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Neonates are not adults; there are unusual pathogens, limitations in immunity, need for new ways to treat, and to monitor for adverse effects

Fetuses, newborns, and young infants are often highly susceptible to unusual pathogens that may be relatively benign in adults.[1–10] The debate continues on whether these epidemiological differences arise in the unique strains of pathogens,[1,11–15] immaturity of the immune system,[16–18] environmental factors in intensive care units[19–21] or in specific climatic conditions that allow these pathogens to reach larger numbers and/or densities.[22–24] These conditions have been difficult to treat as the infectious agents affect the fetus/neonate *in utero* and cannot be treated in a timely fashion, the candidate medications have limited efficacy, or the drugs have had unacceptable short- and long-term adverse effects.[22] Now, the possibility of developing effective vaccines has rekindled hope of finding new solutions.[25] Many of the unusual fetal/neonatal pathogens are transmitted by specific animal/insect vectors,[26,27] and the possibility of preventing insects from becoming long-term carriers through community-wide organizational and genetics-based efforts may bring new solutions.[28] Finally, as we understand epigenetics better, our improved understanding of immunity in fetuses and infants may help in finding new solutions.[29,30] Fetal/neonatal susceptibility reflects an age-related manifestation; we know that these changes in gene expression are epigenetic alterations.[31] If we can understand these changes, we might be able to make a difference. Finally, we still need new treatments and monitoring paradigms.[32] Not every treatment is uniformly available or affordable in different parts of the world.[33] Computational systems to assess, monitor, and treat these highly susceptible patients can be one way to make a difference.[34,35] If we know the possibilities, we can educate and motivate our care-providers to acquire and learn these tools.[36]

Our journal, the *Newborn* aims to cover fetal/neonatal problems that begin during pregnancy or occur after birth during the first 1000 days after birth. In this 1st issue of the second volume, we present 8 important articles (**Figure 1**). In an original study, Motta and his team[37] have evaluated the impact of a web-based software specifically designed for neonatal parenteral nutrition (PN) prescription on extrauterine growth restriction (EUGR) in a cohort of very-low-birth-weight (VLBW) infants. This article is very important because EUGR, a multifactorial condition, is increasingly recognized to be a risk factor for adverse long-term consequences for preterm infants.[38,39] They present a retrospective analysis of serial anthropometric measurements and comorbidities in a cohort of 119 VLBW infants treated with parenteral nutrition for at least 5 consecutive days. They show that a web-based system for prescription of neonatal PN may be useful for ensuring adequate intake of nutrients in preterm infants. These findings need further evaluation, both in terms of short- and long-term outcomes in a larger cohort.

There are 3 important reviews focused on the impact of infectious agents on the developing immunity. Kaur and Dudeja[40] present a scholarly review of the pathogenesis of Enteropathogenic *Escherichia coli* (EPEC) infections in infants. EPEC are an important cause of diarrhea in infants and young children all over the world.[41] Newer molecular diagnostic methods have identified typical and atypical strains of EPEC, and epidemiological studies show that atypical strains might be a more important cause of both endemic diarrhea and outbreaks of diarrhea.[42] The virulence mechanisms and physiopathology of the attaching and effacing lesion (A/E) and the type-three-secretion-system (T3SS) are complex.[43,44] A/E strains use a pool of locus of enterocyte effacement (LEE)-encoded and non-LEE-encoded effector proteins to subvert cellular and barrier properties of the intestinal epithelium.[45] More work is needed to understand the mechanisms of diarrhea in EPEC infections.

In two separate articles, Singh *et al.*[46] and Ethawi *et al.*[47] have reviewed perinatal infections by Chikungunya and Zika viruses. Chikungunya virus is widely transmitted in tropical and subtropical areas by Aedes mosquito vectors.[48] Perinatal/neonatal infections are fortunately not seen very frequently, but some infants can develop fever, thrombocytopenia, lymphopenia, pigmentary changes, and a maculopapular rash.[49] A small subgroup of these infants can develop encephalopathy and have poor neurocognitive outcomes.[50,51] There is no specific treatment, but some candidate vaccines are under evaluation.[52,53] Zika virus (ZIKV) is another viral disease transmitted by Aedes mosquitoes.[54] Infected mothers can vertically transmit ZV to their fetuses, particularly during the first and second trimesters.

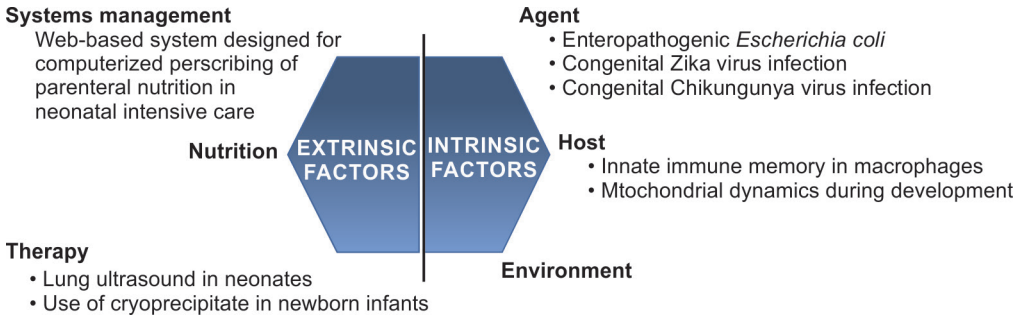

Fig. 1: **Areas of focus in the *Newborn*, volume 2, issue 1.** The *Newborn* has expanded the traditional agent-host-environment trinodal disease model to a hexagonal system. The three additional foci represent extrinsic factors that can affect health; these originate in therapy, nutrition, and systems management. In volume 2, issue 1, we cover 4 of these foci, namely infectious diseases, host factors, therapy, and systems management.

These early-gestation infections can manifest with structural abnormalities of the central nervous system.[55] Unfortunately, we do not have any specific treatment. Evaluation of candidate vaccines is still in an early phase.[56]

There are two extensive reviews focused on macrophages[57] and mitochondria,[58] respectively. In fetuses, neonates, and young infants, macrophages serve a very important role in immune defenses.[59] These cells have thus far been recognized as the primary mediators of innate immunity starting early during development.[60,61] Unlike adaptive immunity, macrophage-mediated defenses have traditionally not been recognized as antigen-specific.[62] However, increasing information suggests that macrophage responses do strengthen with repeated immunological triggers. This concept of innate memory in macrophages has been described as "trained immunity" or "innate immune memory (IIM)." This cellular memory is rooted in epigenetic and metabolic reprogramming.[63]

The second review is focused on mitochondria. As we recognize, mitochondria are dynamic membrane-bound organelles in eukaryotic cells.[64] These are important for the generation of chemical energy needed to power various cellular functions, and also support metabolic, energetic, and epigenetic regulation in various cells. These organelles most likely evolved about 2 billion years ago from α-proteobacteria, a subgroup of the purple non-sulfur bacteria, which most likely belonged to the order *Rickettsiales*.[65] This article provides extensive information about the ontogeny, ultrastructure, structure-function correlation, and biogenesis of mitochondria, and clinical manifestations of mitochondrial dysfunction.

Verma *et al*. have provided a very important review of point-of-care (POC) lung ultrasound, a new modality for assessing the severity of lung disease.[66,67] In the first part of the article, they have defined and discussed various findings in POC lung ultrasound. The second part describes the detection and serial evolution of diagnostic findings in conditions such as respiratory distress syndrome, transient tachypnea of newborn, atelectasis, pneumonia, air-leaks, and bronchopulmonary dysplasia/chronic lung disease of the newborn. These bedside assessments can help in timely evaluation and clinical management of these conditions.[68]

Finally, we have a review article focused on cryoprecipitate, a transfusion blood product that can be useful in critically ill neonates with coagulopathy.[69] Admittedly, it is now being used more often in situations when specific recombinant clotting factors are not available, but it can be life-saving in resource-limited regions of the world.[70,71] Cryoprecipitate is derived from fresh-frozen plasma, and is highly enriched in coagulation factors I (fibrinogen), VIII, and XIII; von Willebrand factor (vWF); and fibronectin.[72] The review presents current information on the preparation, properties, and the clinical importance of cryoprecipitate in treating critically ill neonates.

References

1. Basu S, Tilak R, Kumar A. Multidrug-resistant Trichosporon: an unusual fungal sepsis in preterm neonates. Pathog Glob Health. 2015;109(4):202–206. doi:10.1179/2047773215Y.0000000019
2. Dard C, Chemla C, Fricker-Hidalgo H, et al. Late diagnosis of congenital toxoplasmosis based on serological follow-up: A case report. Parasitol Int. 2017;66(2):186–189. doi:10.1016/j.parint.2016.12.004
3. Goytia VK, Demmler GJ, Pannaraj PS, et al. An unusual cause of sepsis and meningitis in a neonate. Semin Pediatr Infect Dis. 2006;17(4):187, 225–7. doi:10.1053/j.spid.2006.08.003
4. Keus A, Peeters DD, Bekker VV, et al. Neonatal Meningitis and Subdural Empyema Caused by an Unusual Pathogen. Pediatr Infect Dis J. 2019;38(12):e329-e331. doi:10.1097/INF.0000000000002482
5. Kouadio F, Klinger G. Pneumonia, an unusual initial presentation of neonatal herpes infection. Case Rep Crit Care. 2019;2019:9594289. doi:10.1155/2019/9594289
6. Maheshwari A, Stromquist CI, Pereda L, et al. Mixed infection with unusual fungi and staphylococcal species in two extremely premature neonates. J Perinatol. 2004;24(5):324–6. doi:10.1038/sj.jp.7211077
7. McAllister MM, Funnell O, Donahoe SL, et al. Unusual presentation of neosporosis in a neonatal puppy from a litter of bulldogs. Aust Vet J. 2016;94(11):411–414. doi:10.1111/avj.12516
8. Scheurer JM, Fanta ML, Colbenson GA, et al. Early-onset neonatal sepsis caused by vertical transmission of Pasteurella multocida. AJP Rep. 2022;12(2):e123–e126. doi:10.1055/a-1830-2903
9. Sert A, Yazar A, Odabas D, et al. An unusual cause of fever in a neonate: influenza A (H1N1) virus pneumonia. Pediatr Pulmonol. 2010;45(7):734–736. doi:10.1002/ppul.21245
10. Wood AS, Foraker EE, Di Pentima C. Molecular epidemiology in neonatal pasteurellosis. Pediatr Infect Dis J. 2013;32(12):1402. doi:10.1097/INF.0000000000000004
11. Camacho-Gonzalez A, Spearman PW, Stoll BJ. Neonatal infectious diseases: evaluation of neonatal sepsis. Pediatr Clin North Am. 2013;60(2):367–389. doi:10.1016/j.pcl.2012.12.003
12. Zou H, Jia X, He X, et al. Emerging threat of multidrug resistant pathogens from neonatal sepsis. Front Cell Infect Microbiol. 2021;11:694093. doi:10.3389/fcimb.2021.694093
13. Marodi L. Neonatal innate immunity to infectious agents. Infect Immun. 2006;74(4):1999–2006. doi:10.1128/IAI.74.4.1999-2006.2006
14. E SA-M. Toxoplasmosis: stages of the protozoan life cycle and risk assessment in humans and animals for an enhanced awareness and an improved socio-economic status. Saudi J Biol Sci. 2021;28(1):962–969. doi:10.1016/j.sjbs.2020.11.007
15. Shaapan RM. The common zoonotic protozoal diseases causing abortion. J Parasit Dis. 2016;40(4):1116–1129. doi:10.1007/s12639-015-0661-5
16. Basha S, Surendran N, Pichichero M. Immune responses in neonates. Expert Rev Clin Immunol. 2014;10(9):1171–1184. doi:10.1586/1744666X.2014.942288
17. Tsafaras GP, Ntontsi P, Xanthou G. Advantages and limitations of the neonatal immune system. Front Pediatr. 2020;8:5. doi:10.3389/fped.2020.00005
18. Sadeghi K, Berger A, Langgartner M, et al. Immaturity of infection control in preterm and term newborns is associated with impaired toll-like receptor signaling. J Infect Dis. 2007;195(2):296–302. doi:10.1086/509892
19. Johnson J, Akinboyo IC, Schaffzin JK. Infection prevention in the neonatal intensive care unit. Clin Perinatol. 2021;48(2):413–429. doi:10.1016/j.clp.2021.03.011

20. Bhatta DR, Hosuru Subramanya S, Hamal D, et al. Bacterial contamination of neonatal intensive care units: How safe are the neonates? Antimicrob Resist Infect Control. 2021;10(1):26. doi:10.1186/s13756-021-00901-2
21. Kumar S, Shankar B, Arya S, Deb M, Chellani H. Healthcare associated infections in neonatal intensive care unit and its correlation with environmental surveillance. J Infect Public Health. 2018;11(2):275–279. doi:10.1016/j.jiph.2017.08.005
22. Baker RE, Mahmud AS, Miller IF, et al. Infectious disease in an era of global change. Nat Rev Microbiol. 2022;20(4):193–205. doi:10.1038/s41579-021-00639-z
23. Shehab El-Din EM, El-Sokkary MM, Bassiouny MR, et al. Epidemiology of Neonatal Sepsis and Implicated Pathogens: A Study from Egypt. Biomed Res Int. 2015;2015:509484. doi:10.1155/2015/509484
24. Oliva A, Carmona Y, de La CLE, et al. Characterization of neonatal infections by gram-Negative bacilli and associated risk factors. Havana, Cuba. Infect Dis Rep. 2021;13(1):219–229. doi:10.3390/idr13010025
25. Aggarwal A, Garg N. Newer vaccines against mosquito-borne diseases. Indian J Pediatr. 2018;85(2):117–123. doi:10.1007/s12098-017-2383-4
26. Lee H, Halverson S, Ezinwa N. Mosquito-borne diseases. Prim Care. 2018;45(3):393-407. doi:10.1016/j.pop.2018.05.001
27. Weber DJ, Rutala WA. Zoonotic infections. Occup Med. 1999;14(2):247–284.
28. Roiz D, Wilson AL, Scott TW, et al. Integrated Aedes management for the control of Aedes-borne diseases. PLoS Negl Trop Dis. 2018;12(12):e0006845. doi:10.1371/journal.pntd.0006845
29. Ho SM, Johnson A, Tarapore P, Janakiram V, Zhang X, Leung YK. Environmental epigenetics and its implication on disease risk and health outcomes. ILAR J. 2012;53(3–4):289–305. doi:10.1093/ilar.53.3-4.289
30. Lee HS, Barraza-Villarreal A, Hernandez-Vargas H, et al. Modulation of DNA methylation states and infant immune system by dietary supplementation with omega-3 PUFA during pregnancy in an intervention study. Am J Clin Nutr. 2013;98(2):480–487. doi:10.3945/ajcn.112.052241
31. Everson TM, O'Shea TM, Burt A, et al. Serious neonatal morbidities are associated with differences in DNA methylation among very preterm infants. Clin Epigenetics. 2020;12(1):151. doi:10.1186/s13148-020-00942-1
32. Leff SS, Hoffman JA, Gullan RL. Intervention Integrity: New Paradigms and Applications. School Ment Health. 2009;1(3):103–106. doi:10.1007/s12310-009-9013-x
33. Kruk ME, Gage AD, Arsenault C, et al. High-quality health systems in the sustainable development doals era: time for a revolution. Lancet Glob Health. 2018;6(11):e1196–e1252. doi:10.1016/S2214-109X(18)30386-3
34. Kelly CJ, Karthikesalingam A, Suleyman M, et al. Key challenges for delivering clinical impact with artificial intelligence. BMC Med. 2019;17(1):195. doi:10.1186/s12916-019-1426-2
35. Jiang F, Jiang Y, Zhi H, et al. Artificial intelligence in healthcare: past, present and future. Stroke Vasc Neurol. 2017;2(4):230–243. doi:10.1136/svn-2017-000101
36. Jeyakumar T, McClure S, Lowe M, et al. An education framework for effective implementation of a health information system: Scoping Review. J Med Internet Res. 2021;23(2):e24691. doi:10.2196/24691
37. Motta M, Aversa S, Morotti F, Maheshwari A, Tomasi C, Maria Risso F. Extrauterine growth restriction in preterm very low birth weight infants: The use of a web-based system designed for computerized prescribing of parenteral nutrition in neonatal intensive care. Newborn. 2023;2(1):1–10.
38. Makker K, Ji Y, Hong X, et al. Antenatal and neonatal factors contributing to extra uterine growth failure (EUGR) among preterm infants in Boston Birth Cohort (BBC). J Perinatol. 2021;41(5):1025–1032. doi:10.1038/s41372-021-00948-4
39. Gidi NW, Goldenberg RL, Nigussie AK, et al. Incidence and associated factors of extrauterine growth restriction (EUGR) in preterm infants, a cross-sectional study in selected NICUs in Ethiopia. BMJ Paediatr Open. 2020;4(1):e000765. doi:10.1136/bmjpo-2020-000765
40. Kaur P, Dudeja P. Pathophysiology of enteropathogenic Escherichia coli-induced diarrhea. Newborn. 2023;2(1):102–113.
41. Ochoa TJ, Barletta F, Contreras C, et al. New insights into the epidemiology of enteropathogenic Escherichia coli infection. Trans R Soc Trop Med Hyg. 2008;102(9):852–856. doi:10.1016/j.trstmh.2008.03.017
42. Hernandes RT, Elias WP, Vieira MA, et al. An overview of atypical enteropathogenic Escherichia coli. FEMS Microbiol Lett. 2009;297(2):137–149. doi:10.1111/j.1574-6968.2009.01664.x
43. Gaytan MO, Martinez-Santos VI, Soto E, et al. Type three secretion system in attaching and effacing pathogens. Front Cell Infect Microbiol. 2016;6:129. doi:10.3389/fcimb.2016.00129
44. Hecht G, Hodges K, Gill RK, et al. Differential regulation of Na+/H+ exchange isoform activities by enteropathogenic E. coli in human intestinal epithelial cells. Am J Physiol Gastrointest Liver Physiol. 2004;287(2):G370–8. doi:10.1152/ajpgi.00432.2003
45. Ritchie JM, Waldor MK. The locus of enterocyte effacement-encoded effector proteins all promote enterohemorrhagic Escherichia coli pathogenicity in infant rabbits. Infect Immun. 2005;73(3):1466–1474. doi:10.1128/IAI.73.3.1466-1474.2005
46. Singh S, Panghal A, Mane S, et al. Congenital chikungunya virus infections. Newborn. 2023;2(1):45–59.
47. Ethawi Y, Kasniya G, Al Baiti N, Mohammed R, Elzahra F, Huseynova R. Congenital zika virus infections. Newborn. 2023;2(1):91–101.
48. Monteiro VVS, Navegantes-Lima KC, de Lemos AB, et al. Aedes-Chikungunya virus interaction: Key role of vector midguts microbiota and its saliva in the host infection. Front Microbiol. 2019;10:492. doi:10.3389/fmicb.2019.00492
49. Bandyopadhyay D, Ghosh SK. Mucocutaneous manifestations of chikungunya fever. Indian J Dermatol. 2010;55(1):64–67. doi:10.4103/0019-5154.60356
50. Gupta V, Gupta N, Pandita A. Neonate with chikungunya. Clin Case Rep. 2021;9(6):e04351. doi:10.1002/ccr3.4351
51. Barr KL, Vaidhyanathan V. Chikungunya in infants and children: Is pathogenesis increasing? Viruses. 2019;11(3)doi:10.3390/v11030294
52. Schwameis M, Buchtele N, Wadowski PP, et al. Chikungunya vaccines in development. Hum Vaccin Immunother. 2016;12(3):716–731. doi:10.1080/21645515.2015.1101197
53. Erasmus JH, Rossi SL, Weaver SC. Development of vaccines for chikungunya fever. J Infect Dis. 2016;214(suppl 5):S488–S496. doi:10.1093/infdis/jiw271
54. Zhou TF, Lai ZT, Liu S, et al. Susceptibility and interactions between Aedes mosquitoes and Zika viruses. Insect Sci. 2021;28(5):1439–1451. doi:10.1111/1744-7917.12858

55. Moore CA, Staples JE, Dobyns WB, et al. Characterizing the pattern of anomalies in congenital Zika syndrome for pediatric clinicians. JAMA Pediatr. 2017;171(3):288–295. doi:10.1001/jamapediatrics.2016.3982
56. Tebas P, Roberts CC, Muthumani K, et al. Safety and immunogenicity of an anti-Zika virus DNA vaccine. N Engl J Med. 2021;385(12):e35. doi:10.1056/NEJMoa1708120
57. Maheshwari A. Innate immune memory in macrophages. Newborn. 2023;2(1):60–79.
58. He L, Tronstad KJ, Maheshwari A. Mitochondrial dynamics during development. Newborn. 2023;2(1):19–44.
59. Mezu-Ndubuisi OJ, Maheshwari A. Role of macrophages in fetal development and perinatal disorders. Pediatr Res. 2021;90(3):513–523. doi:10.1038/s41390-020-01209-4
60. Newburg DS, Walker WA. Protection of the neonate by the innate immune system of developing gut and of human milk. Pediatr Res. 2007;61(1):2–8. doi:10.1203/01.pdr.0000250274.68571.18
61. MohanKumar K, Namachivayam K, Song T, et al. A murine neonatal model of necrotizing enterocolitis caused by anemia and red blood cell transfusions. Nat Commun. 2019;10(1):3494. doi:10.1038/s41467-019-11199-5
62. Marshall JS, Warrington R, Watson W, et al. An introduction to immunology and immunopathology. Allergy Asthma Clin Immunol. 2018;14(Suppl 2):49. doi:10.1186/s13223-018-0278-1
63. Wu C, Xu Y, Zhao Y. Two kinds of macrophage memory: innate and adaptive immune-like macrophage memory. Cell Mol Immunol. 2022;19(7):852–854. doi:10.1038/s41423-022-00885-y
64. He L, Maheshwari A. Mitochondria in early life. Curr Pediatr Rev. 2023;19(4):395–416. doi:10.2174/1573396319666221221110728
65. Munoz-Gomez SA, Hess S, Burger G, et al. An updated phylogeny of the Alphaproteobacteria reveals that the parasitic Rickettsiales and Holosporales have independent origins. Elife. 2019;8:e42535. doi:10.7554/eLife.42535
66. Raimondi F, Yousef N, Migliaro F, et al. Point-of-care lung ultrasound in neonatology: classification into descriptive and functional applications. Pediatr Res. 2021;90(3):524–531. doi:10.1038/s41390-018-0114-9
67. Rath C, Suryawanshi P. Point of Care Neonatal Ultrasound - Head, Lung, Gut and Line Localization. Indian Pediatr. 2016;53(10):889–899. doi:10.1007/s13312-016-0954-5
68. Kameda T, Mizuma Y, Taniguchi H, et al. Point-of-care lung ultrasound for the assessment of pneumonia: a narrative review in the COVID-19 era. J Med Ultrason. 2021;48(1):31–43. doi:10.1007/s10396-020-01074-y
69. Stanworth SJ. The evidence-based use of FFP and cryoprecipitate for abnormalities of coagulation tests and clinical coagulopathy. Hematology Am Soc Hematol Educ Program. 2007:179–86. doi:10.1182/asheducation-2007.1.179
70. Holcomb JB, Fox EE, Zhang X, et al. Cryoprecipitate use in the PROMMTT study. J Trauma Acute Care Surg. 2013;75(1 Suppl 1):S31–39. doi:10.1097/TA.0b013e31828fa3ed
71. Nair PM, Rendo MJ, Reddoch-Cardenas KM, Burris JK, Meledeo MA, Cap AP. Recent advances in use of fresh frozen plasma, cryoprecipitate, immunoglobulins, and clotting factors for transfusion support in patients with hematologic disease. Semin Hematol. 2020;57(2):73–82. doi:10.1053/j.seminhematol.2020.07.006
72. Kovacic Krizanic K, Pruller F, Rosskopf K, Payrat JM, Andresen S, et al. Preparation and storage of cryoprecipitate derived from amotosalen and UVA-treated apheresis plasma and assessment of in vitro quality parameters. Pathogens. 2022;11(7):805. doi:10.3390/pathogens11070805

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