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Rational development of guidelines for management of neonatal sepsis in developing countries

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Abstract

Purpose of review—This review discusses the rational development of guidelines for the management of neonatal sepsis in developing countries.

Recent findings—Diagnosis of neonatal sepsis with high specificity remains challenging in developing countries. Aetiology data, particularly from rural, community based studies are very limited, but molecular tests to improve diagnostics are being tested in a community-based study in South Asia. Antibiotic susceptibility data are limited, but suggest reducing susceptibility to first and second line antibiotics in both hospital and community acquired neonatal sepsis. Results of clinical trials in South Asia and sub-Saharan Africa assessing feasibility of simplified antibiotic regimens are awaited.

Summary—Effective management of neonatal sepsis in developing countries is essential to reduce neonatal mortality and morbidity. Simplified antibiotic regimens are currently being examined in clinical trials, but reduced antimicrobial susceptibility threatens current empiric treatment strategies. Improved clinical and microbiological surveillance is essential, to inform current practice, treatment guidelines, and monitor implementation of policy changes.

Keywords

Neonatal; infection; guidelines; sepsis; infant

Introduction

Substantial improvements in maternal and child health have been achieved since 2000, with reductions in child deaths from infectious diseases.[1] However, reducing neonatal deaths, and stillbirths, remains challenging.[2] Of the estimated 6.3 million deaths in children under five

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years in 2013,[3] 2.8 million (44%) of these deaths were in the neonatal period (0-27 days), and 0.42 (95%CI 0.27-0.69) million of neonatal deaths were due to sepsis.[1]

The global burden of morbidity due to neonatal infection was estimated at ~3% of all Disability Adjusted Life Years (DALYs),[4] but this estimate excludes long-term morbidity, due to a lack of data on impairment outcomes.[5] With an estimated 6.9 (95%CI 5.5-8.3) million cases of possible severe bacterial infection (pSBI) in neonates in South Asia, sub-Saharan Africa and Latin America in 2012, improving our understanding of this burden is essential.[6]

Reducing the burden of neonatal mortality and morbidity depends on the scale-up of essential interventions, which if universally achieved could reduce neonatal mortality by over two thirds.[7] These interventions include prevention and management of preterm birth, basic and comprehensive obstetric care, immediate new-born care (including resuscitation and antisepsis measures), supportive care, especially for preterm neonates (including kangaroo mother care) and effective management of neonatal infections.[7-9]

Improving management of neonatal infections depends on effective guidelines, and overcoming barriers to implement them.[7] Here the challenges of the rational development of guidelines in developing countries for the management of neonatal sepsis are identified and discussed.

Diagnosis

Neonatal diseases are difficult to diagnose clinically because signs and symptoms are much more non-specific for infectious syndromes (sepsis, pneumonia or meningitis) than in older children. The same clinical signs can be present, for example, in neonates born preterm (<37 weeks' gestation), with intra-partum complications, or viral illnesses, with or without concurrent bacterial infection.[6]

In developing countries diagnoses are usually made by health care workers without specialist training. To support diagnoses of "possible severe bacterial infection" (pSBI) and guide treatment, clinical algorithms have been developed, described in the Integrated Management of Childhood Illness.[10] These algorithms have been informed by research, including the first WHO Young Infants Clinical Signs Study (YICSS),[11] and the second YICSS, which included a focus on neonates in the first week of life.[12] In the second YICSS study, seven clinical signs (fast breathing (respiratory rate >60 breaths per minute), severe chest in-drawing, hyperthermia >37•5°C, hypothermia <35•5°C, no movement or movement only on stimulation, convulsions, poor feeding) had 85% sensitivity and 75% specificity for severe bacterial infection in the first week of life, with an experienced paediatrician's diagnosis as the gold standard.[12] Subsequent meta-analysis of six studies validating the use of this algorithm against physician diagnosis (with supporting laboratory data) found a similarly high sensitivity (87%) but specificity was lower (62%).[13] Fast breathing has been identified as having low specificity as a single sign,[14] and hypothermia may be influenced by the environment, for example in Nepal just under half of all neonates were reported to have hypothermia (32.0-36.0°C).[15]

There are particular settings in which low specificity is problematic. If the algorithm is used in the community to facilitate identification and treatment of neonates,[16] and the prevalence of neonatal infection is much lower than in those seeking health care, the positive predictive value using this algorithm will be lower (less than 50%).[6] In clinical trials, low specificity may introduce misclassification of disease, as described for treatment trials of pneumonia.[17] In current clinical trials for simplified antibiotic treatment the YICSS algorithm has been amended to increase specificity; fast breathing is not included as a single sign for case definition, the temperature threshold was increased from ≥37.5 to ≥38.0°C, and poor feeding had to be confirmed by observation. In addition, neonates with convulsions were excluded from the study of simplified treatments, as they were considered to have critical illness. It is important that standardised case definitions for possible severe bacterial infections in neonates are used, but with the flexibility to evolve, as more sensitive and specific clinical signs and diagnostic strategies are identified.

In developed countries clinical diagnosis of severe bacterial infection in neonates is supported by experienced paediatricians and systematic laboratory investigation, including conventional microbiological (blood, cerebrospinal fluid and urine), haematological, and biochemical tests. However, even with the expertise and investigations available in developed countries, diagnosis remains a challenge.[18] Microbiological identification of a pathogen isolated from blood cultures can confirm a clinical diagnosis of neonatal sepsis, and has high specificity, but sensitivity is lower. Although blood culture sensitivity has been improved with automated blood culture systems (such as BACTEC, BactTALERT), it is still likely less than 80%, particularly with small (<1mL) blood volumes, common from neonatal samples, and if the colony forming unit is low (<4 CFU/mL).[19]

Molecular microbiology, using nucleic acid testing (NAT), may improve diagnostics. There are rapid advances in the use of NAT tests to diagnose and determine the aetiology of diarrhoea and meningitis, both in terms of sensitivity and implementation in developing countries.[20-22] However, high sensitivity can present problems in interpretation, and careful case-control studies are required to establish attributable fractions of disease using these methods.[23] Experience of molecular methods to improve diagnosis in developing countries are more limited for neonatal sepsis than for pneumonia,[24] diarrhoea,[20] or meningitis,[25] but NAT using the Taqman Array Card is being used in a large ongoing multi-site study of the Aetiology of Neonatal Sepsis in South Asia (ANISA),[2627] with results awaited.

In both developed and developing settings, there is a risk of overtreatment for neonatal sepsis, as sensitivity is prioritised over specificity, due to high case fatality risk if neonatal sepsis is untreated. However, unnecessary treatment is not without risk in terms of possible side-effects of treatment, especially with over-dosing, reported in a fifth of neonatal cases in a study in district hospitals in the Kilimanjaro region of Tanzania.[28] Unnecessary treatment and admission to hospital also increases the risk of invasive fungal infections, hospital acquired bacterial infections, and reduced antibiotic susceptibility.[29] A rapid diagnostic test, if it were available, would transform care,[30] directing treatment to those who needed it, and preventing unnecessary antibiotic use.

Aetiology

Differences in the aetiology of neonatal sepsis in developed and developing countries may reflect true differences in disease epidemiology, as well as differences in the levels of care available to support survival of preterm and/or low birth weight neonates. They may also be due to study methodologies, including the quality of microbiological investigations, and study design, particularly whether community or health facility based. There are very limited community based studies,[31,32] of neonatal infection in developing countries.

In early onset neonatal sepsis (0-6 days of life), the most commonly reported pathogens in developing countries include Gram negatives (*Escherichia coli*, *Klebsiella pneumoniae)* and Gram positives (*Staphylococcus aureus*).[33-35] These early-onset infections may include hospital acquired infections, if associated with hospital delivery in developing countries, where inadequate hygiene and anti-sepsis measures contribute to early-onset infections.[36] For late onset neonatal sepsis the most common pathogens reported in developing countries are mainly Gram positive, including *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Streptococcus agalactiae* and some Gram negative non-typhoidal *Salmonellae sp.*.[33-35]

Streptococcus agalactiae (Group B Streptococcus, GBS) although the leading pathogen in early onset infections in developed countries,[37,38] is less consistently reported in developing countries, particularly studies of community acquired bacteraemia. However, in a recent systematic review, although in Southeast Asia the estimated burden of GBS disease in infants was low (0.02/1000 live births (95%CI 0.00-0.07)), Africa was estimated to have the highest incidence of GBS in infants worldwide (1.21/1000 live births (95%CI 0.50-1.91)), although based on only four studies,[39-42] meeting selection criteria.[43] In contrast, the WHO study in The Gambia, Ethiopia, The Philippines and Papua New Guinea in the 1990s investigated 2398 infants attending as outpatients,[44] and isolated GBS in blood cultures from only two infants. Most recently, the WHO study in Bangladesh, Bolivia, Ghana, India, Pakistan and South Africa investigated 782 infants, and there were no isolates of GBS.[45] These differences may reflect true differences, particularly in disease-causing serotypes,[46] however, this study excluded the most severely ill neonates, and it is possible that with delays in accessing care, neonates with GBS died prior to arrival, especially in early onset GBS sepsis,[43] for which the case fatality risk is three times higher in developing countries (12·6%, 95% CI 10·8–14·9) than in developed countries (4·6%, 2·1–9·1).[43]

The role of coagulase negative Staphylococci (CoNS) in neonatal sepsis in developing countries is not defined; in developed countries they are the leading cause of late onset sepsis,[37] but occur mainly in very preterm neonates in intensive care, with ventilator support and indwelling devices.[47] In developing countries, the burden of preterm birth is high,[48,49] but mortality is also very high.[1,49] Supportive care is much more limited, so indwelling devices and invasive ventilation are much less frequently used,[50] and, if in use, are restricted to referral centres in urban settings. In this context, it is unclear the extent to which CoNS acts as a neonatal pathogen; it is sometimes reported,[51-56] but at other times excluded as a contaminant.[39,45,57-60]

Issues of contamination are important for other common skin colonisers, such as *Staphylococcus aureus.* Whilst *S.aureus* does cause disease, the dominance of *S. aureus* reported in some studies in developing countries,[41,45,61] may in part be due to contamination from skin colonisation and inadequate site sterilisation when blood cultures are taken.[45]

Treatment

Empirical treatment for neonatal sepsis, recommended in current WHO guidelines is intravenous ampicillin (or penicillin) plus gentamicin for 7 days.[62] Cloxacillin is an alternative if Staphylococcal infection is suspected. Third generation cephalosporins, increasing in availability, particularly in Asia,[13] are used as second line for those not responding after 48-72 hours of treatment. Despite the inconsistent literature on GBS infections, neonatal treatment (but not intra-partum antibiotic prophylaxis) is also recommended for 48 hours (and then review) for neonates born to mothers with PROM (≥18h), maternal fever ≥38°C before delivery or during labour, and foul-smelling amniotic fluid.[62]

Treatment guidelines include admission to hospital, but care seeking can be low (varying from 10-100% in low and middle income countries).[63] Clinical trials based in Africa and south Asia are assessing whether current antibiotic regimens can be simplified, to facilitate access to care.[14] The Simplified Antibiotic Therapy Trial (SATT) Bangladesh, SATT Pakistan and African Neonatal Sepsis Trial (AFRINEST)), with harmonised protocols,[64] aim to evaluate standard 7 day treatment (daily injection procaine penicillin and gentamicin) compared to combinations of injectable antibiotics and oral amoxicillin.[14]

The success of treatment, however, depends on pathogens being susceptible to treatment choices. Data are limited, but there is increasing evidence for reduced susceptibility in pathogens causing both hospital acquired infections,[36] and community acquired infections, particularly *Klebsiella sp*, and *Staphylococcus aureus*.[33,65,66] In an assessment of WHO treatment guidelines, for hospital acquired infection, around a third of neonatal sepsis isolates were estimated to be susceptible to first line antibiotics,[36] and a half of Gram negatives (*Klebsiella sp* and *E.Coli*) to second line treatment.[36] *Klebsiella pneumoniae* is a particularly important neonatal pathogen, both in terms of its prevalence, ability to persist in environments,[67,68] and cause persisting outbreaks of hospital acquired infections, which can be highly resistant to treatment.[68]

Community-based studies with antibiotic susceptibility data are limited, but in a systematic review including 11 studies, 57% of bacterial isolates were estimated to be susceptible to benzylpenicillin/ampicillin and gentamicin, and 56% susceptible to third generation cephalosporins.[33] Recent work supports these findings; 40 Gram negative neonatal pathogens were isolated as part of the WHO study across six countries and 38/39 (97%) showed resistance to ampicillin, 17/39 (44%) to gentamicin and 19/31 (61%) to third generation cephalosporins.[45] Alternative therapeutic options, such as fluoroquinolones and carbapenems, are limited and expensive for developing countries.

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Supportive care

Respiratory support, intravenous fluids, phototherapy, temperature and glucose regulation as well as prevention of hospital acquired infections, are essential components of care. Limitations in resources mean that interventions for supportive care must be pragmatic. A report of neonatal care in training centres across Kenya found that all hospitals had oxygen, and 19/22 had resuscitation and phototherapy equipment.[50] Pragmatic interventions to improve respiratory support, beyond the provision of oxygen, have been recently described, using bubble CPAP in Uganda and Malawi, with promising findings.[69,70] Similar progress needs to be made in terms of controlled fluid delivery to neonates; there were only 12/22 training centres across Kenya with paediatric burettes.[50] Uncontrolled or inadequate provision of intravenous fluids likely results in many undetected cases of electrolyte imbalance and consequent morbidity and mortality. Simple bedside tests are available for testing glucose levels, and temperature regulation can be improved by Kangaroo Mother Care, but these interventions need adequate staffing and health system support for implementation.

Improving the evidence

In contrast to the networks being set up in developed countries to report and monitor neonatal infections,[37] there are few health facilities in developing countries undertaking systematic clinical surveillance. Embedding clinical surveillance and using admission pro-forma facilitates clinical audit and monitoring and improves care. It will be increasingly possible to add microbiological diagnostic techniques to clinical surveillance platforms to improve understanding of the aetiology of disease and inform treatment guidelines. Reduced antibiotic susceptibility in both hospital and community acquired infections represents an increasing threat to empiric treatment strategies, and more data are urgently needed.[3671] Methods such as whole genome sequencing will be able to shed new light on the epidemiology of infectious diseases worldwide, including transmission,[72] and antibiotic susceptibility.[73] Understanding these mechanisms in developing countries, and identifying drivers of reduced antibiotic susceptibility are essential to inform prevention and control.

Conclusion

Effective management of neonatal sepsis in developing countries is essential to achieve further reductions in child mortality. Simplified antibiotic regimens are currently being examined in clinical trials, but reduced antimicrobial susceptibility threatens current empiric treatment strategies. Improved clinical and microbiological surveillance is essential, to inform current practice, treatment guidelines, and monitor implementation of policy changes.

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Abbreviations

(ANISA)	Aetiology of Neonatal Sepsis in South Asia
(CoNS)	Coagulase Negative Staphylococci
(CFU)	Colony Forming Units
(CPAP)	Continuous positive air pressure
(DALYs)	Disability Adjusted Life Years
(GBS)	Group B Streptococcus
(NAT)	Nucleic Acid Testing
(pSBI)	Possible Severe Bacterial Infection
(WHO)	World Health Organisation
(YICSS)	WHO Young Infants Clinical Signs Study

References and recommended reading

*of special interest **of outstanding interest

1. Liu L, Oza S, Hogan D, et al. Global, regional, and national causes of child mortality in 2000-13, with projections to inform post-2015 priorities: an updated systematic analysis. Lancet. 2015; 385(9966):430–40. [PubMed: 25280870]
2. Lawn JE, Blencowe H, Oza S, et al. Every Newborn: progress, priorities, and potential beyond survival. Lancet. 2014; 384(9938):189–205. [PubMed: 24853593]
3. UNICEF. The UN Inter-Agency Group for Child Mortality Estimation. UNICEF; New York: 2013.
4. Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2013; 380(9859):2197–223. [PubMed: 23245608]
5. Seale AC, Blencowe H, Zaidi A, et al. Neonatal severe bacterial infection impairment estimates in South Asia and sub-Saharan Africa for 2010. Pediatric Research. 2013; 74(S1):73–5. [PubMed: 24366464]

*6. Seale AC, Blencowe H, Manu AA, et al. Estimates of possible severe bacterial infection in neonates in sub-Saharan Africa, south Asia, and Latin America for 2012: a systematic review and meta-analysis. Lancet Infect Dis. 2014; 14(8):731–41. [PubMed: 24974250] Provides the first estimates of the number of cases of possible severe bacterial infection in neonates in developing countries needing treatment.

*7. Dickson KE, Simen-Kapeu A, Kinney MV, et al. Every Newborn: health-systems bottlenecks and strategies to accelerate scale-up in countries. Lancet. 2014; 384(9941):438–54. [PubMed: 24853600] Describes the problems and proposes solutions to scaling up interventions known to be effective to reduce neonatal morbidity and mortality.

8. Imdad A, Mullany LC, Baqui AH, et al. The effect of umbilical cord cleansing with chlorhexidine on omphalitis and neonatal mortality in community settings in developing countries: a meta-analysis. BMC Public Health. 2013; 13(Suppl 3):S15. [PubMed: 24564621]
9. Conde-Agudelo A, Diaz-Rossello JL. Kangaroo mother care to reduce morbidity and mortality in low birthweight infants. Cochrane Database Syst Rev. 2014:CD002771. [PubMed: 24752403]
10. World Health Organisation. [accessed 08/02/2015 2015] Integrated Management of Childhood Illness (IMCI). http://www.who.int/maternal_child_adolescent/topics/child/imci/en/
11. Weber MW, Carlin JB, Gatchalian S, Lehmann D, Muhe L, Mulholland EK. Predictors of neonatal sepsis in developing countries. Pediatr Infect Dis J. 2003; 22(8):711–7. [PubMed: 12913772]

12. Young Infants Clinical Signs Study Group. Clinical signs that predict severe illness in children under age 2 months: a multicentre study. Lancet. 2008; 371(9607):135–42. [PubMed: 18191685]

13. Lee AC, Chandran A, Herbert HK, et al. Treatment of infections in young infants in low- and middle-income countries: a systematic review and meta-analysis of frontline health worker diagnosis and antibiotic access. PLoS Med. 2014; 11(10):e1001741. [PubMed: 25314011]

**14. Zaidi AKM, Baqui AH, Qazi SA, et al. Scientific Rationale for Study Design of Community-based Simplified Antibiotic Therapy Trials in Newborns and Young Infants With Clinically Diagnosed Severe Infections or Fast Breathing in South Asia and subSaharan Africa. Pediatr Infect Dis J. 2013; 32:S7–S11. [PubMed: 23945577] This paper describes the rationale for the ongoing clinical trials of antibiotic treatment for neonatal infection in South Asia and Africa

15. Mullany LC, Katz J, Khatry SK, Leclerq SC, Darmstadt GL, Tielsch JM. Incidence and seasonality of hypothermia among newborns in southern Nepal. Arch Pediatr Adolesc Med. 2010; 164(1):71–7. [PubMed: 20048245]

16. Baqui AH, El-Arifeen S, Darmstadt GL, et al. Effect of community-based newborn-care intervention package implemented through two service-delivery strategies in Sylhet district, Bangladesh: a cluster-randomised controlled trial. Lancet. 2008; 371(9628):1936–44. [PubMed: 18539225]

*17. Mulholland K, Carlin JB, Duke T, Weber M. The challenges of trials of antibiotics for pneumonia in low-income countries. The lancet Respiratory medicine. 2014; 2(12):952–4. [PubMed: 25466342] This article highlights the difficulties of undertaking clinical antibiotic trials in developing countries.

18. Meem M, Modak JK, Mortuza R, Morshed M, Islam MS, Saha SK. Biomarkers for diagnosis of neonatal infections: A systematic analysis of their potential as a pointof-care diagnostics. J Glob Health. 2011; 1(2):201–9. [PubMed: 23198119]

19. Schelonka RL, Chai MK, Yoder BA, Hensley D, Brockett RM, Ascher DP. Volume of blood required to detect common neonatal pathogens. J Pediatr. 1996; 129(2):275–8. [PubMed: 8765627]

20. Kotloff KL, Nataro JP, Blackwelder WC, et al. Burden and aetiology of diarrhoeal disease in infants and young children in developing countries (the Global Enteric Multicenter Study, GEMS): a prospective, case-control study. Lancet. 2013; 382(9888):209–22. [PubMed: 23680352]

21. McAuliffe GN, Anderson TP, Stevens M, et al. Systematic application of multiplex PCR enhances the detection of bacteria, parasites, and viruses in stool samples. J Infect. 2013; 67(2):122–9. [PubMed: 23603249]

22. Liu J, Kabir F, Manneh J, et al. Development and assessment of molecular diagnostic tests for 15 enteropathogens causing childhood diarrhoea: a multicentre study. Lancet Infect Dis. 2014; 14(8): 716–24. [PubMed: 25022434]

23. Blackwelder WC, Biswas K, Wu Y, et al. Statistical methods in the Global Enteric Multicenter Study (GEMS). Clin Infect Dis. 2012; 55(Suppl 4):S246–53. [PubMed: 23169937]

24. Hammitt LL, Kazungu S, Morpeth SC, et al. A preliminary study of pneumonia etiology among hospitalized children in Kenya. Clin Infect Dis. 2012; 54(Suppl 2):S190–9. [PubMed: 22403235]

25. Massenet D, Birguel J, Azowe F, et al. Epidemiologic pattern of meningococcal meningitis in northern Cameroon in 2007-2010: contribution of PCR-enhanced surveillance. Pathogens and global health. 2013; 107(1):15–20. [PubMed: 23432859]

*26. Diaz MH, Waller JL, Napoliello RA, et al. Optimization of Multiple Pathogen Detection Using the TaqMan Array Card: Application for a Population-Based Study of Neonatal Infection. PLoS One. 2013; 8(6):e66183. [PubMed: 23805203] Describes the use of the TaqMan Array Card for the ongoing etiology study of neonatal infection in South Asia

27. Mother Child Link Registry Study Summary - ANISA. [accessed 16/11/2014 2014] 2014. http://www.linkregistry.org/StudySummary.aspx?objectid=8

28. Mbwele B, Reddy E, Reyburn H. A rapid assessment of the quality of neonatal healthcare in Kilimanjaro region, northeast Tanzania. BMC Pediatr. 2012; 12:182. [PubMed: 23171226]

29. Aiken AM, Mturi N, Njuguna P, et al. Risk and causes of paediatric hospital acquired bacteraemia in Kilifi District Hospital, Kenya: a prospective cohort study. Lancet. 2011; 378(9808):2021–7. [PubMed: 22133536]

30. Molyneux E. Severe neonatal bacterial infections: when numbers matter. Lancet Infect Dis. 2014; 14(8):665–7. [PubMed: 24974251]

31. Darmstadt GL, Saha SK, Choi Y, et al. Population-based incidence and etiology of community-acquired neonatal bacteremia in Mirzapur, Bangladesh: an observational study. J Infect Dis. 2009; 200(6):906–15. [PubMed: 19671016]

32. Zaidi AK, Thaver D, Ali SA, Khan TA. Pathogens associated with sepsis in newborns and young infants in developing countries. Pediatr Infect Dis J. 2009; 28(1 Suppl):S10–8. [PubMed: 19106757]

33. Downie L, Armiento R, Subhi R, Kelly J, Clifford V, Duke T. Community acquired neonatal and infant sepsis in developing countries: efficacy of WHO's currently recommended antibiotics--systematic review and meta-analysis. Arch Dis Child. 2012; 98:146–54. [PubMed: 23142784]

34. Seale A, Mwaniki M, Newton CR, Berkley JA. Maternal and early onset neonatal bacterial sepsis: burden and strategies for prevention in sub-Saharan Africa. Lancet Infect Dis. 2009; 9(7):428–38. [PubMed: 19555902]

35. Vergnano S, Sharland M, Kazembe P, Mwansambo C, Heath PT. Neonatal Sepsis: An international perspective. Archives of Disease of Children Fetal and Neonatal Edition. 2005; 90:220–4.

*36. Zaidi AK, Huskins WC, Thaver D, Bhutta ZA, Abbas Z, Goldmann DA. Hospitalacquired neonatal infections in developing countries. Lancet. 2005; 365(9465):1175–88. [PubMed: 15794973] Review of hospital acquired neonatal infections in developing countries, highlights reducing antibiotic susceptiibility in neonatal pathogens.

37. Vergnano S, Menson E, Kennea N, et al. Neonatal infections in England: the NeonIN surveillance network. Arch Dis Child Fetal Neonatal Ed. 2011; 96(1):F9–F14. [PubMed: 20876594]

38. Stoll BJ, Hansen NI, Sanchez PJ, et al. Early onset neonatal sepsis: the burden of group B Streptococcal and E. Pediatrics. 2011; 127(5):817–26. [PubMed: 21518717]

39. Berkley J, Lowe BS, Mwangi I, Williams T, Bauni E, Mwarumba S, Ngetsa C, Slack MPE, Njenga S, Hart CA, Maitland K, English M, Marsh K, Scott JAG. Bacteremia among Children Admitted to a Rural Hospital in Kenya. The New England Journal of Medicine. 2005; 352:39–47. [PubMed: 15635111]

40. Gray K, Bennett SL, French N, Phiri AJ, Graham SM. Invasive Group B Streptococcal Infections in infants, I. Emerging Infectious Diseases. 2007; 13(2):223–9. [PubMed: 17479883]

41. Ojukwu J, Abonyi LE, Ugwu J, Orji IK. Neonatal Septicaemia in high risk babies in South-Eastern Nigeria. Journal of Perinatal medicine. 2006; 34(2):166–72. [PubMed: 16519624]

42. Cutland C, Madhi SA, Zell ER, Kuwanda L, Laque M, Groome M, Gorwitz R, Thigpen MC, Patel R, Velaphi SC, Adrian P, Klugman K, Schuchat A, Schrag SJ, PoPS Trial Team. Chlorhexidine maternal-vaginal and neonate body wipes in sepsis and vertical transmission of pathogenic bacteria in South Africa: a randomised, controlled trial. Lancet. 2009; 374(9705):1909–16. [PubMed: 19846212]

43. Edmond KM, Kortsalioudaki C, Scott S, et al. Group B streptococcal disease in infants aged younger than 3 months: systematic review and meta-analysis. Lancet. 2012; 379(9815):547–56. [PubMed: 22226047]

44. The WHO Young Infants Study Group. Bacterial etiology of serious infections in young infants in developing countries: results of a multicentre study. Pediatr Infect Dis J. 1999; 19(10):S17–22.

45. Hamer DH, Darmstadt GL, Carlin JB, et al. Etiology of Bacteremia in Young Infants in Six Countries. Pediatr Infect Dis J. 2014; 34(1):el–8.

46. Jones N, Bohnsack JF, Takahashi S, et al. Multilocus sequence typing system for group B streptococcus. J Clin Microbiol. 2003; 41(6):2530–6. [PubMed: 12791877]

47. Shane AL, Stoll BJ. Neonatal sepsis: progress towards improved outcomes. J Infect. 2014; 68(Suppl 1):S24–32. [PubMed: 24140138]

48. Blencowe H, Cousens S, Oestergaard MZ, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet. 2012; 379(9832):2162–72. [PubMed: 22682464]

49. March of Dimes, The Partnership for Maternal Newborn and Child Health, Save the Children, WHO. Born Too Soon: The Global Action Report on Preterm Birth. World Health Organization; Geneva: 2012.
50. Aluvaala J, Nyamai R, Were F, et al. Assessment of neonatal care in clinical training facilities in Kenya. Arch Dis Child. 2015; 100(1):42–7. [PubMed: 25138104]
51. Ogunlesi TA, Ogunfowora OB, Osinupebi O, Olanrewaju DM. Changing trends in newborn sepsis in Sagamu, Nigeria: bacterial aetiology, risk factors and antibiotic susceptibility. J Paediatr Child Health. 2011; 47(1-2):5–11. [PubMed: 20973858]
52. Dagnew M, Yismaw G, Gizachew M, et al. Bacterial profile and antimicrobial susceptibility pattern in septicemia suspected patients attending Gondar University Hospital, Northwest Ethiopia. BMC research notes. 2013; 6:283. [PubMed: 23875886]
53. Enweronu-Laryea CC, Newman MJ. Changing pattern of bacterial isolates and antimicrobial susceptibility in neonatal infections in Korle Bu Teaching Hospital, Ghana. East Afr Med J. 2007; 84(3):136–40. [PubMed: 17600983]
54. Mokuolu AJN, Adesiyun O. Neonatal Septicaemia in Ilorin: Bacterial pathogens and antibiotic sensitivity pattern. African Journal of Medicine and Medical Sciences. 2005; 31(2):127–30. [PubMed: 12518907]
55. Acquah SE, Quaye L, Sagoe K, Ziem JB, Bromberger PI, Amponsem AA. Susceptibility of bacterial etiological agents to commonly-used antimicrobial agents in children with sepsis at the Tamale Teaching Hospital. BMC Infect Dis. 2013; 13:89. [PubMed: 23419199]
56. Moyo S, Aboud S, Kasubi M, Maselle SY. Bacteria isolated from bloodstream infections at a tertiary hospital in Dar es Salaam, Tanzania--antimicrobial resistance of isolates. S Afr Med J. 2010; 100(12):835–8. [PubMed: 21414278]
57. Mhada TV, Fredrick F, Matee MI, Massawe A. Neonatal sepsis at Muhimbili National Hospital, Dar es Salaam, Tanzania; aetiology, antimicrobial sensitivity pattern and clinical outcome. BMC Public Health. 2012; 12:904. [PubMed: 23095365]
58. Mulholland EK, Ogunlesi OO, Adegbola RA, et al. Etiology of serious infections in young Gambian infants. Pediatr Infect Dis J. 1999; 18(10 Suppl):S35–41. [PubMed: 10530572]
59. Lochan H, Bamford C, Eley B. Blood cultures in sick children. S Afr Med J. 2013; 103(12):918–20. [PubMed: 24300629]
60. Talbert A, Mwaniki M, Mwarumba S, et al. Invasive Bacterial Infections in Neonates and Young Infants Born Outside Hospital Admitted to a Rural Hospital in Kenya. Pediatr Infect Dis J. 2010; 29(10):945–9. [PubMed: 20418799]
61. Adejuyigbe, EA k-NA.; Adisa, B. Bacterial isolates in the sick young infant in IleIfe, Nigeria. J Trop Pediatr. 2004; 50(6):323–7. [PubMed: 15537715]
62. WHO. Pocket Book of Hospital Care for Children. Second Edition. 2013.
63. Herbert HK, Lee AC, Chandran A, Rudan I, Baqui AH. Care seeking for neonatal illness in low- and middle-income countries: a systematic review. PLoS Med. 2012; 9(3):e1001183. [PubMed: 22412355]
*64. Wall SN, Mazzeo CI, Adejuyigbe EA, et al. Ensuring quality in AFRINEST and SATT: clinical standardization and monitoring. Pediatr Infect Dis J. 2013; 32(Suppl 1):S39–45. [PubMed: 23945575] Highlights the process of standardisation and monitoring needed for comparisons to be made across multi-center studies
65. Thaver D, Ali SA, Zaidi AK. Antimicrobial resistance among neonatal pathogens in developing countries. Pediatr Infect Dis J. 2009; 28(1 Suppl):S19–21. [PubMed: 19106758]
66. Lubell Y, Ashley EA, Turner C, Turner P, White NJ. Susceptibility of communityacquired pathogens to antibiotics in Africa and Asia in neonates--an alarmingly short review. Trop Med Int Health. 2011; 16(2):145–51. [PubMed: 21078009]
67. Chandrashekar MR, Rathish KC, Nagesha CN. Reservoirs of nosocomial pathogens in neonatal intensive care unit. Journal of the Indian Medical Association. 1997; 95(3):72–4. 7. [PubMed: 9212573]
*68. Stoesser N, Giess A, Batty EM, et al. Genome sequencing of an extended series of NDM-producing Klebsiella pneumoniae isolates from neonatal infections in a Nepali hospital characterizes the extent of community- versus hospital-associated transmission in an endemic

setting. Antimicrobial agents and chemotherapy. 2014; 58(12):7347–57. [PubMed: 25267672] Study uses whole genome sequencing to understand transmission in a developing country setting

69. Kawaza K, Machen HE, Brown J, et al. Efficacy of a low-cost bubble CPAP system in treatment of respiratory distress in a neonatal ward in Malawi. PLoS One. 2014; 9(1):e86327. [PubMed: 24489715]
70. McAdams RM, Hedstrom AB, DiBlasi RM, et al. Implementation of Bubble CPAP in a Rural Ugandan Neonatal ICU. Respir Care. 2014; 60(3):437–45. [PubMed: 25389349]
71. Vernet G, Mary C, Altmann DM, et al. Surveillance for antimicrobial drug resistance in under-resourced countries. Emerg Infect Dis. 2014; 20(3):434–41. [PubMed: 24564906]
72. Shah MA, Mutreja A, Thomson N, et al. Genomic epidemiology of Vibrio cholerae O1 associated with floods, Pakistan, 2010. Emerg Infect Dis. 2014; 20(1):1320.
73. Hall JM, Corea E, Sanjeewani HD, Inglis TJ. Molecular mechanisms of betalactam resistance in carbapenemase-producing Klebsiella pneumoniae from Sri Lanka. J Med Microbiol. 2014; 63(Pt 8):1087–92. [PubMed: 24855071]

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Key Points

- Molecular diagnostics to determine aetiology of neonatal sepsis are being tested.
- Clinical trials to assess simplified antibiotic treatments are underway.
- Reduced antibiotic susceptibility to first and second line treatments is an urgent concern.
- Systematic, standardised surveillance of neonatal sepsis in health facilities is essential.