Hepatitis C virus and the kidney

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Hepatitis C virus and the kidney

- Hepatitis C virus (HCV) infection is more prevalent and is associated with higher mortality in patients receiving dialysis and in kidney transplant recipients than in the general population.
- Kidney transplant recipients who are HCV-positive are also at higher risk of allograft and liver failure than are HCV- negative recipients.
- HCV infection is associated with a higher incidence and faster progression of diabetes mellitus and chronic kidney disease (CKD).

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Hepatitis C virus and the kidney

- Viral hepatitis kills 1.45 million people worldwide each year.
- Hepatitis C virus (HCV) infection affects between 5% to 15% of kidney transplant (KT) recipients in the developed world, rates that are up to 10-fold higher than in the general population.

1-Hepatitis C virus and the kidney NATURE RevIewS | NEPHROLOGY volume 15 | FEBRUARY 2019
2-Direct-acting antiviral therapy for hepatitis C virus infection in the kidney transplant recipient Kidney International (2018) 93, 560–567

Hepatitis C virus and the kidney

- CKD is a common disease with a global prevalence of around 10%.
- Hepatitis C and CKD are epidemiologically related for two main reasons:
  - first: because patients with CKD can be exposed to the virus through dialysis units
  - Second: because HCV infection can directly induce renal disease. HCV infection in patients with CKD also increases the risk of and rate of progression to end- stage renal disease (ESRD).

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Hepatitis C virus and the kidney

- HCV infection is associated with worse graft and patient survival and has been extremely difficult to cure after transplant due to the poor efficacy, intolerable side effects, and risk of acute rejection associated with interferon-a (IFN) and ribavirin use.
- Current DAA regimens have high antiviral potency and can achieve sustained virologic response (SVR) rates of >95%.

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EPIDEMIOLOGY OF HCV

- Exposure to HCV was very common among patients with CKD and mainly related to nosocomial transmission in haemodialysis units or to the receipt of contaminated blood transfusions or allografts.
- Improved hygiene and screening practices as well as the introduction of erythropoiesis- stimulating agents for the treatment of renal anaemia, have markedly reduced the risk of HCV infection among patients with CKD.

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EPIDEMIOLOGY OF HCV

The prevalence of HCV infection remains much higher among patients with late- stage CKD than among the general population owing to the persisting nosocomial risk of HCV infection, especially in haemodialysis units, and the suboptimal screening of blood donors in many low-income countries.

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HCV AS A CAUSE OF CKD

- HCV infection is associated with three different kidney lesions:
  - Mixed cryoglobulinaemia (cryoglobulinaemic nephropathy)
  - Membranoproliferative glomerulonephritis
  - Membranous nephropathy

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CAUSES OF RENAL DYSFUNCTION

HCV infection exerts adverse effects on the kidney via two major mechanisms:

- Immune- mediated tissue damage, including effects resulting from HCV lymphotrophism and cryoglobulinaemia
- Direct effects of the virus on renal tissue.

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IMMUNE- MEDIATED EFFECTS

The renal deposition of immune complexes that contain HCV antigens is the main mechanism that drives glomerular inflammation in the context of HCV infection, leading to the production of anti-HCV IgG antibodies, anti- endothelial antibodies and activation of complement.

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DIRECT RENAL EFFECTS OF HCV

- HCV might contribute to tissue damage by directly infecting the endothelium, tubular epithelial cells and renal infiltrating leukocytes.
- Kidney tissue might express CD81 which is suspected to be the receptor by which HCV infects hepatocytes and B lymphocytes. Infected endothelial cells might undergo apoptosis.

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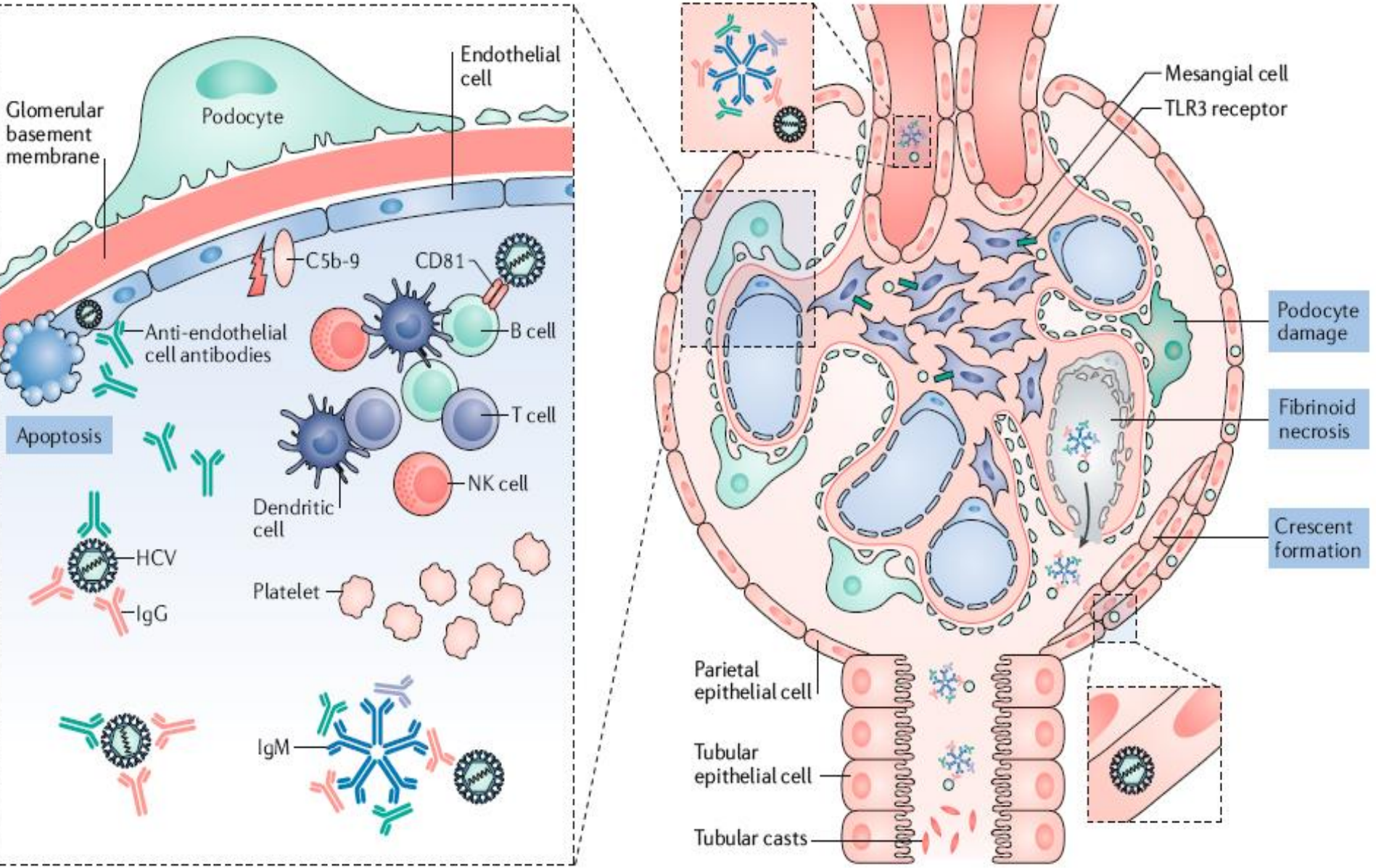

Fig. 2 | **Mechanisms of kidney damage following HCV infection.** Hepatitis C virus (HCV) infection exerts adverse effects on the kidney via two major mechanisms: immune-mediated tissue damage including effects resulting from cryoglobulinaemia and direct effects of the virus on renal tissue. The renal deposition of immune complexes that contain

SCREENING RECOMMENDATION

- HCV infection is often asymptomatic and screening for anti- HCV antibodies by enzyme immunoassay (EIA) is required to detect infection in high- risk populations, including patients on dialysis.
- KDIGO also recommends one time screening for HCV infection for all patients at the time of first diagnosis of CKD.
- Kidney transplantation candidates should be tested for HCV infection during evaluation for transplantation.

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Treatment options for HCV infection

- Interferon, which was given in combination with ribavirin .
- The 48-week course of interferon was associated with several adverse events, including flu- like symptoms, neurocognitive disorders, fatigue and myelo suppression.
- Ribavirin therapy was associated with pruritus, depression and severe haemolytic anaemia.

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LIMITATION OF THIS COMBINATION THERAPY

- The low rate of SVR (15–50% depending on HCV genotype)
- The rate of severe adverse events
- The renal metabolism of ribavirin
- Immunestimulating properties of interferon contraindicated its use in kidney transplant recipients.

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Treatment options for HCV infection

- combinations of two:
  - sofosbuvir–ledipasvir
  - elbasvir–grazoprevir
  - sofosbuvir–velpatasvir
  - glecaprevir–pibrentasvir
- three second- generation DAAs:
  - sofosbuvir–velpatasvir–voxilaprevir

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Treatment options for HCV infection

- For a period of 8–16 weeks depending on the stage of liver fibrosis, virus genotype and subtype, baseline viral load, prior therapeutic history of the patient, and the presence of drug-resistant HCV variants.
- This approach in which combinations of DAAs are used to target all HCV genotypes has high antiviral potency with SVR rates >95%.

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TREATMENT OF HCV INFECTION IN CKD

- International guidelines recommend that all HCV- infected patients are considered for treatment.
- Patients with CKD should receive priority treatment to reduce the risk of hepatic and extra-hepatic complications, particularly renal deterioration and diabetes mellitus in these high-risk individuals.

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HCV INFECTION AND CKD STAGE 1–3

- Treatment recommendations for patients with HCV infection and CKD with estimated glomerular filtration rate (eGFR) >30 ml/min/1.73 m2 are the same as those for the general population.
- Combination therapy with sofosbuvir and velpatasvir, sofosbuvir and ledipasvir or grazoprevir and elbasvir for 8–12 weeks depending on the HCV genotype and subtype, and the extent of underlying liver Disease.

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HCV INFECTION AND CKD STAGE 1–3

- The pangenotypic combinations of sofosbuvir, velpatasvir and voxilapreviror glecaprevir and pibrentasvir can be given for 8 weeks in patients without cirrhosis or for 12 weeks in patients with cirrhosis.
- The presence of decompensated cirrhosis contraindicates the use of protease inhibitors. In these patients a protease inhibitor- free combination (for example,sofosbuvir and velpatasvir) should be used for 12 weeks in combination with ribavirin.

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HCV INFECTION AND CKD STAGE 4–5

- Although of limited use in patients with decompensated cirrhosis, protease inhibitors are good candidates for the treatment of patients with CKD stage 4–5 as they are mainly metabolized by the liver and do not require dose adjustment for patients with stage 4 or 5 CKD.
- NS5A inhibitors are also metabolized by the liver and are similarly useful for this patient group.

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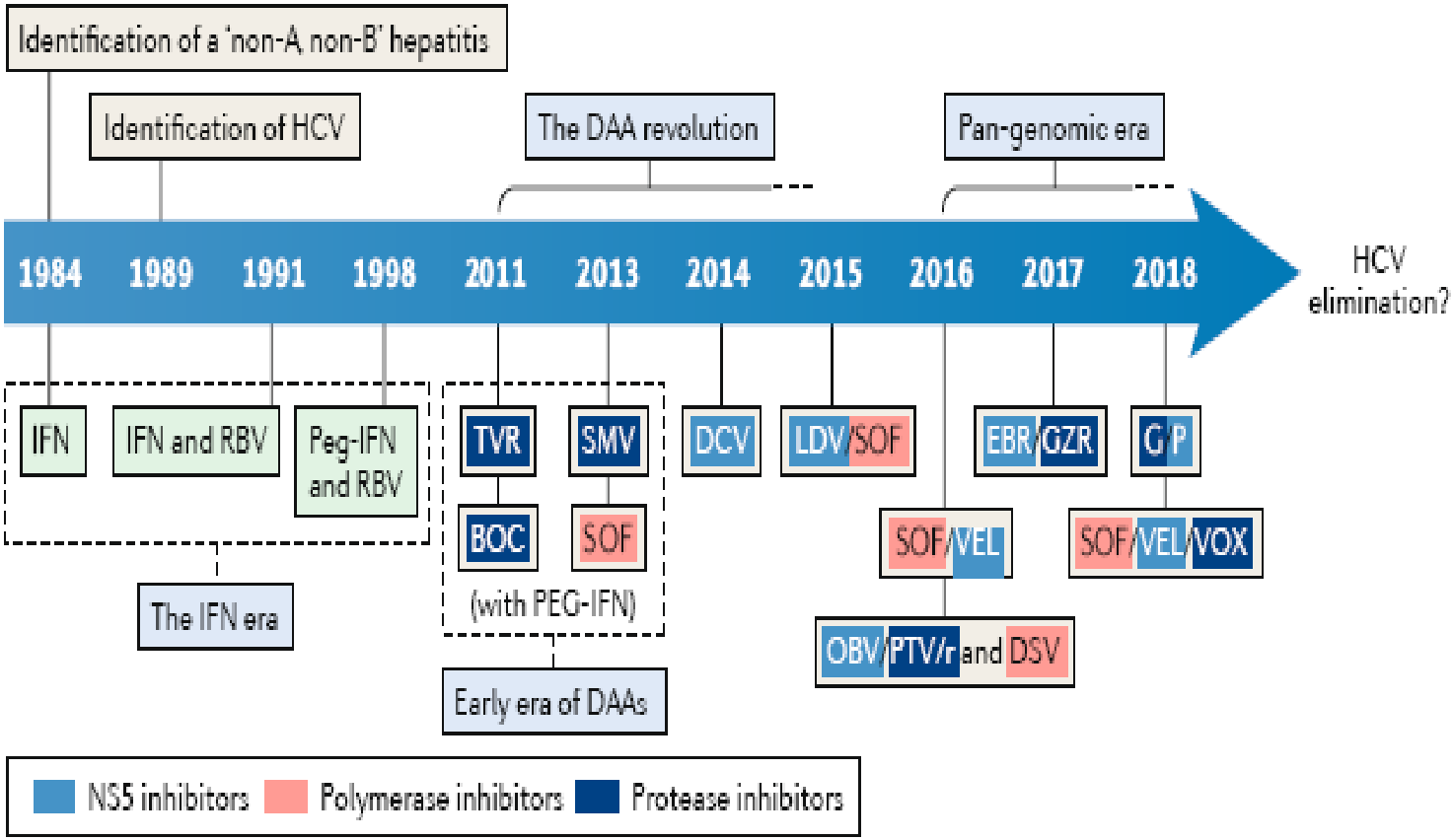
History of antiviral therapies for HCV infection.



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Direct acting antivirals and their targets

Class	Target	Examples	Notes
Protease inhibitors	NS3/NS4A	• Simeprevir • Asunaprevir • Paritaprevir • Grazoprevir • Voxilaprevir	• Not suitable for use in patients with decompensated cirrhosis • No dose adjustment needed in patients with CKD stage 4–5
Non-nucleosidic polymerase inhibitors	NS5B	• Dasabuvir • Beclabuvir	No dose adjustment needed in patients with CKD stage 4–5
Nucleosidic polymerase inhibitors	NS5B	Sofosbuvir	Not recommended for patients with eGFR <30 ml/min/1.73 m^2
NS5A replication complex inhibitors	NS5A	• Daclatasvir • Ombitasvir • Elbasvir • Velpatasvir	Metabolized in the liver; no dose adjustment needed in patients with CKD stage 4–5

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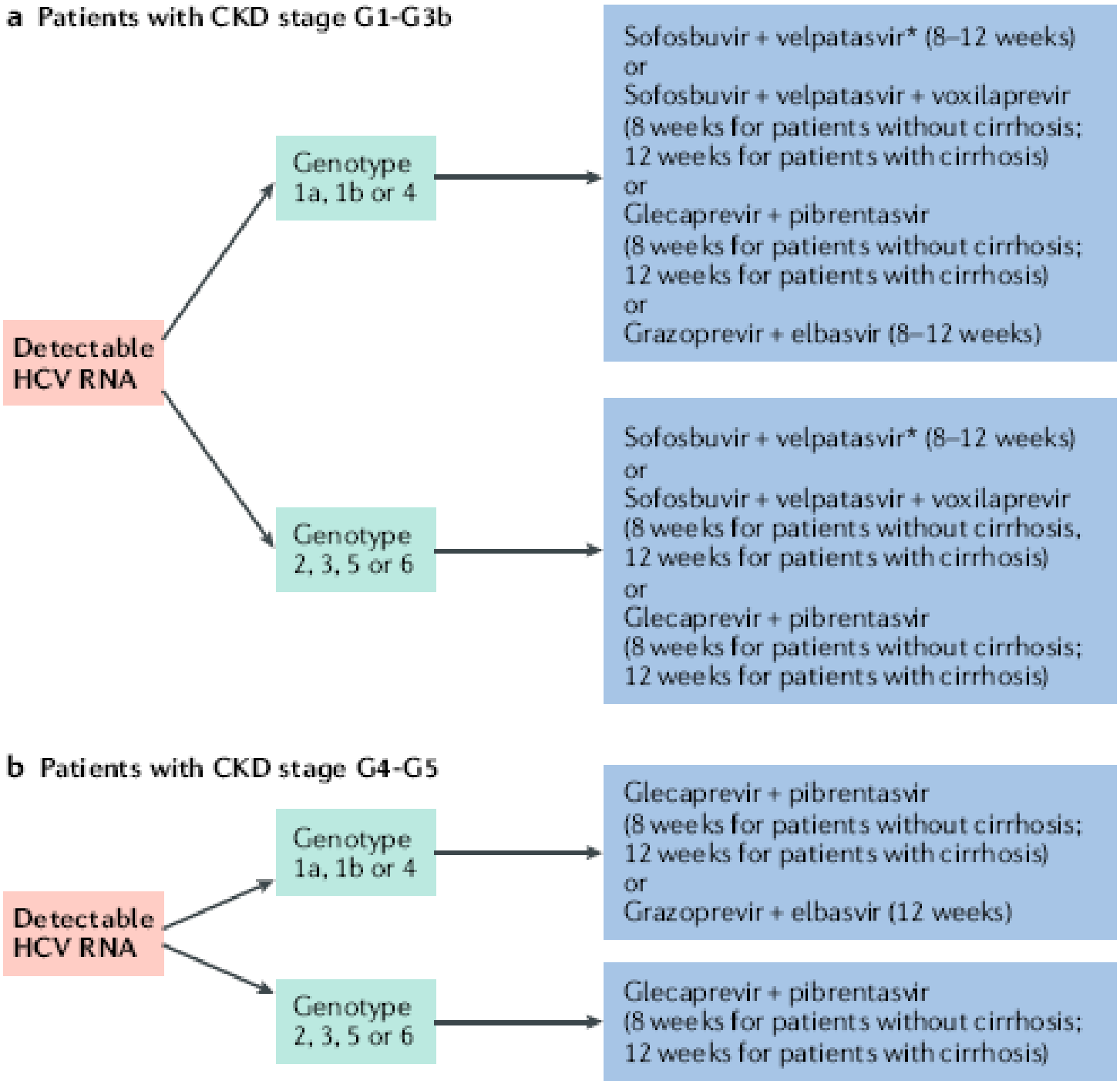

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Kidney function	HCV genotype	Recommended regimen(s)	Strength of evidence	Alternate regimen(s)	Strength of evidence
CKD G4–G5 (GFR < 30 ml/min per 1.73 m²) including HD, KTR[b]	1a	Grazoprevir/elbasvir	1B	Ritonavir-boosted paritaprevir, ombitasvir, and dasabuvir (also known as PrOD or 3D regimen) with ribavirin	2D
		Glecaprevir/pibrentasvir	1B	Daclatasvir/asunaprevir	2C
	1b	Grazoprevir/elbasvir	1B	Ritonavir-boosted paritaprevir, ombitasvir, and dasabuvir (also known as ProD or 3D regimen)	2D
		Glecaprevir/pibrentasvir	1B	Daclatasvir/asunaprevir	2C
	2,3	Glecaprevir/pibrentasvir	1B		
	4	Grazoprevir/elbasvir	2D		
		Glecaprevir/pibrentasvir	1B		
	5,6	Glecaprevir/pibrentasvir	2D		
CKD G5 PD	n/a (reasonable to follow proposed regimens for HD)				
KTR (GFR ≥ 30 ml/min per 1.73 m²)	1a	Sofosbuvir with ledipasvir, daclatasvir or simeprevir	1B	Sofosbuvir/ribavirin	2D
		Glecaprevir/pibrentasvir[c]	1C		
	1b	Sofosbuvir with ledipasvir, daclatasvir or simeprevir	1B		
		Glecaprevir/pibrentasvir[c]	1C		
	2, 3, 5, 6	Glecaprevir/pibrentasvir[c]	1D	Sofosbuvir/daclatasvir/ribavirin[d]	2D
	4	Sofosbuvir with ledipasvir, daclatasvir or simeprevir	1D		
		Glecaprevir/pibrentasvir[c]	1D		

SOFOSBUVIR- BASED REGIMENS IN CKD

- Sofosbuvir is a first- in-class NS5B inhibitor that is available as a single tablet formulation together with the NS5A inhibitors ledipasvir or velpatasvir.
- Sofosbuvir is eliminated by the kidney.
- The standard dose of sofosbuvir (400 mg per day) is not recommended for patients with GFR <30 which might be associated with overexposure to sofosbuvir and its metabolite.
- Elevated serum NGAL levels in patients on sofosbuvir suggests that this agent might cause tubular damage.

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HCV INFECTION ON TRANSPLANT OUTCOMES

- Chronic HCV infection has been independently associated with a number of adverse outcomes in KT recipients, including increased risk of acute rejection, chronic allograft nephropathy, diabetes, and de novo glomerulonephritis.

Direct-acting antiviral therapy for hepatitis C virus infection in the kidney transplant recipient
Kidney International (2018) 93, 560–567

ANTIVIRAL THERAPY IN TRANSPLANTATION

- Before the introduction of DAA therapy, waitlisted HCV- positive patients were treated before kidney transplantation owing to the risk of graft dysfunction or rejection with interferon-based therapy.
- IFN-based therapies are poorly efficacious, causing flu-like symptoms, neuropsychiatric side effects, and provoking autoimmunity.
- Ribavirin, which is added to IFN therapy to improve the likelihood of cure, often causes anemia by provoking hemolysis ,and is also ideally avoided after KT.

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ANTIVIRAL THERAPY IN TRANSPLANTATION

- Currently, the timing of HCV treatment tends to depend on the severity of liver damage and on graft availability:
  - treatment can be initiated after transplantation if a graft is readily available (for example, in case of a living donor)
  - before transplantation (most often just after listing) if not.

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ANTIVIRAL THERAPY IN TRANSPLANTATION

Delaying antiviral therapy in transplant candidates who do not have concerning levels of liver fibrosis might facilitate access to donor organs by enabling earlier transplantation with an HCV-infected allograft followed by initiation of antiviral treatment after transplantation .

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ANTIVIRAL THERAPY IN TRANSPLANTATION

I. Difficulty in predicting time to renal transplantation
II. the potential for drug–drug interactions with calcineurin inhibitors
III. the poor prognosis of patients with CKD and HCV infection

many clinicians are inclined to treat patients with HCV infection and CKD as soon as possible; that is, before kidney transplantation.

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DAAs in KT recipient

DAAs have been remarkably well tolerated in the

KT population.

Direct-acting antiviral therapy for hepatitis C virus infection in the kidney transplant recipient
Kidney International (2018) 93, 560–567

When to treat: before or after KT

After KT

Treatment of HCV be delayed until the post-transplant period:

> any patient who is waiting for a deceased donor transplant who is willing to accept an HCV infected donor organ, provided they are not at risk of clinically significantly worsening liver disease.

Direct-acting antiviral therapy for hepatitis C virus infection in the kidney transplant recipient
Kidney International (2018) 93, 560–567

When to treat: before or after KT

Before KT

Patients who are not candidates for KT:

- who are listed at transplant centers that do not utilize HCV-infected kidneys
- patients with live donors
- with significant extrahepatic manifestations of HCV such as cryoglobulinemic vasculitis
- who are at significant risk of progressive liver disease prior to KT
- those with strong personal preference to be treated on dialysis

should undergo DAA therapy on dialysis.

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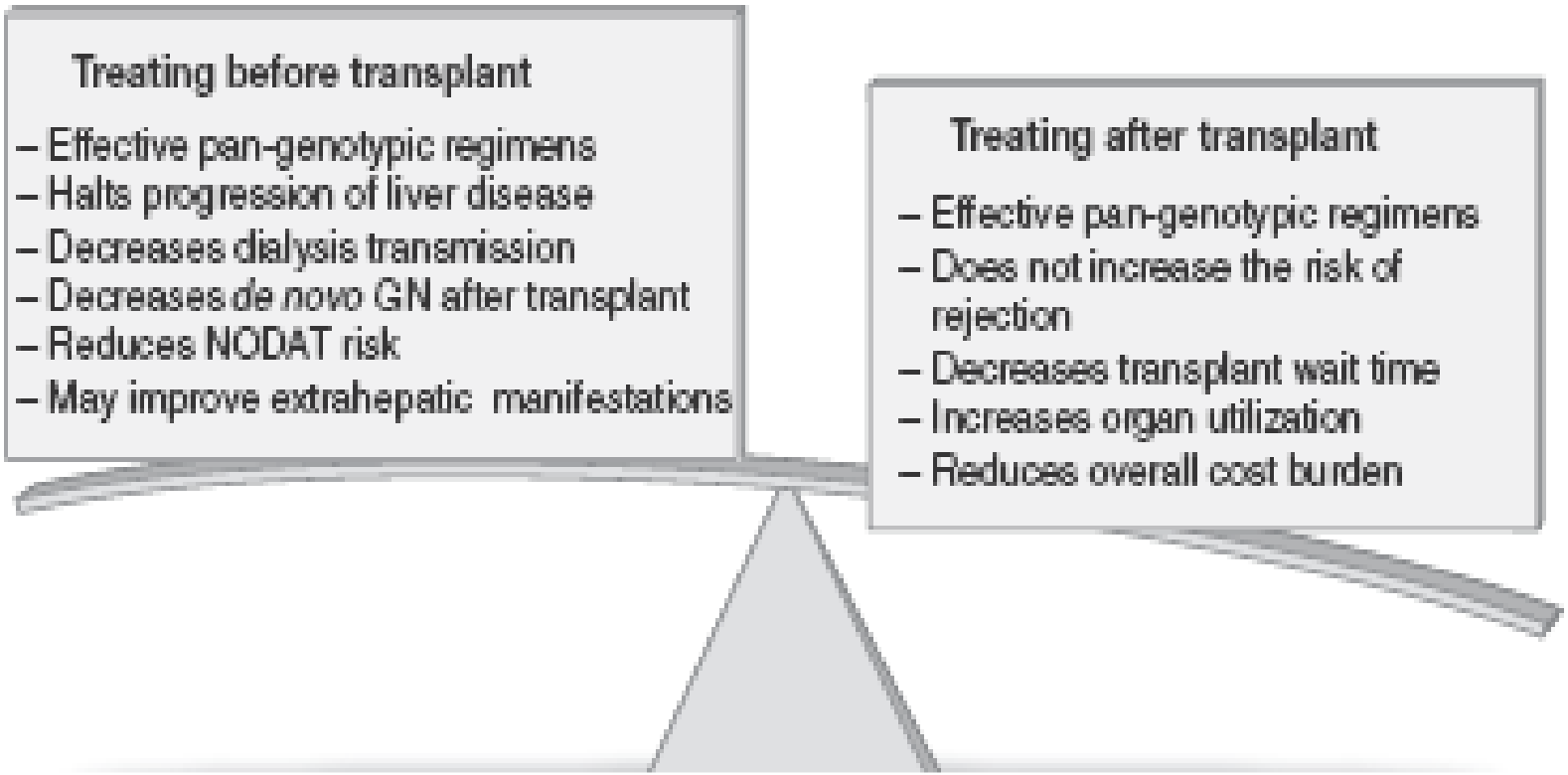
BEFORE OR AFTER KIDNEY TRANSPLANT.



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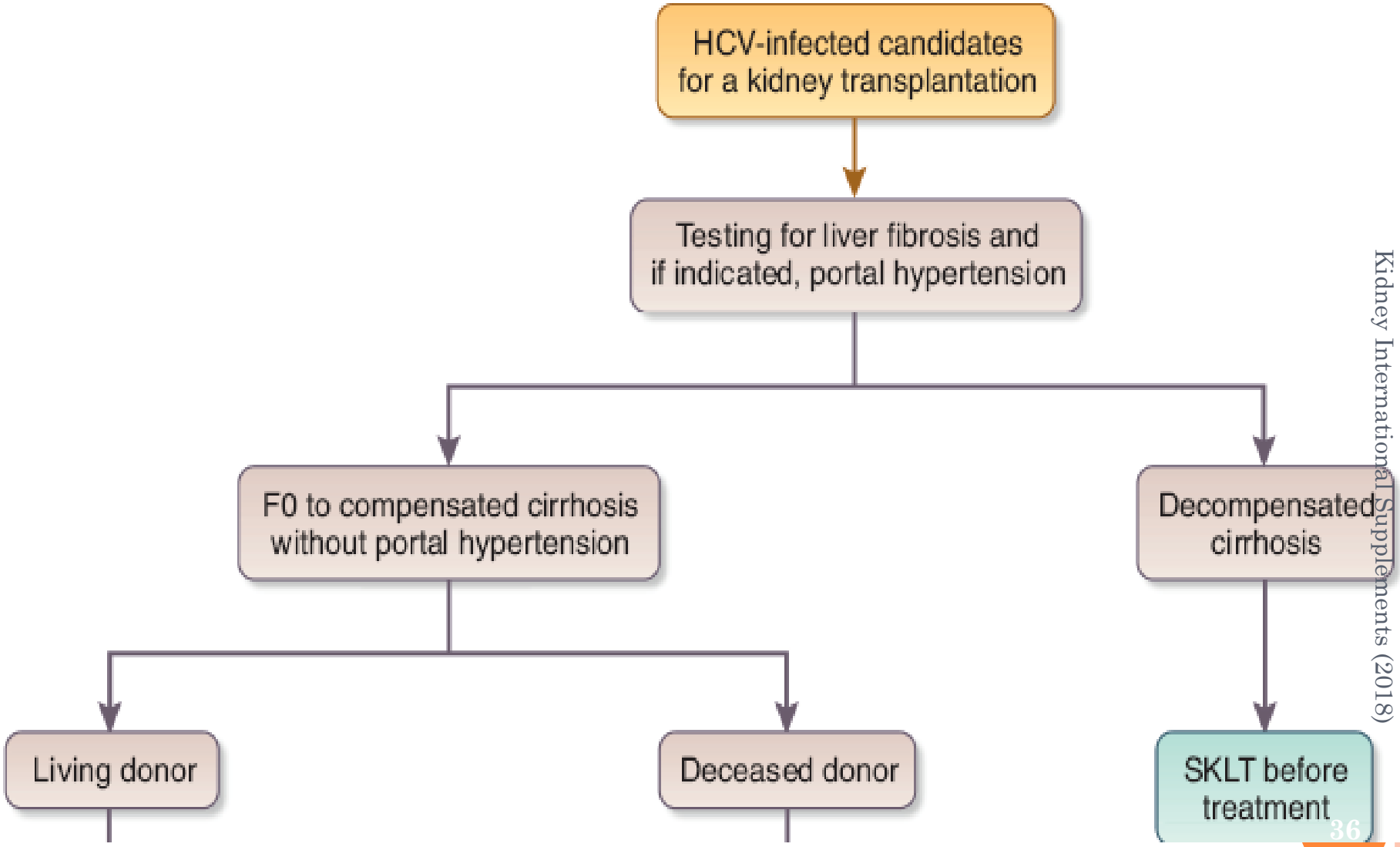
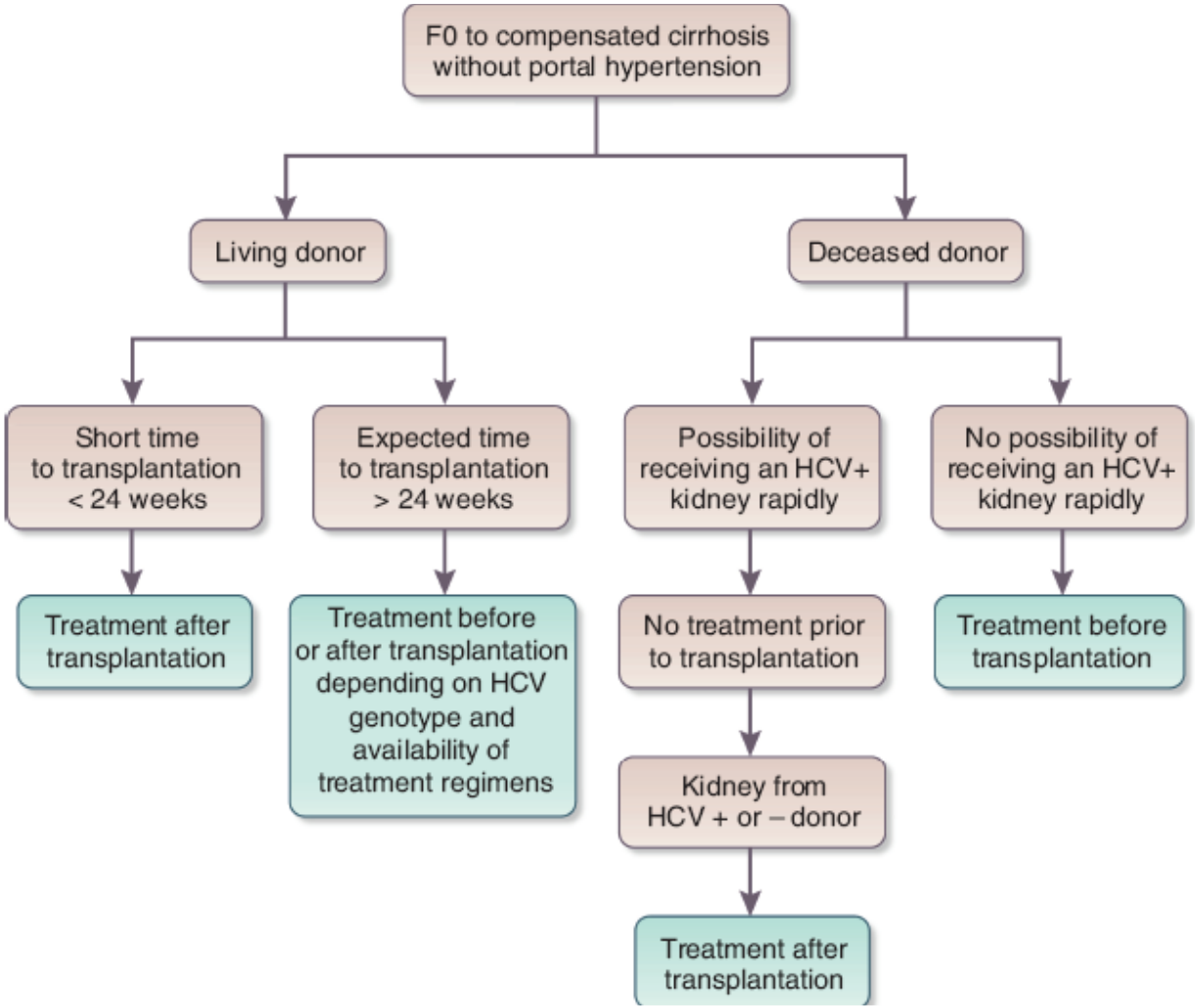


Kidney International Supplements (2018)


F0 to compensated cirrhosis without portal hypertension
Living donor
Deceased donor
Short time to transplantation < 24 weeks
Expected time to transplantation > 24 weeks
Possibility of receiving an HCV+ kidney rapidly
No possibility of receiving an HCV+ kidney rapidly
Treatment after transplantation
Treatment before or after transplantation depending on HCV genotype and availability of treatment regimens
No treatment prior to transplantation
Treatment before transplantation
Kidney from HCV + or – donor
Treatment after transplantation

After KT treatment

- waiting until at least 6 months after transplant, when the risk of acute rejection has decreased and patients may be less sensitive to lower calcineurin inhibitor levels.
- Waiting 6 months also allows confirmation that the patient was not “super-infected” with a new genotype of HCV from their donor.

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Kidney International (2018) 93, 560–567

After KT treatment

pan-genotypic HCV regimenssuch

sofosbuvir -velpatasvir

glecaprevir -pibrentasvir

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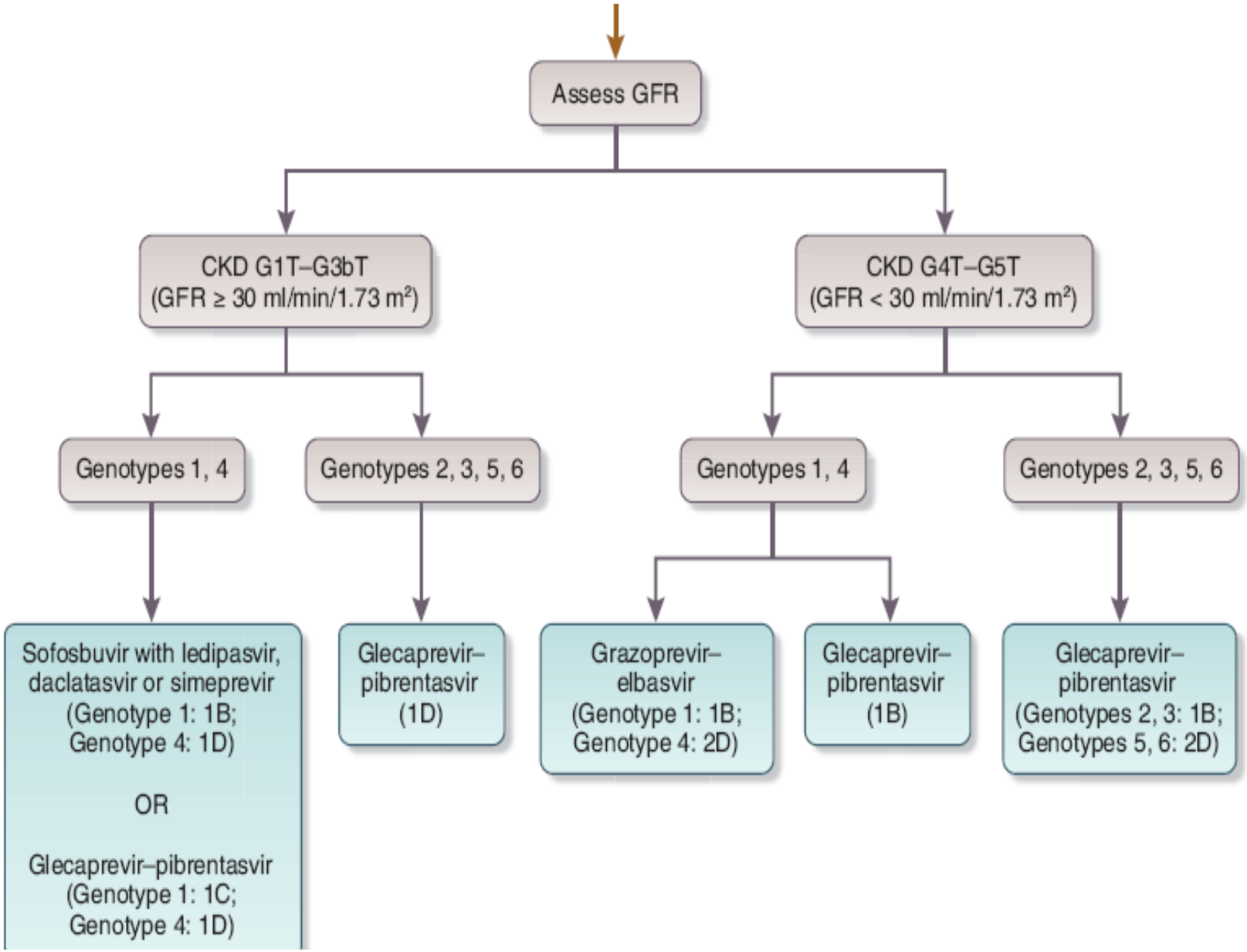
Assess GFR
CKD G1T–G3bT (GFR ≥ 30 ml/min/1.73 m²)
CKD G4T–G5T (GFR < 30 ml/min/1.73 m²)
Genotypes 1, 4
Genotypes 2, 3, 5, 6
Genotypes 1, 4
Genotypes 2, 3, 5, 6
Sofosbuvir with ledipasvir, daclatasvir or simeprevir (Genotype 1: 1B; Genotype 4: 1D)
OR
Glecaprevir–pibrentasvir (Genotype 1: 1C; Genotype 4: 1D)
Glecaprevir–pibrentasvir (1D)
Grazoprevir–elbasvir (Genotype 1: 1B; Genotype 4: 2D)
Glecaprevir–pibrentasvir (1B)
Glecaprevir–pibrentasvir (Genotypes 2, 3: 1B; Genotypes 5, 6: 2D)

HCV-POSITIVE KIDNEYS INTO HCV-NEGATIV RECIPIENTS

- The early results of the THINKER trial showed that HCV-infected organs could be transplanted into recipients who do not have HCV infection, and the virus could be eradicated shortly after KT.

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Kidney International (2018) 93, 560–567

HCV-POSITIVE KIDNEYS INTO HCV-NEGATIV RECIPIENTS

An ideal DAA regimen for this scenario

1. Need to be safe in patients with low eGFR so it could be used in patients with delayed graft function
2. Should have few to no interactions with immunosuppressant medications
3. Ideally treat all genotypes of HCV infection.

Direct-acting antiviral therapy for hepatitis C virus infection in the kidney transplant recipient
Kidney International (2018) 93, 560–567