SOLID ORGAN TRANSPLANTS

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Learning outcomes

1. Define and understand the context of solid organ transplantation, and classify graft types
2. Describe immunosuppression as it pertains to solid organ transplantation
3. Outline the systemic complications and oral manifestations of solid organ transplantation and immunosuppression
4. Perform a dental work-up prior to solid organ transplant using a structured management framework

01 Solid organ transplantation

DEFINITIONS

Solid organ transplantation

A solid organ transplant is a highly effective treatment for advanced organ failure, achieved by transplanting a healthy organ from a living or a deceased donor.

- Transplanted organs may come from
  - Living donor
  - Deceased donor: organs are retrieved after either brain death or circulatory death (cadaveric)
- Clinical and ethical guidelines for donation and allocation exist in most countries
- First successful kidney transplant: 1954 — between living identical twins
- Survival improved markedly only in the 1980s
- Transplantation saves lives in terminal organ failure and improves quality of life

DEFINITIONS

Types of grafts and transplants

Type of graft	Procedure	Source
Autograft	Autologous	Self
Allograft	Allogeneic	Genetically different individual of the same species
Isograft	Syngeneic	Genetically identical individual (monozygotic twin)
Xenograft	Xenogeneic	Different species

Organs

- Common: Kidney, liver, heart, lung, pancreas
- Less common: small bowel
- Kidney is by far the most frequently transplanted organ

Tissues, cells and fluids

- Blood or blood components, blood vessels
- Bone, bone marrow / stem cells
- Cornea, skin, face, hand, trachea
- Heart valve, pancreas islet cells

Indications for transplantation

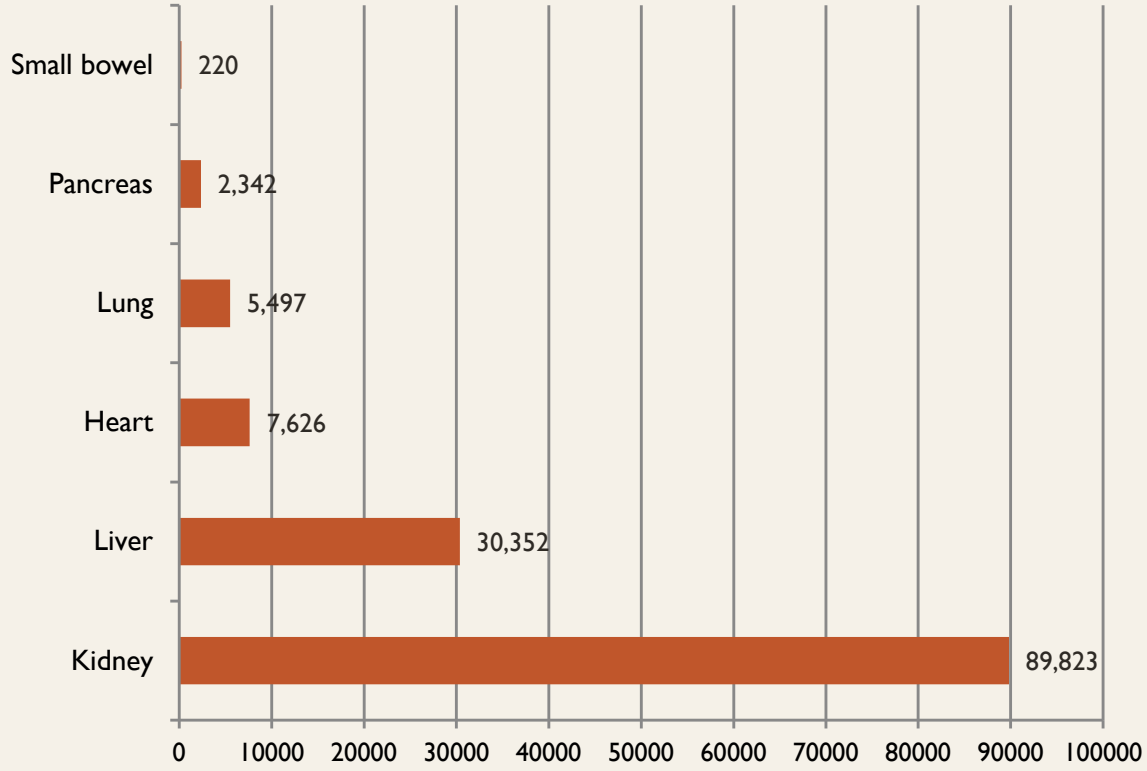
Disease severity

- Untreatable end-stage organ disease
- Limited life expectancy
- Substantial limitation of daily activities

Recipient suitability

- Ambulatory patient with rehabilitation potential
- Acceptable nutritional status
- Satisfactory psychosocial profile and emotional support
- Absence of other severe concomitant disease

Global transplant activity, 2017



WHO World Transplant Registry 2017

- ~135 860 solid organ transplants performed worldwide
- 40% of kidney transplants came from living donors
- 19% of liver transplants came from living donors

EPIDEMIOLOGY

Graft and patient survival

Organ	Donor source	Graft 1-year	Graft 5-year	Patient 1-year	Patient 5-year
Heart	Deceased	90.6%	85.4%	90.0%	78.6%
Lung	Deceased or living (rare)	92.3%	73.5%	85.8%	56.1%
Kidney	Deceased or living	94.4%	83.6%	97.3%	89.7%
Liver	Deceased or living	91.8%	84.6%	89.3%	76.5%
Pancreas	Deceased or living (rare)	93.4%	87.2%	96.4%	88.3%
Intestine	Deceased or living (rare)	Insufficient data	Insufficient data	75.2%	55.5%

Organ Procurement and Transplantation Network (OPTN) and Scientific Registry of Transplant Recipients (SRTR) 2019. OPTN/SRTR 2017 Annual Data Report. Am J Transplant 2019;19(S2):1–516.

ANZOD Registry. 2019 Annual Report, Section 12: Deceased Organ Transplant Outcome Data, Adelaide: Australia and New Zealand Dialysis and Transplant Registry; 2019.

- Survival has improved significantly over the last decade; the best outcomes follow adult kidney transplantation
- Compared with remaining on the waiting list, a cadaveric graft doubles and a living-donor graft quadruples the chance of survival
- Repeat kidney, liver or heart transplantation performs less well — repeat liver transplantation adds only 1.5 life-years per recipient

EPIDEMIOLOGY

A world and transcultural view

Profound geographical inequity

- Demand exceeds donation everywhere
- Activity ranges from >70 per million population in developed countries to 0–2.4 per million in developing countries
- Careful medical and ethical decisions about allocation are critical

Donation schemes vary

- Donor registration; directed living donation to friends and relatives
- Paired and pooled living donation; altruistic donor chains
- Some countries use 'opt out' rather than 'opt in' consent to raise donation rates

Ethics and beliefs

- The Declaration of Istanbul on Organ Trafficking and Transplant Tourism (updated 2018) unites member states against unethical practice
- Transplantation may be refused by some Jehovah's Witnesses and Orthodox Jews

02 Immunosuppression

Immunosuppression

- Because most grafts are allografts, the recipient must be immunosuppressed for life to prevent T-cell alloimmune rejection
- Most immunosuppressants target T lymphocytes — the primary mediators of rejection
- These drugs have a narrow therapeutic index – therapeutic blood monitoring required
  - Blood counts, liver function, kidney function, blood glucose, lipids
  - Immunosuppressant drug levels
  - Other transplant complications
- Three regimen types exist: induction, maintenance and treatment of rejection

The therapeutic balance

Too little
Rejection, graft loss, return to organ failure

Too much
Toxicity, opportunistic infection, malignancy

Immunosuppressive regimens

Regimen	Description	Drugs commonly used
Induction	Begun before, at or immediately after transplantation to deplete or modulate T-cell responses Doses not continued long-term (usually <3 month)	Corticosteroids; cell-depleting agents (alemtuzumab, ATG, ALG, muromonab) or receptor blockers (basiliximab, daclizumab)
Maintenance	Long-term prevention of acute rejection and graft deterioration Mono- or combination therapy Doses reduced 2–4 months post-transplant, once acute rejection risk is lower	Calcineurin inhibitors (ciclosporin, tacrolimus); mTOR inhibitors (sirolimus, everolimus); antiproliferatives (mycophenolate, azathioprine); corticosteroids
Rejection	Treatment of acute rejection mediated by cellular (T-lymphocyte) and/or humoral (circulating anti-HLA antibody) responses	Cellular rejection: high-dose corticosteroids, lymphocyte-depleting antibody. Antibody-mediated rejection: steroids, plasma exchange, IVIg, rituximab

Drug classes and dental implications (1 of 2)

Class / example	Mechanism	Dental implications and interactions
Corticosteroids (prednisolone)	Block transcription of cytokine genes: IL-1, IL-2, IL-3, IL-5, IL-6, TNF-α, interferons	Impaired wound healing; opportunistic infection; steroid supplementation; increased MRONJ risk; avoid aspirin and NSAIDs (GI bleeding)
Ciclosporin (calcineurin inhibitor)	Inhibits IL-2 production; stimulates TGF-β	Gingival hyperplasia; impaired healing; circumoral paraesthesia; bleeding; avoid clarithromycin and ketoconazole
Tacrolimus (calcineurin inhibitor)	Inhibits IL-2 production	Oral ulceration; circumoral paraesthesia; avoid clarithromycin, aciclovir, azole antifungals, NSAIDs
Azathioprine (antiproliferative)	Inhibits purine synthesis and CD28 signalling	Stomatitis; opportunistic infection; bleeding; emesis (dental erosion risk); avoid muscle relaxants

↳ have a sense for immunosuppressants in general
to avoid NSAIDs for methotrexate

Drug classes and dental implications (2 of 2)

Class / example	Mechanism	Dental implications and interactions
Mycophenolate mofetil (antiproliferative)	Inhibits purine synthesis and glycosylation	Stomatitis; opportunistic infection; bleeding; emesis; avoid aciclovir
Methotrexate (antiproliferative)	Inhibits purine and pyrimidine synthesis	Oral ulceration; bleeding; MRONJ risk; avoid NSAIDs (drug toxicity) and beta-lactams
Polyclonal antibodies (ATG, ALG)	Complement-mediated lysis, opsonisation, receptor blockade	Bleeding; opportunistic infection
Monoclonal antibodies (muromonab, alemtuzumab, basiliximab)	Lysis or blockade of CD3, CD52 or the IL-2 receptor	Emesis; wound infection
mTOR inhibitors (sirolimus, everolimus)	Block IL-2-induced cell cycle progression (G1 to S phase)	Oral ulceration; dysgeusia; impaired healing; MRONJ risk; bleeding; emesis; avoid macrolides and azole antifungals

Relative potency and toxicity

	Ciclosporin	Tacrolimus	Sirolimus	Azathioprine	Mycophenolate	Corticosteroids
Immunosuppressive potency	+++	+++±	++±	+	++	+
Nephrotoxicity	++	++	–	–	–	–
Hepatotoxicity	±	±	+	+	–	–
Neurotoxicity	+	++	–	–	–	–
Marrow suppression	–	–	+	+	+	–
Diabetes	+	++	–	–	–	++
Diarrhoea	–	–	+	–	++	–
Hirsutism / hypertrichosis	++	–	–	–	–	++

due to tacrolimus + steroids

– no effect; + mild; ++ moderate; +++ high ++++ extreme.

Adapted from Taylor, Watson and Bradley (2005), Crit Rev Oncol Hematol 56: 23–46.

03 Systemic complications and general management

Rejection: three time courses

Type	Timing	Mechanism
Hyperacute	Minutes to hours	Recipient's pre-existing antibodies against donor HLA
Acute	One week to three months	Cellular (T-lymphocyte) and humoral immunity
Chronic	Months to years	Follows multiple episodes of acute rejection

- Non-immunological graft dysfunction also occurs: surgical and vascular complications, comorbidities, infection and drug side-effects
- Recurrent organ and multiorgan disease may affect the graft
- Dental relevance: during a rejection episode the patient is acutely unwell, on escalated immunosuppression, and elective dentistry must be deferred

Immunological compatibility

HLA tissue typing

- Number of antigens mismatched at each HLA locus
- Fewer mismatches, better graft survival

Humoral sensitisation

- Presence of anti-HLA antibodies against the donor
- A negative crossmatch is required to proceed

ABO blood group

- Is the graft a target for preformed anti-ABO antibody?
- Incompatibility causes hyperacute rejection

Immunological rejection remains the major barrier to transplant success — matching reduces, but never abolishes, the need for immunosuppression.

Solid organ transplant complications

- Recurrent organ and multiorgan disease
- Solid organ transplant rejection
- Non-immunologic graft dysfunction
- Immunosuppression
- Post-transplant lymphoproliferative disorders
- Graft vs Host Disease
- Immune Reconstitution Syndrome

GENERAL MANIFESTATIONS

General risks of immunosuppressant therapy

Haematological

- Bone marrow suppression
- Cytopenias: anaemia, neutropenia, thrombocytopenia
- Bleeding tendency

Organ toxicity

- Nephrotoxicity
- Hepatotoxicity
- Neurotoxicity
- Cardiovascular disease

Metabolic / endocrine

- Secondary diabetes
- Adrenal suppression
- Osteoporosis and osteopenia

Infection

- Viral, fungal and bacterial
- Opportunistic organisms
- May be life-threatening and present atypically or with muted signs

Malignancy

- More than 50% cutaneous (SCC, BCC, melanoma)
- Also virally induced tumours (HPV skin & lip carcinoma, HHV-8 Kaposi sarcoma, EBV lymphoma)
- Requires lifelong surveillance — including of the lips and oral mucosa

Graft-versus-host disease

- Acute (aGvHD): traditionally within the first 100 days; a major challenge because of morbidity and mortality
  - Severe intestinal inflammation, mucosal sloughing, diarrhoea, abdominal pain, nausea and vomiting
  - Skin: diffuse red maculopapular rash
  - Oral: resembles lichen planus, with a higher risk of malignant transformation
- Chronic (cGvHD): normally after 100 days; moderate to severe disease adversely affects long-term survival
- GvHD is unusual after solid organ transplantation but is a major issue after haemopoietic stem cell transplantation

Classification rests on clinical findings, not a fixed time period.

Challenging the 100-day rule…

- Classic acute: within 100 days, acute features only
- Persistent, recurrent or late-onset acute: beyond 100 days, acute features only
- Classic chronic: any time, diagnostic chronic features, no acute features
- Overlap syndrome: any time, features of both ('acute on chronic')

04 Oral complications

Oral infections

Fungal

- Candidiasis — the most common oral infection in these patients
- May be pseudomembranous, erythematous or angular
- N.B. caution: azole antifungals interact with calcineurin and mTOR inhibitors

Viral

- Herpes simplex virus
- Varicella zoster virus
- Cytomegalovirus
- Often more extensive, more painful and slower to resolve than in immunocompetent patients

EBV-associated

- Oral hairy leucoplakia — Epstein–Barr virus
- White corrugated non-removable plaque, typically lateral tongue
- A marker of immunosuppression

Governing principle

Because infection in an immunosuppressed patient can be serious, maintenance of good oral care and aggressive treatment of odontogenic infection are crucially important.

Mucosal, gingival and dental changes

- Fungal (candida), viral (HSV, HZV, CMV, EBV) infection
- Malignancy (virally-driven, cutaneous)
- Petechiae, gingival bleeding
- Hyposalivation
- Oral ulceration and stomatitis
- Anaemia: Mucosal pallor, angular cheilitis, glossitis, fissured/burning tongue, ulcers
- Impaired healing
- Dental erosion
- Dysguesia (mTOR inhibitors), circumoral paraesthesia (tacrolimus), gingival overgrowth (ciclosporin)



Sirolimus-induced oral ulceration



Ciclosporin-induced gingival hyperplasia.

Organ-specific considerations

Transplant	Key dental modifications
Heart	Adequate pain and anxiety control to reduce cardiac stress; bleeding risk from anticoagulants/antiplatelets; caution with intravascular adrenaline (consider adrenaline-free solutions); oral side-effects of antihypertensive drugs; consider antibiotic prophylaxis if IE risk; pacemakers and electromagnetic interference; 'silent' MI may occur without angina
Lung	Pre-transplant mouth breathing causes dry mouth and exacerbation of periodontal disease; caution with respiratory depressants (e.g. opioids); semi-reclined position; airway protection (e.g. rubber dam, high-volume suction, minimise aerosols); preoperative chlorhexidine rinse (to reduce oral bacterial load); pulse oximetry
Kidney	Consider residual renal impairment; avoid nephrotoxic drugs (e.g. NSAIDs); bleeding risk (thrombocytopenia, platelet dysfunction, defective vWF, reduced thromboxane); altered bone metabolism (MRONJ risk if on antiresorptives)
Liver	Nutritional deficiencies (angular cheilitis, glossitis, fissured tongue, ulceration); bleeding risk (reduced coagulation factors and thrombocytopenia) - preoperative FBC and coagulation studies, local haemostatic measures, petechiae / ecchymosis / gingival bleeding; avoid hepatotoxic and hepatically metabolised drugs; infection risk
Pancreas	Often performed with a kidney transplant; hypoglycemia – pre-operative BGLs, monitor for sudden changes in BGLs leading to insulin shock

05 Dental workup prior to solid organ transplant

Timeframes for future-proofing

Pre-transplant



Immediate post-



Stable post-



– Confirm coagulation and blood chemistry returned to normal; blood counts satisfactory

Timeframes for future-proofing

Pre-transplant

months – years

- Dental work-up period
- Work-up timeframe set by other specialties
- Transplant waitlist
- On maintenance modality

Immediate post-transplant

0 – 3 months

- Induction immunosuppression
- Recovery
- Emergency dental tx in hospital setting
- Delay elective dental tx

Stable post-transplant

>3 – 6 months

- Maintenance immunosuppression
- ~3 months once graft is stable and functional
- ~6 months until stable for dental tx
- Confirm coagulation and blood chemistry returned to normal; blood counts satisfactory

Acute or chronic rejection

1 wk – 3 mths; months – years

- Rejection immunosuppression
- S&S of organ failure + histological graft rejection
- Only tx emergencies
- Delay elective dental tx 3–6 months

ORAL MANAGEMENT

Risk assessment

Medical

- Infection risk
- Bleeding and anaemia
- Adrenal suppression
- Secondary diabetes
- Increased malignancy risk
- Hypertension
- Drug interactions and metabolism
- Organ-specific risks

Dental

- Oral complications: mucositis, ulceration, stomatitis
- Dental erosion (emesis)
- Impaired wound healing
- MRONJ risk

Social

- Possible fatigue affecting attendance and cooperation
- Support network and transport to appointments

Access to care

Immediate post-transplant (first 3 months)

- Delay elective treatment at least 3 months, ideally until 6 months post-transplant
- If emergency care required: close medical consultation, conservative treatment selection, consider a hospital setting

Stable post-transplant period

- Six months may be needed before the recipient is stable enough for dental treatment
- Confirm blood counts, coagulation and blood chemistry are satisfactory first

Setting

- Pre-transplant patients may be managed in primary care; seek advice or refer if needed
- Refer to specialist setting if in the immediate post-transplant or chronic rejection period

Timing of treatment

- Book surgical appointments in the morning and early in the week (bleeding risk)

ORAL MANAGEMENT

Education and prevention

Focus on preventive care

- Lifelong oral health maintenance, framed around the patient's medically compromised status
- Effective daily oral hygiene
- Active recall programme with 3–6 monthly appointments
- Routine surveillance for malignancy: squamous cell carcinoma, Kaposi sarcoma, lymphoma

ORAL MANAGEMENT

Surgical considerations

BEFORE

- Assess the risks specific to the type of organ failure
- Liaise with the physician or transplant team on the plan and on antibiotic prophylaxis
- Consider preoperative blood tests: FBC, coagulation, biochemistry

DURING

- Lubricant or barrier cream to protect the lips and soft tissues from trauma
- Careful manipulation of the cheek and soft tissues — caution with suction
- Local anaesthesia: aspirating syringe, vasoconstrictor unless contraindicated
- Sedation: caution— anaemia, drug interactions with immunosuppressants, impaired clearance
- General anaesthesia: not recommended (as above)

AFTER

- Local haemostatic measures if bleeding risk
- Consider chlorhexidine mouthwash for 1–2 weeks after invasive procedures
- Review the wound — healing is impaired and infection presents late
- Analgesia: paracetamol (avoid NSAIDs and aspirin)

Surgical antibiotic prophylaxis?

The argument for

- Increased infection risk in the immunosuppressed transplant patient
- Many transplant centres recommend prophylaxis for procedures producing a transient bacteraemia
- The consequences of a disseminated infection can be severe

The argument against

- No data indicate that this is effective practice; protocols vary between countries
- Choosing the best antibiotic is difficult — oral flora is altered by immunosuppression and by repeated background prophylaxis
- Multiple interactions exist between immunosuppressants and antibiotics

May justify prophylaxis**:** invasive dental procedures - active dental infections (e.g. periodontal or dental abscess), increased dosage of immunosuppressants
May not require prophylaxis: good oral health, stable grafts, not undergoing extensive dental procedures

Given the lack of scientific evidence of benefit, usage should be determined on an individual patient basis, in consultation with the transplant team.

depend

PRIOR TO SOT IMMUNOSUPPRESSION

Pre-treatment recommendations

Eliminate infection and disease

- Extract all **non-restorable teeth and retained roots** (not fully covered by bone or radiolucency present) no less than 10 days (preferably 3 weeks) prior to commencement of therapy
- Extract all **severely periodontally compromised** teeth (periodontal pockets ≥6 mm, advanced mobility, furcation involvement ≥ grade II)
- Extraction or endodontic treatment of **non-vital teeth ± periapical pathology**, allowing sufficient time to evaluate the success of treatment
- Extraction, endodontic treatment or temporary restoration of carious teeth **close to pulpal exposure**
- Consider extraction of **partially erupted teeth** (including third molars)

Stabilise and prepare

- Consider **removal of orthodontic appliances**
- Perform **denture adjustments** (if required)
- Perform **scale and clean** (periodontal debridement) to stabilise periodontal disease
- Smooth **sharp edges** of teeth/restorations
- Provide **elective dental treatment** (only as time/necessity permit)

THINKING IT THROUGH

Solid organ transplant

Rationale

- Immunosuppression → reduced ability to fight infection

Medical, dental and social considerations

- Risk assessment and treatment modifications required; depends on specific organ type
- Institute preventive oral health care program

Areas of the mouth

- Entire mouth — soft tissues and dentition

Optimal timeframes

- Find out timeframe — often a waitlist for an appropriate donor
- Time available pre-transplant to optimise the patient
- Need to remain "dentally fit" until the time of transplant
- Managing infections medium-term (moving target)
  - Eliminate acute dental infections pre-transplant
  - Avoid elective dental treatment in the immediate post-transplant period (3 months)
  - Ideally wait until stable post-transplant period (6 months)

Treatment approaches

- Aggressive (e.g. extractions) vs conservative (e.g. RCTs) options — depends on timeframe and patient motivation

Questions?

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