

Dewa Ayu Putri Sri Masyeni



TROMBOSITOPENIA PADA INFEKSI DENGUE

*Mekanisme, Implikasi
Dan Tata Laksana Terkini*

TROMBOSITOPENIA

pada Infeksi Dengue

Mekanisme, Implikasi, dan Tata Laksana Terkini

Oleh

Dewa Ayu Putri Sri Masyeni

EDITOR:

Putu Saraswati Laksmi Dewi



PENERBIT KBM INDONESIA

Adalah penerbit dengan misi memudahkan proses penerbitan buku buku penulis di tanah air Indonesia. Serta menjadi media sharing proses penerbitan buku.

TROMBOSITOPENIA PADA INFEKSI DENGUE: Mekanisme, Implikasi dan Tata Laksana Terkini

*Copyright @2025 By Dewa Ayu Putri Sri Masyeni
All right reserved*

Penulis

Dewa Ayu Putri Sri Masyeni

Desain Sampul

Aswan Kreatif

Tata Letak

Sofita HM

Editor

Putu Saraswati Laksmi Dewi

Background isi buku di ambil dari <https://www.freepik.com/>

Official

Depok, Sleman-Jogjakarta (Kantor)

Penerbit Karya Bakti Makmur (KBM) Indonesia

Anggota IKAPI/No. IKAPI 279/JTI/2021

081357517526 (Tlpn/WA)

Website

<https://penerbitkbm.com>

www.penerbitbukumurah.com

Email

naskah@penerbitkbm.com

Distributor

<https://penerbitkbm.com/toko-buku/>

Youtube

Penerbit KBM Sastrabook

Instagram

@penerbit.kbmindonesia

@penerbitbukujogja

ISBN: 978-634-202-361-7

Cetakan ke-1, Mei 2025

15 x 23 cm, iv + 67 halaman

Isi buku diluar tanggungjawab penerbit
Hak cipta merek KBM Indonesia sudah terdaftar di DJKI-Kemenkumham
dan isi buku dilindungi undang-undang.

Dilarang keras menerjemahkan, memfotokopi, atau
memperbanyak sebagian atau seluruh isi buku ini
tanpa seizin penerbit karena beresiko sengketa hukum

Sanksi Pelanggaran Pasal 113
Undang-Undang No. 28 Tahun 2014 Tentang Hak Cipta

1. Setiap Orang yang dengan tanpa hak melakukan pelanggaran hak ekonomi sebagaimana dimaksud dalam Pasal 9 ayat (1) huruf i untuk Penggunaan Secara Komersial dipidana dengan pidana penjara paling lama 1 (satu) tahun dan/atau pidana denda paling banyak Rp 100.000.000 (seratus juta rupiah).
2. Setiap Orang yang dengan tanpa hak dan/atau tanpa izin Pencipta atau pemegang Hak Cipta melakukan pelanggaran hak ekonomi Pencipta sebagaimana dimaksud dalam Pasal 9 ayat (1) huruf c, huruf d, huruf f, dan/atau huruf h untuk Penggunaan Secara Komersial dipidana dengan pidana penjara paling lama 3 (tiga) tahun dan/atau pidana denda paling banyak Rp 500.000.000,00 (lima ratus juta rupiah).
3. Setiap Orang yang dengan tanpa hak dan/atau tanpa izin Pencipta atau pemegang Hak Cipta melakukan pelanggaran hak ekonomi Pencipta sebagaimana dimaksud dalam Pasal 9 ayat (1) huruf a, huruf b, huruf e, dan/atau huruf g untuk Penggunaan Secara Komersial dipidana dengan pidana penjara paling lama 4 (empat) tahun dan/atau pidana denda paling banyak Rp 1.000.000.000,00 (satu miliar rupiah).
4. Setiap Orang yang memenuhi unsur sebagaimana dimaksud pada ayat (3) yang dilakukan dalam bentuk pembajakan, dipidana dengan pidana penjara paling lama 10 (sepuluh) tahun dan/atau pidana denda paling banyak Rp 4.000.000.000,00 (empat miliar rupiah).

KATA PENGANTAR

Selamat membaca buku dengan judul " Trombositopenia pada infeksi dengue: mekanisme, implikasi dan tata laksana terkini" Buku ini ditulis sebagai respons terhadap tantangan global yang ditimbulkan oleh infeksi dengue, dimana infeksi virus dengue menjadi penyakit yang semakin meluas tidak hanya terjadi di daerah tropis dan sub-tropis bahkan telah meluas ke daerah non-endemis akibat semakin meningkatnya perjalanan internasional sehingga menjadi perhatian kesehatan masyarakat di berbagai belahan dunia.

Infeksi dengue, yang disebabkan oleh virus dengue dan ditularkan melalui gigitan nyamuk Aedes, dapat bervariasi dalam tingkat keparahan, mulai dari demam ringan hingga infeksi berat yang mengancam jiwa dan memicu kematian pada kelompok populasi tertentu. Dalam beberapa tahun terakhir, penelitian mengenai biomarker, indikator biologis yang dapat menunjukkan adanya penyakit atau tingkat keparahannya, telah menunjukkan potensi yang signifikan dalam meningkatkan pemahaman kita tentang kondisi ini.

Melalui buku ini, kami berusaha untuk menyajikan berbagai temuan terbaru dan pendekatan inovatif dalam manajemen trombositopenia pada infeksi dengue. Kami berharap buku ini dapat menjadi sumber informasi yang berguna bagi para peneliti, profesional kesehatan, dan mahasiswa yang tertarik dengan bidang ini.

Kami ingin mengucapkan terima kasih kepada semua kontributor dan peneliti yang telah berkontribusi dalam

pengembangan pengetahuan tentang “Trombositopenia pada infeksi dengue: mekanisme, implikasi dan tata laksana terkini”. Semoga buku ini bermanfaat dan dapat mendorong penelitian lebih lanjut dalam upaya mengurangi dampak infeksi dengue di seluruh dunia.

Selamat membaca!

Bali, 2025

Penulis

DAFTAR ISI

KATA PENGANTAR	i
DAFTAR ISI	iii
BAB 1 PENDAHULUAN	1
BAB 2 MODALITAS PENGOBATAN INFEKSI DENGUE DI MASA DEPAN.....	15
A. Anti Virus	16
B. Antibodi Monoclonal.....	20
C. Obat dengan Target Host.....	21
D. Terapi lain.....	23
BAB 3 PERKEMBANGAN VAKSIN DENGUE	25
BAB 4 MEKANISME TROMBOSITOPENIA PADA INFEKSI DENGUE	33
BAB 5 IMPLIKASI TROMBOSITOPENIA PADA INFEKSI DENGUE	45
DAFTAR PUSTAKA.....	53
PROFIL PENULIS.....	67

- primary and secondary dengue virus infections. *Nat Rev Immunol* [Internet]. 2019;19(4):218–30. Available from: <http://dx.doi.org/10.1038/s41577-019-0123-x>
8. Yacoub S, Wills B. *Predicting outcome from dengue*. *BMC Med* [Internet]. 2014 Dec 4;12(1):147. Available from: <http://bmcmmedicine.biomedcentral.com/articles/10.1186/s12916-014-0147-9>
 9. World Health Organization (WHO), UNICEF. *Handbook for clinical management of dengue*. 2012;
 10. Karyanti MR, Uiterwaal CSPM, Hadinegoro SR, Widyahening IS, Saldi SRF, Heesterbeek JAPH, et al. *The Value of Warning Signs From the WHO 2009 Dengue Classification in Detecting Severe Dengue in Children*. *Pediatr Infect Dis J* [Internet]. 2024 Jul 19;43(7):630–4. Available from: <https://journals.lww.com/10.1097/INF.0000000000004326>
 11. Juliansen A, Heriyanto RS, Budiputri CL, Meliani F, Muljono MP, Chandra S, et al. *Warning Signs in Predicting Severe Pediatric Dengue Infection*. *J Pediatr Infect Dis* [Internet]. 2022 May 30;17(03):119–25. Available from: <http://www.thieme-connect.de/DOI/DOI?10.1055/s-0042-1745838>
 12. Zhang H, Zhou YP, Peng HJ, Zhang XH, Zhou FY, Liu ZH, et al. *Predictive Symptoms and Signs of Severe Dengue Disease for Patients with Dengue Fever: A Meta-Analysis*. *Biomed Res Int* [Internet]. 2014;2014:1–10. Available from: <http://www.hindawi.com/journals/bmri/2014/359308/>
 13. Adam AS, Pasaribu S, Wijaya H, Pasaribu AP. *Warning sign as a predictor of dengue infection severity in children*. *Med J Indones* [Internet]. 2018 Sep 9;27(2). Available from: <https://mji.ui.ac.id/journal/index.php/mji/article/view/2200>
 14. World Health Organization. *Comprehensive Guideline for Prevention and Control of Dengue and Dengue Haemorrhagic Fever*. Revised and expanded edition. In 2011.
 15. Palanichamy Kala M, St. John AL, Rathore APS. *Dengue: Update on Clinically Relevant Therapeutic Strategies and Vaccines*. *Curr Treat Options Infect Dis* [Internet]. 2023 Apr

- 18;15(2):27–52. Available from:
<https://link.springer.com/10.1007/s40506-023-00263-w>
16. Zou J, Lee LT, Wang QY, Xie X, Lu S, Yau YH, et al. Mapping the Interactions between the NS4B and NS3 Proteins of Dengue Virus. Dermody TS, editor. *J Virol* [Internet]. 2015 Apr;89(7):3471–83. Available from:
<https://journals.asm.org/doi/10.1128/JVI.03454-14>
 17. Whitehorn J, Nguyen CVV, Khanh LP, Kien DTH, Quyen NTH, Tran NTT, et al. *Lovastatin for the Treatment of Adult Patients With Dengue: A Randomized, Double-Blind, Placebo-Controlled Trial*. Clin Infect Dis [Internet]. 2016 Feb 15;62(4):468–76. Available from:
<https://academic.oup.com/cid/article/62/4/468/2463096>
 18. Tricou V, Minh NN, Van TP, Lee SJ, Farrar J, Wills B, et al. *A Randomized Controlled Trial of Chloroquine for the Treatment of Dengue in Vietnamese Adults*. Halstead SB, editor. *PLoS Negl Trop Dis* [Internet]. 2010 Aug 10;4(8):e785. Available from:
<https://dx.plos.org/10.1371/journal.pntd.0000785>
 19. Nguyen NM, Tran CNB, Phung LK, Duong KTH, Huynh H le A, Farrar J, et al. A Randomized, Double-Blind Placebo Controlled Trial of Balapiravir, a Polymerase Inhibitor, in Adult Dengue Patients. *J Infect Dis* [Internet]. 2013 May 1;207(9):1442–50. Available from:
<https://academic.oup.com/jid/article-lookup/doi/10.1093/infdis/jis470>
 20. Low JG et al. Efficacy and safety of celgosivir in patients with dengue fever (CELADEN): a phase 1b, randomised, double-blind, placebo-controlled, proof-of-concept trial. *Lancet Infect Dis*. 2014;14(8):p706–715.
 21. Wagstaff KM, Sivakumaran H, Heaton SM, Harrich D, Jans DA. *Ivermectin is a specific inhibitor of importin α/β -mediated nuclear import able to inhibit replication of HIV-1 and dengue virus*. *Biochem J* [Internet]. 2012 May 1;443(3):851–6. Available from:
<https://portlandpress.com/biochemj/article/443/3/851/80615>

- /Ivermectin-is-a-specific-inhibitor-of-importin
22. Tay MYF, Fraser JE, Chan WKK, Moreland NJ, Rathore AP, Wang C, et al. *Nuclear localization of dengue virus (DENV) 1–4 non-structural protein 5; protection against all 4 DENV serotypes by the inhibitor Ivermectin*. *Antiviral Res* [Internet]. 2013 Sep;99(3):301–6. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0166354213001599>
 23. Suputtamongkol Y, Avirutnan P, Mairiang D, Angkasekwinai N, Niwattayakul K, Yamasmith E, et al. *Ivermectin Accelerates Circulating Nonstructural Protein 1 (NS1) Clearance in Adult Dengue Patients: A Combined Phase 2/3 Randomized Double-blinded Placebo Controlled Trial*. *Clin Infect Dis* [Internet]. 2021 May 18;72(10):e586–93. Available from: <https://academic.oup.com/cid/article/72/10/e586/6104252>
 24. Good SS, Shannon A, Lin K, Moussa A, Julander JG, La Colla P, et al. *Evaluation of AT-752, a Double Prodrug of a Guanosine Nucleotide Analog with In Vitro and In Vivo Activity against Dengue and Other Flaviviruses*. *Antimicrob Agents Chemother* [Internet]. 2021 Oct 18;65(11). Available from: <https://journals.asm.org/doi/10.1128/AAC.00988-21>
 25. Hussin A. Rothan, Zulqarnain Mohamed, Mohammadjavad Paydar NAR& RY. *Inhibitory effect of doxycycline against dengue virus replication in vitro*. *Arch Virol*. 2013;159:711–8.
 26. Fredeking T, Zavala-Castro J, Gonzalez-Martinez P et al. *Dengue patients treated with doxycycline showed lower mortality associated to a reduction in IL-6 and TNF levels*. *Recent Patents Anti-Infect Drug Disc*. 2015;10(51–58):2.
 27. Pambhar V, Mathur N, Mehta A et al. *Effect of doxycycline and doxycycline with carica papaya on thrombocytopenia and leucopenia in acute dengue fever patients*. *J Pham Med Prim Care*. 2022;11(6):3270–5.
 28. Courageot MP, Frenkiel MP, Duarte Dos Santos C, Deubel V, Desprès P. *α-Glucosidase Inhibitors Reduce Dengue Virus Production by Affecting the Initial Steps of Virion Morphogenesis in the Endoplasmic Reticulum*. *J Virol*

- [Internet]. 2000 Jan;74(1):564–72. Available from: <https://journals.asm.org/doi/10.1128/JVI.74.1.564-572.2000>
29. Rathore APS, Paradkar PN, Watanabe S, Tan KH, Sung C, Connolly JE, et al. *Celgosivir treatment misfolds dengue virus NS1 protein, induces cellular pro-survival genes and protects against lethal challenge mouse model*. Antiviral Res [Internet]. 2011 Dec;92(3):453–60. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0166354211004529>
 30. Sung C, Wei Y, Watanabe S, Lee HS, Khoo YM, Fan L, et al. *Extended Evaluation of Virological, Immunological and Pharmacokinetic Endpoints of CELADEN: A Randomized, Placebo-Controlled Trial of Celgosivir in Dengue Fever Patients*. Michael SF, editor. PLoS Negl Trop Dis [Internet]. 2016 Aug 10;10(8):e0004851. Available from: <https://dx.plos.org/10.1371/journal.pntd.0004851>
 31. Warfield KL, Plummer EM, Sayce AC, Alonzi DS, Tang W, Tyrrell BE, et al. *Inhibition of endoplasmic reticulum glucosidases is required for in vitro and in vivo dengue antiviral activity by the iminosugar UV-4*. Antiviral Res [Internet]. 2016 May;129:93–8. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0166354216301218>
 32. Perry ST, Buck MD, Plummer EM, Penmasta RA, Batra H, Stavale EJ, et al. *An iminosugar with potent inhibition of dengue virus infection in vivo*. Antiviral Res [Internet]. 2013 Apr;98(1):35–43. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0166354213000193>
 33. Callahan M, Treston AM, Lin G, Smith M, Kaufman B, Khaliq M, et al. *Randomized single oral dose phase 1 study of safety, tolerability, and pharmacokinetics of Iminosugar UV-4 Hydrochloride (UV-4B) in healthy subjects*. Reiner RC, editor. PLoS Negl Trop Dis [Internet]. 2022 Aug 8;16(8):e0010636. Available from: <https://dx.plos.org/10.1371/journal.pntd.0010636>

34. Glasner DR, Ratnasiri K, Puerta-Guardo H, Espinosa DA, Beatty PR, Harris E. *Dengue virus NS1 cytokine-independent vascular leak is dependent on endothelial glycocalyx components*. Kuhn RJ, editor. PLOS Pathog [Internet]. 2017 Nov 9;13(11):e1006673. Available from: <https://dx.plos.org/10.1371/journal.ppat.1006673>
35. Rathore APS, St. John AL. *Cross-Reactive Immunity Among Flaviviruses*. Front Immunol [Internet]. 2020 Feb 26;11. Available from: <https://www.frontiersin.org/article/10.3389/fimmu.2020.00334/full>
36. Rey FA, Stiasny K, Vaney M, Dellarole M, Heinz FX. *The bright and the dark side of human antibody responses to flaviviruses: lessons for vaccine design*. EMBO Rep [Internet]. 2018 Feb 27;19(2):206–24. Available from: <https://www.embopress.org/doi/10.15252/embr.201745302>
37. Marasco WA, Sui J. *The growth and potential of human antiviral monoclonal antibody therapeutics*. Nat Biotechnol [Internet]. 2007 Dec 7;25(12):1421–34. Available from: <https://www.nature.com/articles/nbt1363>
38. Budigi Y, Ong EZ, Robinson LN, Ong LC, Rowley KJ, Winnett A, et al. *Neutralization of antibody-enhanced dengue infection by VIS513, a pan serotype reactive monoclonal antibody targeting domain III of the dengue E protein*. de Silva AM, editor. PLoS Negl Trop Dis [Internet]. 2018 Feb 9;12(2):e0006209. Available from: <https://dx.plos.org/10.1371/journal.pntd.0006209>
39. St John AL, Rathore AP, Raghavan B, Ng ML, Abraham SN. *Contributions of mast cells and vasoactive products, leukotrienes and chymase, to dengue virus-induced vascular leakage*. Elife [Internet]. 2013 Apr 30;2. Available from: <https://elifesciences.org/articles/00481>
40. Malavige GN, Wijewickrama A, Fernando S, Jeewandara C, Ginneliya A, Samarasekara S, et al. *A preliminary study on efficacy of rupatadine for the treatment of acute dengue infection*. Sci Rep [Internet]. 2018 Mar 1;8(1):3857. Available

- from: <https://www.nature.com/articles/s41598-018-22285-x>
41. Rathore APS, Mantri CK, Aman SAB, Syenina A, Ooi J, Jagaraj CJ, et al. Dengue virus-elicited tryptase induces endothelial permeability and shock. *J Clin Invest* [Internet]. 2019 Aug 26;129(10):4180–93. Available from: <https://www.jci.org/articles/view/128426>
 42. Masri MF Bin, Mantri CK, Rathore APS, John AL St. *Peripheral serotonin causes dengue virus-induced thrombocytopenia through 5HT₂ receptors*. *Blood* [Internet]. 2019 May 23;133(21):2325–37. Available from: <https://ashpublications.org/blood/article/133/21/2325/272751/Peripheral-serotonin-causes-dengue-virus-induced>
 43. Jiménez de Oya N, Blázquez AB, Casas J, Saiz JC, Martín-Acebes MA. *Direct Activation of Adenosine Monophosphate-Activated Protein Kinase (AMPK) by PF-06409577 Inhibits Flavivirus Infection through Modification of Host Cell Lipid Metabolism*. *Antimicrob Agents Chemother* [Internet]. 2018 Jul;62(7). Available from: <https://journals.asm.org/doi/10.1128/AAC.00360-18>
 44. Htun HL, Yeo TW, Tam CC, Pang J, Leo YS, Lye DC. *Metformin Use and Severe Dengue in Diabetic Adults*. *Sci Rep* [Internet]. 2018 Feb 20;8(1):3344. Available from: <https://www.nature.com/articles/s41598-018-21612-6>
 45. Nandini C, Madhunapantula S V., Bovilla VR, Ali M, Mruthunjaya K, Santhepete MN, et al. Platelet enhancement by Carica papaya L. leaf fractions in cyclophosphamide induced thrombocytopenic rats is due to elevated expression of CD110 receptor on megakaryocytes. *J Ethnopharmacol* [Internet]. 2021 Jul;275:114074. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0378874121003019>
 46. Khazali AS, Hadrawi WH, Ibrahim F, Othman S, Nor Rashid N. *Thrombocytopenia in dengue infection: mechanisms and a potential application*. *Expert Rev Mol Med*. 2024;26:e26.
 47. Yang S, Wang L, Wu Y, Wu A, Huang F, Tang X, et al. Apoptosis in megakaryocytes: Safeguard and threat for

- thrombopoiesis. *Front Immunol* [Internet]. 2023 Jan 4;13. Available from:
<https://www.frontiersin.org/articles/10.3389/fimmu.2022.1025945/full>
48. Khazali AS, Hadrawi WH, Ibrahim F, Othman S, Nor Rashid N. *Thrombocytopenia in dengue infection: mechanisms and a potential application*. *Expert Rev Mol Med* [Internet]. 2024 Oct 14;26:e26. Available from:
https://www.cambridge.org/core/product/identifier/S1462399424000188/type/journal_article
 49. Noisakran S, Gibbons RV, Songprakhon P, Jairungsri A, Ajariyakhajorn C, Nisalak A, Jarman RG, Malasit P, Chokeyhaibulkit K PG. *Detection of dengue virus in platelets isolated from dengue patients*. *Southeast Asian J Trop Med Public Heal*. 2009;40(2):253–62.
 50. Onlamoon N, Noisakran S, Hsiao HM, Duncan A, Villinger F, Ansari AA, et al. *Dengue virus-induced hemorrhage in a nonhuman primate model*. *Blood* [Internet]. 2010 Mar 4;115(9):1823–34. Available from:
<https://ashpublications.org/blood/article/115/9/1823/27246/Dengue-virusinduced-hemorrhage-in-a-nonhuman>
 51. Riswari SF, Tunjungputri RN, Kullaya V, Garishah FM, Utari GSR, Farhanah N, et al. *Desialylation of platelets induced by Von Willebrand Factor is a novel mechanism of platelet clearance in dengue*. Fernandez-Sesma A, editor. *PLOS Pathog* [Internet]. 2019 Mar 8;15(3):e1007500. Available from:
<https://dx.plos.org/10.1371/journal.ppat.1007500>
 52. Hottz E, Tolley ND, Zimmerman GA, Weyrich AS, Bozza FA. *Platelets in dengue infection*. *Drug Discov Today Dis Mech* [Internet]. 2011 Jun;8(1–2):e33–8. Available from:
<https://linkinghub.elsevier.com/retrieve/pii/S1740676511000113>
 53. Hottz ED, Oliveira MF, Nunes PCG, Nogueira RMR, Valls-de-Souza R, Da Poian AT, et al. *Dengue induces platelet activation, mitochondrial dysfunction and cell death through mechanisms that involve DC-SIGN and caspases*. *J Thromb*

- Haemost* [Internet]. 2013 May;11(5):951–62. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S1538783622136159>
54. Chuansumrit A, Chaiyaratana W. *Hemostatic derangement in dengue hemorrhagic fever*. *Thromb Res* [Internet]. 2014 Jan;133(1):10–6. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0049384813004428>
 55. Koupenova M, Livada AC, Morrell CN. Platelet and Megakaryocyte Roles in Innate and Adaptive Immunity. *Circ Res* [Internet]. 2022 Jan 21;130(2):288–308. Available from: <https://www.ahajournals.org/doi/10.1161/CIRCRESAHA.121.319821>
 56. Teo A, Tan HD, Loy T, Chia PY, Chua CLL. *Understanding antibody-dependent enhancement in dengue: Are afucosylated IgG1s a concern?* Evans MJ, editor. *PLOS Pathog* [Internet]. 2023 Mar 30;19(3):e1011223. Available from: <https://dx.plos.org/10.1371/journal.ppat.1011223>
 57. Rodenhuis-Zybert IA, van der Schaar HM, da Silva Voorham JM, van der Ende-Metselaar H, Lei HY, Wilschut J, et al. *Immature Dengue Virus: A Veiled Pathogen?* Gale M, editor. *PLoS Pathog* [Internet]. 2010 Jan 8;6(1):e1000718. Available from: <https://dx.plos.org/10.1371/journal.ppat.1000718>
 58. Alonzo MTG, Lacuesta TL V., Dimaano EM, Kurosu T, Suarez L anne C, Mapua CA, et al. Platelet Apoptosis and Apoptotic Platelet Clearance by Macrophages in Secondary Dengue Virus Infections. *J Infect Dis* [Internet]. 2012 Apr 15;205(8):1321–9. Available from: <https://academic.oup.com/jid/article-lookup/doi/10.1093/infdis/jis180>
 59. Ojha A, Nandi D, Batra H, Singhal R, Annarapu GK, Bhattacharyya S, et al. *Platelet activation determines the severity of thrombocytopenia in dengue infection*. *Sci Rep* [Internet]. 2017 Jan 31;7(1):41697. Available from: <https://www.nature.com/articles/srep41697>
 60. Jeon K, Kim M, Lee J, Lee JS, Kim HS, Kang HJ, et al. *Immature*

platelet fraction: A useful marker for identifying the cause of thrombocytopenia and predicting platelet recovery. Medicine (Baltimore) [Internet]. 2020 Feb;99(7):e19096. Available from:

<https://journals.lww.com/10.1097/MD.00000000000019096>

61. Dadu T, Sehgal K, Joshi M, Khodaiji S. *Evaluation of the immature platelet fraction as an indicator of platelet recovery in dengue patients.* Int J Lab Hematol [Internet]. 2014 Oct 12;36(5):499–504. Available from: <https://onlinelibrary.wiley.com/doi/10.1111/ijlh.12177>
62. Looi KW, Matsui Y, Kono M, Samudi C, Kojima N, Ong JX, et al. *Evaluation of immature platelet fraction as a marker of dengue fever progression.* Int J Infect Dis [Internet]. 2021 Sep;110:187–94. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S1201971221006044>
63. Lam PK, Ngoc TV, Thu Thuy TT et al. *The value of daily platelet counts for predicting dengue shock syndrome: results from a prospective observational study of 2301 Vietnamese children with dengue.* PLoS Negl Trop Dis. 2017;11(4):e0005498.
64. Makroo R, Raina V, Kumar P, Kanth R. Role of platelet transfusion in the management of dengue patients in a tertiary care hospital. *Asian J Transfus Sci* [Internet]. 2007;1(1):4. Available from: <https://journals.lww.com/10.4103/0973-6247.28065>
65. Masyeni S, Wardhana IMW, Nainu F. *Cytokine profiles in dengue fever and dengue hemorrhagic fever: A study from Indonesia.* Narra J [Internet]. 2024 Mar 8;4(1):e309. Available from: <https://narraj.org/main/article/view/309>
66. Megawati D, Masyeni S, Yohan B, Lestarini A, Hayati RF, Meutiawati F, et al. *Dengue in Bali: Clinical characteristics and genetic diversity of circulating dengue viruses.* PLoS Negl Trop Dis. 2017;11(5):e0005483.
67. Chlebicki MP, Ang B, Barkham T, Laude A. *Retinal Hemorrhages in 4 Patients with Dengue Fever.* Emerg Infect

- Dis [Internet]. 2005 May;11(5):770-2. Available from: http://wwwnc.cdc.gov/eid/article/11/5/04-0992_article.htm
68. Chamnanchanunt S, Kanagaraj D, Thanachartwet V, Desakorn V RP. Early predictors of clinically significant bleeding in adults with dengue infection. *Southeast Asian J Trop Med Public Heal*. 2012;43(4):890-9.
 69. Siahaan AMP, Tandean S, Saragih EB, Nainggolan BWM. *Spontaneous acute subdural hematoma in dengue fever: Case report and review of the literature*. *Int J Surg Case Rep* [Internet]. 2022 Sep;98:107512. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S2210261222007581>
 70. Castilho BM, Silva MT, Freitas ARR, Fulone I, Lopes LC. *Factors associated with thrombocytopenia in patients with dengue fever: a retrospective cohort study*. *BMJ Open* [Internet]. 2020 Sep 13;10(9):e035120. Available from: <https://bmjopen.bmj.com/lookup/doi/10.1136/bmjopen-2019-035120>
 71. Renuka M, Selvam V, Logia P, Parasuraman V, Rajagopalan RE. Predictors of Clinically Significant Bleeding in Thrombocytopenic Dengue Patients Admitted to Intensive Care Unit: A Retrospective Study. *Indian J Crit Care Med* [Internet]. 2023 Nov 30;27(12):888-94. Available from: <https://www.ijccm.org/doi/10.5005/jp-journals-10071-24574>
 72. Laoprasopwattana K, Binsaii J, Pruekprasert P, Geater A. Prothrombin Time Prolongation was the Most Important Indicator of Severe Bleeding in Children with Severe Dengue Viral Infection. *J Trop Pediatr* [Internet]. 2017 Aug 1;63(4):314-20. Available from: <http://academic.oup.com/tropej/article/63/4/314/2848022/P-rothrombin-Time-Prolongation-was-the-Most>
 73. Rao SV, Jacob GG, Raju NA, Ancheri SA. Spontaneous arterial hemorrhage as a complication of dengue. *Indian J Crit Care Med* [Internet]. 2016 May;20(5):302-4. Available from: <https://www.ijccm.org/doi/10.4103/0972-5229.182201>
 74. Mourão MPG, Lacerda MVG, Macedo VO, Mourão MPG,

- Lacerda MVG, Macedo VO, et al. *Thrombocytopenia in patients with dengue virus infection in the Brazilian Amazon*. Platelets [Internet]. 2007 Jan 7;18(8):605–12. Available from: <http://www.tandfonline.com/doi/full/10.1080/09537100701426604>
75. Orsi FA, Angerami RN, Mazetto BM, Quaino SK, Santiago-Bassora F, Castro V, et al. *Reduced thrombin formation and excessive fibrinolysis are associated with bleeding complications in patients with dengue fever: a case-control study comparing dengue fever patients with and without bleeding manifestations*. BMC Infect Dis [Internet]. 2013 Dec 28;13(1):350. Available from: <https://bmcinfectdis.biomedcentral.com/articles/10.1186/1471-2334-13-350>
 76. Bhuiyan T, Das A, Rahim A, Islam MR. A case of unusual hemorrhage as a complication of dengue fever in a tertiary hospital in Dhaka. *J Med* [Internet]. 2024 Jan 4;25(1):100–1. Available from: <https://www.banglajol.info/index.php/JOM/article/view/70537>
 77. Lye DC, Archuleta S, Syed-Omar SF et al. *Prophylactic platelet transfusion plus supportive care versus supportive care alone in adults with dengue and thrombocytopenia: a multicentre, open-label, randomised, superiority trial*. Lancet. 2017;389(10079):1611–8.
 78. Chakraborty S, Alam S, Sayem M, Sanyal M, Das T, Saha P, et al. *Investigation of the efficacy and safety of eltrombopag to correct thrombocytopenia in moderate to severe dengue patients - a phase II randomized controlled clinical trial*. EClinicalMedicine. 2020;29–30.
 79. Jenkins JM, Williams D, Deng Y, Uhl J, Kitchen V, Collins D, et al. *Phase 1 clinical study of eltrombopag, an oral, nonpeptide thrombopoietin receptor agonist*. Blood [Internet]. 2007;109(11):4739–41. Available from: <http://dx.doi.org/10.1182/blood-2006-11-057968>
 80. Assir MZK, Kamran U, Ahmad HI, Bashir S, Mansoor H,

- Anees S Bin, et al. *Effectiveness of Platelet Transfusion in Dengue Fever: A Randomized Controlled Trial*. *Transfus Med Hemotherapy* [Internet]. 2013;40(5):362–8. Available from: <https://karger.com/TMH/article/doi/10.1159/000354837>
81. Lye DC, Archuleta S, Syed-Omar SF, Low JG, Oh HM, Wei Y, et al. *Prophylactic platelet transfusion plus supportive care versus supportive care alone in adults with dengue and thrombocytopenia: a multicentre, open-label, randomised, superiority trial*. *Lancet* [Internet]. 2017 Apr;389(10079):1611–8. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0140673617302696>
 82. Tunjungputri RN, Riswari SF, Pramudo SG, Kuntjoro L, Alisjahbana B, Nugraha HG, et al. *Effect of oseltamivir phosphate versus placebo on platelet recovery and plasma leakage in adults with dengue and thrombocytopenia; a phase 2, multicenter, double-blind, randomized trial*. McElroy AK, editor. *PLoS Negl Trop Dis* [Internet]. 2022 Jan 7;16(1):e0010051. Available from: <https://dx.plos.org/10.1371/journal.pntd.0010051>
 83. Lye DC, Lee VJ, Sun Y, Leo YS. *Lack of Efficacy of Prophylactic Platelet Transfusion for Severe Thrombocytopenia in Adults with Acute Uncomplicated Dengue Infection*. *Clin Infect Dis* [Internet]. 2009 May;48(9):1262–5. Available from: <https://academic.oup.com/cid/article-lookup/doi/10.1086/597773>
 84. Kurukularatne C, Dimatatac F, Teo DLT, Lye DC, Leo YS. *When less is more: Can we abandon prophylactic platelet transfusion in Dengue fever?* *Ann Acad Med Singapore*. 2011;40(12):539–45.
 85. Thomas L, Kaidomar S, Kerob-Bauchet B, Moravie V, Brouste Y, King JP, et al. *Prospective observational study of low thresholds for platelet transfusion in adult dengue patients*. *Transfusion* [Internet]. 2009 Jul;49(7):1400–11. Available from: <https://onlinelibrary.wiley.com/doi/10.1111/j.1537-2995.2009.02132.x>

86. Chuansumrit A, Teeraratkul S, Wanichkul S, Treepongkaruna S, Sirachainan N, Pakakasama S, et al. *Recombinant-activated factor VII for control and prevention of hemorrhage in nonhemophilic pediatric patients*. Blood Coagul Fibrinolysis [Internet]. 2010 Jun;21(4):354–62. Available from: <http://journals.lww.com/00001721-201006000-00010>
87. Sathyapalan DT, Padmanabhan A, Moni M, P-Prabhu B, Prasanna P, Balachandran S, et al. Efficacy & safety of *Carica papaya leaf extract (CPLE) in severe thrombocytopenia ($\leq 30,000/\mu\text{l}$) in adult dengue – Results of a pilot study*. Price MA, editor. PLoS One [Internet]. 2020 Feb 19;15(2):e0228699. Available from: <https://dx.plos.org/10.1371/journal.pone.0228699>
88. Nirupam N, Kumar S, Badatya S, Chhapola V, Sharma R, Kumar V. Intravenous Anti-D immunoglobulin for control of life threatening bleed in dengue hemorrhagic fever with severe thrombocytopenia. *J Pediatr Infect Dis* [Internet]. 2015 Jul 28;07(03):127–30. Available from: <http://www.thieme-connect.de/DOI/DOI?10.3233/JPI-120358>
89. Varma S, Shafiq N, Singhal M, Pannu A. Safety and efficacy of a single dose of Anti-D (WinRho[®]) in severe thrombocytopenia secondary to dengue virus infection. *Indian J Crit Care Med* [Internet]. 2017 Feb;21(2):80–4. Available from: https://www.ijccm.org/doi/10.4103/ijccm.IJCCM_386_16
90. De Castro Rac, De Castro Jaa, Barez Myc, Frias M V., Dixit J, Genereux M. Thrombocytopenia Associated With Dengue Hemorrhagic Fever Responds To Intravenous Administration Of Anti-D (Rho-D) Immune Globulin. *Am J Trop Med Hyg* [Internet]. 2007 Apr;76(4):737–42. Available from: <https://www.ajtmh.org/view/journals/tpmd/76/4/article-p737.xml>
91. Pothapregada S, Kamalakannan B TM. Role of platelet transfusion in children with bleeding in dengue fever. *J Vector Borne Dis*. 2015;52(4):304–8.

PROFIL PENULIS

Buku ini ditulis oleh dosen Fakultas Kedokteran dan Ilmu kesehatan Universitas Warmadewa, Bali, Dr.dr. Dewa Ayu Putri Sri Masyeni, SpPD, KPTI. Beliau adalah seorang klinisi di bidang Ilmu Penyakit Dalam, lebih spesifik lagi pada Penyakit Tropis dan Infeksi. Pengalaman beliau sebagai klinisi dan juga akademisi yang memiliki kewajiban Tridharma perguruan tinggi telah melahirkan lebih dari 44 karya ilmiah yang dipublikasi pada jurnal internasional bereputasi/terindex scopus sampai bulan Oktober 2023, selain banyak karya ilmiah yang telah dipublikasi pada jurnal terakreditasi Sinta.

Selain itu beliau juga aktif pada mengajar dan praktisi pada bidang travel medicine/kedokteran wisata dan telah aktif menuliskan hasil riset di bidang kedokteran wisata. Selain hasil karya yang telah bisa dibaca pada jurnal-jurnal bereputasi, karya berupa buku khususnya buku ajar juga telah dimanfaatkan oleh mahasiswa kedokteran. Beliau juga telah banyak diundang untuk melaksanakan review artikel pada jurnal internasional bereputasi. Berbagai hibah/grant telah beliau capai baik hibah tingkat nasional dari Kementerian Pendidikan dan Kebudayaan Riset dan Teknologi Indonesia sejak tahun 2017, 2020, 2021, 2022, tetapi juga hibah internasional dari International Society of Travel Medicine (ISTM) tahun 2016 dan 2021. Beliau juga aktif sebagai editorial board jurnal internasional bereputasi Scopus Q2, World Journal of Clinical Cases .