

Methods of Increasing Graft Survival

Allograft compatibility · immunosuppression · immune complications

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Learning objectives

- Explain why HLA matching has different priorities across solid organs.
- Trace the pharmacologic interruption of T-cell activation and proliferation.
- Match major rejection mechanisms to the interventions.
- Explain infection, malignancy, and tolerance as limits of graft survival.

A graft survives through several protective layers

Protection is a combined immunologic and clinical strategy.

Before implantation

- Reduce donor–recipient incompatibility.
- Avoid preformed antibody reactions.

After implantation

- Suppress T-cell activation and clonal expansion.
- Address antibody-mediated injury.

Over time

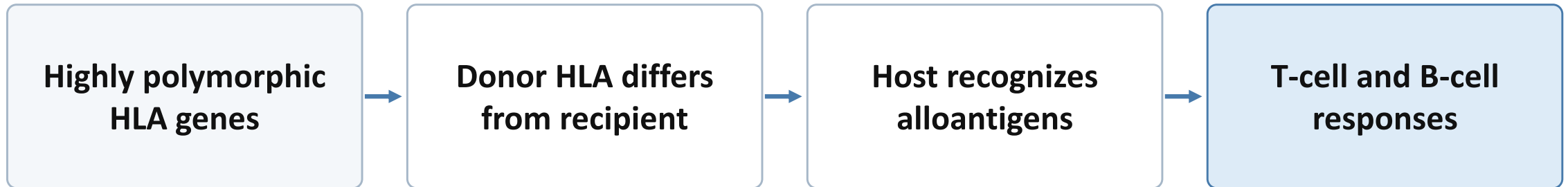
- Prevent progressive immune injury.
- Balance immune suppression against infections and cancers.

Allografts create an alloimmune problem

- Allografts are transplanted between genetically different members of one species.
- Recipient lymphocytes can recognize graft antigens as foreign.
- T lymphocytes and antibodies can each mediate rejection.
- Graft-survival strategies must account for both cellular and humoral immunity.

HLA polymorphism creates donor–recipient disparity

The principal antigenic differences provoking allograft rejection involve HLA alleles.



- Genetic identity is exceptional: Identical twins are the special case.
- HLA matching decreases disparities but does not replace other protective strategies.

HLA matching: Kidney versus other major organs

Kidney transplantation

- Matching important HLA alleles provides substantial benefit.
- HLA-A, HLA-B, and HLA-DR.
- Both alleles at each named locus matter.

Liver, heart, and lung

- HLA matching as usually not performed.
- Anatomic compatibility may dominate.
- Clinical urgency and storage time also influence organ selection.

Kidney allocation: The HLA loci emphasized

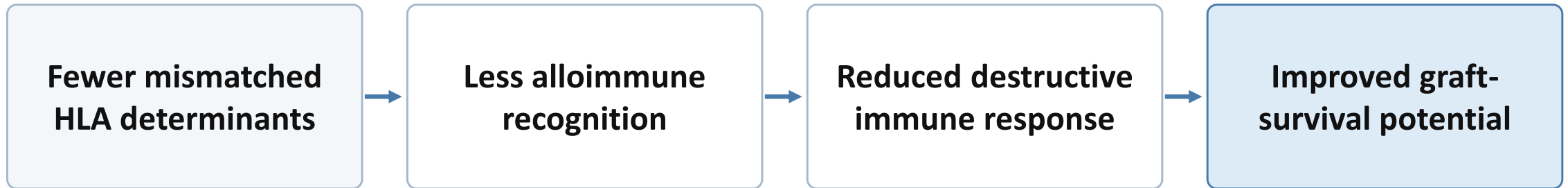
- HLA-A and HLA-B are class I HLA loci.
- HLA-DR is a class II HLA locus.
- Matching of both alleles of HLA-A, -B, and -DR as particularly useful.
- Improved compatibility reduces important alloantigenic differences encountered by the host.

What “both alleles” means at the named HLA loci

Locus	Alleles considered	Teaching implication
HLA-A	Two donor / two recipient alleles	Assess differences across both alleles.
HLA-B	Two donor / two recipient alleles	A single matching allele does not mean a fully matched locus.
HLA-DR	Two donor / two recipient alleles	Class II disparity is relevant to T-cell responses.

Locus-level matching and overall genetic identity are not interchangeable.

Why better HLA matching can protect a kidney graft



- The causal interpretation follows the recognized role of HLA alloantigens in graft rejection.
- HLA matching is beneficial but not a guarantee against rejection.

Donor selection involves competing priorities

Immunologic compatibility

- Donor–recipient HLA differences can drive rejection.
- A closer match is beneficial for kidney transplantation.

Organ and recipient realities

- Anatomical suitability must be considered.
- Severe recipient illness can make timing decisive.
- Time in storage is also a constraint.

The relative weight of HLA matching is organ-dependent.

Application: Why the best HLA match may not be selected

A critically ill heart-transplant candidate needs a suitable donor urgently. A more closely HLA-matched organ may involve substantial delay.

Which priorities does the textbook describe as potentially overriding HLA matching?

- Anatomic compatibility and severity of the underlying illness.
- The need to minimize organ storage time.

Preventing hyperacute rejection requires antibody awareness

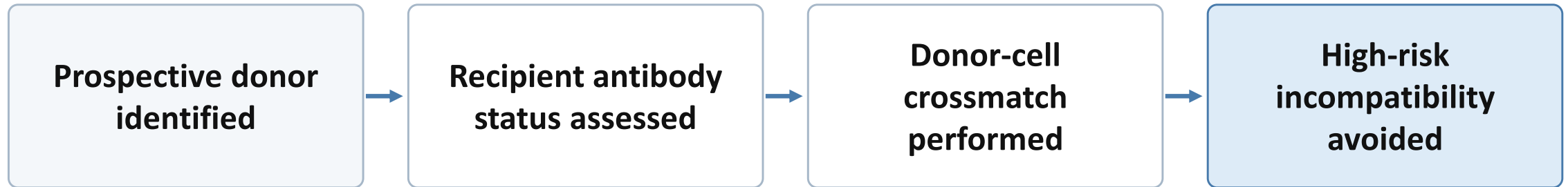
- Hyperacute rejection is mediated by antibodies already present before implantation.
- These antibodies recognize graft endothelial antigens.
- Relevant antibody targets include blood group antigens and donor HLA molecules.
- Matching and antibody testing address a danger not prevented by delaying T-cell responses alone.

Why a recipient may already possess anti-HLA antibodies

Prior exposure	Immunologic consequence
Previous transplantation	Recipient may have encountered nonself HLA antigens.
Blood transfusion	Exposure to allogeneic cells can induce anti-HLA antibodies.
Pregnancy	Exposure to fetal alloantigens can sensitize the recipient.

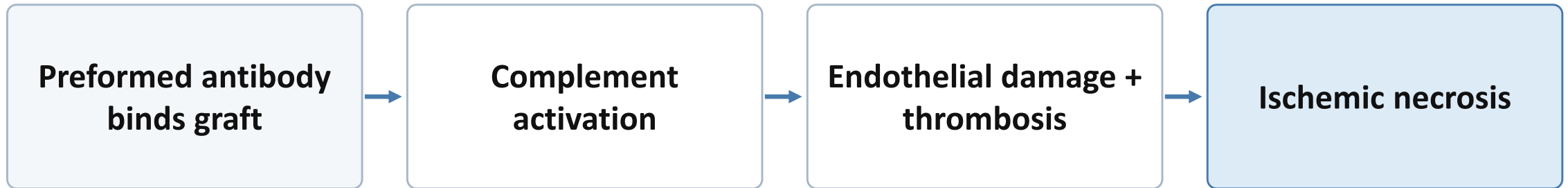
These are sensitization mechanisms, not a claim that every exposure causes antibodies.

Crossmatching blocks the preformed-antibody pathway



- ABO matching and donor-cell crossmatching to the rarity of hyperacute rejection.
- Crossmatching and later immunosuppression address different phases of alloimmunity.

Hyperacute rejection is an endothelial catastrophe



- Because antibodies exist beforehand, injury can begin once perfusion is restored.
- This mechanism explains the high priority of preventing incompatible transplantation.

Selection measures cannot substitute for immunosuppression

Before graft implantation

- Choose compatible donor and recipient where feasible.
- Match blood group and assess donor-reactive antibodies.
- Consider HLA matching in the organ-specific context.

After graft implantation

- Alloreactive lymphocytes can still activate.
- T-cell responses may damage parenchyma and vessels.
- Except with identical twins, immunosuppressive therapy is necessary.

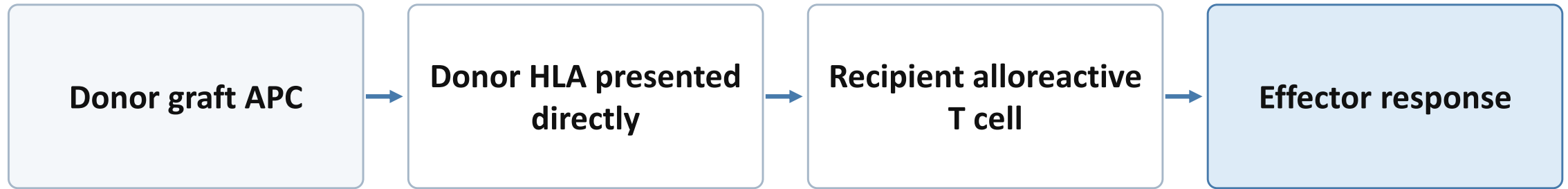
Rejection mechanisms determine treatment targets

Pattern	Principal mechanism	Implication
Hyperacute	Preformed antibody → complement → thrombosis	Prevent incompatibility before implantation.
Acute cellular	Alloreactive T cells injure parenchyma/vessels	Reduce T-cell activation and responses.
Acute antibody-mediated	Antibody-dependent endothelial injury	Address the antibody-mediated component.
Chronic	Persistent vascular injury and fibrosis	Acute-rejection therapies have limitations.

Acute T-cell rejection is a central prevention target

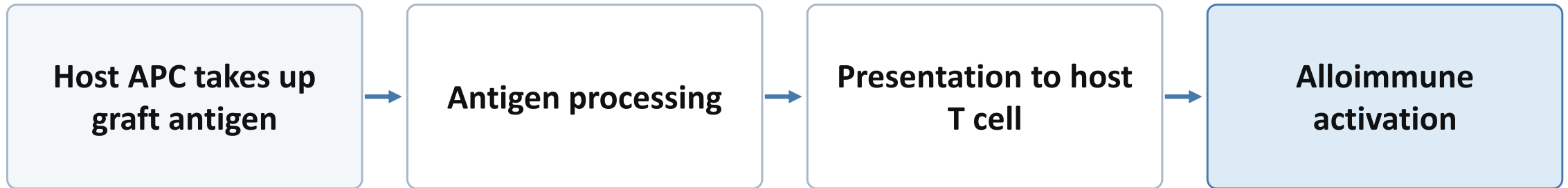
- Acute rejection may occur in days or weeks, or after later reduction of immunosuppression.
- CD8+ cytotoxic T lymphocytes can directly injure graft cells.
- CD4+ T lymphocytes can produce cytokines and recruit inflammatory cells.
- Accordingly, many immunosuppressive strategies target T-cell activation.

Direct recognition can activate recipient T cells



- The direct pathway is emphasized in the source as important in acute CTL-mediated rejection.
- Blocking downstream activation can reduce the consequences of direct recognition.

Indirect recognition broadens the allograft response



- The indirect pathway particularly with chronic rejection.
- Compatibility strategies reduce the antigenic differences driving both pathways.

The two effector arms of cellular rejection

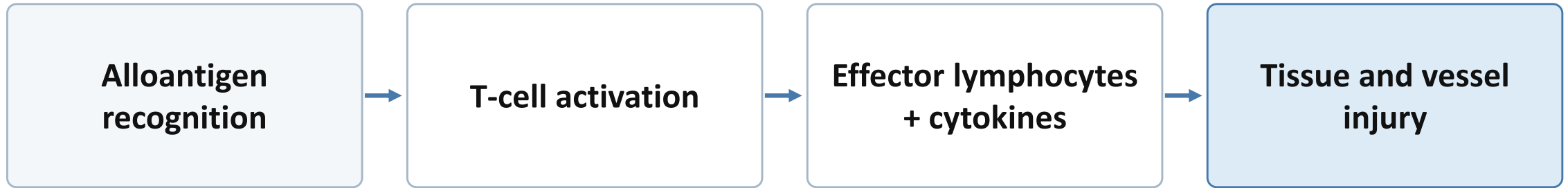
CD8+ cytotoxic T cells

- Recognize relevant graft targets.
- Can directly kill graft parenchymal cells.
- Produce cellular tissue injury.

CD4+ helper T cells

- Respond to allogeneic antigen presentation.
- Produce cytokines.
- Promote recruitment of inflammatory cells and vascular injury.

T-cell activation amplifies graft injury



- Immunosuppressive drugs intervene before or during amplification of these responses.
- The pathway clarifies why multiple pharmacologic targets can be complementary.

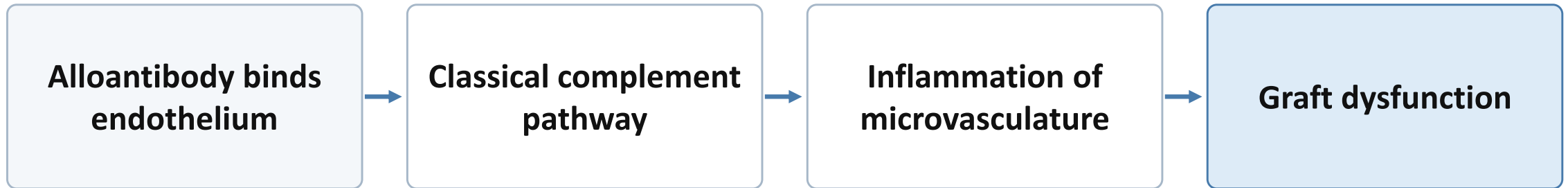
Tubulitis reflects cellular attack on kidney tubules

- Acute cellular rejection may show interstitial inflammatory infiltrates.
- Lymphocytes may accumulate among tubular epithelial cells: Tubulitis.
- Focal tubular epithelial injury may accompany the inflammation.
- The pathologic pattern is consistent with effector T-cell activity.

Endotheliitis identifies vascular cellular rejection

- Lymphocytes may enter the space beneath graft vascular endothelium.
- Endothelial swelling and intimal arteritis can be present.
- Severe vascular involvement may include injury and necrosis of vessel walls.
- These findings link T-cell responses to loss of vascular integrity.

Antibody-mediated rejection uses a distinct route



- Kidney lesions may include glomerulitis and peritubular capillaritis.
- C4d deposition may indicate activation of complement by antibodies.

Histopathology helps identify the dominant immune mechanism

Finding in kidney graft	Interpretation
Tubulitis + interstitial inflammation	Typical acute T-cell–mediated rejection pattern.
Endotheliitis / intimal arteritis	Vascular pattern of cellular rejection.
Glomerular / peritubular capillaritis	Typical microvascular inflammation of antibody-mediated rejection.
C4d deposition	Evidence of complement activation in antibody-mediated injury.

Immunosuppression is ordinarily indispensable

- All donor–recipient combinations except identical twins require immunosuppressive treatment.
- Even a carefully selected graft can provoke immune recognition.
- Immunosuppressants limit rejection but impair protective immune responses.
- The benefit must therefore be considered alongside treatment-associated infection and cancer risk.

Immunosuppressive drugs act at different steps

The named drug classes suppress distinct functional components of alloimmunity.

Inflammation

- Steroids reduce inflammatory responses.
- They do not eliminate pre-existing HLA differences.

Cell expansion

- Mycophenolate mofetil inhibits lymphocyte proliferation.
- This curtails amplification after activation.

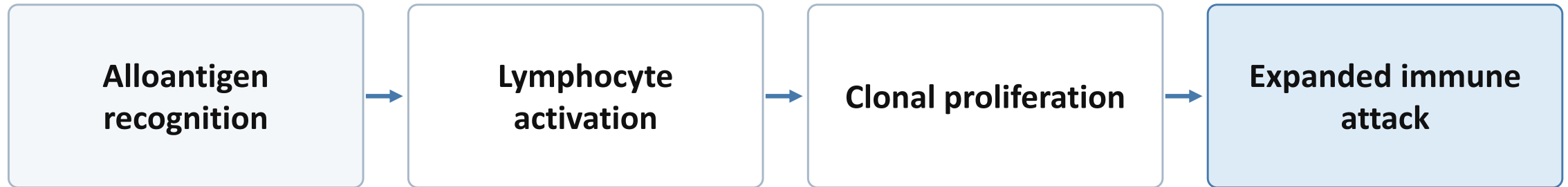
Activation signaling

- Tacrolimus and cyclosporine inhibit calcineurin.
- Reduced NFAT activation limits T-cell cytokine production.

Corticosteroids reduce inflammatory injury

- Steroids are listed among drugs routinely used for immunosuppression.
- Their principal mechanism emphasized here is reduction of inflammation.
- Inflammation is an important downstream consequence of alloreactive T-cell activation.
- Steroid action is conceptually downstream of donor antigen recognition.

Mycophenolate restrains lymphocyte proliferation

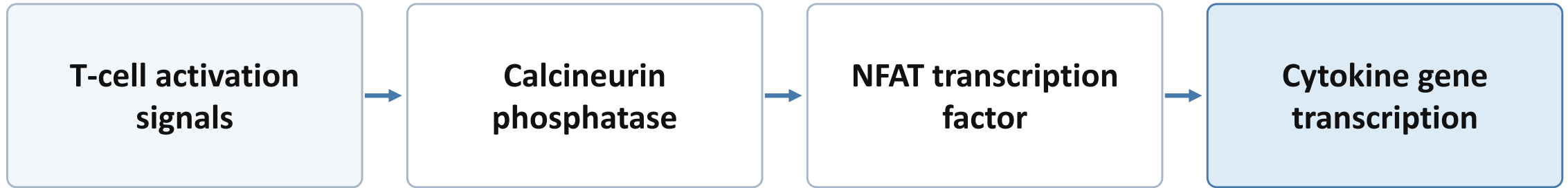


- Mycophenolate mofetil acts on the lymphocyte-proliferation step.
- The source does not assign it a role in correcting donor HLA mismatch.

Calcineurin inhibitors suppress T-cell responses

- Tacrolimus (FK506) and cyclosporine are both calcineurin inhibitors.
- Calcineurin is a phosphatase required for activation of NFAT.
- NFAT promotes transcription of several cytokine genes.
- Inhibition reduces the T-cell signaling needed to mount an antigrraft response.

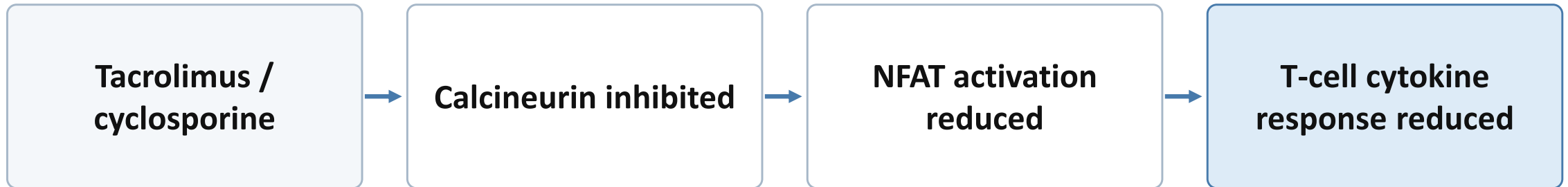
Calcineurin–NFAT links signaling to cytokine genes



- IL-2 as an especially important NFAT-regulated cytokine.
- Inhibiting calcineurin interrupts this sequence before cytokine transcription.

Tacrolimus interrupts NFAT-dependent activation

Pharmacologic inhibition is applied to a specific signaling node.



- The drug action is upstream of the NFAT-driven cytokine program.
- This explains suppression of cellular rejection without altering donor HLA identity.

IL-2 is a key growth signal in the T-cell response

- IL-2 as a growth factor encoded by an NFAT-responsive gene.
- T-cell activation normally induces cytokine gene transcription.
- Calcineurin inhibitors reduce the signaling leading to IL-2 transcription.
- This mechanistic connection explains why calcineurin inhibition constrains T-cell responses.

Steroids, mycophenolate and tacrolimus: Target map

Intervention	Textbook target or effect	Position in response
Steroids	Reduce inflammation	Inflammatory effector phase
Mycophenolate mofetil	Inhibits lymphocyte proliferation	Expansion of immune clones
Tacrolimus	Inhibits calcineurin → NFAT	Activation / cytokine transcription
Cyclosporine	Calcineurin inhibition	Activation / cytokine transcription

A drug mechanism is not a rejection diagnosis

Medication mechanism

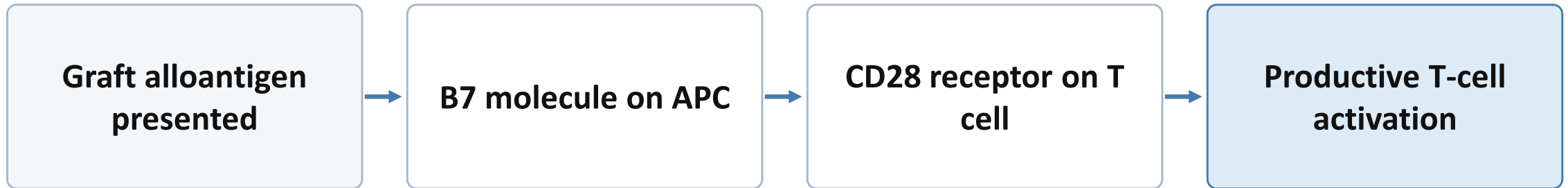
- Blocks a signaling step or inflammatory consequence.
- May broadly suppress protective host immunity.
- Does not identify which lesion is present.

Rejection pathogenesis

- Cellular injury reflects activated T cells.
- Humoral injury reflects antibodies and complement.
- Pathology distinguishes relevant tissue patterns.

Treatment reasoning starts from mechanism, not from drug names alone.

T-cell activation requires costimulatory signaling



- B7 on graft-donor dendritic cells and CD28 on host T cells.
- Interrupting this interaction can decrease the antigraft response early in sensitization.

B7–CD28 costimulation: The interacting partners

Antigen-presenting cell

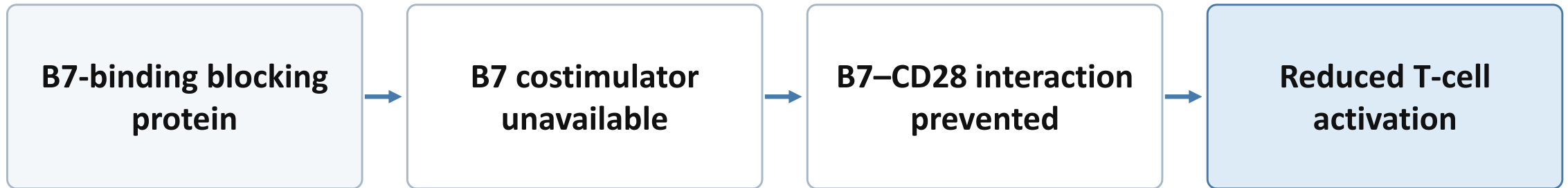
- A dendritic cell can present graft alloantigen.
- Its B7 molecules deliver a costimulatory signal.

Host T lymphocyte

- Receives an antigen-recognition signal.
- CD28 provides the receptor for B7 costimulation.

This is a cell–cell signaling interaction, not an antibody crossmatch.

Blocking B7 interrupts early T-cell sensitization



- The text describes administration of proteins that bind and block B7.
- This targets costimulation rather than calcineurin signaling.

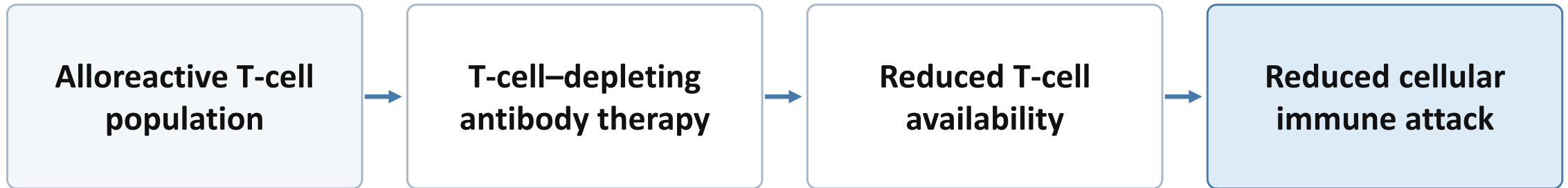
Two distinct interventions in T-cell activation

Feature	Calcineurin inhibition	Costimulation blockade
Target	Intracellular calcineurin	B7 costimulatory molecules
Key consequence	Reduced NFAT-mediated transcription	Interrupts B7–CD28 signaling
Functional position	After T-cell triggering	Early sensitization / activation
Clinical purpose	Suppress alloreactive T-cell responses	Reduce antigrraft T-cell activation

Therapies for established rejection extend beyond maintenance drugs

- T-cell–depleting antibodies among additional rejection treatments.
- Pooled intravenous immunoglobulin (IVIG) is another named approach.
- Plasmapheresis is used for severe antibody-mediated rejection.
- Mechanism-directed assessment distinguishes cellular from antibody-mediated injury.

T-cell–depleting antibodies reduce effector-cell availability

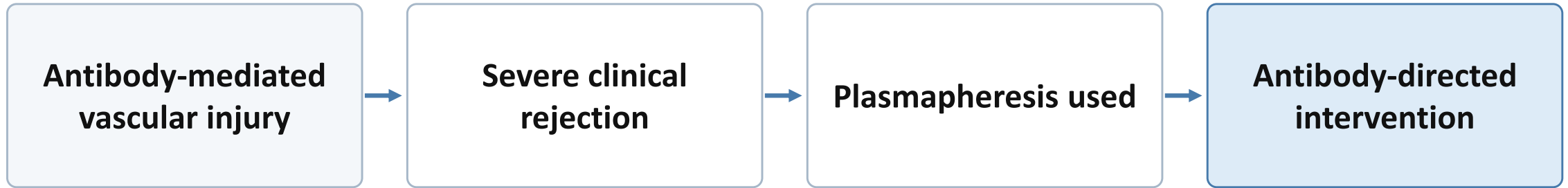


- This as a treatment used for graft rejection.
- The supplied text does not define antibody products, doses, or specific treatment algorithms.

IVIG is mentioned with mechanistic uncertainty

- Pooled intravenous IgG is listed as a therapy used to treat rejection.
- Suppression of inflammation as an effect of IVIG.
- The textbook explicitly states that the mechanisms are unknown.
- A proposed detailed pathway should not be presented as established from this excerpt.

Plasmapheresis targets severe antibody-mediated rejection

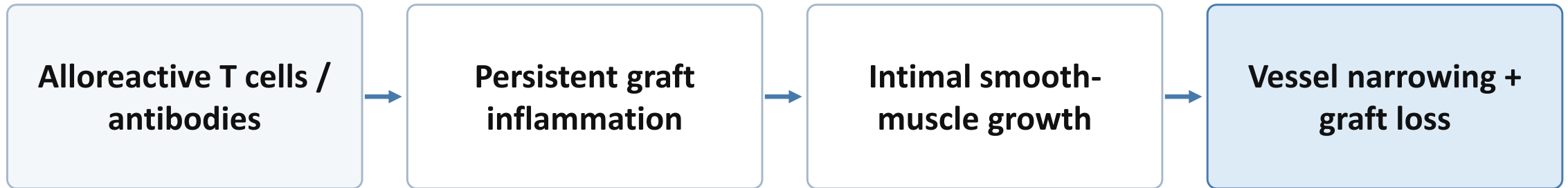


- The textbook places plasmapheresis specifically in severe antibody-mediated rejection.
- No efficacy percentages, procedural details, or dosing schedules are provided.

Selecting a mechanistic response to graft injury

Observed problem	Immune axis emphasized	Interventions discussed
Active cellular rejection	Recipient T-cell responses	T-cell immunosuppression; T-cell–depleting antibodies
Antibody-mediated rejection	Antibody + complement / endothelium	IVIg; Plasmapheresis in severe cases
Hyperacute antibody reaction	Preformed circulating antibody	Prevent through matching and crossmatch
Chronic progressive rejection	Vascular remodeling / fibrosis	Most acute-rejection therapies remain inadequate

Chronic rejection progresses through vascular remodeling



- T-cell cytokines can stimulate smooth-muscle cells and fibroblasts.
- Chronic damage is more refractory to available therapies than acute rejection.

Fibrosis links chronic immune injury to graft decline

- Progressive vascular narrowing reduces long-term graft function.
- Interstitial fibrosis and tubular atrophy may follow vascular injury in kidney grafts.
- Transplant glomerulopathy can include duplicated capillary basement membranes.
- These structural changes explain why preventing acute rejection does not abolish late graft loss.

Acute success is not equivalent to lifelong graft survival

Improved short-term control

- Therapy reduces many acute T-cell rejection episodes.
- Effective suppression helps improve early graft survival.

Long-term vulnerability

- Chronic vascular damage and fibrosis can continue.
- Chronic rejection is refractory to most therapies.
- Complications of immunosuppression accumulate.

A functioning graft is only one dimension of transplant success.

Immunosuppression carries major biologic costs

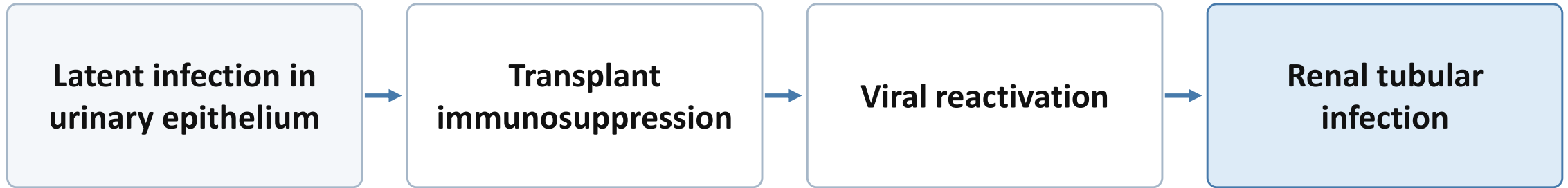
- Suppressing antigrraft immunity also weakens protective host responses.
- Opportunistic infections and cancers as major barriers.
- These complications affect disease-free survival after transplantation.
- More immune suppression is not a risk-free means of prolonging graft function.

Central trade-off: Prevent rejection while preserving protective immunity.

Infection vulnerability spans multiple pathogen classes

Microbial class	Clinical implication
Bacterial	Increased susceptibility with immunosuppression.
Viral	Potential new infection or reactivation of latent viruses.
Fungal	Opportunistic infection risk in the immunosuppressed host.

BK polyomavirus illustrates latent viral reactivation



- The source highlights BK virus as a particularly important kidney-transplant complication.
- Reactivation can threaten allograft function.

BK polyomavirus can itself cause graft failure

- BK virus persists latently in lower genitourinary epithelial cells of healthy persons.
- Under immunosuppression, it may reactivate and involve renal tubules.
- Renal infection can damage a transplanted kidney and impair function.
- Graft dysfunction therefore does not automatically establish acute immune rejection.

Graft dysfunction: Rejection and infection are distinct

Immune rejection

- Recipient anti-graft T cells or antibodies drive tissue injury.
- Suppressing this immune response protects the graft.

BK virus–associated injury

- Latent virus reactivates under immunosuppression.
- Tubular infection can impair graft function.
- Additional suppression cannot be assumed harmless.

The same treatment that protects against rejection can increase infection risk.

Malignancy risks follow sustained immune suppression

Several cancers among transplant recipients.

Skin cancer

- Overall skin-cancer risk is increased.
- A clinically important long-term complication.

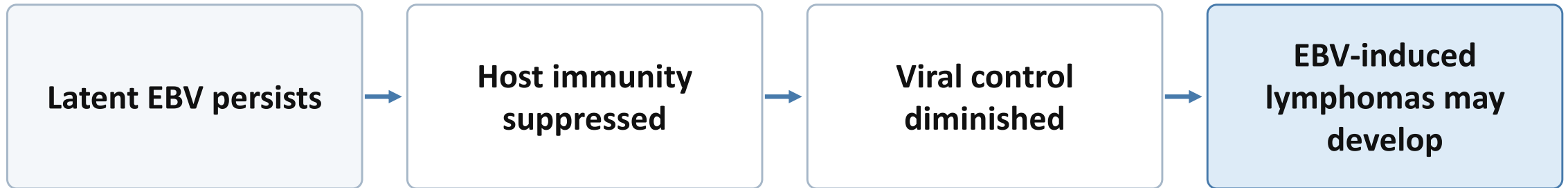
EBV-associated lymphoma

- EBV-related lymphoid malignancy risk rises.
- Latent oncogenic viral reactivation may contribute.

HPV-associated carcinoma

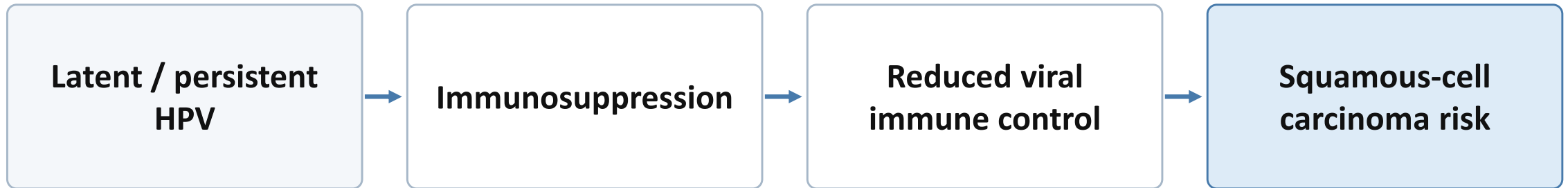
- HPV-related squamous cell carcinoma is described.
- Oncogenic viral reactivation is implicated.

EBV-related lymphoma links immune control to cancer risk



- This is a mechanistic teaching schematic consistent with the source's stated association.
- No incidence, risk ratio, screening protocol, or diagnostic criterion is asserted.

HPV-associated carcinoma is another oncogenic-virus risk

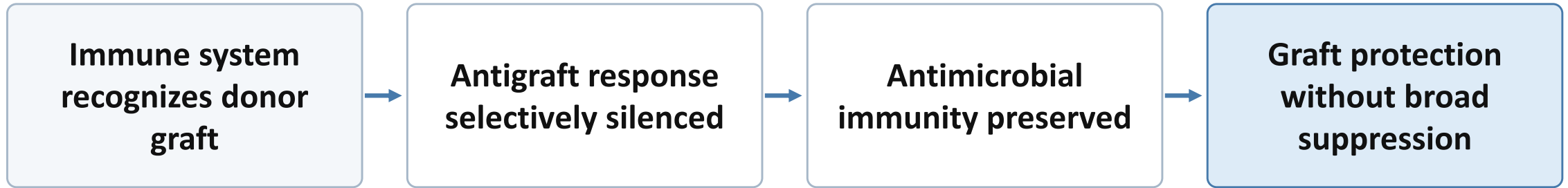


- HPV-induced squamous cell carcinomas among transplant-associated malignancies.
- The exact cancer site and risk estimates are not specified in the excerpt.

The goal is disease-free survival, not only graft function

- Successful transplantation aims to preserve a functioning graft.
- Opportunistic infection can cause serious morbidity.
- Skin cancers and virus-associated malignancies may compromise long-term outcomes.
- Graft survival should therefore be interpreted with recipient safety in mind.

Donor-specific tolerance is the theoretical ideal



- The source states that efforts to induce such tolerance have not yet succeeded.
- The diagram describes the intended goal, not an achieved clinical pathway.

Broad suppression differs from donor-specific tolerance

Conventional immunosuppression

- Lowers immune responses to graft alloantigens.
- Also diminishes defensive responses to microbes.
- Creates infection and oncologic risks.

Desired donor-specific tolerance

- Would selectively reduce antigraft reactivity.
- Would preserve responses to pathogens.
- Remains an unrealized goal in the cited text.

Case reasoning: Early vascular graft injury

A renal allograft rapidly develops vascular thrombosis after perfusion. The recipient had prior exposure to allogeneic cells.

Which prevention step addresses the relevant mechanism?

- Assess preformed donor-reactive antibodies before transplantation.
- ABO compatibility and donor-cell crossmatching reduce the risk of hyperacute rejection.

Case reasoning: Later decline after immunosuppression change

A transplant recipient develops abrupt loss of graft function after immune-suppressing treatment is reduced.

Which pathophysiologic process should the clinician consider?

- Acute rejection can occur late when immunosuppression is tapered or stopped.
- Cellular and antibody-mediated patterns need mechanistic distinction.

Case reasoning: Deteriorating kidney graft with viral risk

A kidney-transplant recipient receiving sustained immunosuppression develops impaired allograft function.

Why is immune rejection not the only explanation?

- BK polyomavirus can reactivate during immunosuppression.
- Renal tubular infection may itself cause graft failure.

Integrated methods of improving graft survival

Stage / aim	Protective strategy	Main limitation
Organ selection	HLA matching where beneficial; Anatomic / urgency / storage considerations	Priorities vary by organ.
Avoid immediate loss	ABO compatibility; Donor antibody crossmatch	Does not eliminate later alloimmunity.
Prevent cellular rejection	Steroids, mycophenolate, calcineurin inhibitors, B7 blockade	General immune suppression carries risks.
Treat established rejection	T-cell depleting antibodies; IVIG; Plasmapheresis for severe AMR	Chronic injury remains difficult to reverse.
Future selectivity	Donor-specific immune tolerance	Not yet successful in textbook account.

Consolidated mechanistic principles

- HLA disparities are central alloantigens; Donor selection reduces but rarely removes this difference.
- Calcineurin–NFAT–IL-2 signaling and B7–CD28 costimulation provide distinct T-cell targets.
- Antibodies, complement, and graft endothelium require separate mechanistic attention.
- Infection, malignancy, and chronic rejection limit the benefit of even effective acute immunosuppression.

Integrated discussion: What should an effective strategy balance?

A donor organ is suitable, preformed-antibody incompatibility has been excluded, and a lifelong need to maintain the graft remains.

Which four considerations should frame the discussion?

- Organ-specific matching and donor suitability; Control of alloreactive T cells.
- Recognition of antibody-mediated injury; Protection against infection and malignancy.

Primary textbook and source scope

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. Chapter 6: Diseases of the Immune System.
- Primary assigned heading: “Methods of Increasing Graft Survival,” printed pages 210–211.
- Mechanistic parent context: “Rejection of Tissue Transplants” and “Patterns and Mechanisms of Graft Rejection,” printed pages 208–210.
- No external prescribing guidelines or nontextbook treatment outcomes are incorporated into this lecture.