Manejo clínico das arboviroses

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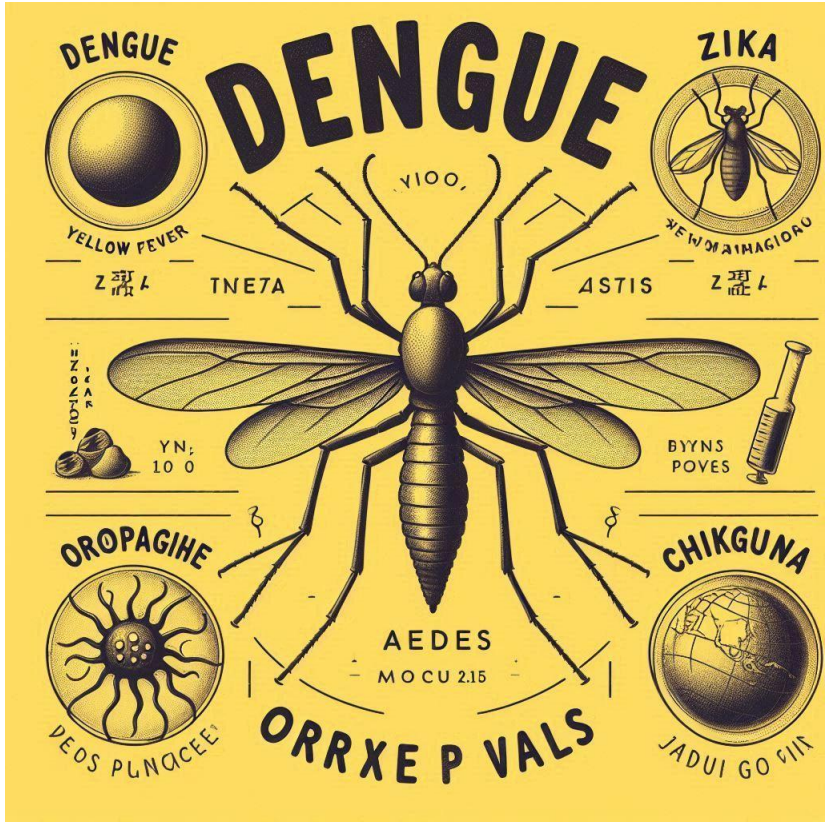
Faculdade de Medicina da Universidade de São Paulo



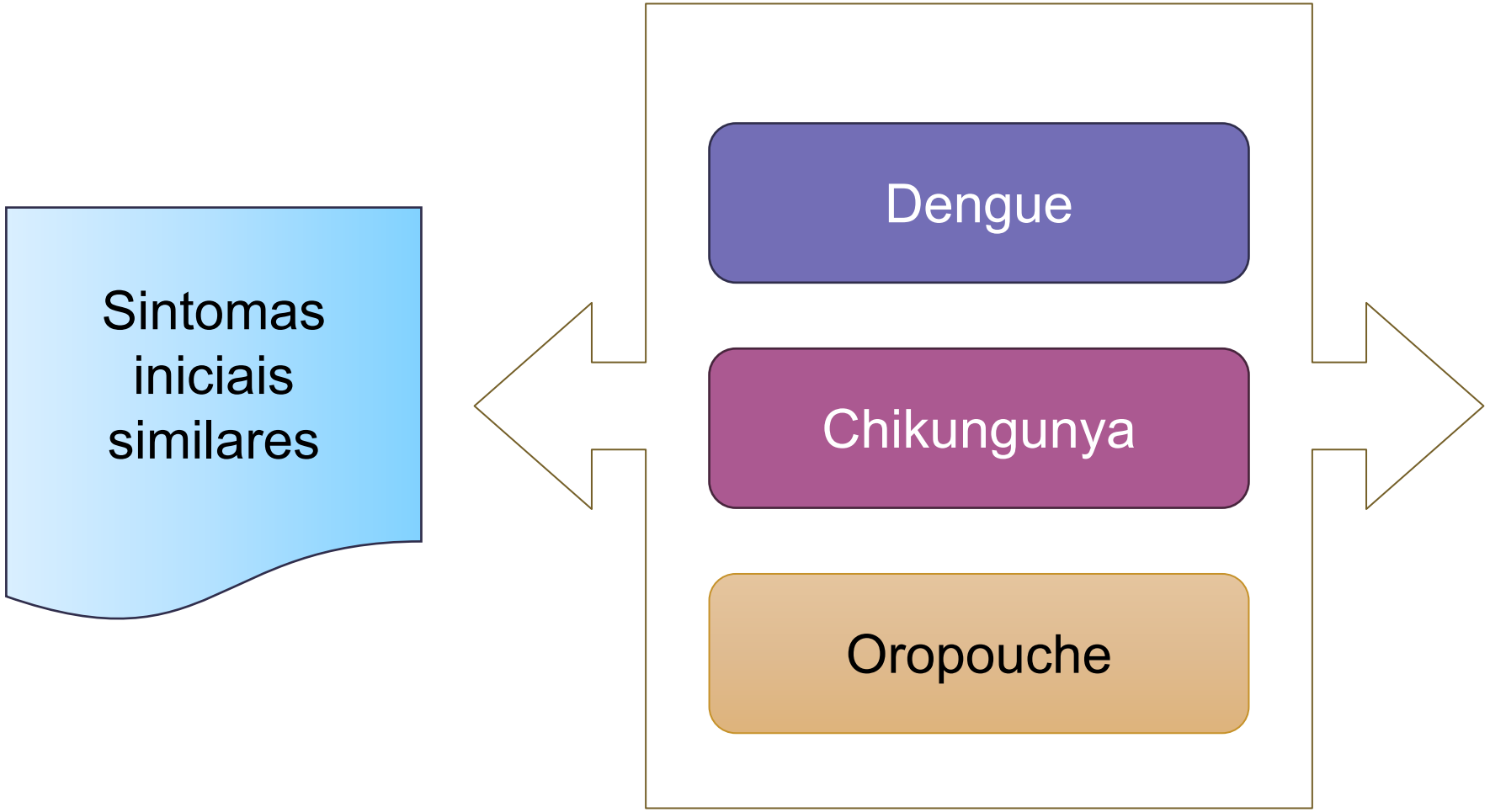
Conflito de interesse

Nada a declarar

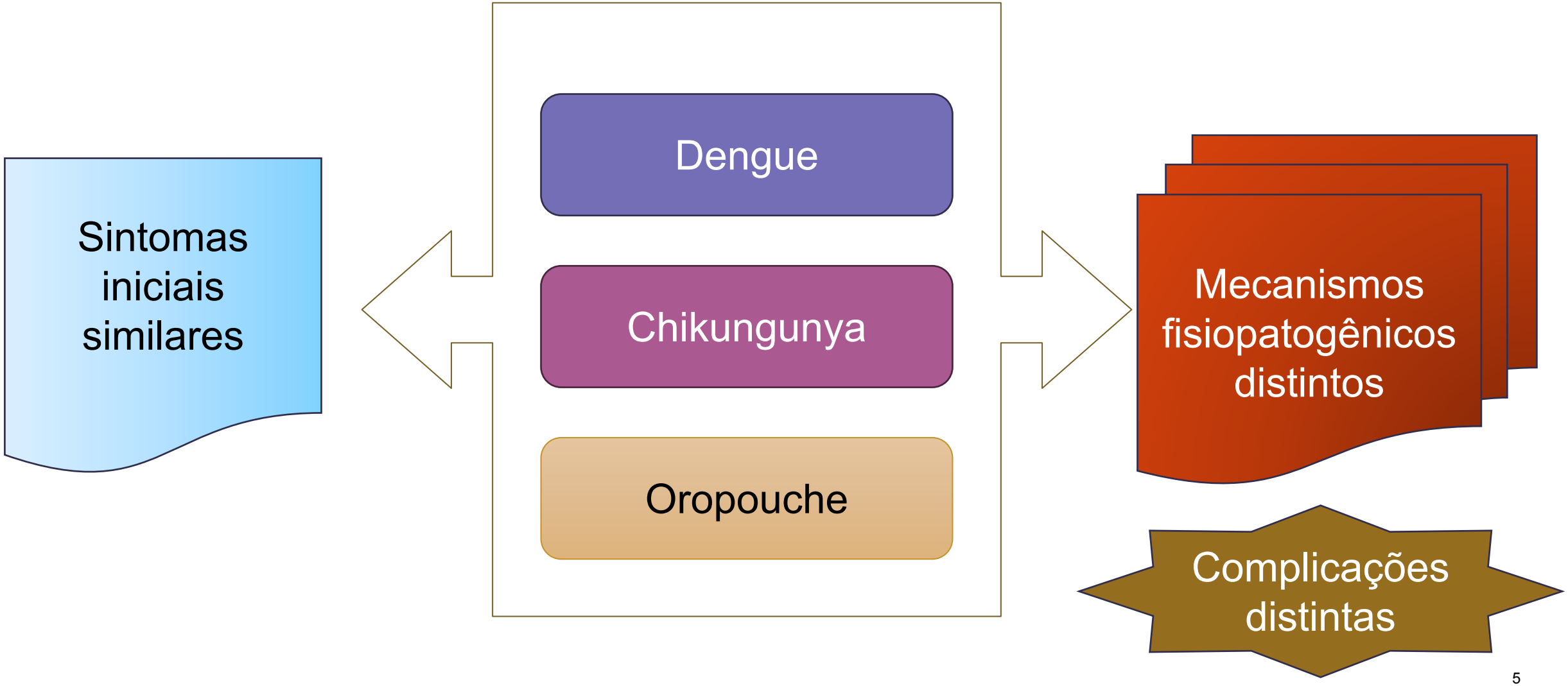
Tópicos

- Dengue
- Chikungunya
- Oropouche
- Zika
- Febre amarela

Arboviroses



Arboviroses

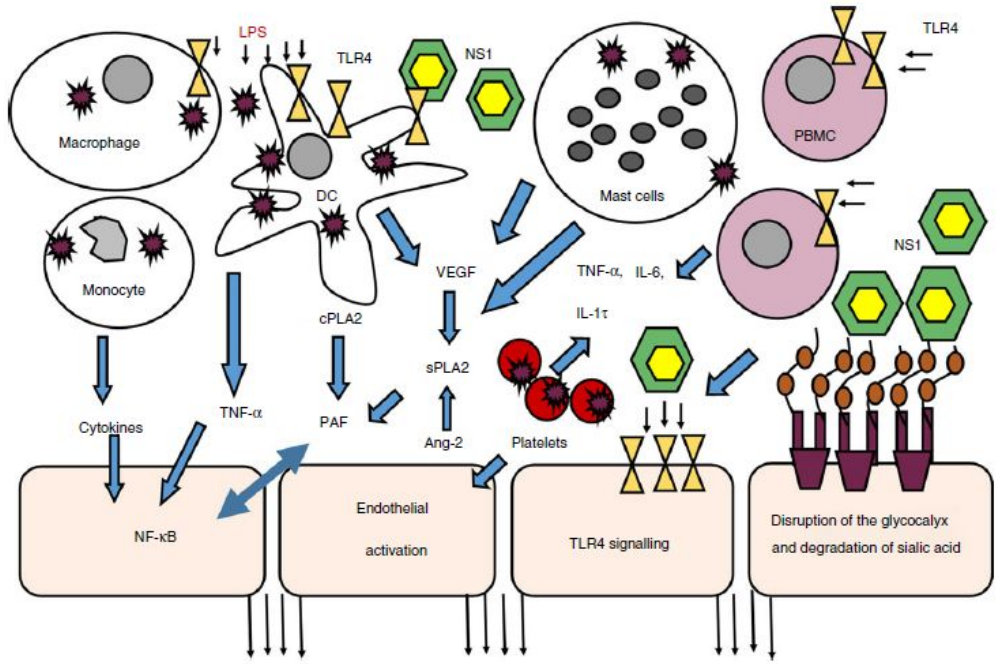


DENGUE

Dengue - Fisiopatogenia

Características particulares na dengue

Extravasamento vascular

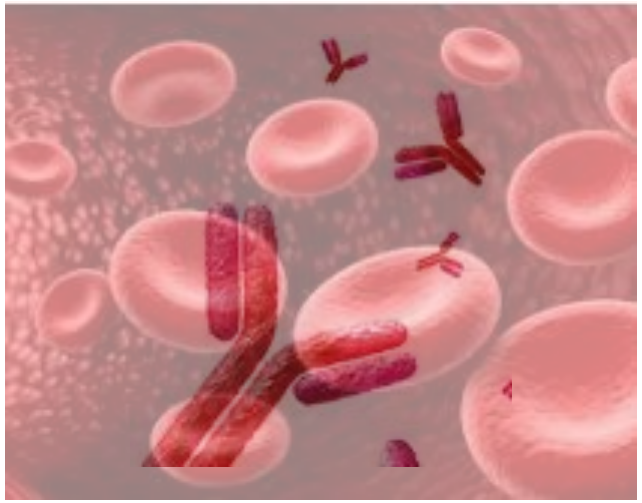


- DENV Infecção célula endotelial
- NS1 disruptura endotelial e destruição da barreira reguladora de permeabilidade vascular e células de adesão.
- Efeito inflamatório (tempestade de citocinas)
- Ativação sistema de complemento aumento de anafilatoxina C3a e C5a ação na superfície endotelial

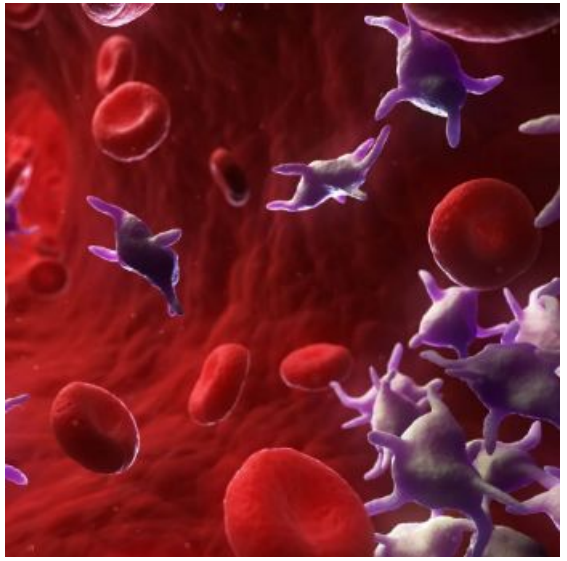
Dengue - Fisiopatogenia

Plaquetopenia

Supressão medular



Destruição periférica imunomediada

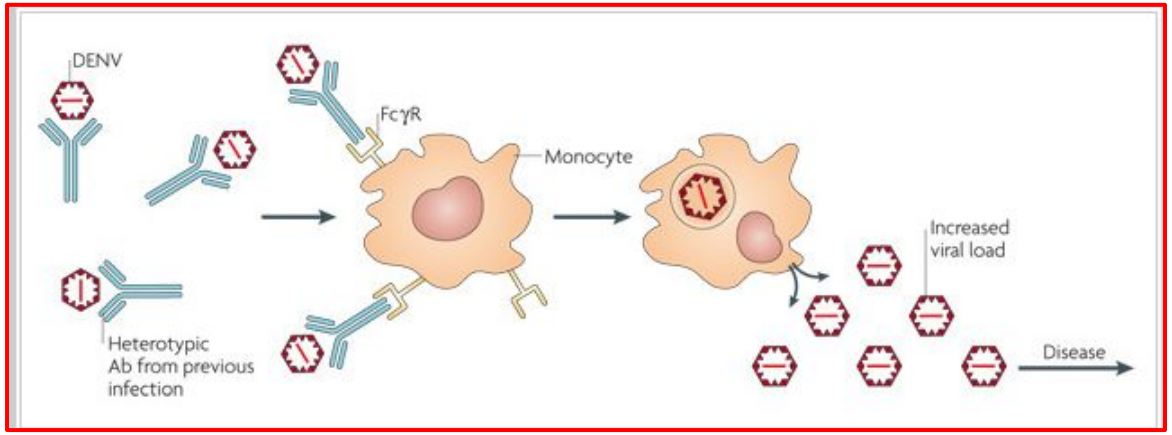


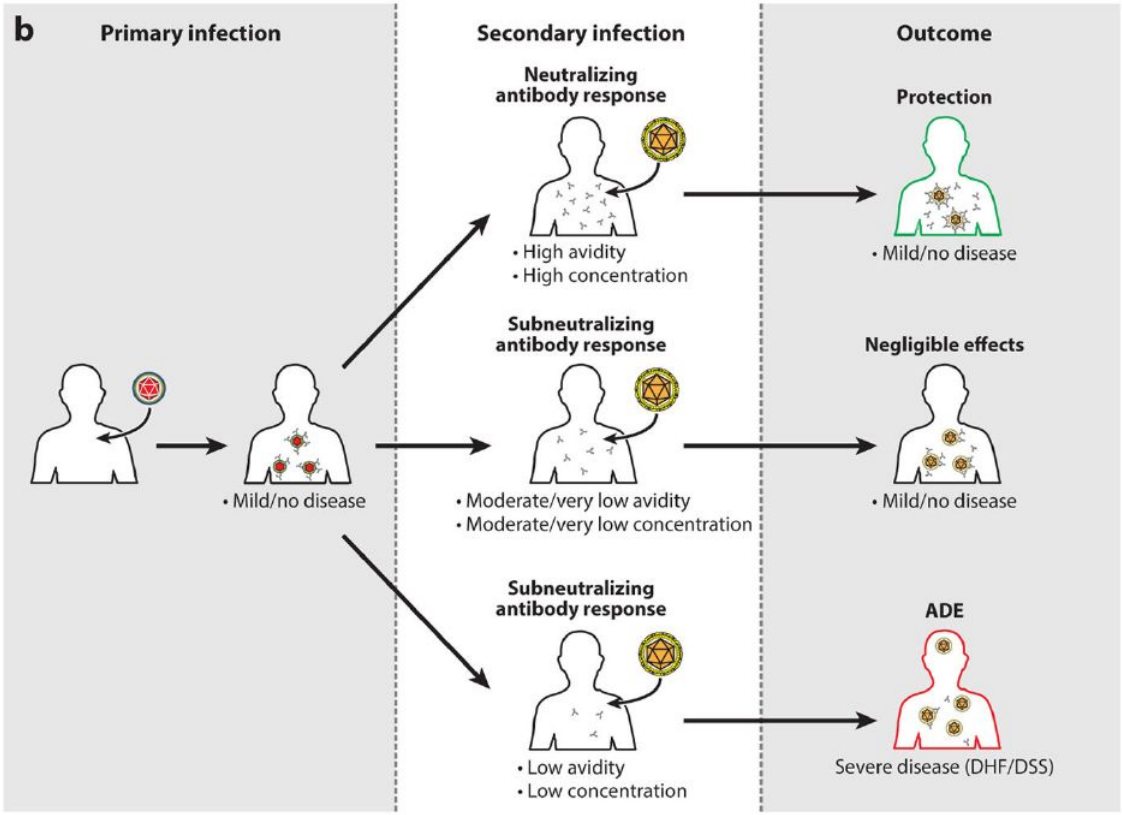
Infecção viral direta

Dengue - Fisiopatogenia

2ª infecção mais grave

Antibody-dependent enhancement (ADE)



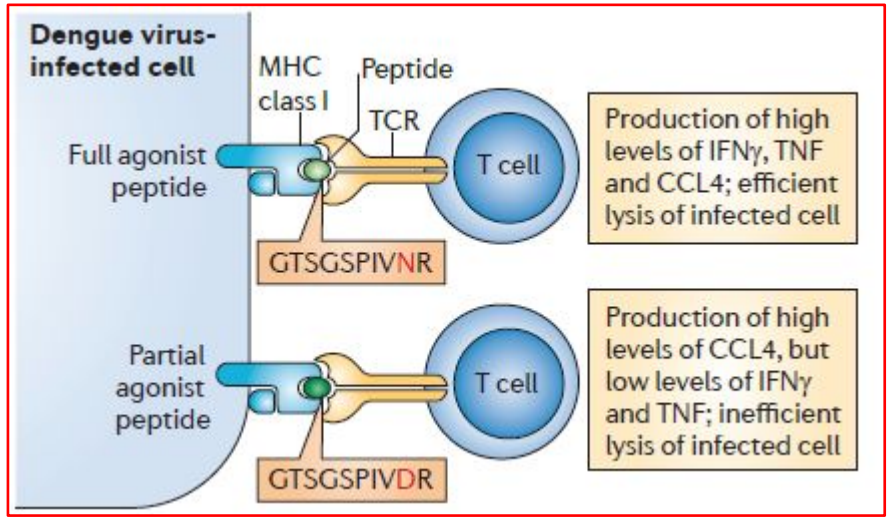


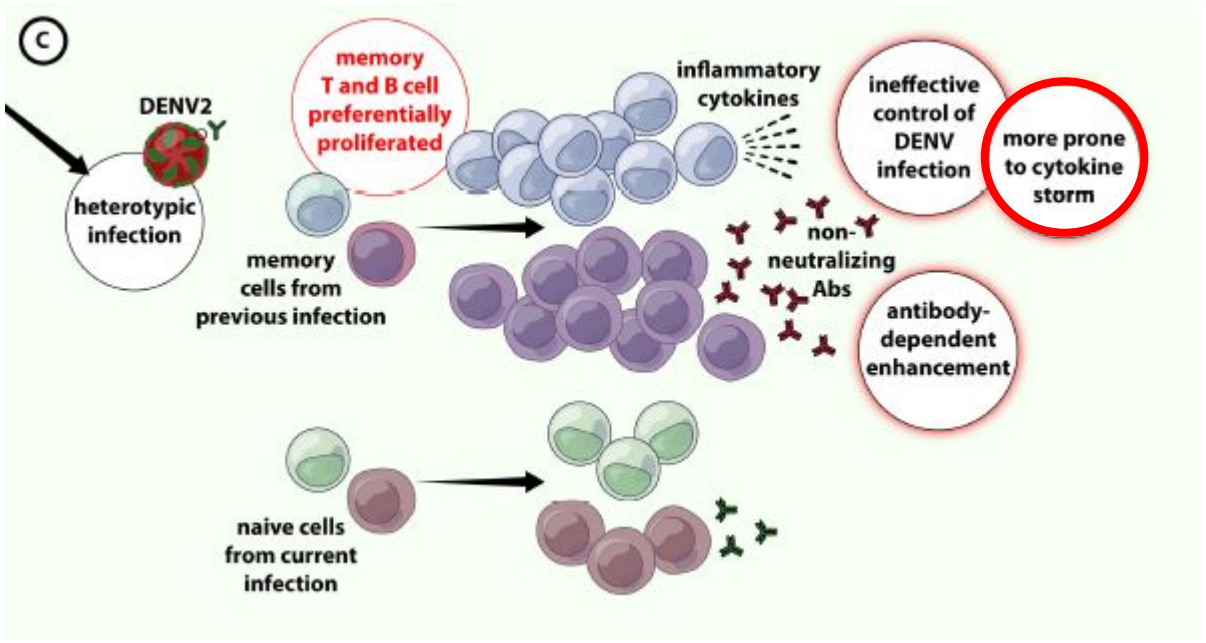
WHITEHEAD ET AL. PROSPECTS FOR A DENGUE VIRUS VACCINE. NATURE REV MICROBIOL,2007
NGONO & SHRESTA. IMMUNE RESPONSE TO DENGUE AND ZIKA. ANNU REV IMMUNOL, 2018

Dengue - Fisiopatogenia

2ª infecção mais grave

Original Antigenic Sin

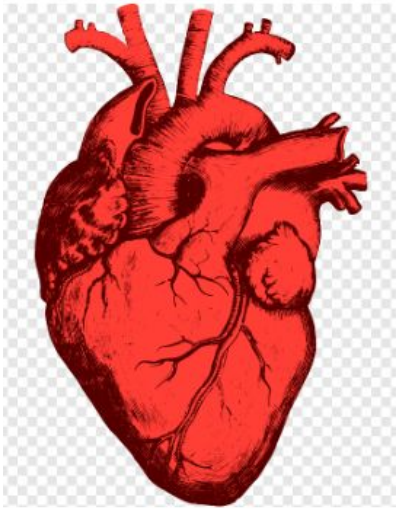


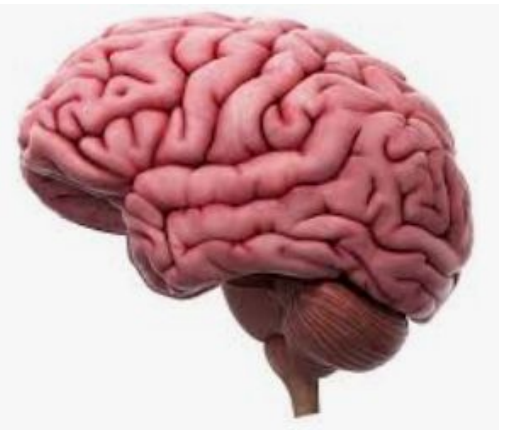


YONG YK ET AL. DENGUE INFECTION –RECENT ADVANCES IN DISEASE PATHOGENESIS IN THE ERA OF COVID-19. FRONT. IMMUNOL, 2022

Dengue - Fisiopatogenia

Órgãos alvos





Dengue - Fisiopatogenia

Órgãos alvos

Review > Viruses. 2019 Dec 9;11(12):1136. doi: 10.3390/v11121136.

Insight into the Tropism of Dengue Virus in Humans

Feroza Begum [1,2], Sandeepan Das [1,2], Debica Mukherjee [1,2], Sweety Mal [1], Upasana Ray [1,2]

Table 1. Overview of DENV-infected cells in humans as identified in human autopsy and various in vitro studies.

Human Organs/Tissues	Primary Cells/Cell Lines	Presence of DENV Antigens/RNA	References
Skin	a. Primary epidermal keratinocytes and HaCaT cells	Negative sense (−) RNA, envelope (E) and non-structural (NS) proteins NS5 and NS3	[28,121,122]
	b. Primary dermal mast cells, HMC1 and KU812 cell lines	Positive-sense (+) RNA and viral capsid (C)	[29–31,123]
	c. Dermal DCs (CD1c+ and CD14+) and Langerhan cells	NS1, E and positive-sense (+) RNA	[21,25,27]
	d. Monocyte-derived DCs in dermis	NS1 and E	[25,26,124]
	e. Dermal macrophages	Positive-sense (+) RNA and E	[21,27,125–127]
	f. Fibroblasts	NS3	[28]
	g. Lymphatic endothelium	NS3	[28]
	h. Human microvascular endothelium line-1 (HMEC-1)	E and NS1	[128–133]
Draining Lymph nodes	a. Macrophages	DENV RNA and NS3	[13,18,34]
	b. Immunoblasts	Unspecified	[34]
	c. Lymphocytes	Unspecified	[34]
	d. Plasma cells	Unspecified	[34]
Spleen	a. Macrophages in red pulp	Negative-sense (−) and positive-sense (+) RNA, NS3, E and NS1	[13–15,18,20,34,35,37]
	b. Splenic endothelium and sinusoidal endothelium	NS3	[18,130,131]
	c. Immunoblasts in white pulp	Positive-sense (+) RNA and an unspecified DENV antigen	[15,34]
	d. Lymphocytes in white pulp	Positive-sense (+) RNA and an unspecified DENV antigen	[15,34]
	e. Lymphocytes in red pulp	Positive-sense (+) RNA and an unspecified DENV antigen	[15]
	f. Giant cells (binucleated or multinucleated)	Positive-sense (+) RNA and an unspecified DENV antigen	[15]
	g. Plasma cells	Unspecified	[34]
	h. Mononuclear cells (macrophages and DCs) in white pulp	NS3, NS1 and E	[18,35]
	i. Germinal centers in lymphoid follicle	Positive-sense (+) RNA and an unspecified DENV antigen	[15]
	j. Centroblasts in white pulp	Positive-sense (+) RNA and an unspecified DENV antigen	[15]
Central Nervous System	a. Vascular endothelium and human brain microvascular endothelial cells (HBMEC)	Positive-sense (+) RNA	[74,130,131,133,134]
	b. Neurons	Positive-sense (+) RNA and NS3	[34,74,133]
	c. Astrocytes	Positive-sense (+) RNA and NS3	[18,34,74,135]
	d. Microglia	Positive-sense (+) RNA	[34,74]
	e. Lymphocytes, Purkinje cells and granular cells	Unspecified	[34]
Kidney	a. Immunoblasts	Unspecified	[34]
	b. Histiocytes	Unspecified	[34]
	c. Plasma cells	Unspecified	[34]
	d. Lymphocytes	Unspecified	[34]

Dengue - Fisiopatogenia

Órgãos alvos

Review > Viruses. 2019 Dec 9;11(12):1136. doi: 10.3390/v11121136.

Insight into the Tropism of Dengue Virus in Humans

Feroza Begum [1,2], Sandeepan Das [1,2], Debica Mukherjee [1,2], Sweety Mal [1], Upasana Ray [1,2]

Table 1. *Cont.*

Human Organs/Tissues	Primary Cells/Cell Lines	Presence of DENV Antigens/RNA	References
Liver	a. Hepatocytes, HepG2, Huh7, Huh75.1 and Huh7.5	Negative-sense (−) and positive-sense (+) RNA and NS3	[13,14,20,34,135–139]
	b. Kuppfer cells	Negative-sense (−) and positive-sense (+) RNA and NS3	[13–15,20,34]
	c. Vascular/sinusoidal endothelium	Negative-sense (−) and positive-sense (+) RNA and NS3	[13–15,20,34,130]
Lung	a. Alveolar macrophages	Negative-sense (−) RNA and NS3	[14,15,20,34]
	b. Type II pneumocytes	Negative-sense (−) RNA and NS3	[14,20,34]
	c. Vascular endothelium and human pulmonary endothelial cell (EC) line (HPMEC-ST1.6R)	Negative-sense (−) and positive-sense (+) RNA and NS3	[14,15,20,34,130,140]
Intestine	a. Plasma cells in lamina propria	Unspecified	[34]
	b. Mononuclear cells in lamina propria	Unspecified	[34]
Heart	a. Myocardial endothelium	Negative-sense (−) RNA and NS3	[20,104]
	b. Myocardial interstitial cells	Unspecified	[104]
	c. Cardiomyocytes	Negative-sense (−) RNA and NS3	[20,104]
	d. Monocytes/macrophages	Negative-sense (−) RNA and NS3	[20]
Stomach	a. Lymphocytes in mucosa	Unspecified	[34]
	b. Plasma cells in lamina propria	Unspecified	[34]
Blood	a. Peripheral blood monocyte/macrophage (PBMC)-derived primary B cells and B cell lines (Raji cells, Wil 2WT, BM, LK63, Daudi and 8866)	Negative-sense (−) RNA, an unspecified DENV antigen (primary B cells) and DENV RNA (BM and LK63, Daudi, Raji) (Wil 2WT and 8866)	[141–145]
	b. PBMC-derived T cells and T cell lines (JK44, JK49, CB2.8, CB6.17, HSB-2, Molt-4 and Jurkat)	DENV NS3, C, NS1 (Primary T cells), DENV RNA (Molt-4 and Jurkat) and an unspecified antigen (JK44, JK49, CB2.8, CB6.17 and HSB-2)	[143,145–147]
	c. Activated monocytes and U937 cells	prM and NS3	[17,125,127,128,148–150]
	d. Blood-derived DCs	Negative-sense (−) and positive-sense (+) RNA, DENV E and NS1	[25,124,126,151,152]

Dengue - Fisiopatogenia

Órgãos alvos

Case Reports › BMC Infect Dis. 2021 Apr 1;21(1):311. doi: 10.1186/s12879-021-05959-2.

Systemic dengue infection associated with a new dengue virus type 2 introduction in Brazil – a case report

Marielton Dos Passos Cunha [1], Amaro Nunes Duarte-Neto [2], Shahab Zaki Pour [3], Ludhmila Abrahão Hajjar [4], Fernando Pereira Frassetto [2], Marisa Dolhnikoff [2], Paulo Hilario do Nascimento Saldiva [2], Paolo Marinho de Andrade Zanotto [5]

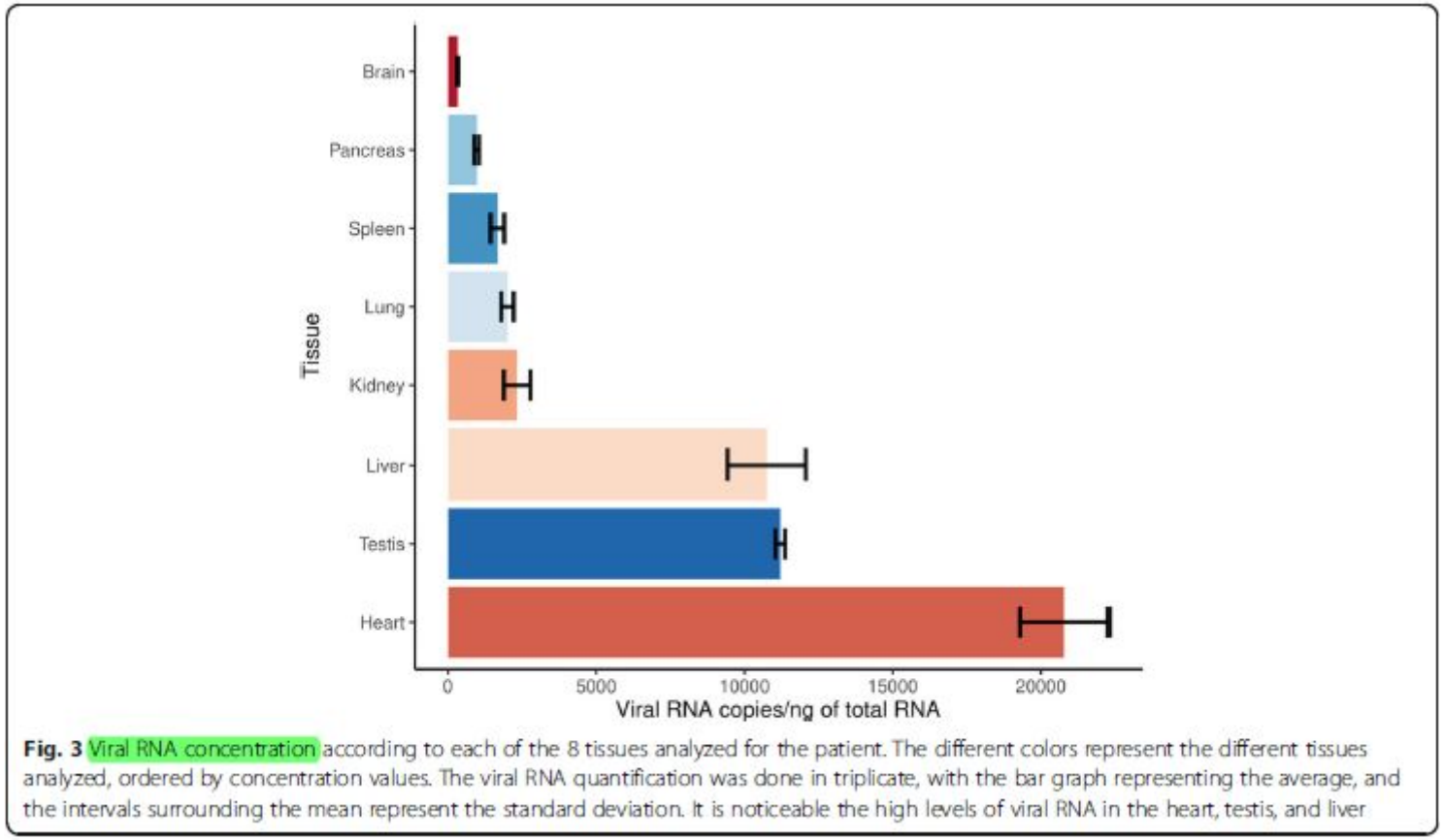


Fig. 3 Viral RNA concentration according to each of the 8 tissues analyzed for the patient. The different colors represent the different tissues analyzed, ordered by concentration values. The viral RNA quantification was done in triplicate, with the bar graph representing the average, and the intervals surrounding the mean represent the standard deviation. It is noticeable the high levels of viral RNA in the heart, testis, and liver

Dengue - Fisiopatogenia

Fases da doença

Review > Virus Res. 2023 Jan 15:324:199018. doi: 10.1016/j.virusres.2022.199018. Epub 2022 Dec 7.

Dengue virus infection – a review of pathogenesis, vaccines, diagnosis and therapy

Boon Hui Kok [1], Hui Ting Lim [1], Chin Peng Lim [1], Ngit Shin Lai [1], Chiuan Yee Leow [2], Chiuan Herng Leow [3]

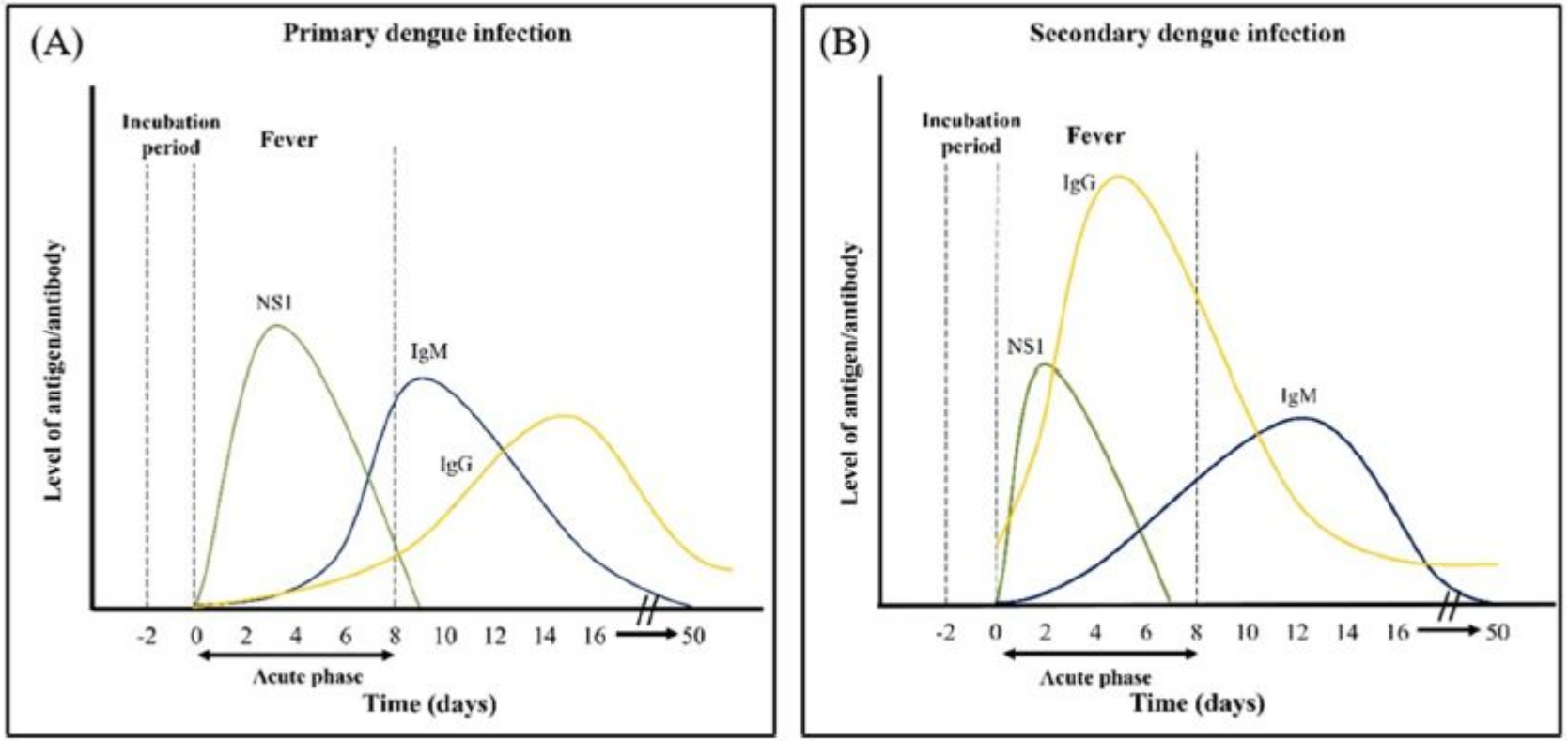
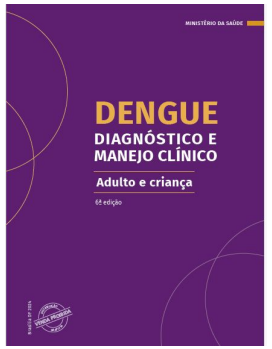
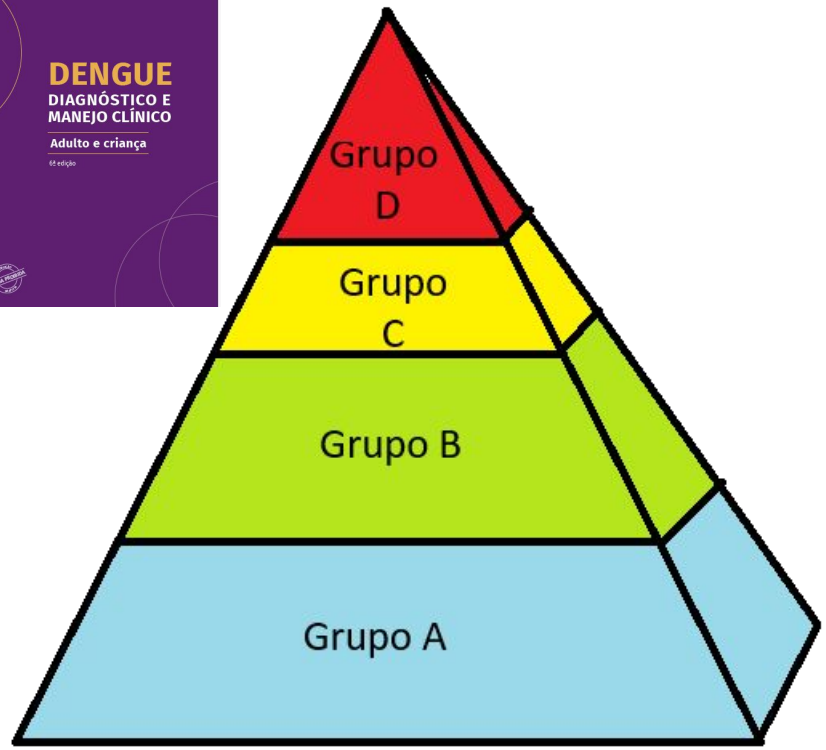


Fig. 4. The level of NS1, IgM and IgG for primary and secondary dengue infection. (A) During primary infection, NS1 and IgM are detectable starting day 0 onwards and day 3 onwards, respectively, while IgG can only be detected on day 10 onwards. (B) For secondary infection, IgG level is used to differentiate both primary and secondary infection by presenting very significant level during acute phase due to rapid anamnestic IgG reaction.

Dengue – Manifestação e manejo

Espectro clínico





SUSPEITA DE DENGUE

Relato de febre, usualmente entre dois e sete dias de duração, e duas ou mais das seguintes manifestações: náusea, vômitos; exantema; mialgia, artralgia; cefaleia, dor retro-orbital; petéquias; prova do laço positiva e leucopenia. Também pode ser considerado caso suspeito toda criança com quadro febril agudo, usualmente entre dois e sete dias de duração, e sem foco de infecção aparente.

Notificar todo caso suspeito de dengue

Tem sinal de alarme ou gravidade?

Não

Pesquisar sangramento espontâneo de pele ou induzido (prova do laço, condição clínica especial, risco social ou comorbidades).

Não

Grupo A

Dengue sem sinais de alarme, sem condição especial, sem risco social e sem comorbidades.

Sim

Grupo B*

Dengue sem sinais de alarme, com condição especial, ou com risco social e com comorbidades.

Sim

Grupo C

Sinais de alarme presentes e sinais de gravidade ausentes

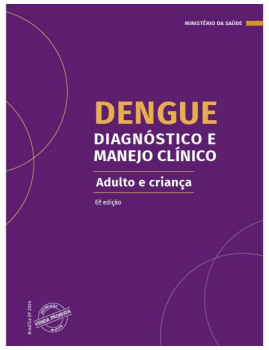
- Dor abdominal intensa (referida ou à palpação) e contínua.
- Vômitos persistentes.
- Acúmulo de líquidos (ascite, derrame pleural, derrame pericárdico).
- Hipotensão postural e/ou lipotimia.
- Hepatomegalia maior do que 2 cm abaixo do rebordo costal.
- Sangramento de mucosa.
- Letargia e/ou irritabilidade.
- Aumento progressivo do hematócrito.

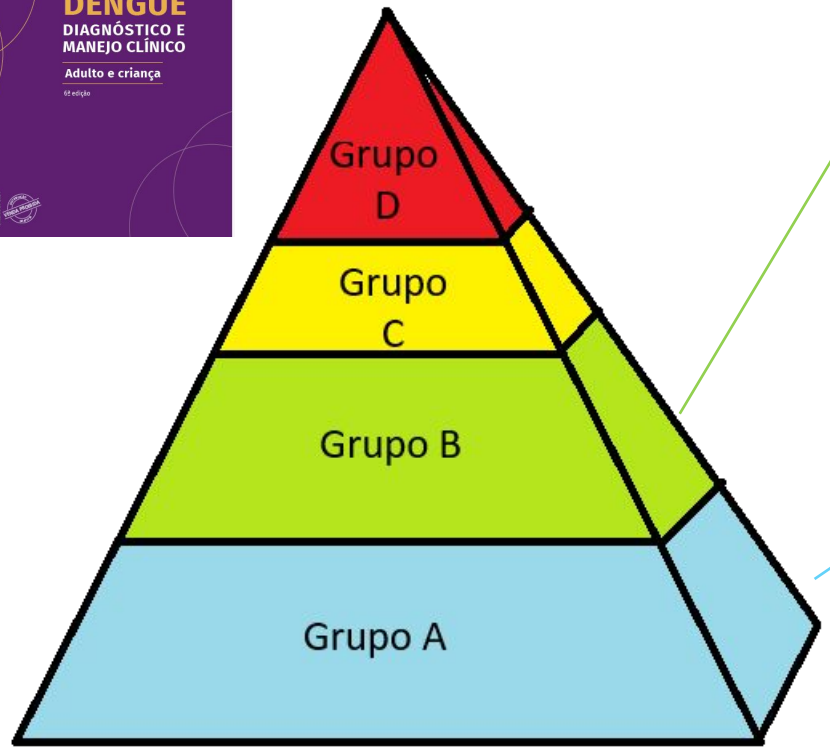
Grupo D

Dengue grave

- Extravasamento grave de plasma, levando ao choque evidenciado por taquicardia; extremidades distais frias; pulso fraco e filiforme; enchimento capilar lento (> 2 segundos); pressão arterial convergente (< 20 mm Hg); taquipneia; oliguria (< 1,5 ml/kg/h); hipotensão arterial (fase tardia do choque); cianose (fase tardia do choque); acumulação de líquidos com insuficiência respiratória.
- Sangramento grave.
- Comprometimento grave de órgãos.

Dengue – Manifestação e manejo





Sem sinais de alarme
Com comorbidades
de risco
Com risco social

Sem sinais de alarme
Sem comorbidades
de risco
Sem risco social

Exames (Ht)

**Hidratação oral ~ 60ml/Kg/d **
manter-se euvolêmico (urina clara)

- Soro caseiro
- Sais de reidratação oral
- Sucos, água de coco

Sintomáticos

- Antitérmico*
- Analgésico*

Orientação sinais de gravidade

Dengue – Manifestação e manejo

Paracetamol

Randomized Controlled Trial > Lancet Glob Health. 2019 May;7(5):e664-e670.
doi: 10.1016/S2214-109X(19)30032-4.

Effect of standard dose paracetamol versus placebo as antipyretic therapy on liver injury in adult dengue infection: a multicentre randomised controlled trial

Vasin Vasikasin [1], Thanawith Rojdumrongrattana [2], Worayon Chuerboonchai [3], Thanawhan Siriwiwattana [2], Wittaya Thongtaeparak [2], Suchada Niyasom [4], Nawarat Lertliewtrakool [3], Sitawee Jitsiri [3], Dhitiwat Changpradub [5]

	Paracetamol (n=48)	Placebo (n=40)	Risk ratio (95% CI)	p value
Discontinuation of study medications	18 (38%)	10 (25%)	1·29 (0·88–1·87)	0·210
Elevated aspartate transaminase	18 (38%)	9 (23%)	1·36 (0·94–1·96)	0·129
Elevated alanine transaminase	14 (29%)	4 (10%)	1·60 (1·13–2·26)	0·034
Discontinuation before fever resolution	5 (10%)	6 (15%)	0·81 (0·41–1·60)	0·517
Severe dengue	3 (6%)	0	1·89 (1·55–2·31)	0·248
Upper gastrointestinal tract bleeding	2 (4%)	0	..	..
Acute kidney injury	1 (2%)	0	..	..
Shock	0	0	..	..
Liver failure	0	0	..	..
Death	0	0	..	..

Data are n (%) unless otherwise indicated.

Table 4: **Safety analyses (safety population)**

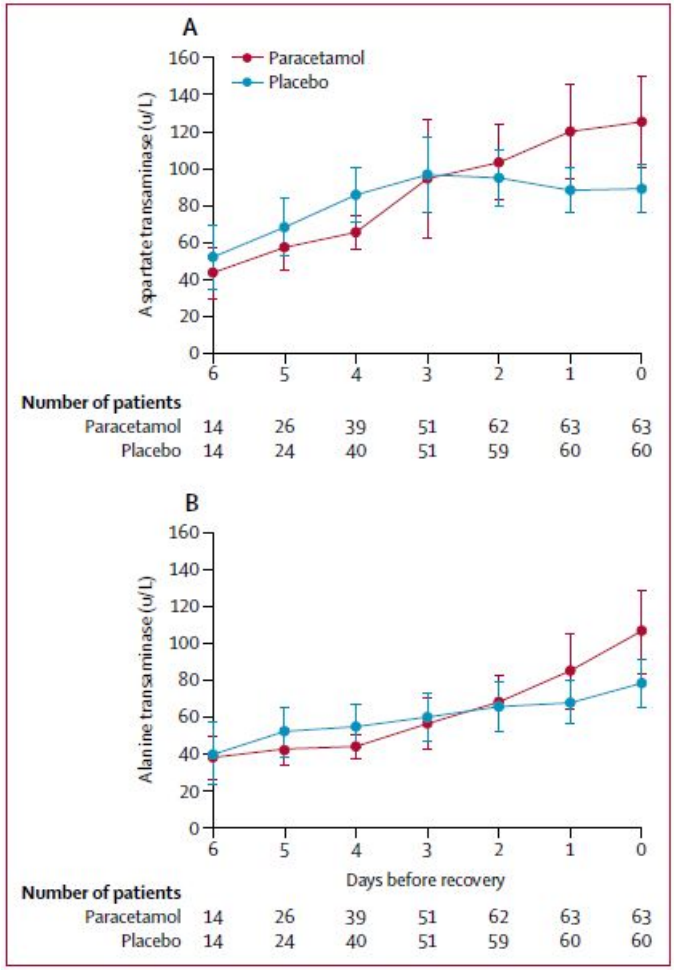


Figure 2: **Mean serum aspartate transaminase (A) and alanine transaminase (B) concentrations**
Error bars are 95% CI.

Dengue – Manifestação e manejo

Paracetamol

Rev Med Virol. 2024 Jul;34(4):e2564. doi: 10.1002/rmv.2564.

Liver involvement in dengue: A systematic review

Valentine Campana [1 2], Catherine Inizan [3], Jean-David Pommier [4], Luce Yemadje Menudier [5], Muriel Vincent [5], Marc Lecuit [6 7], Xavier De Lamballerie [8], Myrielle Dupont-Rouzeyrol [3], Bernadette Murgue [8], André Cabié [1 2]

Lesão hepática

- Mecanismo multifatorial

Uso de paracetamol

- Associada ao aumento de ALT/AST (HR 4,8 [$IC_{95\%}$ 2,4-10])
- Dose cumulativa >8g □ risco de alteração da função hepática (OR 4,62 [$IC_{95\%}$ 1,37-13])

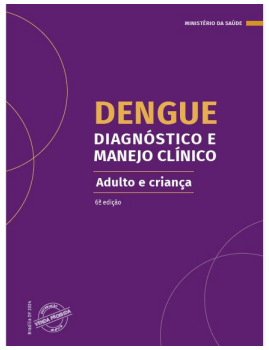
Aumento de AST/ALT

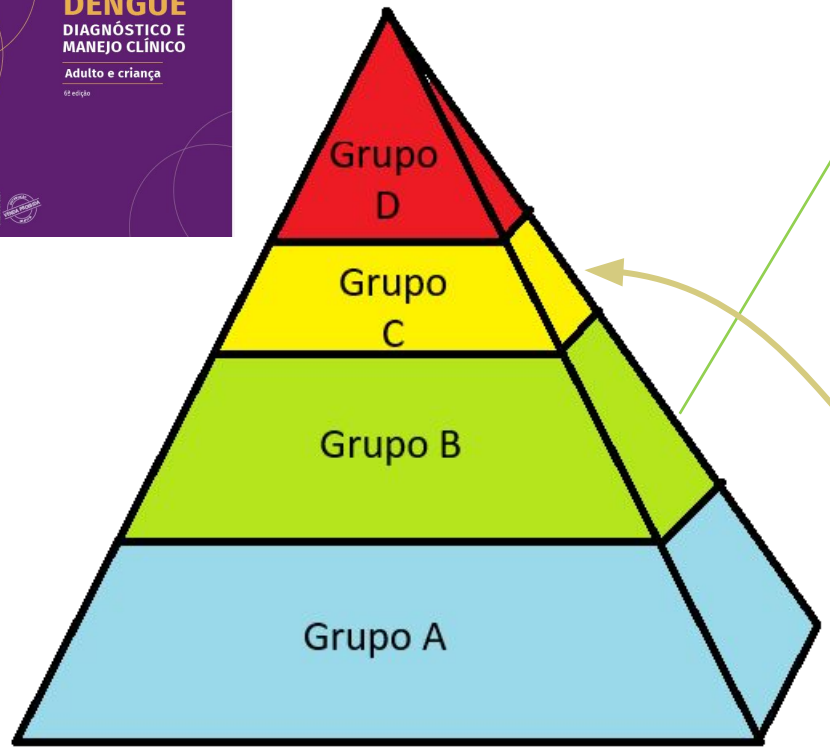
- Preditor independente de dengue grave (OR 2,67)
- Mais frequente em pacientes com choque
- Mais frequente nos casos de desfecho fatal

ALT/AST >1.000IU/L:

- 53,6 – 71% dos casos de óbito

Dengue – Manifestação e manejo



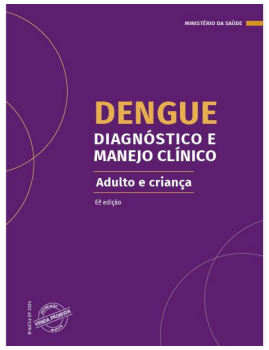


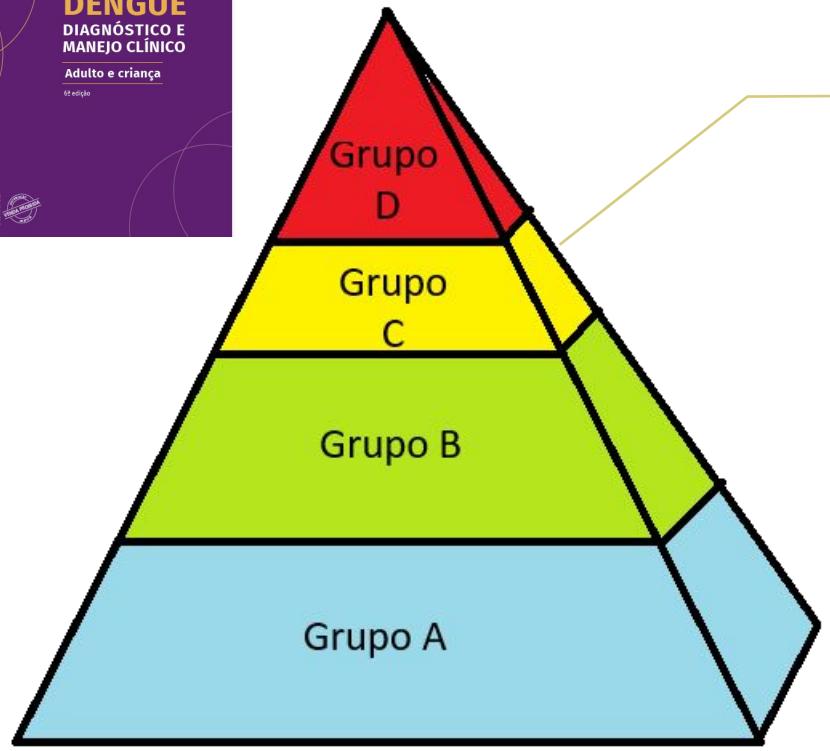
Sem sinais de alarme
Com comorbidades
de risco
Com risco social

Exames
(Ht)

Hemoconcentração
ou
sinais de alarme

Dengue – Manifestação e manejo





Sinais de alarme, sem sinais de gravidade

- Dor abdominal, vômitos
- Acúmulo de líquidos (torácica, abdominal, pericárdico)
- Hipotensão/ lipotimia
- Hepatomegalia
- Letargia e/ou irritabilidade
- ↑ progressivo de Ht

Dengue – Manifestação e manejo

Sinais de alarme, sem sinais de gravidade

- Dor abdominal, vômitos
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- Hipotensão/ lipotimia
- Hepatomegalia
- Letargia e/ou irritabilidade
- ↑ progressivo de Ht

Dor abdominal, vômitos, hepatomegalia	Hipoperfusão do trato digestivo? Lesão hepática? Sangramento?	Transaminases, lactato, Ht
Hipotensão/ Lipotimia Letargia e/ou irritabilidade	Hipovolemia intravascular? Disfunção outros órgãos?	Albumina, ureia, creatinina, eletrólitos, gasometria, ECO
Acúmulo de líquidos	Extravasamento de líquidos	Ht, exames de imagem

Dengue – Manifestação e manejo

Sinais de alarme, sem sinais de gravidade

- Dor abdominal, vômitos
- Acúmulo de líquidos (torácica, abdominal, pericárdico)
- Hipotensão/ lipotimia
- Hepatomegalia
- Letargia e/ou irritabilidade
- ↑ progressivo de Ht

RESSUSCITAÇÃO VOLÊMICA

Dor abdominal, vômitos, hepatomegalia	Hipoperfusão do trato digestivo? Lesão hepática? Sangramento?	Transaminases, lactato, Ht
Hipotensão/ Lipotimia Letargia e/ou irritabilidade	Hipovolemia intravascular? Disfunção outros órgãos?	Albumina, ureia, creatinina, eletrólitos, gasometria, ECO
Acúmulo de líquidos	Extravasamento de líquidos	Ht, exames de imagem

Dengue – Manifestação e manejo

Sinais de alarme, sem sinais de gravidade

- Dor abdominal, vômitos
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- Letargia e/ou irritabilidade
- ↑ progressivo de Ht

RESSUSCITAÇÃO VOLÊMICA

Reavaliação 2hs

Melhora dos sinais vitais (PA, nível de consciência, diurese) e laboratorial (Ht)

Reavaliação periódica e manter hidratação endovenosa

Critérios de alta:

- Estabilidade hemodinâmica 48hs
- Afebril 24hs
- Melhora clínica
- Estabilidade Ht
- Plaquetas estável/ ascensão

Dengue – Manifestação e manejo

Sinais de alarme, sem sinais de gravidade

- Dor abdominal, vômitos
- Acúmulo de líquidos (torácica, abdominal, pericárdico)
- Hipotensão/ lipotimia
- Hepatomegalia
- Letargia e/ou irritabilidade
- ↑ progressivo de Ht

RESSUSCITAÇÃO VOLÊMICA

Reavaliação 2hs

Sem melhora clínica ou Ht

RESSUSCITAÇÃO VOLÊMICA

Cuidados com grupos de risco para edema agudo dos pulmões:

- Cardiopatas
- Desnutridos
- Asmáticos
- Dialíticos

Dengue – Manifestação e manejo

Sinais de alarme, sem sinais de gravidade

- Dor abdominal, vômitos
- Acúmulo de líquidos (torácica, abdominal, pericárdico)
- Hipotensão/ lipotimia
- Hepatomegalia
- Letargia e/ou irritabilidade
- ↑ progressivo de Ht

RESSUSCITAÇÃO VOLÊMICA

Reavaliação 2hs

Sem melhora clínica ou Ht

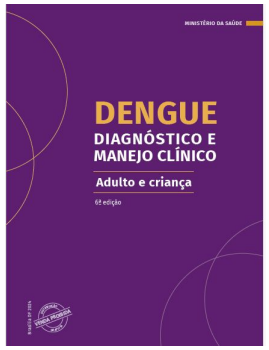
RESSUSCITAÇÃO VOLÊMICA

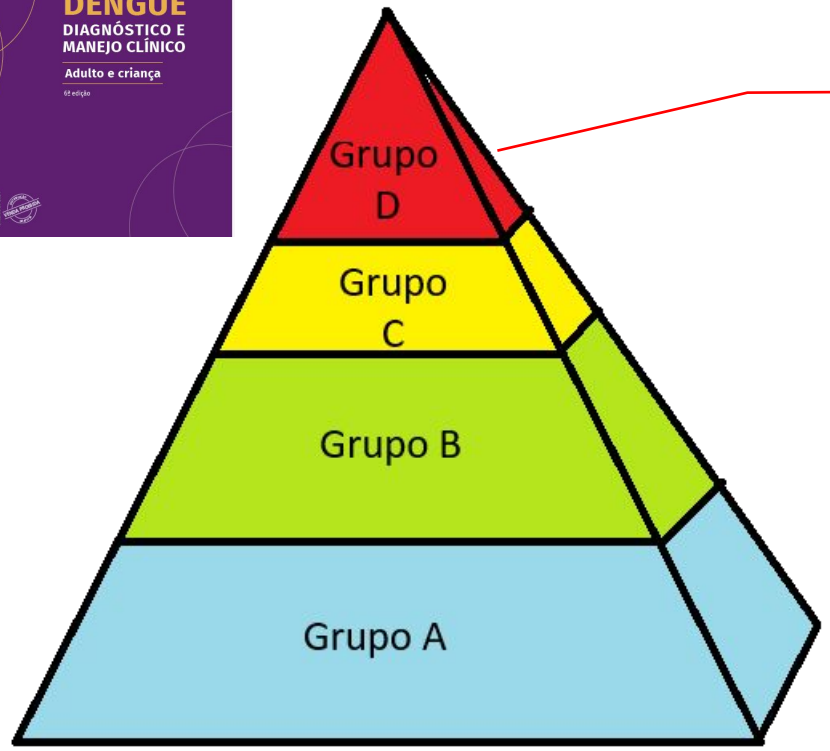
Cuidados com grupos de risco para edema agudo dos pulmões:

- Cardiopatas
- Desnutridos
- Asmáticos
- Dialíticos

"soro + albumina" UTI

Dengue – Manifestação e manejo





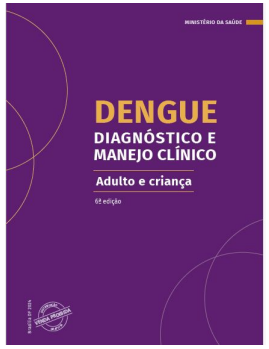
Sinais de alarme e sinais de gravidade

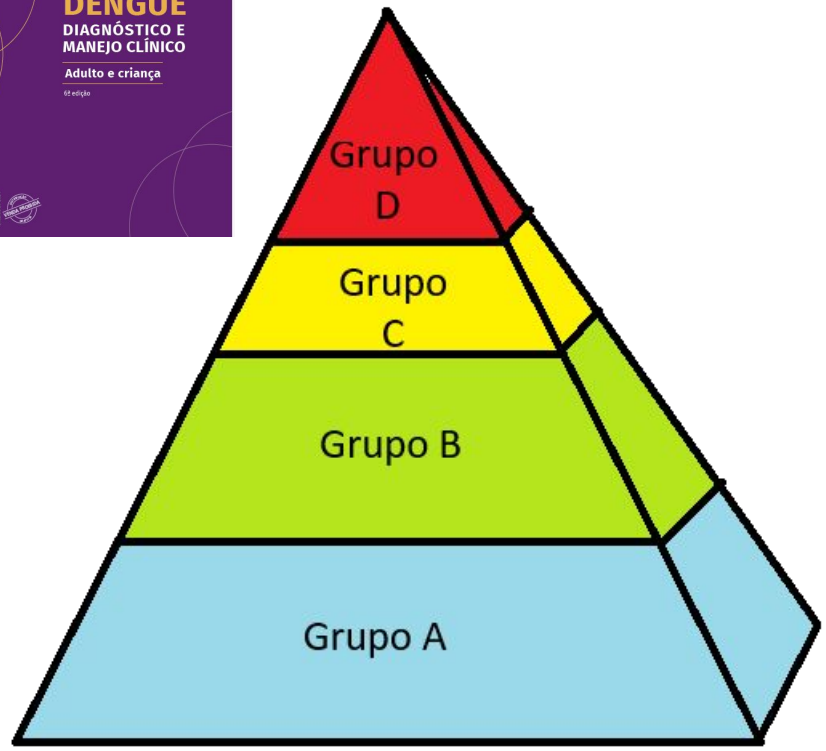
- Sinais de má perfusão periférica
- Hipotensão com pinçamento de PAs x Pad
- Choque
- Cianose
- Sangramento grave
- Disfunção de outros órgãos

UTI

RESSUSCITAÇÃO VOLÊMICA

Dengue – Manifestação e manejo





UTI

Escaneie o QRCODE e tenha acesso direto a videoaula.

Dengue – Manifestação e manejo

Transfusão profilática de plaqueta

- Transfusão profilática se plaqueta < 30 mil/µL x suporte habitual
- Randomização 1:1
- 43 grupo transfusão x 40 grupo controle

Transfusion Medicine and Hemotherapy

Original Article

Transfus Med Hemother 2013;40:362–368
DOI: 10.1159/000354837

Received: May 31, 2012
Accepted: December 13, 2012
Published online: September 11, 2013

Effectiveness of Platelet Transfusion in Dengue Fever: A Randomized Controlled Trial

Muhammad Zaman Khan Assir[a] Umair Kamran[a] Hafiz Ijaz Ahmad[b] Sadia Bashir[a]
Hassan Mansoor[a] Saad Bin Anees[a] Javed Akram[c]

Summary

Background: Scientific data regarding effects of platelet transfusion on platelet count in dengue-related thrombocytopenia is scanty. **Methods**: A single center, randomized non-blinded trial was conducted on adult patients with dengue fever and platelet counts less than 30,000/µl. Patients were randomized to treatment and control group. Treatment group received single donor platelets. Patients with post-transfusion platelet increment (PPI) ≥10,000/µl and/or corrected count increment (CCI) ≥5,000/µl 1 h post-transfusion were considered responders. Primary outcome was platelet count increments at 24 and 72 h. **Results**: 87 patients were enrolled, and 43 (48.2%) received platelet transfusion. Mean PPI and CCI at 1 h post-transfusion in the treatment group were 18,800/µl and 7,000/µl respectively. 22 (53.6%) patients in the treatment group were non-responders. more likely to be non-responders. Platelet transfusion neither prevented development of severe bleeding nor shortened time to cessation of bleeding. Three severe transfusion reactions and two deaths occurred in treatment group. **Conclusion**: In this trial, almost half the patients showed no response to a high-dose platelet transfusion. Platelet transfusion did not prevent development of severe bleeding or shorten time to cessation of bleeding and was associated with significant side effects. Therefore, platelet transfusion should not be routinely done in the management of dengue fever.

Dengue – Manifestação e manejo

Transfusão profilática de plaqueta

- Transfusão de plaqueta profilática se < 20mil/µL x suporte habitual
- Randomização 1:1
- 182 grupo controle x 187 grupo transfusão

Prophylactic platelet transfusion plus supportive care versus supportive care alone in adults with dengue and thrombocytopenia: a multicentre, open-label, randomised, superiority trial

David C Lye, Sophia Archuleta, Sharifah F Syed-Omar, Jenny G Low, Helen M Oh, Yuan Wei, Dale Fisher, Sasheela S L Ponnampalavanar, Limin Wijaya, Linda K Lee, Eng-Eong Ooi, Adeeba Kamarulzaman, Lucy C Lum, Paul A Tambyah, Yee-Sin Leo

	By day 7 or hospital discharge	
	Transfusion group (n=187)	Control group (n=182)
Total	40 (21%)	48 (26%)
Gingival	21 (11%)	32 (17%)
Epistaxis	8 (4%)	9 (5%)
Haemoptysis	3 (2%)	1 (1%)
Haematuria	0	1 (1%)
Haematemesis	0	0
Melaena	0	4 (2%)
Haematemesis or melaena not controlled by endoscopic procedure	0	0
Menorrhagia	0	2 (1%)
Inter-menstrual bleed	0	1 (1%)
Menorrhagia or inter-menstrual bleed not controlled by progesterone	0	0
Haematoma	7 (4%)	8 (4%)
Usual menses	4 (2%)	4 (2%)
Others	4 (2%)	2 (1%)

	By day 21	
	Transfusion group (n=187)	Control group (n=182)
Total	42 (22%)	49 (27%)
Gingival	21 (11%)	33 (18%)
Epistaxis	8 (4%)	9 (5%)
Haemoptysis	3 (2%)	1 (1%)
Haematuria	0	1 (1%)
Haematemesis	0	0
Melaena	0	4 (2%)
Haematemesis or melaena not controlled by endoscopic procedure	0	0
Menorrhagia	0	2 (1%)
Inter-menstrual bleed	0	1 (1%)
Menorrhagia or inter-menstrual bleed not controlled by progesterone	0	1 (1%)
Haematoma	7 (4%)	8 (4%)
Usual menses	6 (3%)	4 (2%)
Others	4 (2%)	2 (1%)

Dengue – Manifestação e manejo

Transfusão profilática de plaqueta

- 11 estudos; 1904 pacientes
- Sem evidência do benefício de transfusão profilática de plaqueta
- SEM evidência do benefício de transfusão plaqueta + PFC

Trans R Soc Trop Med Hyg 2017; **111**: 433–439
doi:10.1093/trstmh/trx079 Advance Access publication 29 January 2018

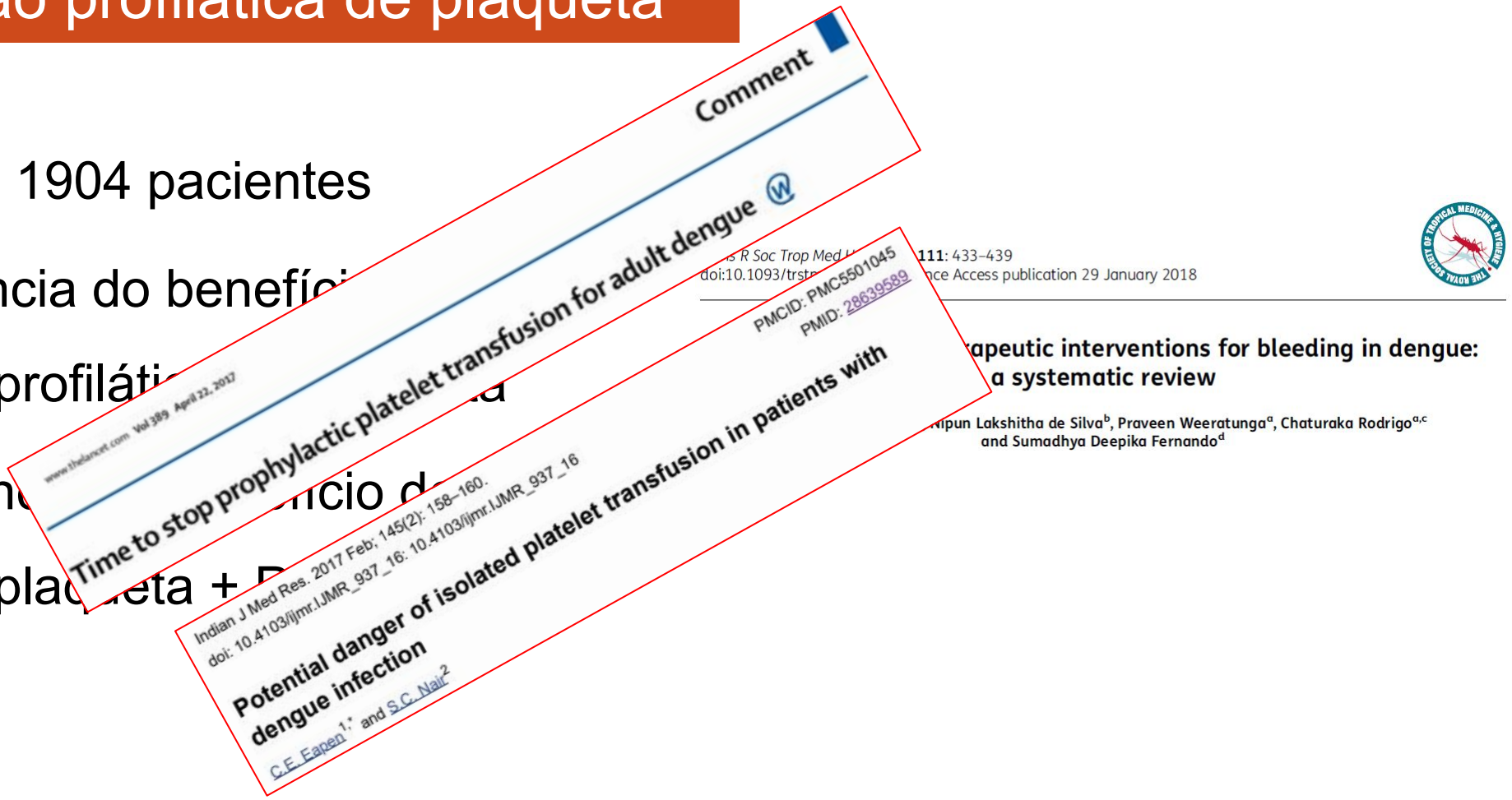
Prophylactic and therapeutic interventions for bleeding in dengue: a systematic review

Senaka Rajapakse[a,*], Nipun Lakshitha de Silva[b], Praveen Weeratunga[a], Chaturaka Rodrigo[a,c] and Sumadhya Deepika Fernando[d]

Dengue – Manifestação e manejo

Transfusão profilática de plaqueta

- 11 estudos; 1904 pacientes
- Sem evidência do benefíci
  transfusão profiláti
- SEM evidên ncio d
  transfusão pla eta +



FEBRE CHIKUNGUNYA

CHIKUNGUNYA - FISIOPATOGENIA

Patogenia

- CHIKV infecta fibroblastos, queratinócitos e células endoteliais na pele Exantema
- Disseminação Sistêmica: linfonodos, fígado, baço, SNC, fibroblastos cardíacos
- Destruição Tecidual: A infecção de células musculares e sinoviais causa necrose tecidual e dor articular.

CHIKUNGUNYA - FISIOPATOGENIA

Resposta Imune após infecção viral:

- **Ativação imune:** A infecção ativa respostas imunes inatas, incluindo a produção de interferons e citocinas pró-inflamatórias (IL-6, RANKL).
- **Evasão Imune:** CHIKV suprime a sinalização JAK-STAT e a formação de grânulos de estresse para evitar a resposta imune.
- **Inflamação Crônica:** A persistência de RNA viral e antígenos em macrófagos sinoviais e fibroblastos contribui para a inflamação crônica e a artralgia.

CHIKUNGUNYA - FISIOPATOGENIA

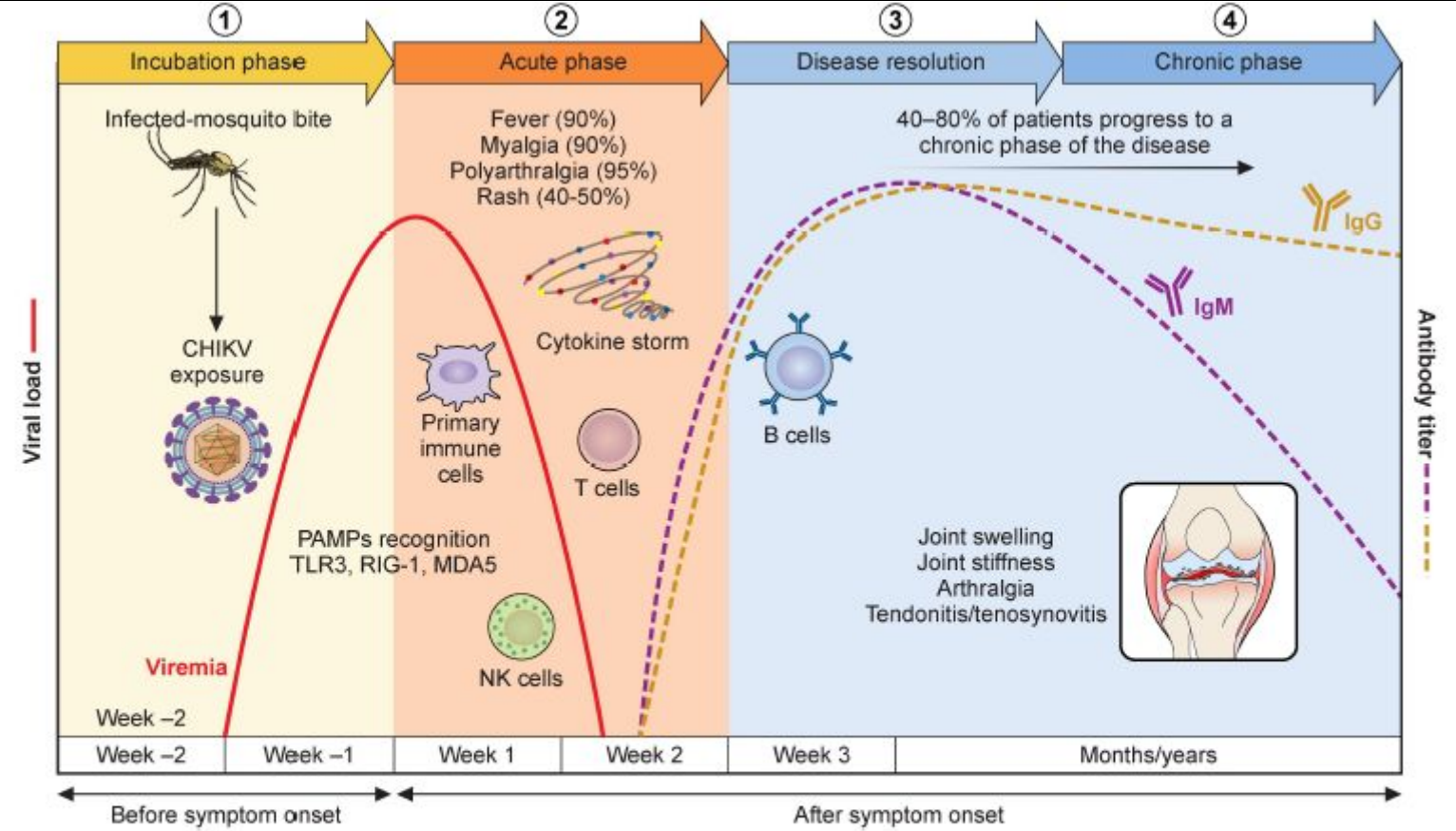


Figure 3. Timeline of chikungunya virus pathogenesis.

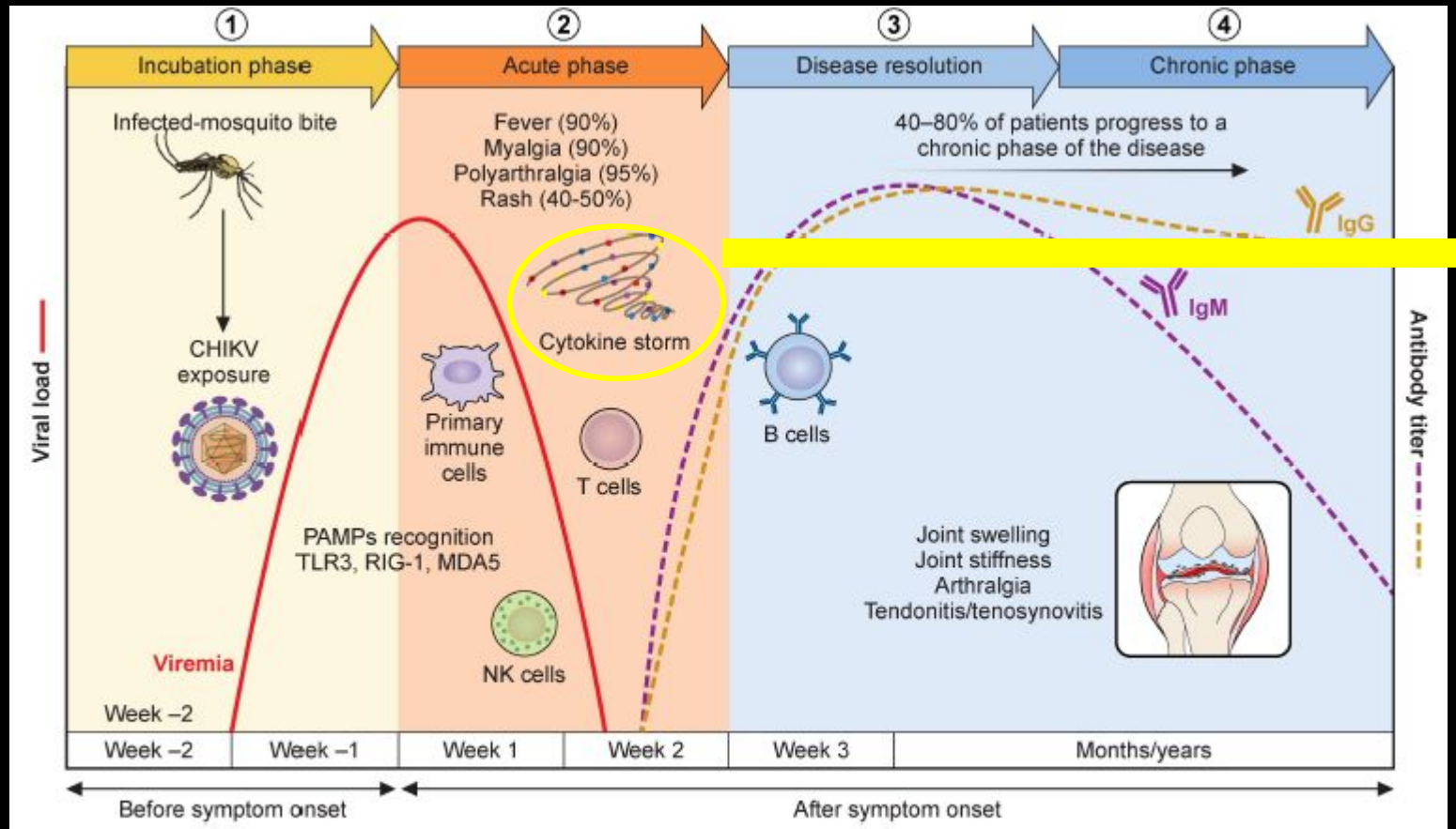
Schematic of the timeline of CHIKV-induced disease divided into four phases: incubation, acute, disease, resolution, and chronic illness. Typical viral load (pink line), symptoms, cytokine storm, involved immune cells, and antibody titres (orange and purple dotted lines) are depicted along the infection timeline.

Review > Virulence. 2024 Dec;15(1):2396484. doi: 10.1080/21505594.2024.2396484. Epub 2024 Sep 1.

Pathogenicity and virulence of chikungunya virus

Wesley Freppel [1], Laurie A Silva [2], Kenneth A Stapleford [3], Lara J Herrero [1]

CHIKUNGUNYA - FISIOPATOGENIA



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Manifestações agudas graves

Review > Virulence. 2024 Dec;15(1):2396484. doi: 10.1080/21505594.2024.2396484. Epub 2024 Sep 1.

Pathogenicity and virulence of chikungunya virus

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CHIKUNGUNYA – Clínica e manejo

PLoS One. 2022 Apr 7;17(4):e0260939. doi: 10.1371/journal.pone.0260939. eCollection 2022.

Chikungunya Death Risk Factors in Brazil, in 2017: A case-control study

Rhaquel de Morais Alves Barbosa Oliveira [1], Francisca Kalline de Almeida Barreto [1], Geovana Praça Pinto [2], Isabella Timbó Queiroz [2], Fernanda Montenegro de Carvalho Araújo [2 3], Kilma Wanderley Lopes [4], Regina Lúcia Sousa do Vale [4], Daniele Rocha Queiroz Lemos [2], John Washington Cavalcante [5 6], André Machado Siqueira [7], Lívia Carla Vinhal Frutuoso [8 9], Elisabeth Carmen Duarte [8], Antônio Silva Lima Neto [4], André Ricardo Ribas Freitas [10], Luciano Pamplona de Góes Cavalcanti [1 2 5]

Fatores relacionados ao risco de óbito (82 óbitos x 164 vivos)

- Cardiopatias crônicas (OR 3,8)
- Insuficiência renal crônica (OR 12,77)
- Dor abdominal (OR 3,74)
- Apatia (OR 11,62)
- Dispneia (OR 50,61)

CHIKUNGUNYA – Clínica e manejo

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CHIKUNGUNYA – Clínica e manejo

Indian J Crit Care Med. 2018 Jan;22(1):5-9. doi: 10.4103/ijccm.IJCCM_336_17.

Clinical Profile, Intensive Care Unit Course, and Outcome of Patients Admitted in Intensive Care Unit with Chikungunya

Anish Gupta [1], Deven Juneja [1], Omender Singh [1], Suneel Kumar Garg [1], Varun Arora [1], Desh Deepak [1]

Table 1: Most common presenting complaints (*n*=60)

Parameter	*n* (%)
Fever	58 (96.67)
Altered mental status	34 (56.67)
Joint pains	23 (38.33)
Breathlessness	18 (30)
Vomiting	12 (20)
Oligura/anuria	8 (13.33)
Cough	7 (11.67)
Rash	5 (8.33)
Loose motions	5 (8.33)
Seizure	4 (6.67)
Bleeding	2 (3.33)
Abdominal pain	2 (3.33)
Hemiparesis	1 (1.67)
Quadriparesis	1 (1.67)
Chest pain	1 (1.67)

Table 2: Intensive Care Unit admission criteria (*n*=60)

ICU admission criteria	*n* (%)
Altered mental status	31 (51.67)
Sepsis and shock	10 (16.67)
Respiratory failure	9 (15)
Post-CPR status	3 (5)
Seizures	2 (3.33)
Arrhythmia	1 (1.67)
Myasthenia crisis	1 (1.67)
AKI	1 (1.67)
GBS	1 (1.67)
Hemiparesis	1 (1.67)

ICU: Intensive Care Unit; CPR: Cardiopulmonary resuscitation; AKI: Acute kidney injury; GBS: Guillain-Barré Syndrome

CHIKUNGUNYA – Clínica e manejo

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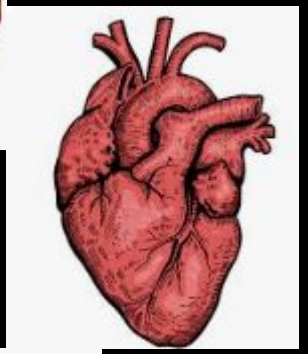
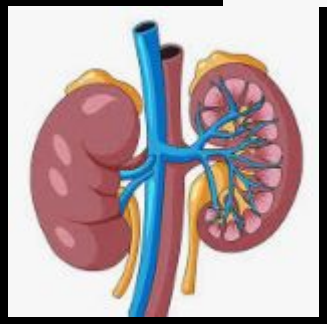
Table 3: Comparison of baseline patient characteristics between survivors and nonsurvivors

Parameter	Overall ($n=60$), n (%)	Survivors ($n=38$), n (%)	Nonsurvivors ($n=22$), n (%)	P
Age (years)	65.72±17.4	63.05±19.3	70.32±12.8	0.12
Gender				
Male	43	25	18	0.241
Female	17	13	4	
Comorbidities	51 (85)	32 (84.21)	19 (86.36)	0.822
APACHE II score	17.28±7.9	12.84±5.3	24.96±5.6	<0.0001
SOFA score	7.15±4.2	5.05±2.6	10.95±3.7	<0.0001
Cardiovascular failure	22 (36.67)	7 (18.42)	15 (68.18)	<0.0001
Respiratory failure	17 (28.3)	5 (13.16)	12 (54.55)	0.001
Renal failure	15 (25)	2 (0.35)	13 (56.52)	<0.0001
Neurology failure	15 (25)	8 (21.05)	7 (31.82)	0.372
Coagulation failure	7 (11.67)	1 (2.63)	6 (27.27)	0.004
Hepatobiliary failure	Nil	Nil	Nil	NA
Lactate	2.88±3.3	2.02±1.91	4.37±4.6	0.004
Vasopressor support	28 (46.67)	11 (28.95)	17 (77.27)	<0.0001
Renal replacement therapy	16 (26.67)	1 (2.63)	15 (68.18)	<0.0001
Mechanical ventilation	35 (58.33)	15 (39.47)	20 (90.91)	<0.0001
ICU length of stay	10.23±10.9	10.39±11.4	9.95±10.2	0.881
Hospital length of stay	15.15±13.1	15.79±13.6	14.04±12.4	0.624
Number of days on MV	5.88±9.5	5.03±10	7.36±8.5	0.363
Number of sessions of RRT	0.9±2.3	0.026±0.16	2.41±3.3	<0.0001
Number of days on vasopressors	2.1±3.2	1.11±2.1	3.82±4	<0.0001

$P<0.05$ is considered significant. APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential organ failure assessment; MV: Mechanical ventilation; RRT: Renal replacement therapy; NA: Not available; ICU: Intensive Care Unit





CHIKUNGUNYA – Clínica e manejo

Review › Trop Med Infect Dis. 2021 Jun 22;6(3):108. doi: 10.3390/tropicalmed6030108.

Cardiomyopathy and Death Following Chikungunya Infection: An Increasingly Common Outcome

Elizabeth M Traverse [1], Hannah K Hopkins [1], Vedana Vaidhyanathan [2], Kelli L Barr [1]

Abstract: Chikungunya virus (CHIKV) is vectored by *Aedes aegypti* and *Aedes albopictus* mosquitoes and is found throughout tropical and sub-tropical regions. While most infections cause mild symptoms such as fever and arthralgia, there have been cases in which cardiac involvement has been reported. In adults, case reports include symptoms ranging from tachycardia and arrythmia, to myocarditis and cardiac arrest. In children, case reports describe symptoms such as arrythmia, myocarditis, and heart failure. Case reports of perinatal and neonatal CHIKV infections have also described cardiovascular compromise, including myocardial hypertrophy, ventricular dysfunction, myocarditis, and death. Myocarditis refers to inflammation of the heart tissue, which can be caused by viral infection, thus becoming viral myocarditis. Since viral myocarditis is linked as a causative factor of other cardiomyopathies, including dilated cardiomyopathy, in which the heart muscle weakens and fails to pump blood properly, the connection between CHIKV and the heart is concerning. We searched Pubmed, Embase, LILACS, and Google Scholar to identify case reports of CHIKV infections where cardiac symptoms were reported. We utilized NCBI Virus and NCBI Nucleotide to explore the lineage/evolution of strains associated with these outbreaks. Statistical analysis was performed to identify which clinical features were associated with death. Phylogenetic analysis determined that CHIKV infections with cardiac symptoms are associated with the Asian, the East Central South African, and the Indian Ocean lineages. Of patients admitted to hospital, death rates ranged from 26–48%. Myocarditis, hypertension, pre-existing conditions, and the development of heart failure were significantly correlated with death. As such, clinicians should be aware in their treatment and follow-up of patients.

Keywords: CHIKV; chikungunya; myocarditis; cardiomyopathy; cardiovascular

- Relatos de casos de taquiarritmia e arritmia, miocardite e parada cardíaca em adultos
- Os mesmos quadros em crianças
- Em recém-nascidos, miocardiopatia hipertrófica, disfunção ventricular, miocardite grave e óbito por disfunção cardíaca

CHIKUNGUNYA – Clínica e manejo

Acta Trop. 2023 Jan:237:106705. doi: 10.1016/j.actatropica.2022.106705. Epub 2022 Sep 30.

High levels of cardiovascular biomarkers in fatal Chikungunya virus infection

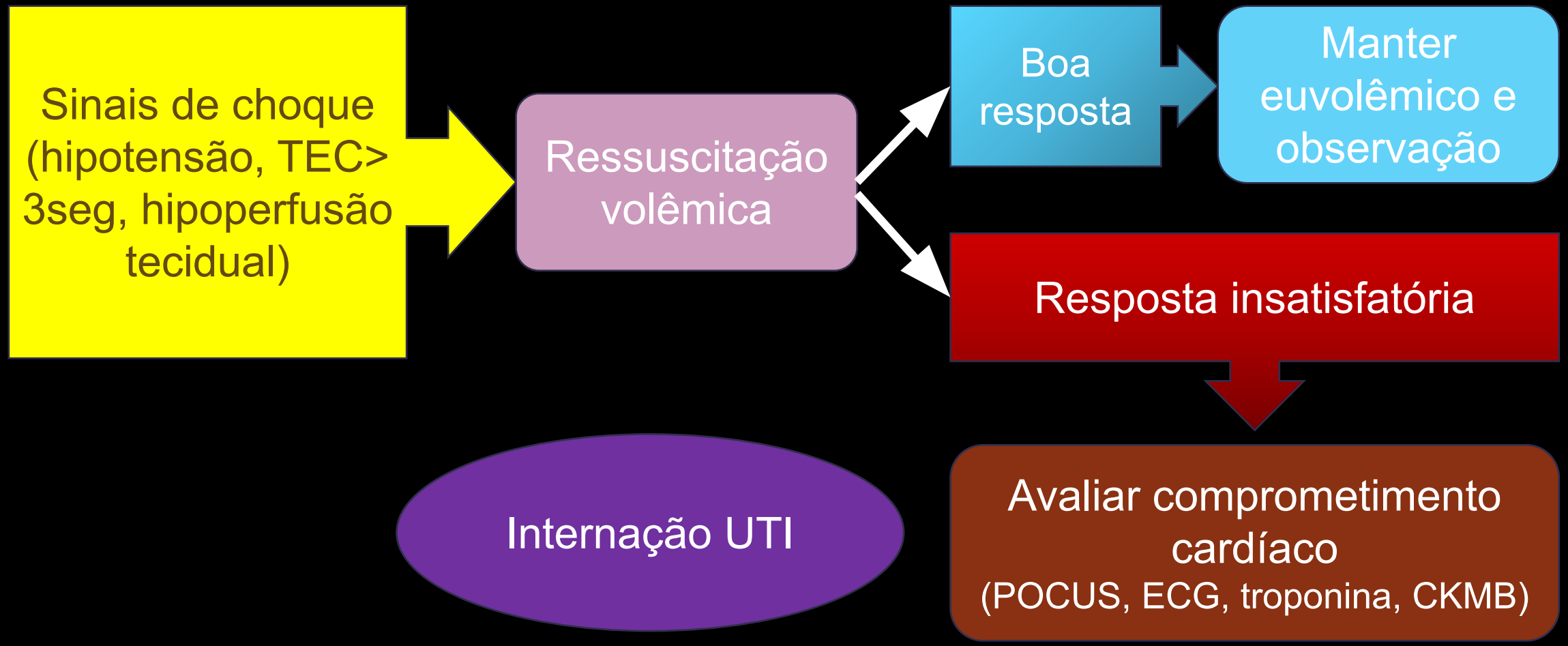
Jorge Acosta-Reyes [1], Angélica Rico [2], Brayan Bayona-Pacheco [3], Edgar Navarro-Lechuga [4], Fabian Leonardo Muñoz [5], Alfonso Campo [6], Karen Beracaza [3], Diego Viasus [3], Marcela Mercado [7]

Table 2
Levels of cardiovascular biomarkers between fatal and no fatal patients with Chikungunya viral infections, Colombia.

Cardiovascular biomarker	Cases (fatal patients) median	IQR	Controls (no fatal patients) median	IQR	P value**
B-type natriuretic peptide (BNP)	68.6	6.86–415.6	68.6	68.6–248.9	0.893
Creatine kinase MB isoenzyme (CK-MB)	50,000	26,259.6–50,000	2086.4	1051.4–50,000	0.000
Chemokine ligand 6 (CXCL6/GCP-2)	174.5	91.5–386.8	143	102.3–182.9	0.254
Endocan-1	6232.4	4152.8–10,524.2	2605.3	1923.8–4389.6	0.000
Fatty-acid-binding protein 3 (FABP3)	100,000	69,999.1–100,000	2782.3	1756.9–5483.1	0.000
Fatty-acid binding protein 4 (FABP4)	276,476.0	38,222.9–500,000	11,640.9	7024.3–18,572.8	0.000
N-terminal pro b-type natriuretic peptide (NTproBNP)	599.7	301.9–774.6	510.4	331.3–850.4	0.673
Oncostatin-M (OSM)	103.2	55.8–174.9	27.8	14.8–45.2	0.000
Troponin I	292.2	68.6–795.7	88.9	68.6–513.2	0.063

** Mann-Whitney U test.

CHIKUNGUNYA – Clínica e manejo



CHIKUNGUNYA – Clínica e manejo

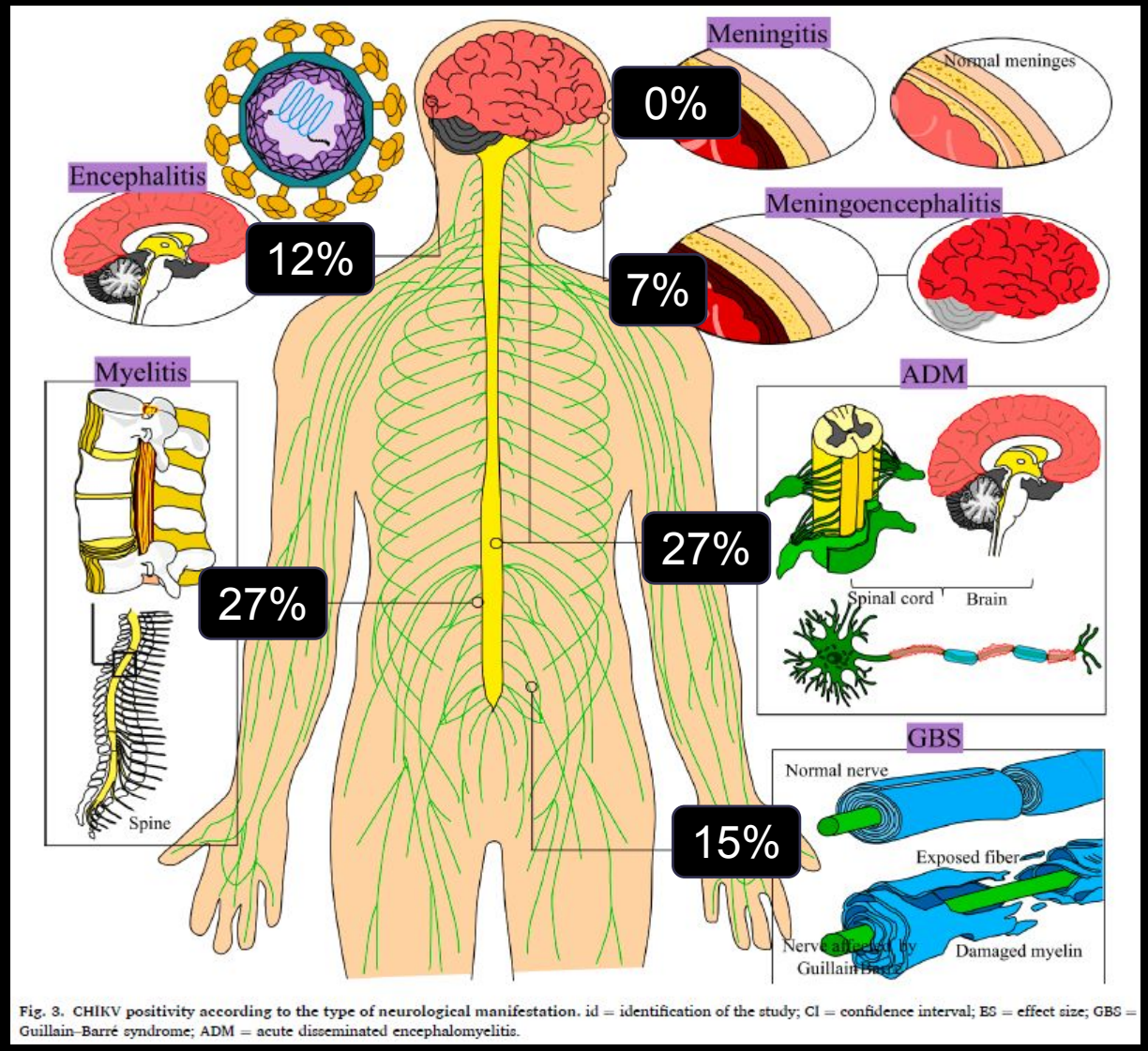


Fig. 3. CHIKV positivity according to the type of neurological manifestation. id = identification of the study; CI = confidence interval; ES = effect size; GBS = Guillain–Barré syndrome; ADM = acute disseminated encephalomyelitis.

Meta-Analysis > Infect Dis Now. 2024 Aug;54(5):104938. doi: 10.1016/j.idnow.2024.104938. Epub 2024 Jun 15.

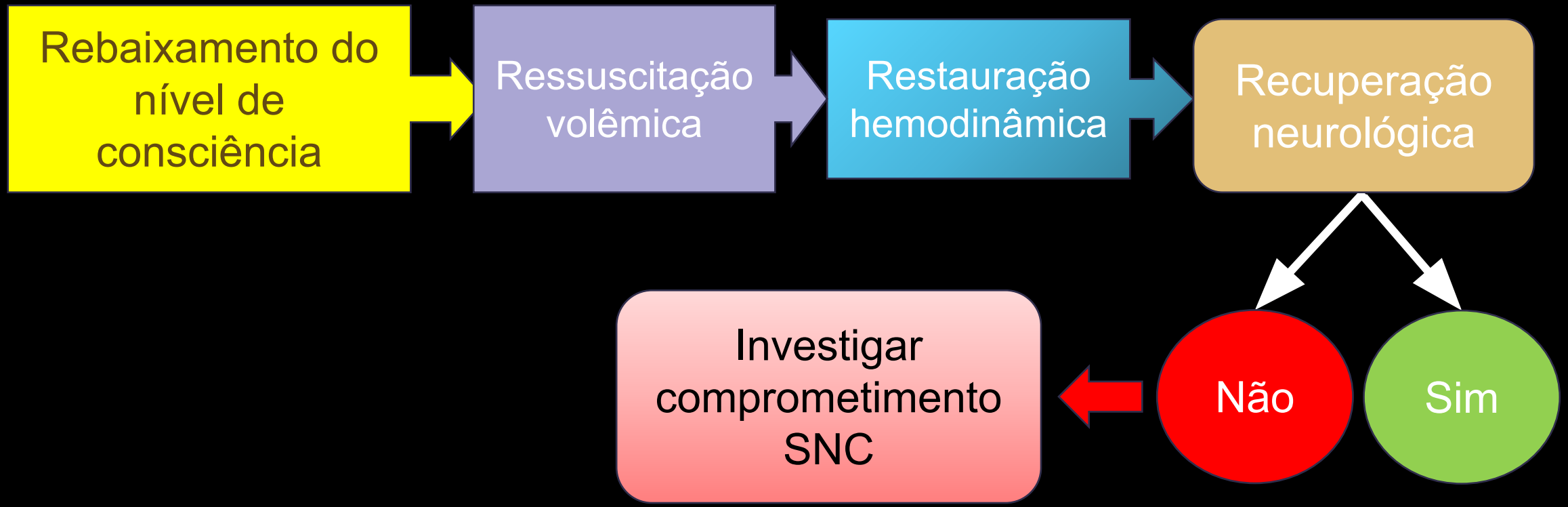
A meta-analysis of Chikungunya virus in neurological disorders

Vivaldo G da Costa [1], Marielena V Saivish [2], Paola F Sinhorini [3], Maurício L Nogueira [4], Paula Rahal [5]

Revisão sistemática e meta-análise

- 19 artigos (2009 a 2022) 7.319 pacientes
- Ocorrência de alteração neurológica: 12% ($IC_{95\%}$ 6-19)

CHIKUNGUNYA – Clínica e manejo



CHIKUNGUNYA – Clínica e manejo

> J Pediatric Infect Dis Soc. 2024 Oct 3:piae102. doi: 10.1093/jpids/piae102. Online ahead of print.

Perinatal and Neonatal Chikungunya virus Transmission: a case series

A Fátima C P A Di Maio Ferreira [1], Ana M Bispo de Filippis [2], Maria Elisabeth L Moreira [3], Simone B de Campos [4], Trevon Fuller [5], Fernanda C R Lopes [6], Patrícia Brasil [7]

- 58 gestantes (1 assintomática)
- 17 infecção durante 1º/2º trimestre todos RN negativos
- 41 infecção no 3º trimestre (1 assintomática)
  - 12 infecção > 7 dias do parto RN negativos
  - 29 infecção próximo do parto
    - 2 RN termo, negativos
    - 9 RN com sintomas, mas não confirmou infecção (falso negativo?)
    - 18 PCR/IgM positivo

CHIKUNGUNYA – Clínica e manejo

Sintomas nos RN

- Hipoatividade (25%)
- Febre (22%)
- Encefalite (18%)
- Rash (18%)
- Insuf. Respiratória (18%)
- Irritabilidade (12%)
- Hipercromia (12%)
- Lesão vesico-bolhosa (12%)
- Apneia (8%)
- Baixo ganho de peso (5%)

Alteração laboratorial: plaquetopeni
CIVD (40%)

J Pediatric Infect Dis Soc. 2024 Oct 3:piae102. doi: 10.1093/jpids/piae102. Online ahead of print.

Perinatal and Neonatal Chikungunya virus Transmission: a case series

A Fátima C P A Di Maio Ferreira [1], Ana M Bispo de Filippis [2], Maria Elisabeth L Moreira [3], Simone B de Campos [4], Trevon Fuller [5], Fernanda C R Lopes [6], Patrícia Brasil [7]

Figure 3. Clinical manifestations of CHIKV infection in neonates. (A) Post chikungunya pigmentary disorder, (B) chik sign, (C) scaled skin syndrome like presentation, (D) irritability and crusty perioral lesions, (E) roseoliform rash and respiratory distress, and (F) vesicolobullous lesions.

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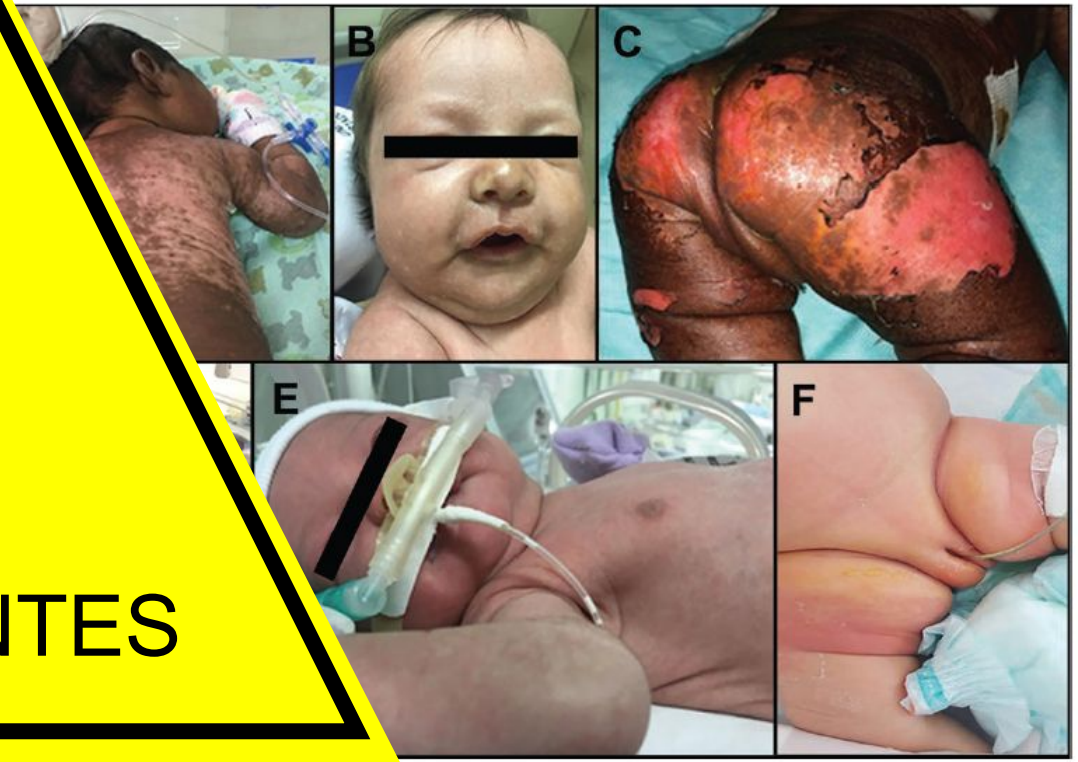

Figure 3. Clinical manifestations of CHIKV infection in neonates. (A) Post chikungunya pigmentary disorder, (B) chik sign, (C) scaled skin syndrome like presentation, (D) irritability and crusty perioral lesions, (E) roseoliform rash and respiratory distress, and (F) vesicolobullous lesions.

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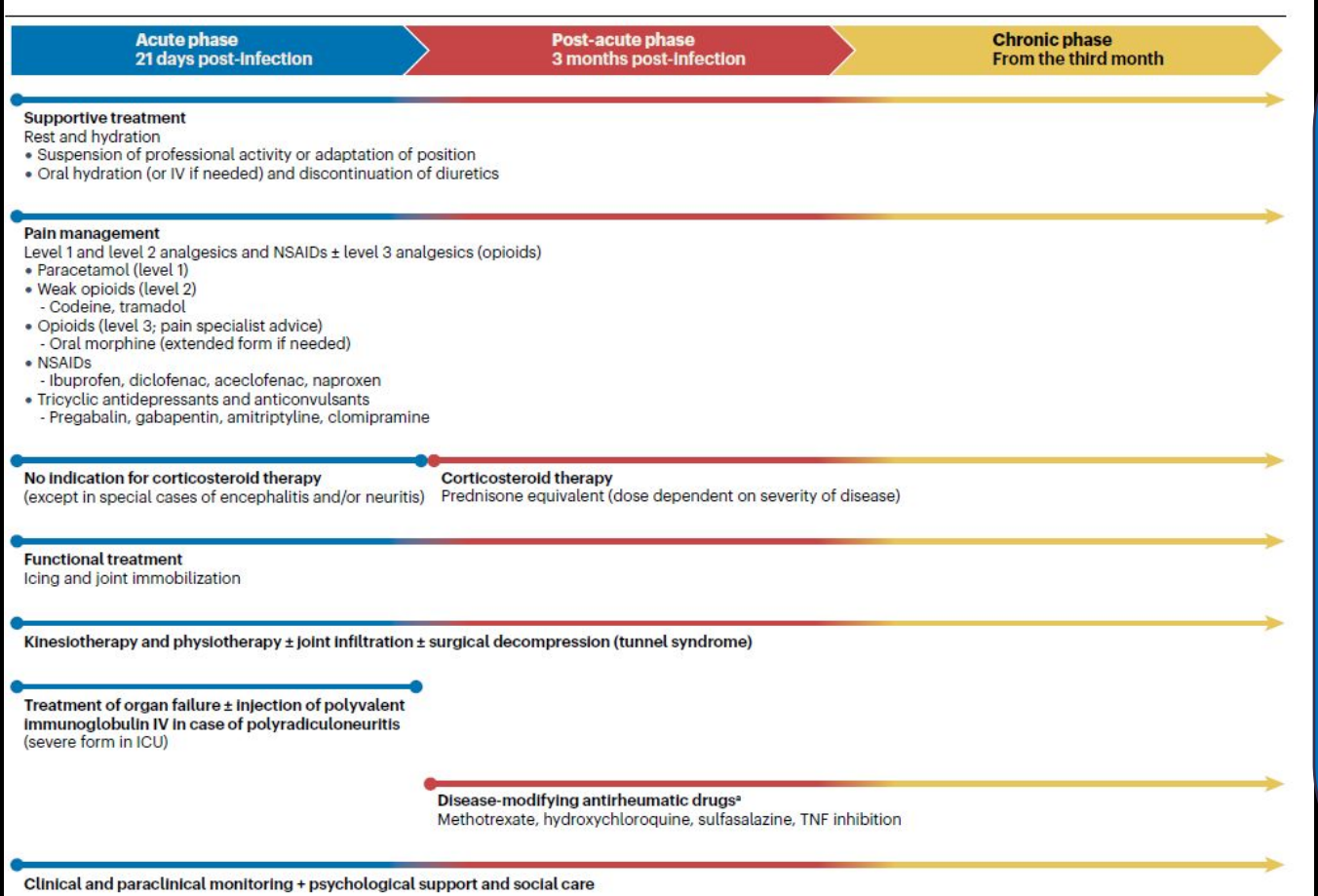
GESTANTES

CHIKUNGUNYA – Clínica e manejo



Manejo da dor (fase aguda: 21d)

- Repouso e hidratação oral
- Analgésicos (dipirona/ paracetamol)
- Opioides fracos (codeína, tramadol)
- AINE (ibuprofeno, diclofenaco, naproxena...)
- Tricíclicos (pregabalina, gabapentina, amitriptilina)
- Não utilizar corticosteroides na fase aguda

Bartholomeeusen et al. Chikungunya fever. Nat Rev Dis Primes 2023

CHIKUNGUNYA – Clínica e manejo

FEBRE DE OROPOUCHE

Oropouche

- Fisiopatogenia
- Histologia
- Manifestações clínicas
- Tratamento

Oropouche

Review > Viruses. 2018 Apr 4;10(4):175. doi: 10.3390/v10040175.

Oropouche Fever: A Review

Hercules Sakkas [1,2], Petros Bozidis [3], Ashley Franks [4], Chrissanthy Papadopoulou [5]

Modelos animais

Neuroinvasiva

Lesão hepatocelular

Aborto
Transmissão fetal

Oropouche

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Transmissão fetal

Modelos animais

E em humanos???

Oropouche

Review > Lancet Infect Dis. 2024 Jul;24(7):e439-e452. doi: 10.1016/S1473-3099(23)00740-5. Epub 2024 Jan 25.

Emergence of Oropouche fever in Latin America: a narrative review

Konrad M Wesselmann [1], Ignacio Postigo-Hidalgo [2], Laura Pezzi [3], Edmilson F de Oliveira-Filho [2], Carlo Fischer [2], Xavier de Lamballerie [3], Jan Felix Drexler [4]

Quadro clínico

- Incubação 3~10 dias
- Febre, cefaleia, artralgia, mialgia, calafrios
- Náusea, vômito
- Fotofobia, dor retro-orbitária
- Exantema

Sintomáticos (evitar medicações hepatotóxicas)

Evolução bifásica (recrudescência dos sintomas (1ª fase 2-4 dias, 2ª fase a partir de 7~10 dias do início, duração até 1 mês)

Oropouche

Review > Lancet Infect Dis. 2024 Jul;24(7):e439-e452. doi: 10.1016/S1473-3099(23)00740-5. Epub 2024 Jan 25.

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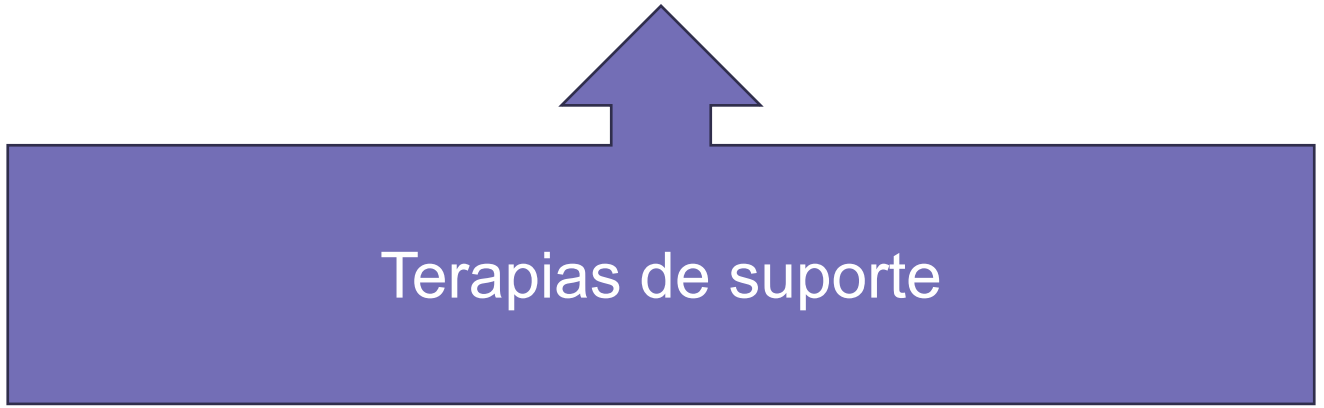
Complicações

- Comprometimento SNC (meningite asséptica ou meningoencefalite)
- Fenômenos hemorrágicos



Oropouche

Case Reports > Emerg Infect Dis. 2024 Nov;30(11):2370-2374. doi: 10.3201/eid3011.241132. Epub 2024 Sep 13.

Fatal Oropouche Virus Infections in Nonendemic Region, Brazil, 2024

Antonio Carlos Bandeira, Felicidade Mota Pereira, Arabela Leal, Sara P O Santos, Ana Claudia Barbosa, Marcia Sao Pedro Leal Souza, Daniele Ribeiro de Souza, Natalia Guimaraes, Vagner Fonseca, Marta Giovanetti, Luiz Carlos Junior Alcantara, André Alvarez A Lessa, Ramon Costa Saavedra, Luiz Marcelo R Tomé, Felipe Campos M Iani, Rivia Mary Barros, Sandra Maria O Purificação, Jaciara Prado de Jesus, Ricardo Rosário Fonseca, Marcio Luis Valença Araújo

Table 1. Laboratory results for patient 1 in a case of fatal Oropouche virus infections in nonendemic region, Brazil, 2024*

Variable	Time after admission	
	6 hours	13 hours
Hematocrit, %	50.3	20.9
Hemoglobin, %	16.7	7.0
Mean corpuscular volume, fL (reference <80 fL)	82	88
Mean corpuscular hemoglobin, pg (reference 27–31 pg)	27	29
Leukocytes, cells/mm^3	44,700	24,500
Neutrophils, %	71	80
Band forms, %	8	10
Metamyelocytes, %	1	1
Lymphocytes, %	16	6
Platelets, cells/mm^3	125,000	43,000
Bleeding time, min	ND	1
Clotting time, min	ND	>30
Clot retraction	ND	Complete
Aspartate aminotransferase, U/L	ND	970
Alanine aminotransferase, U/L	7	404
GGT, U/L	559	144
TB/DB, mg/dL	2.78/1.52	ND
Creatinine, mg/dL	4.1	2.3

*GGT, gamma-glutamyl transferase; ND, not done; TB/DB, total bilirubin/direct bilirubin.

Table 2. Laboratory test results for patient 2 in a case of fatal Oropouche virus infections in nonendemic region, Brazil, 2024*

Variable	Time after admission	
	At admission	10 hours
Hematocrit, %	38.7	43.7
Hemoglobin, %	13.5	14.0
Mean corpuscular volume, fL (reference <80 fL)	86	82
Mean corpuscular hemoglobin, pg (reference 27–31 pg)	30	26
Leukocytes, cells/mm^3	9,500	19,400
Neutrophils, %	59	58
Band forms, %	0	0
Metamyelocytes, %	0	0
Lymphocytes, %	34	36
Platelets, cells/mm^3	147,000	91,000
Prothrombin time, sec	ND	>120
Partial thromboplastin time, sec	ND	>120
Bleeding time, min	ND	5
Clotting time, min	ND	>30
TB/DB, mg/dL	ND	2.71/1.54
Creatinine, mg/dL	ND	3.6
NS1	Nonreactive	ND

*Patient was transferred to a second hospital after initial admission. ND, not done; NS1, rapid immunochromatographic test for dengue virus; TB/DB, total/direct bilirubin.

Oropouche

› N Engl J Med. 2024 Oct 30. doi: 10.1056/NEJMc2412812. Online ahead of print.

A Case of Vertical Transmission of Oropouche Virus in Brazil

Carlos Garcia Filho [1], Antônio Silva Lima Neto [2], Ana Maria Peixoto Cabral Maia [1], Luiz Osvaldo Rodrigues da Silva [1], Robson da Costa Cavalcante [1], Higor da Silva Monteiro [3], Kamilla Carneiro Alves Marques [1], Rebeca de Souza Oliveira [1], Sami de Andrade Cordeiro Gadelha [4], Deborah Nunes de Melo [3], Anacelia Gomes de Matos Mota [4], Shirlene Telmos Silva de Lima [5], Karene Ferreira Cavalcante [5], Larissa Maria Façanha Duarte [5], Ítalo José Mesquita Cavalcante [5], Leda Maria Simões Mello [5], Carlos Henrique Alencar [3], Cintia Damasceno Dos Santos Rodrigues [6], Carla Santos de Oliveira [6], Fernanda de Bruycker-Nogueira [6], Felipe Gomes Naveca [6], André Ricardo Ribas Freitas [7], Luciano Pamplona de Góes Cavalcanti [8]

› Lancet Infect Dis. 2024 Oct 15:S1473-3099(24)00651-0. doi: 10.1016/S1473-3099(24)00651-0. Online ahead of print.

Oropouche virus and potential birth defects

Karin Nielsen-Saines [1], Patricia Brasil [2]

Review › Viruses. 2024 Sep 9;16(9):1435. doi: 10.3390/v16091435.

Oropouche Virus (OROV) in Pregnancy: An Emerging Cause of Placental and Fetal Infection Associated with Stillbirth and Microcephaly following Vertical Transmission

David A Schwartz [1], Pradip Dashraath [2], David Baud [3]

› Lancet Infect Dis. 2024 Oct 15:S1473-3099(24)00617-0. doi: 10.1016/S1473-3099(24)00617-0. Online ahead of print.

Newborns with microcephaly in Brazil and potential vertical transmission of Oropouche virus: a case series

Fernanda Eduarda das Neves Martins [1], Jannifer Oliveira Chiang [1], Bruno Tardelli Diniz Nunes [1], Bethania de Freitas Rodrigues Ribeiro [2], Lívia Carício Martins [1], Lívia Medeiros Neves Casseb [1], Daniele Freitas Henriques [1], Consuelo Silva de Oliveira [1], Ethel Leonor Noia Maciel [3], Rafael da Silva Azevedo [1], Layna de Cássia Campos Cravo [1], André Rodrigues Façanha Barreto [4], André Luiz Santos Pessoa [5], Arnaldo Jorge Martins Filho [6], Jorge Rodrigues de Sousa [7], Lavinia Schuler-Faccini [8], Juarez Antônio Simões Quaresma [9], Pedro Fernando da Costa Vasconcelos [10], Raimunda do Socorro da Silva Azevedo [11]

Oropouche

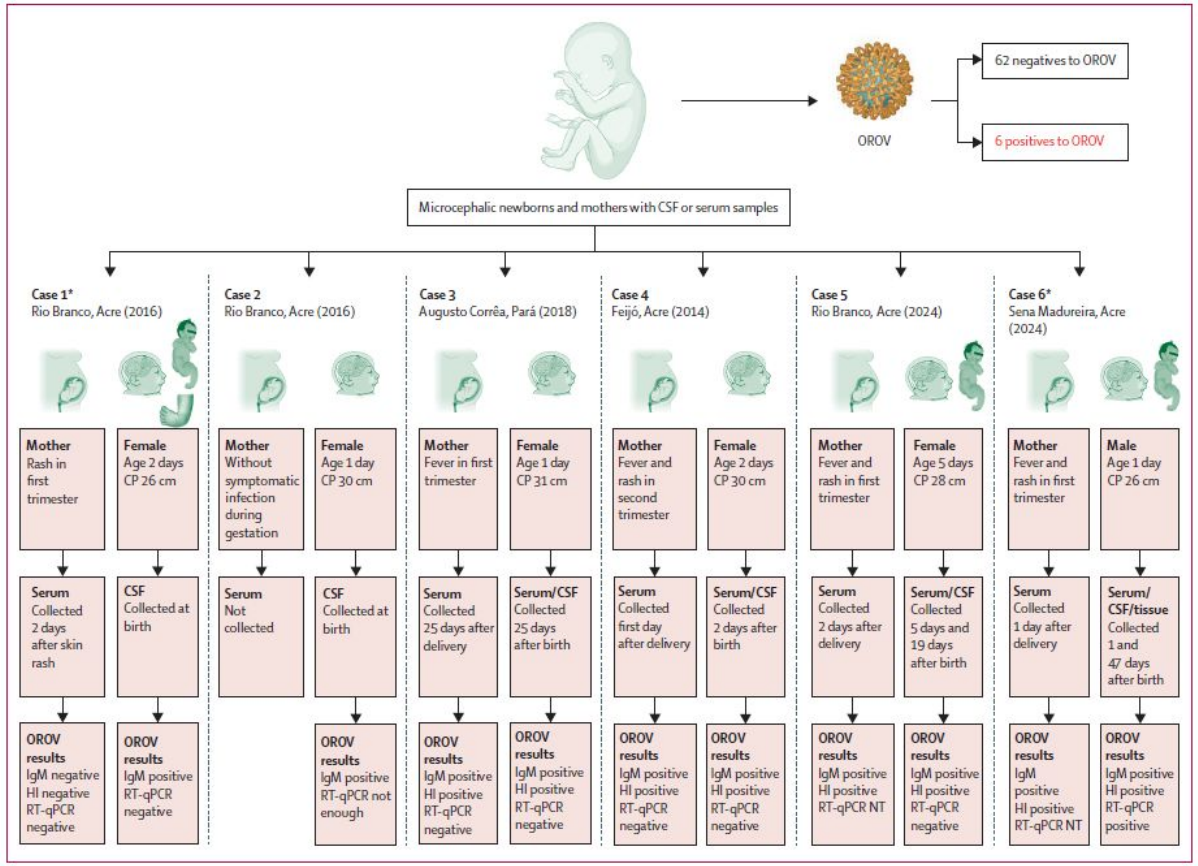


Figure 1: Presentation of six cases of newborns with microcephaly and other congenital alterations who presented positive laboratory results for Oropouche virus
CP=cephalic perimeter. CSF=cerebrospinal fluid. HI=haemagglutination inhibition. NT=not tested. OROV=Oropouche virus. qPCR=quantitative PCR. *The newborn died.

› Lancet Infect Dis. 2024 Oct 15:S1473-3099(24)00617-0. doi: 10.1016/S1473-3099(24)00617-0.
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Transmissão vertical

- 5 gestantes sintomáticas, 1 assintomática □ 4 no 1º trimestre, 1 no 2º trimestre
- Todos RN femininos
- Todos RN com IgM+ e PCR- no LCR
- 1 RN faleceu aos 47 dias de vida

Oropouche

Diagnóstico Tratamento

- Monitoramento dos casos
- Investigação dos casos graves

(serviços de referência)

- Estudos dos óbitos