTRs.

Table 2: Potential side effects of immunosuppressive medications

Side Effect	Immunosuppressant					
	Cortico-Steroids	Cyclo-sporine	Aza-thioprine	Tacrolimus	Mycophenolate Mofetil	Sirolimus
Hypertension	✓	✓		✓		
Anaemia			✓	✓		
Glucose intolerance	✓	✓		Hyper-glycaemia		✓
Hyperlipidaemia	✓	✓		✓	✓	
Hyper/ hypo-kalaemia		✓		✓		✓
Hypo-magnesemia		✓		✓		
Hyperuricemia		✓		✓		
Osteoporosis	✓					
Nausea/ vomiting			✓	✓	✓	
Abdominal pain				✓	✓	
Diarrhoea				✓	✓	
Gas				✓	✓	
Anorexia				✓	✓	
Thrombo-cytopenia			✓			✓
Leukopenia			✓	✓		✓
Gastric diseases	✓				✓	

Side Effect	Immunosuppressant					
	Cortico-Steroids	Cyclo-sporine	Aza-thioprine	Tacrolimus	Mycophenolate Mofetil	Sirolimus
Neurological Disorders	✓	✓				
Others	Protein catabolism, Fluid retention	Nephro-toxicity, gingival hypertrophy	Hepatic dysfunction	Leucocytosis, constipation		

Metabolic Drug Interactions and Impact on Nutrition in Kidney Transplant Recipients

Numerous adverse reactions or instances of treatment ineffectiveness with medications stem from variations or shifts in drug metabolism. The capacity of a patient's body to metabolize drugs, significantly impacted by genetic differences or changes in the activity levels of drug-metabolizing enzymes, can profoundly alter how a drug behaves in the body, influencing its effectiveness or potential for harm.[24] While standard clinical practice often relies on dosing guided by blood concentrations, the wide variability in how individuals metabolize drugs underscores the need for personalized medication approaches, particularly for drugs with narrow therapeutic ranges. Identifying genetic and non-genetic factors that may impact how a specific drug is processed in the body is essential for tailoring pharmacotherapy to recipients, optimizing treatment outcomes while minimizing risks.[25]

Drug Metabolism and Implications for Personalized Medicine

Cytochrome P450 enzymes are critical for metabolizing drugs, steroids, and carcinogens. CYP3A4 and CYP2C9, commonly inhibited enzymes, lead to elevated serum levels when co-administered with calcium channel blockers, anti-diabetics, warfarin, midazolam, and diclofenac.[26] Genetic and non-genetic differences significantly influence drug metabolism, with genetic variations, such as those in CYP3A5, differing across ethnic groups and affecting medication dosing.[7] Non-genetic factors like age, diet, and drug interactions also alter enzyme function.[25]

In transplantation medicine, understanding these factors is crucial for personalized immunosuppressive therapy. CYP enzymes

interactions can impact drug metabolism, requiring tailored dosing to optimize efficacy and minimizing adverse effects, particularly in transplant recipients (Table 3).

Table 3: Pharmacology and cytochrome P450 enzyme involvement in immunosuppressant metabolism

Immunosuppressant	Pharmacology	CYP enzymes
Cortico-Steroids (Prednisone, Methyl-prednisolone)	Inhibition of T-cell migration and production of T-cell lymphokines	CYP3A4/5
Calcineurin inhibitors (Cyclosporine, Tacrolimus)	Selective inhibition of T-cell dependent immune response: Calcineurin inhibition, Inhibition of cytokine production	CYP3A4/5
mTOR inhibitors (Sirolimus, Everolimus)	Inhibition of B- and T-cell proliferation	CYP3A4/5
Purine analogues (Azathioprine)	Inhibition of purine metabolism	Thiopurine S-methyltransferase, Xantine oxidase
Inosine monophosphate dehydrogenase inhibitors (Mycofenolate mofetil, Mycofenolate)	Selective inhibition of inosine monophosphate dehydrogenase, Inhibition of B- and T-cell proliferation	CYP3A4/5

CYP3A4: cytochrome P450 3A4

Understanding Food-Drug Interactions

Food-drug interactions arise when nutrients and medications interact on a physical, chemical, or physiological level, potentially altering the effectiveness of treatment. These interactions may decrease drug bioavailability, leading to treatment failure, or increase it, raising the risk of adverse effects. Nutritional status and diet can alter drug metabolism, and certain dietary components may exert pharmacological effects.[26]

Phytochemicals in fruits and vegetables, known for their health benefits, can influence drug metabolism by affecting enzymes like cytochrome P450 and interacting with drug transporters. Such interactions may alter drug absorption and pharmacokinetics.[27] Table 4 highlights common fruits and vegetables and their potential drug interactions.

Table 4: Inhibition of CYP450 and drug transporters by common food

Food	Mechanism of potential interaction	Clinical relevance
Common/temperate fruit juices		
Grapefruit	Inhibits CYP3A4, CYP1A2, MRP2, OATP-B, p-glycoprotein	↑ TAC level/toxicity[7] ↑ Everolimus level (Potential) exposure ↑ Sirolimus level (Potential) ↑ Cyclosporine level[28]
Seville orange	Inhibits p-glycoprotein, CYP3A4, CYP2C9, OATP	↓ TAC level/toxicity ↑ CYS level/toxicity
Clementine (Mandrin orange)	Inhibits CYP3A4	↑ TAC level/ toxicity[29]
Orange	No reported interactions it might be due to absence of furanocoumarins	Minimal impact drug levels[30]
Tangerine	Inhibits p-glycoprotein, stimulate CYP3A4 (Disomin in tangerine also inhibit CYP3A4 and CYP1A2 *in vitro*)	Not demonstrated to CYS[31]
Lemon	Inhibits CYP3A4, CYP2C9, possibly OATP (because of presence of same polyphenols as in grapefruit juice)	↑ CYS level[32]
Lime	Inhibits CYP3A4, CYP2C9 (because of presence of same polyphenols as in grapefruit juice)	↑ CYS level[32]
Pomegranate	Inhibits CYP3A4, CYP2C9, contains punicalagin that inhibit intestinal sulfo-conjugation	↑ TAC (potential)[33]/ Toxicity[29]
Apple	Inhibits CYP1A1, OATP family (OATP 1, OATP 3, NTCP) due to presence of polyphenols	
Grape	Inhibits CYP3A1, CYP2E1 (due to Resveratrol)	
Mango	Inhibits CYP1A1, CYP1A2, CYP3A1, CYP2C6, CYP2E1, p-glycoprotein (ABCB1) due to qurecetin, glycosylated xanthones, mangiferin	Not demonstrated[30]
Pineapple	Inhibits CYP2C9 (due to bromelain)	Not demonstrated[30]

Food	Mechanism of potential interaction	Clinical relevance
Cranberry	Inhibits CYP3A4, CYP2C9	Not demonstrated[7]
Mulberry	Inhibits CYP3A1, OATP-B, also modulate (activate) CYP3A1 and p-glycoprotein	
Black raspberry	Inhibits CYP3A1	Not demonstrated to TAC[33]
Blue berry	Weak inhibitor of CYP3A4 due to anthocyanins	Not demonstrated to TAC[33]
Guava	Weak inhibitor p-glycoprotein, CYP3A4	Not demonstrated
Tropical fruit juices		
Kiwi	Inhibits CYP3A4	Not demonstrated[30]
Pomelo	Inhibits CYP2C9, CYP3A4 (no effect on P-glycoprotein)	↑ TAC level/toxicity[7] ↓ cyclosporine[30]
Star fruit	Inhibits CYP3A4 (stronger than grape fruit)	↑ TAC level/toxicity ↑ CYS level/toxicity
Passion fruit	Inhibits CYP2C9, CYP3A4	Not demonstrated[30]
Dragon fruit	Inhibits CYP3A4	Not demonstrated[30]
Rambutan	Inhibits CYP3A4	Not demonstrated[30]
Litchi	Inhibits CYP2C9	Not demonstrated[30]
Vegetable fruits		
Tomato	Inhibit CYP1A1, CYP1B1, UGP	
Carrot	Inhibit CYP2E1	
Avocado	Unknown	Interaction with warfarin (unclear)
Red pepper	Inhibit CYP1A1, CYP2A2, CYP3A1, CYP2C1, CYP2B1, CYP2B2, CYP2C6	
Spinach	Inhibit CYP1A2	
Spices		
Turmeric[7]	Inhibits CYP3A4	↑ TAC level/ toxicity with excessive intake[7]

Food	Mechanism of potential interaction	Clinical relevance
Ginger[7]	Inhibits CYP3A4	↑ TAC level/toxicity[29] Not demonstrated[7]
Herbs		
Panax ginseng	Poor inhibition of CYP2D6; Poor inhibition of P-gp; Poor induction of CYP3A; Promotion of Klotho signalling pathway	↓ TAC level/toxicity[29]
Green tea	Inhibition of CYPs; Inhibition of P-gp; Promotion of Klotho signalling pathway	↓ TAC level/toxicity[29]
Echinacea purpurea		In conductive[29]
Hypericum perforatum (St John's Wort)	Induction of CYP3A4; Induction of P-gp	↓ TAC level, ↑ risk of transplant rejection[29] Unaffected MPA[34]

CYP450: cytochrome P450, OATP: organic anion transporting polypeptide, P-gp: p-gylcoprotein, CCBs: calcium channel blockers, CNS: central nervous system, HMG CoA: hydroxyl methyl glutaryl coenzyme A, PDE-5: phosphodiesterase type 5, NTCP: sodium taurocholate co-transporting peptide.

Nutritional assessment and biomarkers in kidney transplantation

Malnutrition poses a significant concern for individuals undergoing kidney transplantation, resulting from a complex interplay of physiological, psychological, and metabolic factors. This multi-faceted issue is influenced by distinct challenges associated with each transplanted organ. In all solid organ transplantations, factors such as anorexia, nausea, vomiting, and difficulties in chewing or swallowing can hinder adequate nutrient intake. Furthermore, psychological aspects such as depression, fatigue, and the necessity for restricted diets add to the complexity. Additionally, the hypermetabolic state induced by both the underlying disease and the surgical procedure worsens nutritional deficiencies, alongside potential interactions between drugs and nutrients. Recognizing the specific factors contributing to malnutrition in various transplant scenarios is crucial for effective management and better patient outcomes. Table 5 summarises the factors contributing to malnutrition in KTRs, ranging from general challenges affecting all solid organs to specific complications related to individual organs.

Table 5: Factors of malnutrition in kidney transplant recipients

Mechanism	Effects
Inflammatory response	Anorexia Muscle catabolism ↑ Energy expenditure
Psychosis	Depression Fatigue
Deterioration of Organ Function	↓ Gastrointestinal absorption Impaired protein synthesis Electrolyte and mineral imbalance Metabolic acidosis Pancreatic insufficiency Small bowel dysfunction
Dietary limitations	Malnutrition Limited access to food Restricted diets
Gastroparesis	Nausea and vomiting Dysphagia
Hypermetabolic state due to disease and/or surgery	Glucose intolerance/Diabetes Hypertriglyceridemia Cholesterol elevation Hypertension
Co-morbidity (cardiovascular disease, hyperparathyroidism, bone disease)	Protein-energy wasting syndrome, loss of lean body mass

Comprehensive Nutrition Assessment

Conducting a thorough nutritional assessment, combining subjective and objective measures, is pivotal for enhancing outcomes in KTRs. Bi-annual assessments recommended to prevent malnutrition and identify risks like protein-energy wasting and obesity.[35] A comprehensive nutrition assessment for KTRs should include several assessment parameters such as physical assessment, history, anthropometric measurement, and biomarkers. Physical assessment evaluates overall nutrition status, focusing on fat and muscle stores and fluid retention, and signs of nutrient deficiencies (e.g., muscle wasting, skin, hair, and oral health). History-taking identifies causes and durations of deficiencies, addressing medical history, dietary intake, gastrointestinal symptoms, medication use, and socio-economic factors. Anthropometric measurements

provide objective data, though they have limitations. Biomarkers, such as serum albumin, pre-albumin, cholesterol, and creatinine, are critical for diagnosing malnutrition and guiding interventions.[36] Body composition analysis using dual-energy X-ray absorptiometry, alongside BMI and body mass, is recommended at initial appointments and every three months thereafter.[35]

Nutrition Assessment Tools

Various tools are available for assessing nutritional status (Table 6).[37] The Subjective Global Assessment (SGA), endorsed by the Kidney Disease Outcomes Quality Initiative, provides a comprehensive evaluation using subjective and objective criteria.[35] The Nutritional Risk Index (NRI) predicts surgical outcomes by assessing malnutrition, while tools like the Malnutrition Universal Screening Tool (MUST) and Nutritional Risk Screening (NRS-2002) are effective for identifying malnutrition risk in hospital settings.[38] Pre-operation nutrition screening (PONS) helps identify individuals at risk of malnutrition before surgery. These tools incorporate anthropometric parameters, laboratory markers, and subjective evaluation.[37] Notably, SGA and NRS-2002 assess both nutritional status and disease severity, with particular consideration given to older age among recipients.

Laboratory Markers

Serum albumin is a predictor of chronic malnutrition and surgical-related complications with lower levels linked to higher mortality and an elevated risk of post-transplant infections.[37] Prealbumin, due to shorter half-life, offers a more sensitive marker for malnutrition, though its accuracy may be reduced in chronic kidney disease.[39] Elevated transferrin levels can indicate iron deficiency or kidney failure.

Creatinine reflects muscle mass and helps assess muscle depletion, common in end-stage kidney disease.[40] Serum cholesterol provides insights into dyslipidaemia, a frequent post-transplant complication, while low levels in chronic kidney disease are associated with malnutrition and higher coronary artery disease risk. Total lymphocyte count has limited utility as a malnutrition marker, especially in elderly KTRs, and is less reliable post-transplant due to immunosuppressive therapy.[41]

Nutritional assessment incorporating subjective and objective measures is essential for optimizing outcomes in KTRs transplant recipients. A comprehensive nutritional assessment using biomarkers such as serum albumin, prealbumin, cholesterol, and creatinine helps diagnosing malnutrition, guiding intervention, and improving long-term outcomes in KTRs.

Table 6: Comparison of parameters in nutritional assessment and screening tools used in transplant surgery

Parameters		Screening			Assessment			
		NRS-2002	PONS	NRI	SGA	PEW	MNA	CONUT
Anthropometric parameters	Weight loss	+	+	–	+	+	+	–
	BMI	+	+	–	–	+		–
	Total body fat					+		
	Muscle mass					+		
	Mid arm muscle circumference					+	+	
	Present weight	–		+	–			–
	Usual body weight	–		+	–			–
History and symptoms	Food intake/ diet history	+	+	–	+	+	+	–
	Gastrointestinal function/symptoms	–		–	+		+	–
	Stress level/ severity of diagnosis	+		–	+		+	–
	Primary diagnosis	–		–	+			–
	Physical symptoms	–		–	+			–
	Functional capacity	–		–	+			–
Biomarkers	Albumin	–	+	+	–	+	+	+
	Pre-albumin					+	+	
	Total cholesterol						+	+
	Total lymphocyte count	–		–	–			+
	Serum creatinine					+		

Nutrition management strategies

Management Strategies

The significance of dietary intake in managing nutritional complications that may arise after transplantation is paramount. Nutritional interventions are integral to transplant care, addressing obesity and malnutrition before transplantation and mitigating risks afterward.[2] Effective weight management involves low-carbohydrate, controlled-fat diets with carbohydrate intake at 55% of total energy to prevent hyperglycaemia and hypertriglyceridemia. Research highlights dietary patterns rich in plant-based foods and low in meat and processed for KTRs. These approaches help reduce the risk of NODAT, and support better post-transplant outcomes.

Table 7 outlines various interventions, ranging from general dietary recommendations and counselling to specific dietary supplementation, tailored to address post-transplant metabolic imbalances.[42]

Table 7: Summary of key dietary guidelines and terms

Dietary intervention	Components
NCEP guidelines	- Less than 10% of total calories from saturated fatty acids - An average of 30% or less of total calories from all fats - Less than 300 mg of cholesterol per day - Dietary energy levels sufficient to reach or maintain a desirable weight
Mediterranean Diet	- Mono-unsaturated to saturated fatty acid ratio: 1.6 to 2.0 - Dietary fibre intake: 41 to 62 g/day per person - Antioxidant capacity of the whole diet: 3,500 to 5,300 Trolox equivalents per person per day - Phytosterol intake: 370 to 555 mg/day per person
Low fat	- 25% of energy intake from lipids - Less than 10% of energy intake from saturated fatty acids - Less than 500 mg of cholesterol per day
Low calorie	Consuming fewer calories than daily expenditure, based on individual needs

Dietary intervention	Components
Low sodium (salt restriction)	Less than 1.5 g of sodium per day from foods; less than 3 g of additional salt per day
Low protein (protein restriction)	0.8 to 0.9 g of protein per kg of body weight per day
AHA diet	- Macronutrient intake (% of total calories): 55% carbohydrates, 15% protein, 30% total fat - Energy intake greater than 25 kcal per kg of ideal body weight per day

NCEP: National Cholesterol Education Program; AHA: American Heart Association.

Route of Nutrition Support

The route of nutrition support for people awaiting kidney transplantation involves several key considerations. Most recipients can consume food pre-transplant, but small bowel transplant candidates often rely on total parenteral nutrition. Recipients experiencing reduced appetite or early fullness should be encouraged to consume nutrient-rich foods and supplements at frequent intervals throughout the day. When oral intake is insufficient, tube feeding is recommended. Gastrointestinal tubes are ideal for short-term use or people with ascites, while gastrostomy or jejunostomy tubes are suitable for long-term access in those without ascites. Total parenteral nutrition is recommended for conditions like ileus, pancreatitis, chylous ascites, or small bowel failure. Formula selection depends on the recipient's needs, with concentrated formulas for fluid overload, branched-chain amino acid formulas for hepatic encephalopathy, and MCT oil-based formulas for fat malabsorption.

Post-transplant nutrition support varies based on graft function, gastrointestinal status, eating ability, and nutrient requirements. Tube feeding is preferred when oral intake is delayed or insufficient, particularly for malnutrition recipients or those facing complications such as graft nonfunction, sepsis, kidney failure, or ventilatory issues.

Nutrition Recommendations and Intervention

When determining nutrient recommendations for KTRs, factors such as nutritional status, body weight, age, gender, metabolic condition, organ failure stage and type, infections, malabsorption, fluid removal procedures like paracentesis or dialysis, and comorbidities must be considered (detailed in Table 8).

Dietary interventions range from general counselling to targeted supplementation, addressing key concerns like weight management, diabetes, and nutrient deficiencies. Strategies include lifestyle modifications focusing on diet and physical activity, supplementation (e.g., magnesium or n-3 fatty acids), and tailored dietary approaches that prioritise balanced nutrition.

Recipients receive personalized dietary guidance through intensive counselling by a registered dietitian or nutritionist. Serving as a dynamic blueprint for tailored nutrition, plans are designed based on recipient's lifestyle, health conditions and goals. These plans serve as adaptable frameworks, continuously refined to align with the patient's changing needs and treatment progress.

Table 8: Nutritional recommendations for kidney transplant recipients

	Before solid organ transplantation	After kidney transplantation	
		Short-term	Long-term
Protein (g/kg) - Maintenance - Repletion	 1.2 - 1.4 1.5 - 2.5	1.3 - 2.0	0.8 - 1.2
Energy (kcal/kg) - Weight maintenance - Weight gain - Weight loss	 25 - 30 30 - 35 500 - 1000 kcal/day	30 - 35	25 - 30
Fat **(% total calories)**	30%	30% - 50%	<30% Cholesterol: < 300 mg Saturated fat: 7% - 10%
Carbohydrate **(% total calorie)**		50 - 70%	45% - 50% Fibre: 25 - 30g
Fluid	HD: Urine 500 - 1000 mL PD: Urine 1000 mL		HD: Urine 500 - 1000 mL PD: Urine 1000 mL

	Before solid organ transplantation	After kidney transplantation	
		Short-term	Long-term
Electrolytes and Minerals			
- Sodium	HD: <2.4 g; PD: 2g	No added salt, Monitor potassium, phosphorus, magnesium	
- Potassium	HD: <2.4 g PD: 3-4g		
- Phosphorus	800 to 1000 mg		
- Calcium	<2000 mg calcium		Calcium: 1000 to 1500 mg
Vitamins			
- B12	3 mcg		
- Folat	1-5 mg		
- B1	1.5-2 mg		
- E	15 IU		
- D	Within DRI (20mcg)		Supplement vitamin D

Adhering to a diet rich in fish, fruits, vegetables, and low-fat dairy product, has been linked to a significant enhancing long-term graft survival and cost-effectiveness.[43,44] Despite the benefits, implementing this dietary approach can be challenging due to differences in cooking methods, which may affect adherence.[45] Nonetheless, the evidence supporting both diets highlights the importance of dietary interventions in optimizing outcomes and improving the well-being of KTRs. Further research is needed to address barriers and integrate these dietary approaches into clinical practice, ultimately fostering better health outcomes and quality of life for kidney transplant recipients.

Food safety guidelines for kidney transplant recipients

Maintaining cleanliness during food preparation helps minimizing foodborne illnesses risks, particularly for immunocompromised KTRs.[46] Proper hand hygiene requires washing hands with warm, soapy water for a minimum of 20 seconds, especially before and after preparing food and prior to eating. Kitchen surfaces, utensils, and equipment should be regularly cleaned and sanitized, especially

after handling raw meat, poultry, seafood, or eggs, to prevent bacterial contamination. Using separate cutting boards and utensils for raw proteins and fresh produce reduces cross-contamination risk. Furthermore, all fruits and vegetables should be washed under cold running water, even if they will be peeled or cooked, to remove bacteria.

Practicing safe food handling helps safeguard recipients from potential pathogens. Healthcare professionals should emphasize keeping raw food separate from ready-to-eat food during storage and preparation to prevent contamination. Avoiding raw or undercooked food and cooking food to the appropriate internal temperatures ensures bacteria are eliminated. Additionally, refrigerating perishables, leftovers, and prepared meals within two hours, or one hour if above 90°F helps maintain food safety.

High-risk foods like unpasteurized dairy, raw sprouts, and processed meats can harbour harmful bacteria and should be avoided or adequately heated to 165°F, especially by immunocompromised transplant recipients. Proper food storage and thawing for food safety. Keep refrigerators at 40°F (4°C) or below and freezers at 0°F (-18°C) to slow bacterial growth. Stored leftovers in shallow containers for quick cooling and consumed within a few days to prevent spoilage. Following these practices helps prevent foodborne illnesses.

Lastly, staying updated on food recalls and advisories is essential, especially for products that pose a risk for immunocompromised individuals. Recipients should communicate with their healthcare providers or transplant teams to follow dietary restrictions and food safety guidelines. By adhering to these measures, healthcare professionals can help reduce the risk of foodborne illnesses in transplant recipients, supporting their recovery and long-term health.[47]

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Chapter 6

Paediatric transplantation

Learning Objectives

- To explain the significance of kidney transplantation in paediatric population.
- To identify selection criteria and pre-procedure management.
- To highlight the possible complications related to the procedure and medication.
- To recognize the possible outcome of paediatric kidney transplant.

Introduction

Paediatric Kidney transplantation is a lifesaving therapeutic modality for children with end-stage kidney disease.[1,2] It is very important that healthcare providers and families be aware of the benefits and potential complications associated with kidney transplantation in children,[3-5] and the current developments that may affect how they go through this complex process. It is important to summarize the whole process, including eligibility criteria, pre-transplant assessment, post-transplant care and long-term results.

When the renal system of a young child needs support, paediatric kidney transplantation is an option. The surgery can provide improved kidney function, improve the quality of life, and allow growth and development in children so they can become healthy adults. In fact, kidney transplantation in children can significantly raise the health status of the child; however, it also has its particular set of issues.[6,7] The benefits include better functioning of the kidneys and an all-around sense of well-being, but it also includes risks of rejection of the kidney and potential side effects of immunosuppressive therapy, making it very unpredictable for both the child and the caregivers.[8-10]

Eligibility criteria and contraindication

A child with a calculated glomerular filtration rate of less than 20 mL/min/1.732 m², who is unlikely to recover or is experiencing end-stage kidney disease due to different reasons such as congenital anomalies of the kidney and urinary tract (CAKUT), congenital nephrotic syndrome (CNS), cystic kidney diseases, kidney dysplasia,

or kidney aplasia, may be eligible for kidney transplantation. The criteria for selecting paediatric candidates is completely different from those applicable to adults. Several factors must be evaluated to confirm the suitability of a child for kidney transplantation, including:

- Presence of uremic symptoms.
- Failure to have normal growth, which may result from inadequate caloric intake or impaired growth hormone function.
- Delayed psychomotor development.
- Metabolic bone disease.
- The stability of the child's social circumstances.

A very cautious selection process is followed in order to optimize the outcome for the child in need. Physicians consider several factors such as age, weight, overall health, and family support to determine if a kidney transplant is appropriate for the candidate.

Pre-transplant evaluation

The steps toward a transplant be complex. Pretransplant evaluation is one of the significant steps in preparing the patient for a transplant and also in creating the best possible outcome following the Surgery.

Age and Weight Considerations

Size does matter in the case of a paediatric kidney transplant. There are certain criteria for age and weight that a child has to meet in order to undergo the procedure safely. It's all about being sure the child is strong enough to handle the surgery.[14]

Tests and Laboratory Screenings

The following tests are indicated for a recipient of kidney transplantation:

- Complete blood cell count (CBC).
- Comprehensive metabolic panel, including serum phosphorus and magnesium.
- Parathyroid hormone test.
- Liver function tests.

- Coagulation test – which include prothrombin time with International Normalized Ratio (INR) and activated partial thromboplastin time.
- Viral tite rs test.
- Human leukocyte antigen (HLA) and panel reactive antibody (PRA) testing.

Matching and compatibility testing is an extremely crucial part in the pre-transplant evaluation process to determine whether the donated kidney is compatible for the recipient. Tissue typing and crossmatching help identify the degree of compatibility between the donor and recipient to minimize the risk of kidney rejection. HLA testing also evaluates the genetic compatibility between the donor and recipient, increasing the chances of a successful transplant.[15,16]

In PRA testing, recipient serum is incubated with white blood cells taken from a group of blood donors with human leukocyte antigen (HLA) type representative of the community. Presence of “T Cells” indicates that the recipient has antibodies against the donor cells. The ratio of donors inducing a reaction in the recipient predicts the likelihood of a positive crossmatch that would prevent transplantation.

Infectious Disease Screening

During the pre-transplant evaluation process, infectious disease screening is crucial to ensure the patient's overall health and the success of the transplant procedure.[17] This typically includes testing for:

- Cytomegalovirus (CMV).
- Herpes simplex virus (HSV).
- Varicella-zoster virus (VZV).
- Epstein-Barr virus (EBV).
- Hepatitis B virus (HBV).
- HIV.

Which can lead to possible complications during and post procedure, if any of the following tests are positive.

Imaging Studies and Diagnostic Procedures

Chest X-rays and computed tomography scans create images of the lungs and thoracic cavities, which can be used by health professionals to assess any structural abnormalities or other conditions that could affect a person's eligibility for receiving a transplant.

Cardiac Imaging Tests, Cardiac and Pulmonary Assessments, Echocardiogram and Stress Tests

Cardiac imaging tests are a thorough examination of the inner structure and working capability of the heart, conducted with high accuracy. Various tests, such as echocardiograms and stress tests, are administered to check the endurance level of the heart against surgical stressors and its recovery time after transplantation.[18,19]

Echocardiograms and stress tests show the pumping ability, rhythm, and general state of the heart, which is very essential in making one prepared for the journey of transplantation.[20,21]

Pulmonary Function Tests

Pulmonary function tests provide a vital screening that details how the lungs take in oxygen and get rid of carbon dioxide. These tests provide information on lung volume and function, and they are very good indicators of an individual's tolerance to surgical procedures and recovery from transplantation. The process can be viewed as a performance review for the lungs to ensure that they will be sufficiently prepared to sustain the individual throughout the transplant process.[22,23]

Psychological and Social Evaluations

Aside from physical health assessments, the pre-transplant evaluation process involves psychological and social evaluations. These tests will help to assess the patient's current mental health and emotional stability in the transplant process. Moreover, social support and compliance evaluation assesses the patient's support system and ability to comply with instructions for post-transplant care in order to be successful.[24,25]

Final Evaluation and Listing for Transplant

The final evaluation, after reviewing all pre-transplant information, determines whether a patient is a candidate for transplantation. It involves analyzing all the results of diagnosis, evaluations, and assessments to reach a very informed decision regarding how prepared the patient is for the transplant. Hence, listing the patient as transplant-eligible, after the suitability is confirmed, becomes a very important step toward obtaining a life-saving kidney transplant.[26] In other words, the whole pre-transplant evaluation serves as a very important basis for successful transplant outcomes in that potential risks are identified, compatibility is ensured, and any pre-existing illnesses of the recipient are identified. In this way, it administers the tests and screenings through which both the patients and healthcare providers can make informed decisions and guarantee better outcomes for post-transplantation. Such team efforts underway during the evaluation phase greatly smooth the transplant process and ultimately redound to the health and well-being of the transplant recipients.[27,28]

Post-transplant care

Post-paediatric kidney transplantation nursing care is very important for the recovery and long-term success of the child who has undergone this procedure. This specialized nursing modality has a comprehensive approach initiated with adequate preparation before the transplant, followed by immediate post-transplant care, long-term care, and follow-up strategies. The focus of nursing care is medication management, the development of signs and symptoms of rejection and complications, nutritional and dietary instruction, and psychosocial support for the patient and family. Close collaboration with the paediatric nephrology team and active involvement of family members in the care plan is crucial part of recovery and reduces the post-transplant possible complication.[29,30]

1. Post-Paediatric Kidney Transplant Nursing Care Preparation

- *Assessment and Education of Patient and Family:*

  It is important that patient and family assessment and education be done before the kidney transplant journey. The assessors need to understand their background medically and their

lifestyle habits and ensure that they understand the complexity of post-transplant care.[31,32]

- *Coordination with Transplant Team*:

  Nursing care does not work in isolation, so it is very important to collaborate with the transplant team to be able to provide coordinated post-transplant care. This will help in facilitating good communication and coordination of any issues that may arise while working towards the holistic well-being of the patient.[33-35]

2. Early Post-Transplant Care Plans

- *Monitoring Vital Signs and Laboratory Values*:

  In the initial phase following transplantation, monitoring of vital signs and laboratory values is such an important aspect in saving the new kidney. Vigilance is the key to catching deviations early on and making the recovery process smooth.[7]

- *Fluid Management: Urine Output Monitoring*:

  Post-transplant patients need fluid management and urine output monitoring. The balance has to be just right so that the kidney function is maintained without any complications arising from it.[36]

3. Medication Management and Monitoring

- *Immunosuppressant Therapy Administration*:

  Immunosuppressant therapy is the unsung hero of kidney transplant care, keeping the body from rejecting its new tenant. The drugs should be given at the proper time, and their effectiveness has to be watched over for a successful long-term transplant.

- *Side Effects Monitoring and Management*:

  It is very important for nurses to observe any possible side effects of the medications, post-transplants. The timely detection and management of these can make a great deal of difference in the recovery journey of the patient.[37-38]

4. Dietary and Nutrition Counselling

- *Post-Transplant Dietary Restrictions*:

  Instructing patients about appropriate dietary choices, along with knowing which foods should be avoided, will help ensure adequate nutrition for the new transplanted kidney and minimize the risk of complications.

- *Fostering Healthy Eating Habits*:

  Nutritional education for patients after a transplant operation is even more than checking on a checklist. It's about establishing a positive rapport between nutrition and health. Nurses play a major role in promoting overall well-being after transplantation through healthy choices around mindful eating.[39-40]

5. Monitoring for Signs of Rejection and Complications

- *Warning Signs and Symptoms*:

  The warning signs after a paediatric kidney transplant should be watched for, which may indicate rejection or other complications. The nurse caring for a child with a kidney transplant has to look out for fever, oedema, reduced urine output, pain at the site of transplantation, or flu-like symptoms.

- *Diagnostic Evaluation and Interpretation*:

  Regular diagnostic tests, such as blood tests, urine tests, and biopsies, are necessary for monitoring the health of the transplanted kidney and for the early detection of possible signs of rejection. It is important to understand these test results in order to adjust treatment plans and ensure optimal outcomes.[41-43]

6. Long-Term Care and Follow-Up Strategies

- *Consistent Monitoring Appointments and Assessments*:

  Regular follow-up appointments with the healthcare team are important for ensuring long-term success post-transplantation. The appointment will help in monitoring the progress of transplantation, solve any problems that may arise, and thus allow for adjustments in the treatment plan.

- *Chronic Conditions Management and Preventive Strategies*:

  Long-term care after paediatric kidney transplant involves not only the management of chronic conditions but also the institution of preventive measures. This may include medication to prevent rejection, lifestyle modifications, and follow-up to maintain the health of the transplanted kidney and overall health.[10,44]

7. Psychosocial Support and Mental Health

- *Assessment of Affective Health*:

  The importance of emotional well-being is similar to that of physical health post transplantation. Assessing the emotional status of children and their families can be helpful in identifying and treating any possible mental health disorder that might arise in the period of recovery.

- *Provide counseling and support services*:

  The use of counseling services and emotional support can greatly impact the overall recovery course and quality of life for paediatric patient's post-kidney transplantation. Children can be helped in coping strategies, mental health aid, and guidance with whatever resources are available to them to improve their emotional well-being.[25,45-47]

8. Consultation with the Paediatric Nephrologists and Family Members

- *Multidisciplinary Care Coordination*:

  The coordination of the paediatric nephrology team with nursing staff and other health providers is indispensable in the provision of comprehensive care post-transplantation. Teamwork guarantees that every aspect of the patient's health is addressed in a proficient and effective manner.

- *Engaging and educating families in care plans*:

  Family members should be incorporated into the care plan following a paediatric kidney transplant in order to facilitate ongoing care and support at home. This approach will help in preparing family members as the child recovers from the surgery, to provide the necessary care and help that can ensure long-term health for the paediatric patient.

Generally speaking, nursing care for a paediatric patient following a kidney transplant forms part of overall care that young recipients of transplants require. It is by the use of guidelines, continuing observation and support, and collaboration with health professionals and family members that nursing practice can greatly contribute to good results and improve the quality of life for these paediatric patients. It is only through a patient-centered approach, with commitment to holistic care, that paediatric transplant nurses can impact the health and well-being of their young patients.[48-49]

Long-term outcomes

The recipient's health, the donor kidney's quality, medication compliance, and the existence of problems are some of the variables that affect kidney transplant results over the long run.[50]

1. Graft Survival

Graft Survival Rates on Average:

- Average lifespan of a living donor kidney: 15–20 years.[51]
- Deceased donor kidney: typically, 10–15 years.

A number of variables, including lifestyle, medical care, and donor-recipient matching, affect graft survival rates.

2. Patient Survival

Improvements in immunosuppressive drugs and post-transplant care have led to a significant improvement in survival rates over time. After a kidney transplant, patient survival is typically better than continuing dialysis.

3. Quality of Life

Compared to dialysis, kidney transplantation frequently results in a marked improvement in quality of life, including improved mental and physical health as well as freedom from the limitations of frequent dialysis sessions.[52]

Complications

Following kidney transplantation, there may be complications that develop immediately post-surgery or overtime. Some common complications are:

1. Rejection

- Acute Rejection: The immune system attacks the new kidney in the first year.
- Chronic Rejection: There is a gradual loss of kidney function over years of growth.

2. Infections

Immunosuppressive agents compromise immunity, predisposing an individual to bacterial, viral, and fungal infections. In transplant recipients, cytomegalovirus (CMV), Epstein–Barr virus (EBV), and polyomavirus (BK) infection are the most common viral infection.

Surgery and immunosuppression commonly cause urinary tract infections (UTIs).

3. Adverse Drug Reactions

- Immunosuppressive drugs are necessary to prevent rejection; however, they increase the susceptibility to infections.
- Hypertension.
- Diabetes.
- Osteoporosis.
- High cholesterol levels.
- Weight gain.

4. Heart Problems

heart disease, which remains one of the leading causes of death even after kidney transplantation, has a greater possibility of attacking kidney transplant recipients.

5. Cancer

Long-term immunosuppression increases the possibility of getting cancer, most commonly skin cancer. Additional cancers such as lungs, liver, or kidney cancer were observed as well.[53] Similarly to that Post Transplant Lymphoproliferative Disease (PTLD) is one the major complication of paediatric kidney transplantation.[54-55]

6. Recurrence of Original Kidney Disease

The transplanted kidney may occasionally have a recurrence of the underlying kidney disease that led to kidney failure.

7. Dysfunction of Graft

Among the causes are:

- Rejection.
- Diseases.
- Kidney illness recurrence.
- Adverse drug reactions.
- Postoperative problems, such as ureteric obstruction or leaking.

8. Post-Transplant Diabetes Mellitus

Immunosuppressive drugs, mainly corticosteroids and calcineurin inhibitors, such as tacrolimus can cause diabetes in patients who had no history of the disease.

9. Problems Affecting the Digestive System

Nausea, vomiting, diarrhoea, or ulcers may be caused by drugs or infections.

10. Bone and Joint Issues

Joint pain and bone thinning, also known as osteopenia or osteoporosis, are adverse effects of immunosuppressive therapy, mainly steroids.

11. Surgical Complications

- The bleeding.
- Blood clots.
- Leakage or obstruction of urine from the kidney transplant.
- Infection at the site of surgery.

12. Metabolic Disorders

- Elevated potassium is known as hyperkalaemia.
- Low levels of phosphate are termed hypophosphatemia.

Other disturbances induced by kidney failure or adverse drug reactions.

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Chapter 7

Psychosocial Support for Kidney Transplantation

Learning objectives

- To describe the physical and emotional effects of having a transplant.
- To recognise the psychosocial effects associated with different transplantation experiences (pre-transplant, cancelled transplant, graft rejection and successful transplant).
- To explain the role of the Multidisciplinary Team (MDT) in responding to psychosocial needs before and after transplantation.
- To identify appropriate interventions, such as referral to a psychotherapist, psychologist or social worker, to support people with the psychosocial aspects of transplantation.

Introduction

Transplantation must be viewed from different perspectives; the medical, pharmacological, pre and post operative phases, and also the psychosocial. While it is accepted that transplantation is regarded as the gold standard to treating kidney disease more effectively than either PD or HD,[1] the road to a successful kidney transplant often involves people on dialysis navigating psychosocial issues which can be debilitating, threatening and difficult to manage.[2] What, therefore, are some of the psychosocial issues those caring for people on dialysis should be conscious of?

While mention will be made of some of the psychosocial issues present in the preoperative period, the emphasis of this chapter will be on the psychosocial issues relevant to the post operative period. Also, transplant is to be understood in this chapter as referring to cadaveric transplant. Live donor transplant raises a number of complex issues[3] which is beyond the scope of this chapter.

The Preoperative period

Illness brings with it significant psychosocial changes. For example, for those who require dialysis treatment these changes include adherence to a strict regime of treatment, a restrictive diet, a change in lifestyle, emotional upheaval which often finds expression in stress, anxiety, and depression.[4]

For nurses this landscape is familiar. One way people eligible for a transplant on dialysis cope is to live in hope of a transplant. 'We all dreamed of the day we'd get the call for a transplant'[5] was how one young person on dialysis described it. This ushers in a period that brings with it its own psychosocial stress – waiting. The anxiety associated with waiting is often expressed in phrases such as 'how long will I have to wait' and 'will I be healthy enough to have a transplant'. In the mind of the person on dialysis waiting brings with it the tension between the possibility of a return to life without dialysis and the risk of deteriorating health while waiting to be called for transplant.

From a more positive perspective, nurses can encourage people on dialysis to use this waiting period as a time of preparation. An example of this could be supporting them to engage with any emotional, physical, or social difficulties they may be experiencing and/or enabling them to develop a healthy lifestyle. Structured support could be offered through support groups for those preparing for transplant.

The Post operative period

The period following transplant has been described as like 'riding an emotional rollercoaster'.[6] There is uncertainty should the transplanted graft take time to function, delight that the transplanted graft is functioning, that the person is now free from dialysis, that the restrictions imposed by dialysis treatment no longer apply. Yet, it should be recognised that complications can arise when adapting to a successful transplant. The requirement to take life-long immunosuppressants medication, the fear of rejection and the need for regular check-ups can be problematic for some.[7] However, the more common psychosocial impacts people experience following transplant are; depression,[7,8] adjustment disorders[9,10] and non-adherence.[10,13,14]

Depression

There are a number of common symptoms which indicate a person is depressed; from low mood to loss of interest, being self-critical to poor concentration. The Patient Health Questionnaire - 9 is a useful tool which can be used to measure the level of depression.

One study estimates the prevalence of depression among people who have had a successful transplant as 20 to 25% of cases.[10] Depression can be triggered if there are complications following transplant. These are anxious times for the person as the sustainability of the transplanted graft may be called into question. Furthermore, the person's subjective health perception, that is, what was imagined before transplant and the reality of what is happening now can result in a depressive episode. If there are clinical indicators of depression referral to a psychotherapist or psychologist or to their primary care physician should be considered. If necessary, their primary care physician can prescribe antidepressant medication.

Adjustment Disorders

Adjustment to life after a successful transplant is not without its difficulties. Adjustment disorders,[9] often induced by a stressful life event or trauma, can occur is people post-transplant. Issues such as responsibility for the transplanted graft, role within the family, lack of social support, and employment can prove problematic. Hence, it should be remembered that following a successful transplant stress does continue which has the 'the potential of debilitating mental health effects'.[10]

Social and family support to help the person through some of the adjustment difficulties they may be experiencing is seen as important. A lack of family support has been shown to increase the risk of post-traumatic stress disorder[11] and non-adherence. To combat this, support groups, either organised in the hospital or locally or online, could offer the support necessary to reduce adjustment difficulties.[12]

Non-Adherence

One issue that contributes significantly to graft loss in those who have a successful transplant is non-adherence.[13,14] According to one study those most likely to be non-adherent are kidney recipients'.[15] What this means in effect is that half of late acute rejections and 15% of graft losses are directly related to issues around non-adherence.[16] How is non-adherence to be understood? In practice it covers the following: 'not taking medications, missing medications, taking too much, not taking enough, wrong timing, wrong dose and/or wrong pill, but may also refer to missing appointments, not booking

appointments, not doing blood work, not returning calls and/or refusal to follow the treatment regimen'.[10]

For those caring for people with a transplant, any one of these factors or a combination of these should act as an alert, a communication that the person is struggling in some way. Swift intervention is vital to ascertain what the issue is, followed by a referral to an appropriate member of the MDT. Depression can also be a factor in non-adherence to medication. If depression is an issue post-transplant the person should be monitored closely and if non-adherence becomes an issue intervention at an early stage can be made.

In practice a three-step approach directed at people who are non-adherent can be beneficial. The first step is an assessment process which should - step two - focus on the underlying causes, leading to - step three - a tailored response that address the individual's issues.[10]

Psychosocial Support

Psychosocial support for people at the pre- and post-transplant stage can come in various forms and at many levels. What should be paramount is the need of the person seeking support. Importantly, many hospitals acknowledge that psychosocial issues following transplant are common and have in place structures of support.[17,18,19]

In any provision of psychosocial care, the first step is assessment of the person requesting support. The fundamental question is: what kind of psychosocial support is this person looking for? Following assessment, the next question is: do I have the professional skills to provide the psychosocial care this person requires, or do I need to refer on to someone who is professionally trained to support this person?

A Multidisciplinary Team (MDT) approach is an effective way to cover the needs of those requiring support following a transplant. Ideally, MDTs should include amongst their number; transplant co-ordinators, medical staff, a social worker, either a psychotherapist, psychologist or psychiatrist, and a dietician. To what extent is a team like this available in your unit? Is there anyone from the list above not part of your team? If so, what does this say about your unit's ability to provide the necessary psychosocial care for those who, following transplant, request it? Diagram 1 outlines the MDT structure in one of the major hospitals in Ireland.

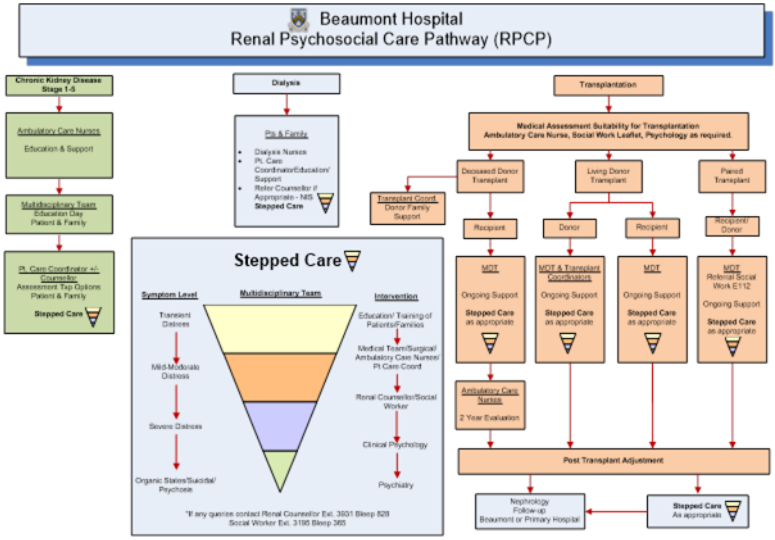


Diagram 1

Conclusion

Dr Thomas, who himself experienced kidney failure and had a successful kidney transplant, writes that 'the improvements following transplantation cannot be overstated but the psychological impact of the event stays with you'.[8] For many people transplanted dealing with the psychosocial impact can be difficult. The difficulty may manifest itself in different ways, in depression, in non-adherence or in difficulties adjusting to life after transplant. Whatever and wherever the difficulties occur, the provision of psychosocial care is essential. Providing such care 'is an investment that underpins and secures medical and nursing achievements.[20]

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Chapter 8

Nursing management approach for kidney transplant patients

Learning objectives

- To highlight important considerations at each stage of the transplant journey.
- To describe the nurse's role in kidney transplant.
- To point out the role of nurses in transplant recipient post-surgery.

Introduction

Kidney transplantation is a surgical procedure considered the best treatment option for the patient with chronic kidney disease.[1] Kidney transplantation will provide the patient a better lifestyle with less cost; this procedure must be done by an expert transplant surgeon. Nurses' responsibilities in this lifesaving process range from holistic preoperative assessments and preparations to vigilant postoperative care, which includes psychosocial and psychiatric support, meticulous medication practices, and close surveillance for infections.[2,3]

Nursing professionals have managed to increase the success of the transplant procedures and to improve the health status of the transplant recipients by taking evidence-based measures and implementing a holistic framework in their care plans.[4,5]

1. Preoperative Assessment and Preparation

1.1. Evaluation of the Kidney Transplant Candidate

Before a patient can receive a kidney transplant, a thorough pre-transplant evaluation is needed. This process involves various tests and assessments to ensure the patient's readiness for the surgery.[6,7]

1.2. Pre-transplant Workup and Testing

During the pre-transplant workup, nurses play an important role in analysing, checking, and detecting all the different laboratory results and imaging tests done for the candidate. This vigilant nursing analysis includes.[8-11]

- Laboratory Tests and Imaging Studies
- Cardiac Assessments
- Pulmonary Function Tests
- Infectious Disease Screening
- Psychological Evaluation
- Multidisciplinary Team Review

Nurses' vigilance and readiness may detect any early potential reason to delay the kidney transplantation; they are managing the waiting list and ensuring all patients have equitable access to be evaluated for transplantation and then listed if appropriate, with ethical and moral responsibilities.[12]

2. Intraoperative care

Nursing roles start from the time when the patient is admitted to the operating room; multiple tasks are fundamental for the surgery's success,[13,14] such as:

- Operating table preparation
- Positioning the patient
- Haemodynamic Monitoring and Management
- Fluid and Electrolyte Balance
- Temperature Regulation
- Blood Glucose Monitoring
- Medication Administration
- Surgical Site Preparation
- Prevention of Complications
- Documentation

3. Postoperative Care and Monitoring

3.1. Immediate Post-Transplant Period

Usually, a kidney transplant recipient will spend the first 48 to 72 hours in the ICU. Nurses will look closely and observe for different

changes and warning signs; nursing vigilance will detect any early signs and act accordingly.[15,16]

- **Haemodynamic Monitoring:** Closely monitoring vital signs (blood pressure, heart rate, temperature, and respiratory rate) and assessing any signs of haemodynamic instability.[17]
- **Renal Function Monitoring:** Monitoring urine output, assessing signs of graft dysfunction, and closely monitoring laboratory values like creatinine and urea levels.[17]
- **Pain Management:** Providing appropriate pain relief measures, including multimodal analgesia, and assessing the effectiveness of pain management strategies.[17]
- **Fluid and Electrolyte Balance:** Managing fluid intake and output, monitoring electrolyte levels, and addressing any imbalances.[17,18]
- **Medication Management:** Administering immunosuppressant medications as prescribed, monitoring for side effects, and educating the patient on medication adherence.[17,18]
- **Psychosocial Support:** Providing emotional support to the patient and their family, addressing anxiety and fear, and facilitating communication with the healthcare team.[17]
- **Early Mobilisation:** Encouraging early mobilisation to prevent complications like deep vein thrombosis and promoting overall recovery.[17]

3.2. Care of the Surgical Wound & Management of Complications

The nursing role will continue as well, following the surgical wounds and management of complications. The highly skilled nurses will observe and look for different signs and symptoms that may lead to early detection of any possible complications.[19,20]

- **Initial Care:** The surgical wound should be kept clean and dry. Dressings may be changed regularly, and the patient should be instructed on proper hand hygiene to prevent infection.
- **Monitoring:** Close monitoring for signs of infection, such as redness, swelling, pus, or increased pain, is essential.
- **Pain Management:** Pain at the surgical site is common and can be managed with prescribed pain medication.

3.3. Management of potential complications

- **Surgical Site Infections (SSI):** These can be a significant concern, with risk factors including diabetes, obesity, and certain immunosuppressants. Treatment may involve antibiotics and potentially surgical debridement.[21]
- **Lymphoceles:** Fluid collections (lymphoceles) around the transplanted kidney can occur and may require drainage or other interventions.[22]
- **Ureteral Complications:** Problems with the ureter, such as leaks or strictures, can occur and may require surgical repair or other treatments.[23,24]
- **Vascular Complications:** Blood clots or problems with blood vessels around the kidney can occur and may require intervention.[25]

4. Medication Management and Adherence

4.1. Medication Management

Nurses help patients create plans for taking and organising their prescriptions, including scheduling refills, using pill organisers, and setting reminders. Nurses will evaluate patients' medication adherence habits in order to spot any obstacles and risk factors for non-adherence.[26]

4.2. Intervention and Support

Nurses use techniques like motivational interviewing, counselling, and liaising with other medical specialists (such as social workers and pharmacists) to enhance adherence.

4.3. Monitoring and Follow-Up

Nurses keep an eye out for drug side effects and complications in patients, offering continuing assistance and modifying treatment regimens as necessary.

5. Infection Prevention and Control

5.1. Patient Education

- Patient education includes teaching patients and their families about the dangers of infections, how to avoid them, and the importance of medication adherence.
- Giving advice on food safety and hygienic measures, including hand hygiene.
- Teaching people how to spot infection signs and symptoms early on.[27]

5.2. Monitoring and Surveillance

- Monitoring patients for signs and symptoms of infection.
- Conducting surveillance for healthcare-associated infections, including urinary tract infections (UTIs) and Clostridium difficile infection (CDI).
- Coordinating laboratory testing for diagnosis and monitoring of infections.
- Collaborating with other healthcare professionals to ensure appropriate antimicrobial prophylaxis and treatment.[28]

6. Psychosocial Support and Education

6.1. Psychosocial Support

- **Emotional Support:** Nurses assist patients in managing the psychological impact of transplantation, such as depression, anxiety, and fear of rejection.
- **Facilitating Communication:** Nurses encourage patients to express their concern and have open communication with the transplant team.
- **Connecting with Resources:** Nurses may help patients liaise with other support teams, such as social support, if needed.
- **Addressing Family Needs:** Nurses can analyse and provide guidance for family support, as it is part of the healing process.[29-32]

6.2. Education

- **Medication Adherence:** Nurses provide the needed information regarding the importance of adherence to immunosuppressant regimens to prevent rejection.[33, 34]
- **Lifestyle Modifications:** Nurses will clarify the possible changes that may happen post-surgery, such as dietary changes, physical activity, and other lifestyle adjustments to promote overall health and well-being.[35]
- **Follow-up Care:** Nurses schedule follow-up visits, stress the value of routine examinations, and reinforce the necessity of constant communication with the transplant team.[35]
- **Infection Prevention:** Nurses instruct patients on infection control prevention measures, like washing their hands and limiting their exposure to possible infection sources.[36]
- **Recognising Symptoms:** Nurses clarify the possible signs and symptoms of infection or rejection and the importance of immediately reporting them.[37]
- **Promoting Self-Management:** By teaching and supporting self-management techniques, nurses enable patients to take an active role in their treatment.

Conclusion

In order to improve patient outcomes, nursing management for kidney transplant recipients takes a comprehensive strategy that keeps into account mental, emotional, and physical aspects. With knowledge and experience, the nursing role aims to offer care and compassion, support, and direction throughout the post-transplant journey.[38-40] In conclusion, nurse management encompasses a wide variety of duties that need to be handled with the highest seriousness and severity, and it cuts across the spectrum of care demands for kidney transplant patients. Through their expertise, empathy, and unwavering dedication, nurses significantly contribute to the patient's experience during the transplant procedure, improving patient outcomes and quality of life. As the primary carers, nurses contribute indirectly and sustainably to the overall outcome of kidney transplantation, they also signpost to the wider healthcare team (dietitians, pharmacists, social workers, physiotherapists); as a

result, they play a crucial role in making sure transplant recipients are in the greatest possible health.[41,42]

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