Management of Newborn Infections During Inpatient Care

Why is management of newborn infections during inpatient care important?
A newborn infection is defined as an infection (evidenced by clinical and/or microbiologic criteria) occurring within the first 4 weeks of life and includes sepsis, bacteremia, pneumonia, meningitis, omphalitis, skin infections, urinary tract infections, tetanus, and diarrhea. Newborns, particularly preterm and low birth weight babies, may be born in the setting of high exposure to pathogens that can breach skin and mucosal barriers, and newborns are more susceptible to severe infections because their immature immune systems lack antigenic experience and are less able to control and recover from infection by potential pathogens. Preterm and low birth weight babies are also more exposed to organisms due to their greater dependency on care providers and the necessity of invasive therapies (i.e. intravenous access, intubation, nasogastric feeding), with inpatient care posing a significant exposure risk to more virulent pathogens.

An estimated 6.9 million newborns in South Asia and sub-Saharan Africa required treatment for possible serious bacterial infection in 2012. Studies have indicated that the rate of neonatal infections in low and middle-income countries is 3 to 20 times higher than in resource-rich countries, with an alarming rate of antibiotic-resistant infections.

The estimates of the incidence of newborn infections in lower- and middle-income countries range from 5.5 infections per 1,000 live births by positive blood culture to 170 infections per 1,000 live births using clinical diagnosis. An additional number of newborns die in the community before a blood culture or clinical diagnosis is made. It is estimated that more than 80% of infection-related deaths in newborns could be avoided if the coverage and quality of currently available preventable measures and effective interventions improved.

How are newborn infections acquired?
Newborn infections can originate from exposures to bacterial, viral, or more rarely to fungal organisms in utero, during labor and delivery, or in the postnatal period. Infections may be transmitted vertically from the mother or horizontally from caregivers and the environment.

Exposures to pathogenic organisms can occur in the postnatal period via contact with organisms on the hands of caregivers, health care workers, family and community members, or contact with infected materials or equipment. Hospital-acquired infections can result from exposure to infected medical equipment/commodities such as incubators, oxygen delivery systems, feeding tubes, monitors, towels or wraps, and invasive procedures and in-dwelling medical devices such as intubation, urinary catheterization, and intravenous lines.

How can poor management of newborn infection cause harm?
The risk of death from infection is high, even in the inpatient setting. Sick newborns often present with nonspecific clinical signs such as difficulty feeding, lethargy or irritability, and temperature instability; these signs may also be associated with prematurity. Newborn infections are difficult to identify and diagnose and disease progression occurs quickly, requiring extreme vigilance by providers, caregivers, and parents. Delays in recognition and treatment may lead to death and significant morbidity, including neurodevelopmental impairment. Severe invasive infections can result in an immunologic inflammatory response syndrome known as sepsis, which causes dysfunction of and damage to organ systems including the circulatory and nervous systems, brain, kidneys, and other organs, and often leads to severe disability or death.

While harms associated with delayed recognition or treatment of newborn infections can be serious, there may be harmful consequences of increased exposure to antibiotics. Newborns receiving antibiotics are often separated from the parents, making bonding and breastfeeding challenging. Because of the challenges differentiating serious bacterial infections from other newborn syndromes, and the severity of the consequences of failing to treat a true infection, antibiotics are prescribed liberally for suspected infection in newborns. There are issues of unnecessary exposure to antibiotics due to unregulated dispensing by drug sellers/pharmacists/chemists, and by clinicians with low thresholds for prescribing antibiotic therapy.

Early antibiotic exposures cause changes to the newborn microbiome, resulting in long term sequelae including increased risk of asthma and allergy, gastrointestinal disturbances and diarrhea. Importantly, early and prolonged exposures can result in increased risk of antibiotic-resistant infection. Necrotizing enterocolitis, late-onset sepsis, and death have all been associated with prolonged antibiotic exposure in newborns. Inappropriate prolonged antibiotic use also leads to longer hospitalizations, often at a substantial cost.

What are the current evidence-based best practices?

Prevention measures
Elements of essential newborn care have been demonstrated to reduce the risk of infection. Such care practices include hand hygiene, appropriate umbilical cord care, as well as early and continued breastfeeding. Intrapartum and in-hospital hand hygiene has been shown to significantly reduce the risk of nosocomial infections in a variety of low-resource settings with improved mortality and outcomes. A recent review reported the application of a 4% chlorhexidine solution to the umbilical stump of an infant born in the community resulted in a 12% reduction in neonatal mortality and 50% reduction in omphalitis, though the effect was not seen for infants born in hospital settings. An exclusive human milk diet has been associated with a reduced risk of serious infections in preterm/low birth weight infants compared to formula diet. The use of probiotics in very low birth weight infants has been investigated, reducing the risk of late-onset sepsis, necrotizing enterocolitis, and all-cause mortality.

Current approaches to management of newborn infections
Clinical manifestations of newborn infections range from subclinical infection to severe manifestations of focal or systemic disease, with symptoms often nonspecific and affecting feeding, breathing, temperature, and alertness patterns of the newborn. Clinical manifestations are influenced by timing of exposure, immune status of the infant, and the virulence of the causative agent.

Newborn sepsis can be classified as early onset or late onset:
- Early onset sepsis refers to bacteremia acquired either before or during delivery (vertical acquisition), manifesting within the first week of life.
- Late onset sepsis refers to bacteremia acquired after delivery from nosocomial or community sources (horizontal acquisition), manifesting between 7 and 28 days of life.

Diagnosis of newborn serious bacterial infections
Serious bacterial infections can be identified by clinical assessment, either biochemically (with biomarkers) or microbiologically. Limited availability of
microbiological diagnostic testing in LMICs is a major barrier to safe antibiotic use and shortening courses of treatment. In settings where families with sick young infants do not accept or cannot access more advanced care, diagnosis in outpatient settings by an appropriately trained health worker is based on the signs of presumed serious bacterial infection.18 Currently available diagnostic tests have significant barriers in their use and interpretation. The actual impact of diagnostics depends on the availability, cost, time to result, and both negative and positive predictive value of the test, as well as the availability, uptake, and effectiveness of the treatment based on the test results.

**Biomarkers**

At this time, there is no accepted biomarker for use in low and middle income countries. The availability, cost, rapidity of results, sensitivity, specificity, predictive value, and the interpretation of results pose challenges for the widespread use of biomarkers. Small studies have described hundreds of biomarkers associated with severe neonatal infections. Biomarkers, alone or in combination, have been used to identify newborn infections: procalcitonin (PCT), C-reactive protein (CRP), tumor necrosis factor-a (TNF-a), interferon-g (IFN-g), interleukin-6 (IL-6), interleukin-8 (IL-8). The majority of these studies have evaluated biomarkers in combination with C-reactive protein (CRP); already in widespread clinical use for the diagnosis of infection. As an acute-phase reactant, CRP alone is less useful in the earliest phases of severe neonatal infection because it does not peak until 12 to 24 hours after infection and can also be triggered by a non-infectious insult, such as trauma.20

**Microbiology**

Variation in the causal agents and microbiome/flora are significant factors to consider with prevention, screening, and treatment protocols for newborns in lower- and middle-income countries. Klebsiella and Escherichia coli are the most common causal organisms for early neonatal sepsis. Women with group B Streptococcus (GBS) colonization increase the risk of early neonatal GBS infection. Gram-negative organisms account for twice as many cases of newborn infection than gram positives in Africa and Asia, which is thought to be attributable to post-delivery exposure. Few reliable epidemiologic data are available from low- and middle-income countries about the incidence of life-threatening, pregnancy-related infections and their microbial etiology,21 due to the very limited availability of microbiological diagnostic testing in LMICs. In a 2016 study from South Asia, the percentage of newborn deaths following suspected newborn infections due to bacteria was 13.8%, 11.8% were due to viruses, and 74% of deaths occurred unknown infection etiology or with no infection.22 Less than 10% of blood cultures from inpatient newborns with suspected serious bacterial infection in lower- and middle-income countries are positive.23 Additional considerations in investigating causal agents are bacterial versus viral. Especially for late-onset sepsis, viral etiologies may be considered, including human simplex virus (HSV), cytomegalovirus (CMV), HIV, or respiratory syncytial virus (RSV) or similar respiratory viruses. Clinical clues to a viral infection, though not specific, may include hematologic disturbance, including low platelet counts and the presence of elevated liver enzymes in addition to physical exam findings.

**Use of antibiotics**

For newborns with possible risk factors for infection, routine practice is to initiate broad-spectrum antibiotics after obtaining samples for cultures (blood, urine, cerebral spinal fluid as appropriate) and await culture results. Current evidence has suggested no benefits from prolonging the course beyond 36 to 48 hours of antibiotics if the blood cultures remain negative. If cultures return positive, antibiotics should be changed to the narrowest spectrum possible.24 In low-resource settings bacterial culture is rarely available, and antibiotic recommendations are based on empiric management. Recent trials have demonstrated that simplified antibiotic courses, including oral amoxicillin with or without injectable gentamicin depending on severity of the clinical presentation, are equally efficacious as the reference course of injectable penicillin plus gentamicin in newborns with serious bacterial infections (excluding critically ill newborns) when referral was not feasible and patient safety with previous reference can be assured.

If viral causes are suspected, prolonged exposure to antibiotics would be of little use, and antiviral therapy should be included. Acyclovir would be recommended for suspected HSV infection, while other antivirals may be considered for HIV. There is not clear evidence for use of other antivirals against RSV, late-onset CMV (with exception being congenital CMV), or other viruses. Widespread use of broad-spectrum antibiotics as first-line drugs present many problems. For many oral and injectable antibiotics regimens, the duration and dose have not been optimized. Selection of agents and not optimized because cultures, sensitivities, biomarkers and drug levels are generally not available. There are many potential side effects (see above harm section) that may result particularly from broad-spectrum antibiotic use, most notably the development of highly resistant strains of bacteria associated with high mortality.

**Table 1: Evidence-based clinical approaches and activities for the prevention, detection, management and referral of newborn infections**

<table>
<thead>
<tr>
<th>Approach</th>
<th>Activity</th>
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<tbody>
<tr>
<td>Prevention</td>
<td>• Infection control practices including hand hygiene; proper sterilization of medical equipment; and clean water and hygienic disposal of waste in the community and in the medical facility</td>
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<td>• Clean cord care, chlorhexidine cord cleansing if appropriate, and clean postnatal practices</td>
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<td></td>
<td>• Breast feeding</td>
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<td></td>
<td>• Interventions to prevent hypothermia: drying, head covering, skin-to-skin contact, and delayed bathing</td>
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<td></td>
<td>• Limit use of invasive procedures/venipuncture</td>
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<td></td>
<td>• Avoiding cot and incubator sharing</td>
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<td></td>
<td>• Appropriate inpatient admission and duration</td>
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<td></td>
<td>• Maternal vaccines (Tetanus, influenza, hepatitis B)</td>
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<td></td>
<td>• Screening and treatment of maternal infections</td>
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<td></td>
<td>• Reduce occurrence and severity of preterm birth</td>
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<td>• Pro/prebiotics</td>
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| Detection                  | • Biomarkers: Culture-independent diagnostics (serial measurements of CRP) and in combination with other biomarkers |
|                           | • Microbiology: Culture methods                                          |

| Management                 | • Special newborn care or neonatal intensive care                        |
|                           | • Algorithmic case management of neonatal sepsis, including injectable and oral antibiotics, and hospital-based care |
|                           | • Antimicrobial resistance and antibiotic stewardship including judicious use, appropriate selection and duration of antibiotic |

| Referral to appropriate facility | • Timely referral to appropriate facility for care, with appropriate pre-referral care |
|                                | • Provide adequate care of the sick newborn during transport without separation from family members |
|                                | • If referral to inpatient care not possible, combination injectable and oral antibiotics for 7 days in select settings |
treatment in light of growing antibiotic resistant infections, a paucity of data on the most appropriate/effective antibiotic regimens, a growing body of literature on the consequences of antibiotic exposure on the individual, including microbiome disturbances and chronic inflammatory illnesses, and the additional resource requirements of extended hospitalizations for antibiotic administration in low-resource settings.\textsuperscript{30,34,35,36}

Localized and serious bacterial infections

The WHO recommends oral antimicrobial therapy and home-based care for young infants with a localized infection, and follow-up by a trained health worker to evaluate status after 2 days.\textsuperscript{33} For newborns with suspected or confirmed serious bacterial infection, the recommendation is for admission to a referral-level facility and intramuscular or parenteral combination antimicrobial therapy of gentamicin, and amoxicillin or penicillin as first-line treatment, or intravenous cloxacillin and gentamicin if staphylococcus infection is suspected.\textsuperscript{38,39} Simplified outpatient antibiotic therapy of injectable gentamicin plus oral amoxicillin is recommended when inpatient referral-level care at a higher-level facility is not feasible or not accepted, with close observation and follow-up by a trained health worker to assess clinical status.\textsuperscript{40}

Malaria and tuberculosis

WHO recommends use of long-lasting insecticidal nets (LLINs), and intermittent preventive therapy for infants (IPTi) in areas of moderate to high transmission in sub-Saharan Africa; and prompt diagnosis and treatment of malaria infections.\textsuperscript{41} Congenital infection by vertical transmission of TB occurs late in pregnancy by transplacental transmission through umbilical veins; or aspiration and swallowing of infected amniotic fluid in utero or intrapartum. In newborns diagnosed with TB, a horizontal spread in the postpartum period by droplet or ingestion from mother or undiagnosed family member is most common.\textsuperscript{42}

System requirements for prevention and management of newborn infections during inpatient care

Infection prevention and control

Although smaller babies are more vulnerable, they require the same infection prevention measures as all inpatient newborns, notably in the special care and intensive care units.\textsuperscript{4} Diligent infection prevention measures in the delivery room and postnatal wards can significantly reduce the incidence of infection and affect the nature of the infecting organisms.\textsuperscript{4} Fundamental components of infection prevention include (i) commodities/supplies for infection prevention, including capacity building, motivation and supervision for proper hand washing; (ii) adequate space to minimize crowding with only one baby per cot or incubator; and (iii) adequate, routine cleaning of surfaces and reprocessing of re-usable items with heat, appropriate disinfectants and/or sterilants.\textsuperscript{4}

Antimicrobial resistance

The emergence of antimicrobial resistance threatens to slow or halt progress in reductions in morbidity and mortality. As circulating pathogens increasingly become resistant to commonly available antibiotics, the efficacy of currently recommended treatment approaches is threatened. WHO warns that the many new antibiotics under development will be insufficient to address the growing number of resistant pathogens, especially multidrug-resistant tuberculosis and resistant gram-negative pathogens.\textsuperscript{43,44}

Infection prevention and disease control strategies, appropriate and judicious use of antibiotics, development of new antibiotic agents and other novel therapies, and improved antimicrobial resistance surveillance are required urgently to address this issue globally.\textsuperscript{45}

Vaccination against infectious diseases with high rates of antimicrobial resistance, such as typhoid, is another WHO priority strategy to address the growing threat of antimicrobial resistance.

There are multiple causes of irrational use of medicines, and in particular antibiotics. A context-specific system change is needed as different countries have widely differing health care. Multiple global recommendations have been made to promote rational use of antibiotics and other medicines\textsuperscript{46} including 2 recent World Health Assembly resolutions\textsuperscript{47,48} and a regional resolution.\textsuperscript{49}

How do we tackle antimicrobial resistance?

- Disease control and infection prevention strategies
- Vaccination of mothers
- Narrow spectrum treatments with diagnostics
- Antibiotic stewardship including guidelines for clinical use of suitable antibiotics
- New drugs
- Repurposing and/or phenotypic reversion of older drugs
- Testing of antibiotic combinations
- Therapeutic antibodies

What actions can be taken to improve the management of newborn infections during inpatient care?

Core actions needed by key stakeholders to ensure quality management of newborn infections

Policy Makers

- Establish/strengthen newborn health committee in facilities with representatives from key stakeholders and professional bodies
- Ensure integration with other programs such as newborn infection prevention and control, water, sanitation and hygiene (WASH), antimicrobial resistance and stewardship, and maternal health
- Develop suitable indicators for national and subnational and additional indicators for hospitals admitting small/baby babies
- Develop standards, guidelines, and teaching aids; and establish policies for competency-based in-service and preservice training

Program Planners/Implementers

- Establish a unit-wide training curriculum for best practices
- Adapt indicators to monitor newborn outcomes and evaluate progress
- Promote partnership across health care unit

Facility Managers/Administrators/Leaders

- Create policies, procedures, and infrastructure that affirm infection prevention and control practices
- Make an explicit commitment to support quality inpatient care that includes the prevention and management of newborn infections
- Develop feedback loops so that newborn outcomes are regularly monitored, reported, and acted upon
- Provide handwashing stations and space for all health care providers and parents to provide care for their newborn during hospitalization

Health Care Providers (physicians, nurses, midwives, ancillary staff)

- Embrace antimicrobial resistance and antibiotic stewardship
- Infuse evidence-based clinical approaches in routine medical and nursing practice, foster interdisciplinary newborn care teams, and participate in quality improvement initiatives
- Educate family members on the unique contribution that they play in the care of their newborn; train family members on the importance of their involvement in hand-hygiene, and infection control practices
- Implement best infection prevention and infection management practices
- At discharge, counsel families on newborn care and infection prevention practices at home, and to recognize danger signs that trigger appropriate early care seeking

Families

- Stay engaged and informed about infection prevention and care practices while the newborn is in an inpatient setting, in follow-up care, or at home
- Inform parents that the antibiotics may not be essential for newborns during sickness, unless recommended by doctors/trained health workers
- Seek medical advice and treatment from qualified professionals

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