Dengue Related Kidney Injury:

Clinical Management in Endemic Regions

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Scenario of Dengue Infection

Paz-Bailey et al *Lancet* 2024; 403: 667–82

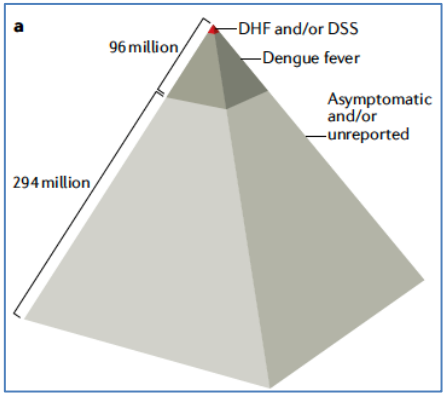
Outline

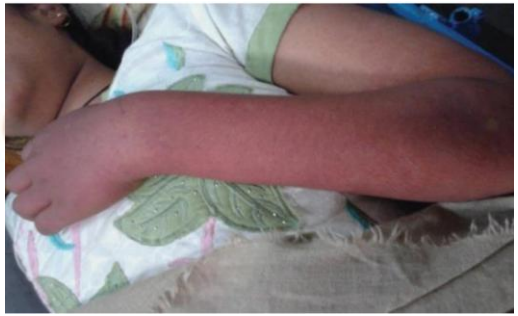
- Clinical course of Dengue infection
- Pathogenesis of complicated Dengue & Renal involvement
- Renal involvement in DENV infection
- Implications & Risk factors
- Discuss practical aspects in prevention & Mx
- Future directions

Phases of Dengue Infection

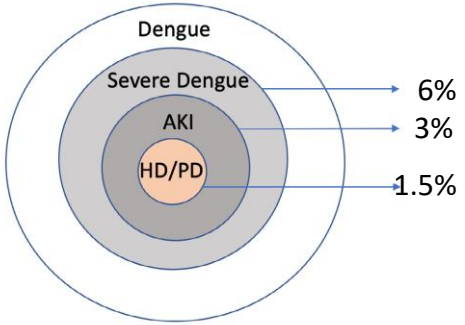
Asymptomatic in ~75% of cases

Incubation	FEBRILE	CRITICAL	RECOVERY
5-7 days	3-7 days	2-3 days	~15 days
	• **High fever (40°C)** • Dehydration • Nausea/Vomiting • Joint and muscle pain • Skin rashes • White blood cells decreased • Liver enlargement	• **Decrease in fever** • **Plasma leakage** • High hematocrit and decreased platelets • Hemorrhages • Organ impairment (hepatitis, encephalitis, myocarditis)	• **Fluid reabsorption** • Hematocrit and white blood cell stabilization • Intense fatigue





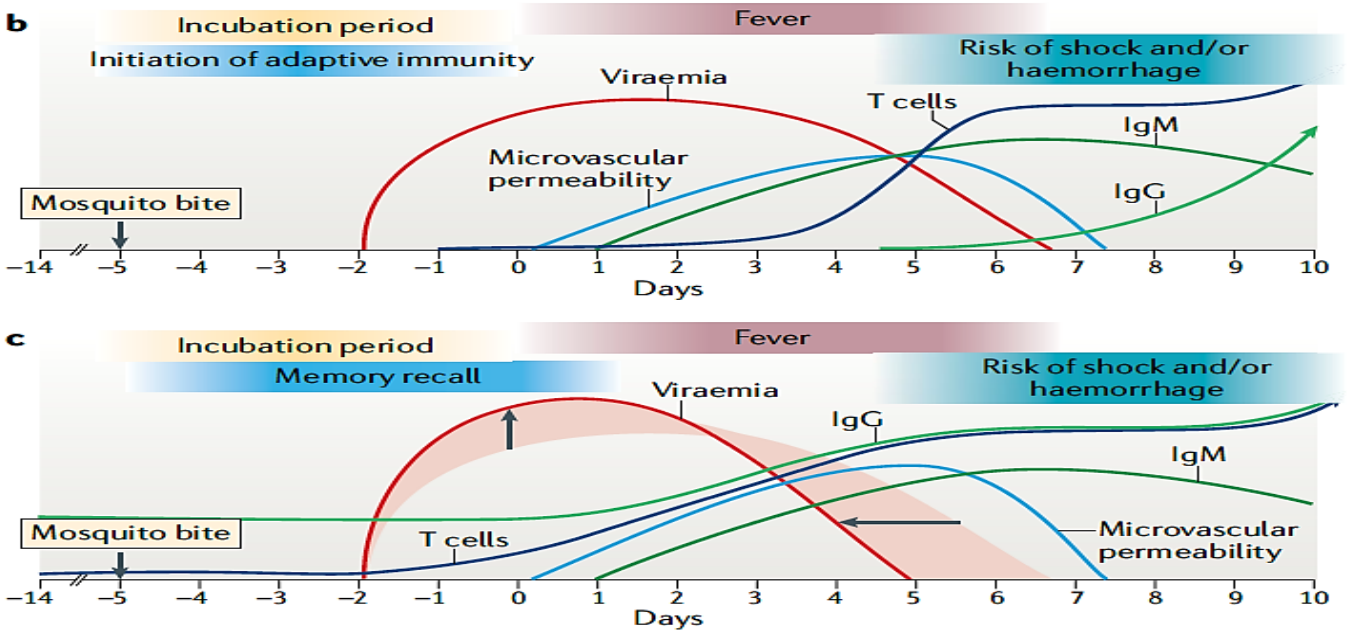
Severe Dengue
- Severe plasma leakage:
-shock
-fluid accumulation with respiratory distress
(Dengue Shock Syndrome)
- Severe hemorrhage (Dengue Hemorrhagic Fever)
- Severe organ damage



Bignardi et al *Braz. J. Nephrol 2022;44(2):232-237*

Primary Vs Secondary Infection

- Ability to utilise pre-existing heterotypic flavivirus antibody for enhancing infection – ADE
- Maximum with DENV-1 following DENV-2 infection



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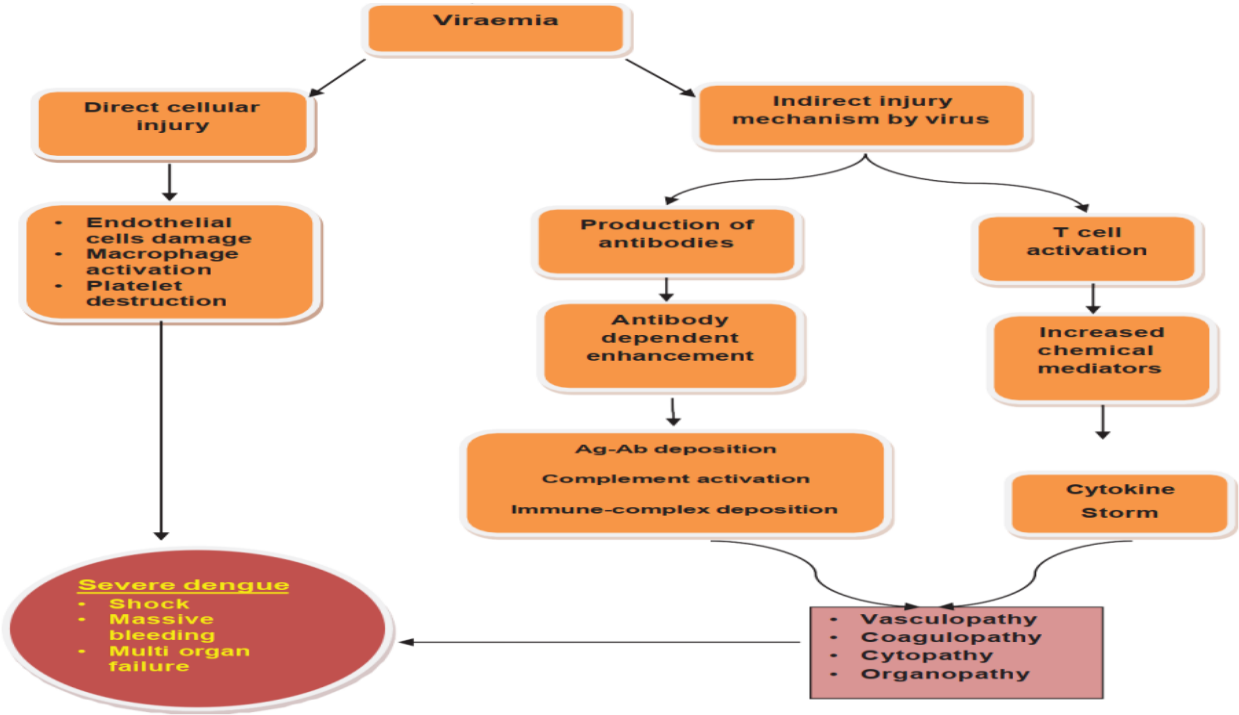
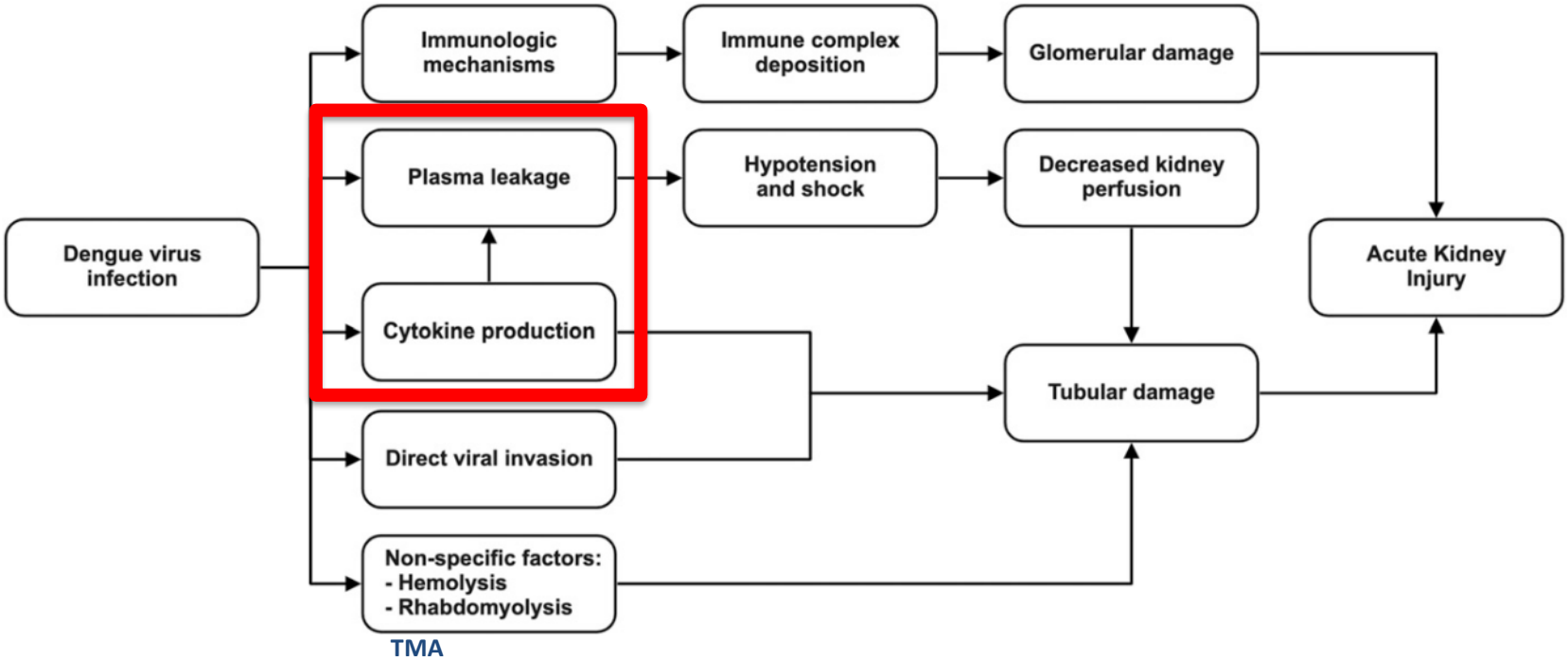
Pathophysiology of Complicated Dengue



Adapted from National Guidelines for Dengue Management 2023

Mechanisms of Renal Involvement-AKI



Diptyanusa Am. J. Trop. Med. Hyg., 105(1), 2021, pp. 24–30

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Renal Involvement in DENV

- Proteinuria
  - Common 70%, correlates with severity of disease & low platelets
  - Rarely nephrotic
  - Self-limiting
- Glomerulonephritis (*denovo*/circulating IC)
  - Nephritic sediment (15% cases)
  - Case reports of IgA, anti-GBM, LN
- AKI

Gurugama et al J Clin Virol. 2018;101:1-6
Kusirisin et al Nephrology. 2023;28:5–20

Prevalence of DA-AKI

Trans R Soc Trop Med Hyg 2024; **118**: 1–11
https://doi.org/10.1093/trstmh/trad067 Advance Access publication 13 September 2023

Prevalence of acute kidney injury among dengue cases: a systematic review and meta-analysis

Ganesh Bushi[a,†], Muhammed Shabil[a], Bijaya Kumar Padhi[b,*,†], Mohammed Ahmed[c], Pratima Pandey[a], Prakasini Satapathy[a,d], Sarvesh Rustagi[e], Keerti Bhusan Pradhan[f], Zahraa Haleem Al-qaim[g], and Ranjit Sah[h,i,*]

- 37 studies, 21,764 participants
- Moderate quality studies, high heterogenicity
- Differing definitions of AKI, pt population & study design
- Pooled prevalence 8% (95% CI 6 to 11)

Risk Factors for DA-AKI

- Advanced age
- Male gender
- DM
- Delay in admission
- DHF, DSS
- Rhabdomyolysis
- Concomitant bacterial infection
- MODS
- Use of nephrotoxic drugs

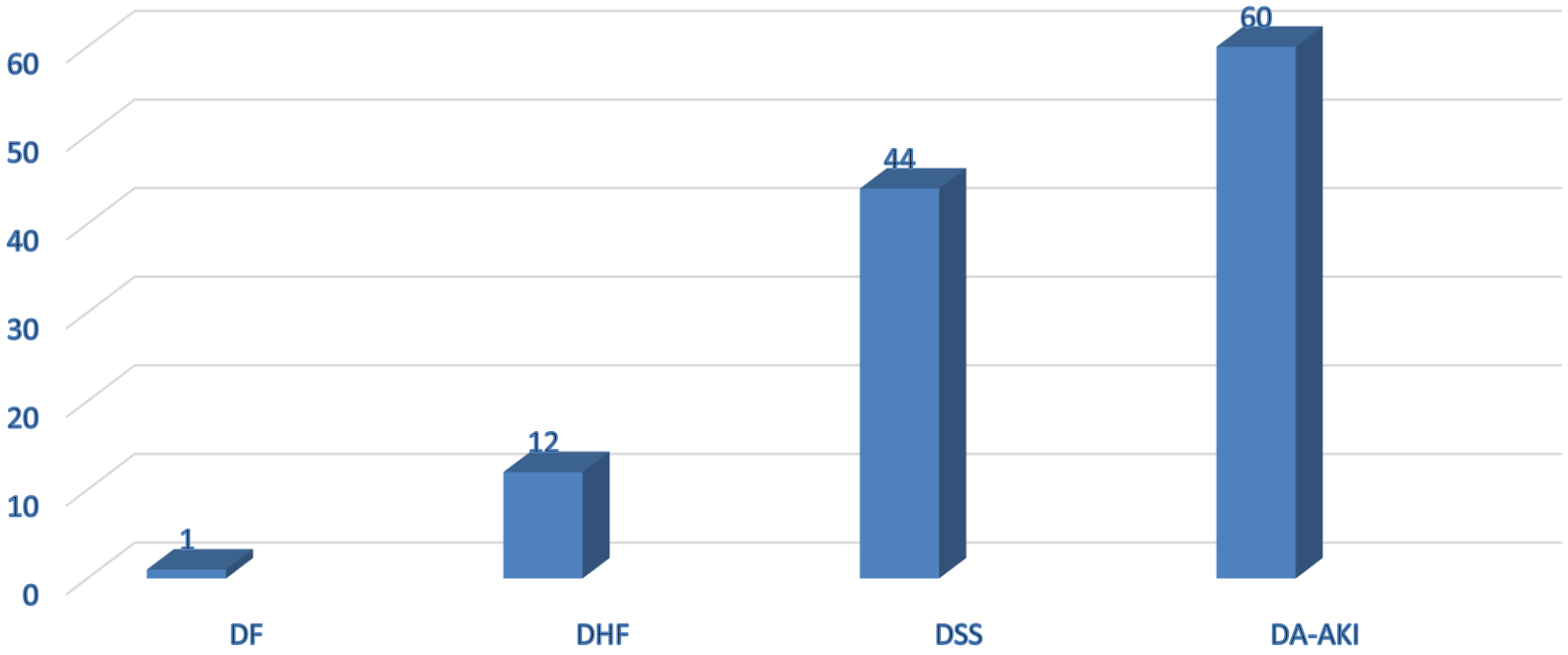
Gurugama et al J Clin Virol. 2018;101:1-6, Patel et al Indian J Nephrol 201; 29(1):15-21, Malhi et al PLoS One 2015 10(9):e0138465.

Implications of DA-AKI

- Longer hospital stay
- Increased mortality
  - Stage 3 AKI: 70% mortality in some series
  - Nearly 100% mortality in dialysis requiring AKI with DSS
  - Acute-on-chronic disease: Worse prognosis
  - Higher mortality reported from South Asia

Bignardi et al *Braz. J. Nephrol 2022;44(2):232-237*
Kuo *et al* Clin. J. Am. Soc. Nephrol.:3 (2008) 1350–1356

% Mortality with DENV Complications



George et al Trop Med Public Health. 1988;19:585-590

Post-AKI Renal Recovery

- Malhi et al
  - 72 patients post-AKI 3 month FU
  - 36/71 (50.7%) eGFR 60-80,16/71 (22.5%) eGFR <60
- Mukhopadhyay et al 2024
  - 41 pt had AA-AKI of 278 pts
  - Only 78% had complete renal recovery by 3 months

Malhi et al PLoS One 2015 10(9):e0138465.
Mukopadhyay etal Kidney International Reports (2023) 8, S1–S473

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Early Identification & Prevention

- Close monitoring of UO & lab parameters sp in high risk group
- Avoid nephrotoxic drugs
- Assessment & maintenance of blood volume
- Optimized fluid administration, controlled infusion rates & tonicity
- Avoid osmolarity disorders, fluid overload & worsening fluid extravasation

Standard Fluid Management

- Precisely calculated fluid regimens key in management of DHF
- 48 hr recommended fluid quota is maintenance fluid +5% deficit (approx. 4.6 L in 50 kg)
- Crystalloid preferred over colloids
- 10ml/kg for pts with shock (over 1 hr in compensated or bolus in decompensated shock)
- Colloid use only if persistent shock despite 2 crystalloid boluses or near completion of fluid quota

Management in CKD

- Suggested fluid regimen (0.9% NS), restrict therapy to 24-36 hr
  - 0.35ml/kg/hr for 24 hrs
  - 3ml/kg/hr for 4 hrs
  - 1ml/kg/hr for 3 hrs followed by oral hydration
- Regular hourly monitoring of clinical signs of hydration status (I/O, skin turgor, postural BP, JVP, Hct, serositis)
- Change in IVC diameter & collapsibility better than Hct
- Target IVC collapsibility index to <30%

Chatterjee et al MRIMS J Health Sci. 2023.

IMMUNOMODULATION IN DENGUE

Opportunities for Intervention

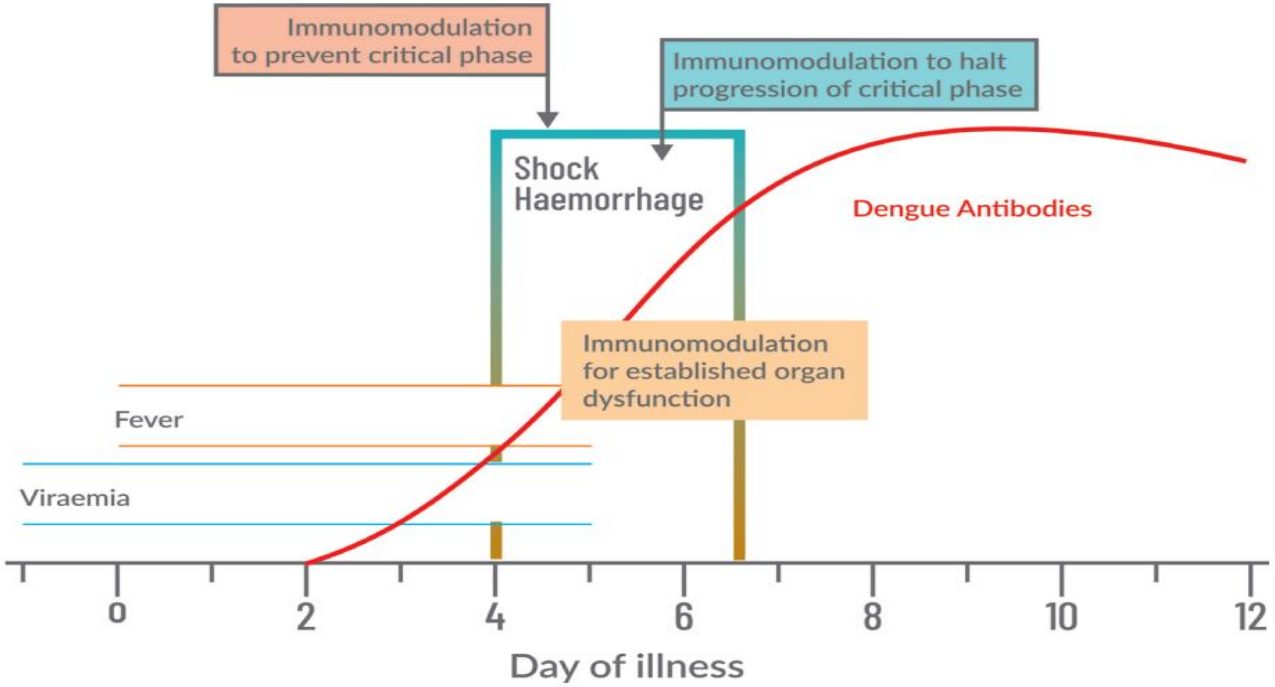

Figure 1 Clinical course of dengue infection with potential time frames for immunomodulation.

Bhat CS, et al. Arch Dis Child Month 2022

Options For Immunomodulation

- Corticosteroids
- IVIg
- Therapeutic monoclonal antibodies

Role of Steroids

Heliyon

ELSEVIER

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19 September 2018

Cite as:
S. M. Rathnasiri Bandara, H. M. M. T. B. Herath. Effectiveness of corticosteroid in the treatment of dengue – A systemic review. Heliyon 4 (2018) e00816.
doi: 10.1016/j.heliyon.2018.e00816

Review Article

Effectiveness of corticosteroid in the treatment of dengue – A systemic review

S. M. Rathnasiri Bandara [a], **H. M. M. T. B. Herath** [b,*]

[a] *Kandy General Hospital, Sri Lanka*

[b] *National Hospital of Colombo, Sri Lanka*

* Corresponding author.

E-mail address: tharukaherath11@gmail.com (H.M.M.T. B. Herath).

- Preliminary stage

  onset of symptoms to the earliest plasma leakage

- Intermediate stage

  onset of critical phase to time before the severe stage of DSS

- Late stage

  severe profound shock

Preliminary Stage

Table 1. The use of corticosteroids at the preliminary stage.

Grading of evidence (GE), steroid protocol (GS), Recommendation (GR)	Authors/Reference/Study year/ number/age of participants/Shock stage of recruited group	Dose and duration of steroid	Results/conclusion	Explanation for the results
GE-II GS-C 1, C2 GR-C	Tam DT et al./(Tam et al., 2012)/ 2012/255/Adult and children/No Shock	Low-dose (0.5 mg/kg) or high-dose (2 mg/kg) oral prednisolone therapy for 3 days. Within dengue fever for ≤72 hours.	No/no significant adverse effects or prolongation of viremia were seen. No reduction in the incidence of shock.	High-dose could reduce the risk of shock by up to 43%.
GE-II GS-B GR-C	Villar LA et al./(Villar et al., 2009)/ 2009/189/Adult and children (age group 5−15 years and >15/No Shock)	IV MP 15 mg/kg single dose, within 120 hours of onset of fever	Yes/reduces the incidence of bleeding and no prolongation of viremia and no significant adverse events	MP has the highest receptor affinity out of corticosteroids and IV root access is used. Treated early in the cause of illness.
GE-III GS-E GR-D	Kularatne S.A.M. et al./(Kularatne et al., 2009)/2009/100/adult/No Shock	IV 4 mg dexamethasone, followed by 2 mg doses every 8 hourly for 24 hours	No/A low dose is used, dexamethasone was not effective in achieving a higher rise of platelet count in dengue infection	Four-day course of high-dose dexamethasone (40 mg/day) is an effective dose. Dexamethasone 10 mg/day was used in this study
GE-III-1 GS-E GR-D	Shashidhara K.C. et al./(Shashidhara et al., 2013)/2013/62/adults/No Shock	IV dexamethasone 8 mg initially, followed by 4 mg every 8 hourly thereafter for 4 days	No/A low dose x used, dexamethasone was not effective in achieving a higher rise of platelet count in dengue infection	Four-day course of high-dose dexamethasone (40 mg/day) is an effective dose. Dexamethasone 12 mg/day was used in this study
GE-III-1 GS-C1, C2 GR-D	Thi Hanh Tien Nguyen et al./ (Nguyen et al., 2013)/2013/225/ children and young adults (aged 5−20 years)/No Shock	Low-dose (0.5 mg/kg) or high-dose (2 mg/kg) regimens of oral prednisolone/Fever for less than 72 hours	No/Early prednisolone therapy has little impact on the host immune response or the clinical evolution of dengue	After corticosteroid administration, It may take longer duration to detect changes of immune markers. In this study, it was checked only day 1 and day 2

Intermediate Stage

Table 2. The use of corticosteroids during intermediate stage.

Grading of evidence (GE), steroid protocol (GS), Recommendation (GR)	Authors/Reference/Study year/ number/age of participants/Shock stage of recruited group	Dose and duration of steroid	Results/conclusion	Explanation for the results
GE-III-2 GS-D-2 GR-D	Fernando S et al./(Fernando and Samarawickrama, 2016)/2015/100/Adult/ Dengue hemorrhagic fever at grade I and grade II	IV HC 50 mg 4 times per day for three days	Yes/92 % had improved within 72 hour/24% of control found to have myocarditis, hemorrhage, pneumonia	Pharmacologically effective drug protocol was used in the trial that maintained therapeutic drug levels.
GE-II and III -2 GS-D3 GR-D	Min M et al./(Min et al., 1975)/1975/98/ Children./shock	IV HC as follows: day 1: 25 mg/ kg, day 2:15/kg, day 3:10 mg/kg, for 3 days	Yes/A statistically significant mortality benefit with steroid	Pharmacologically effective drug protocol was used in the trial.
GE- III GS-D1 GR-D	Dummy Sumarmo, et al./(Sumarmo et al., 1982)/1982/87/Children 8 years/ shock	A single dose of IV HC hemisuccinate, 50 mg/kg.	No/No value in the treatment hydrocortisone	No sustained effective drug dose was maintained. High dose effect last only for a short period. HC has low receptor affinity than MP.
GE-III-2 GS-A GR-D	Futrakul P et al./(Futrakul et al., 1981)/ 1981/22/children 6 months to 14 years	IV MP: 10–30 mg/kg day. Single or repeated dose	Yes/9 out of 11 treatment group survived. All patients in the control groups died	Sustained and effective drug dose was maintained. Single dose may help due to higher receptor affinity of MP
GE-III-2 GS-A GR-D	Futrakul P et al./(Futrakul et al., 1987)/ 1987/9/Children 2.5–13 years	IV MP: 30 mg/kg day. Repeated dose were given to 7 patients	Yes/Significant hemodynamic improvement.	Sustained and effective drug dose was maintained with using a drug with higher receptor affinity.

Late Stage

Table 3. The use of corticosteroids during the late stage.

Grading of evidence (GE), steroid protocol (GS), Recommendation (GR)	Authors/Reference/Study year/ number/age of participants/Shock stage of recruited group	Dose and duration of steroid	Results/conclusion	Explanation for the results
Conditional recommendation against				
WHO suggests against the use of systemic corticosteroids in the treatment of patients with suspected or confirmed severe arboviral disease. [*Conditional recommendation, very low certainty evidence*] • For patients on established corticosteroid therapy, the decision to continue should be made according to anticipated risk/benefit balance.				
GS-D4 GR-D	Martoatmodjo, 1975)/1975/28/ children/Most patients profound shock	(120–180 mg per day).	severe dengue shock syndrome.	mineralocorticoid action of HC could cause increase mortality and morbidity at this stage.

Role of Intravenous Immunoglobulin

- Pleiotropic immunomodulatory role
- Uncontrolled case series have reported some success in using IVIg
- RCT found no role in secondary DENV infection with severe thrombocytopenia

Conditional recommendation against
WHO suggests against the use of immunoglobulins in the treatment of patients with suspected or confirmed severe arboviral disease. [*Conditional recommendation, very low certainty evidence*]

Therapeutic Monoclonal Antibodies

- Pan-serotype if against E protein or its domines

✓ **VIS513**

  - Bind domine III of E protein
  - Can administer either 24 h or 5 days post dengue infection
  - Phase 2 study is on-going in India (CTRI/2021/07/035290)

- **Important limitations**
  - Can lead to ADE at intermediate concentrations
  - Optimal therapeutic window and concentration

Monica Palanichamy Kala et al. Dengue : Update on clinally relevant therapeutic strategies and vaccines, Curr Treat Options Infect Dis (2023) 15:27-52

Timing/Indications for RRT

- Conventional indications of intractable
  - Acidosis
  - Electrolyte abnormalities
  - Fluid overload
  - Uraemia

Factors to consider for RRT initiation

Severity of AKI

Trajectory of renal function

Output with fluid status

Acid-base, electrolyte, uremia

Severity of critical illness

Cause for AKI

Other organ dysfunction

Co-morbidities

Fluid overload

Risks of RRT

Hypotension

Bleeding

Access related

Drug clearance / Nutrition

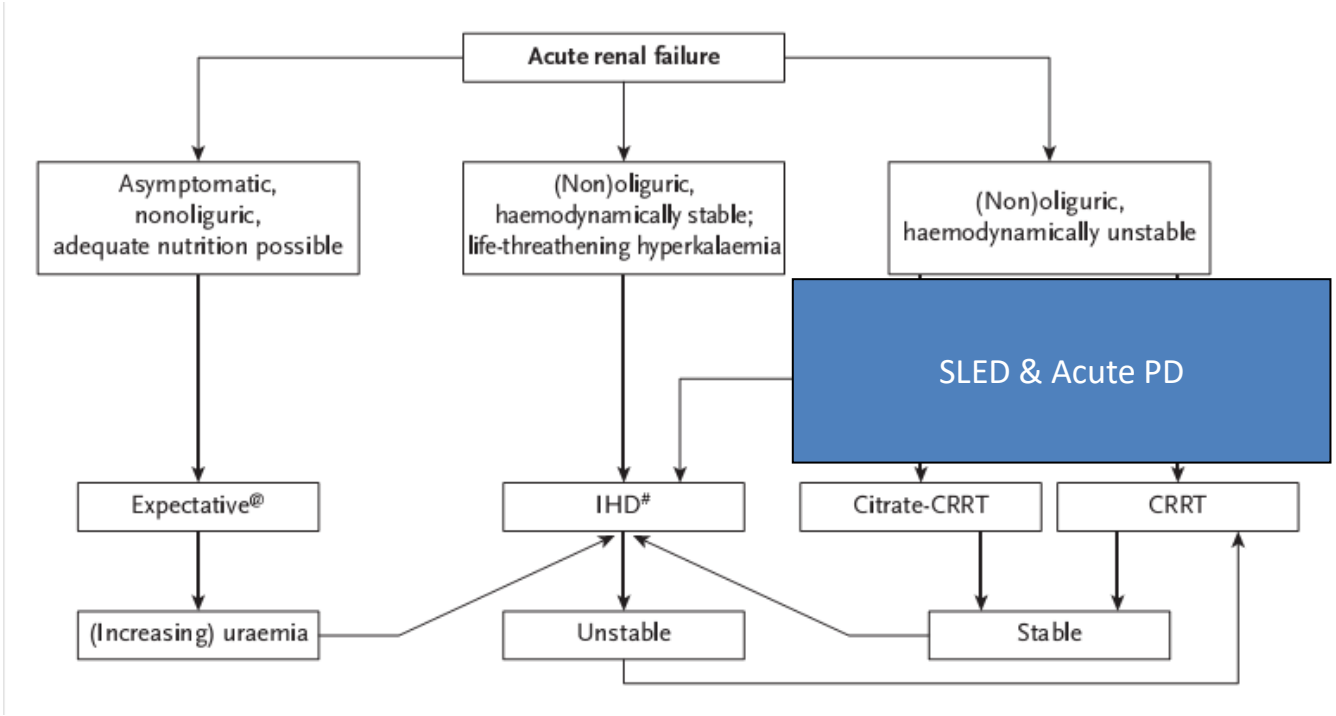
Other factors

Availability

Costing & logistics

Patient wish

RRT Options


Acute renal failure
Asymptomatic, nonoliguric, adequate nutrition possible
(Non)oliguric, haemodynamically stable; life-threathening hyperkalaemia
(Non)oliguric, haemodynamically unstable
SLED & Acute PD
Expectative@
IHD#
Citrate-CRRT
CRRT
(Increasing) uraemia
Unstable
Stable

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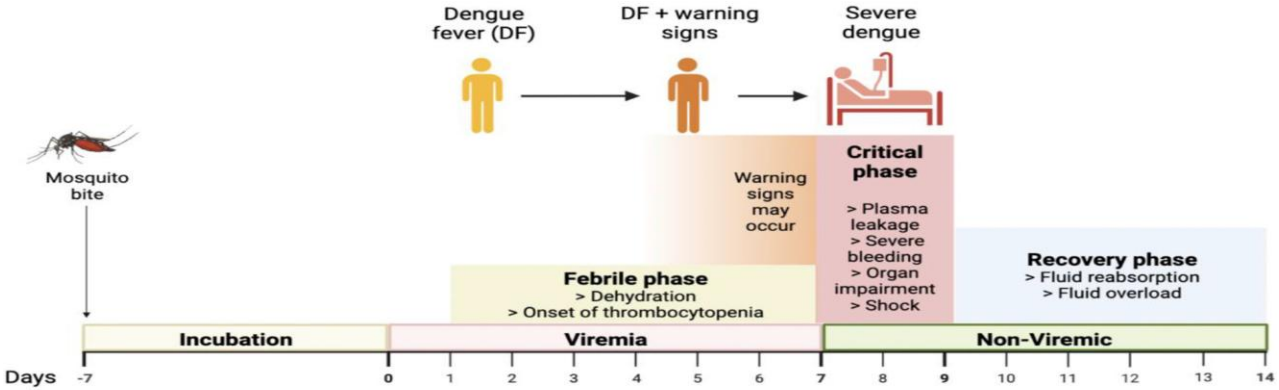
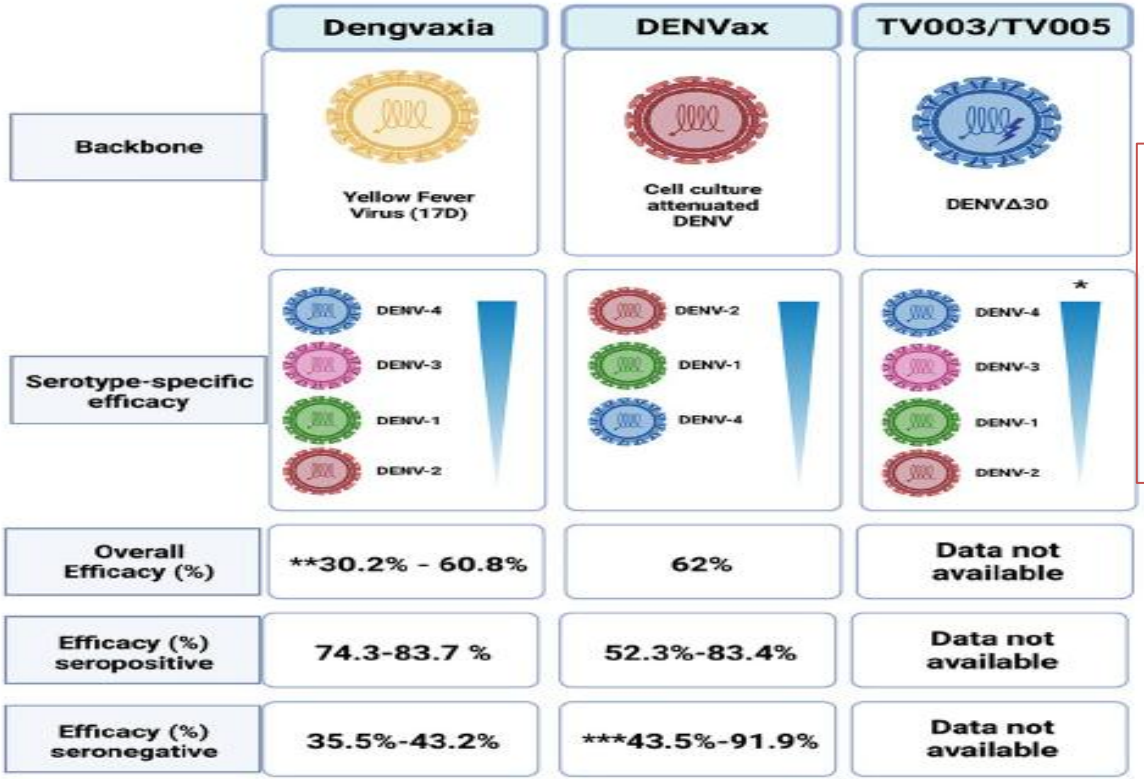
Newer Therapeutic Agents



Current clinical management	**Symptomatic care** • Acetaminophen • Oral rehydration	**Hospitalisation required** • Tapering IV fluids therapy (crystalloids supplemented with colloids); diuresis for fluid overload • Blood/platelet transfusion in case of severe bleeding
Proposed novel therapeutics	**Direct acting anti-virals** • JNJ-A07 • Ivermectin • Doxycycline **Thrombopoietic medications** • Eltrombopag **Others** • CPLE • Vitamin E	**Monoclonal therapeutics** • VIS513 **Host-targeted medications** • Mast cell inhibitors ◦ Ketotifen ◦ Montelukast • Metabolic targets ◦ Metformin

Curr Treat Options Infect Dis (2023) 15:27–52

Dengue Vaccines



Not recommended

- *naïve* patients
- allergic reactions
- outbreak setting
- Immunocompromised hosts

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Daily Mosnodenvir as Dengue Prophylaxis in a Controlled Human Infection Model

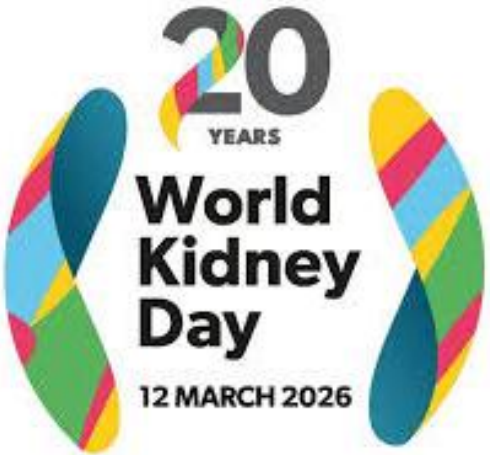
A.P. Durbin,[1] L. Van Wesenbeeck,[2] K.K. Pierce,[3] G. Herrera-Taracena,[4] L. Ebone,[1] A. Buelens,[2] P. Lutton,[3] B.P. Sabundayo,[1] V. Van Eygen,[2] K. De Clerck,[2] I. Fetter,[3] N.V. Voge,[5] X. Fang,[1] N. Goeyvaerts,[2] Y. Vandendijck,[2] J. Mayfield,[1] O. Lenz,[2] S. De Meyer,[2] T.N. Kakuda,[6] H. He,[1] E. Amaro-Carambot,[7] R.D. Akli,[5] M. Carmolli,[3] T. De Marez,[5] S.S. Whitehead,[7] M. Van Loock,[2] and F. Rasschaert[2]

- DAA binds to NS4B protein, inhibiting interaction with NS-3
- Active against all serotypes
- Efficacy as prophylactic agent established
- Efficacy in endemic areas & treatment untested
- Potential viral resistance

Conclusions

- AKI though uncommon, remarkably increases mortality & morbidity in DENV infection
- High index of suspicion, early diagnosis, avoidance of nephrotoxic drugs improves outcomes
- Therapy includes appropriate fluid therapy & supportive management

Thank You!



KIDNEY HEALTH FOR ALL

Caring for People, Protecting the Planet