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Rethinking management of neonates at risk of sepsis

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Health professionals involved in the care of young infants are aware of the consequences of not administering or delaying antibiotics in cases of bacterial sepsis. Those who have seen such cases may be quicker to prescribe antibiotics in the future, even if sepsis is a remote possibility. However, this practice is not without risks. Exposure to broad spectrum antibiotics alters the body's microbiota, increases opportunistic infections and promotes antimicrobial resistance (AMR), which may restrict future treatment options for the child.¹ Therefore, a contextual evaluation of risks and benefits is necessary when prescribing antibiotics.

Given these grave consequences, what should clinicians do when evaluating a young infant at risk of infection? In most settings the standard of practice is to treat all neonates with parenteral antibiotics immediately, as a default. This practice is rooted in times when neonatal mortality was inordinately high and is also based on the premise that neonates are immunologically vulnerable to infections.² However, data suggest that the immune system of the term neonate is well adapted to fight most common bacteria.³ The epidemiology of neonatal sepsis has evolved over the past century with socioeconomic gains and advances in perinatal care. In 2012, the rate of sepsis in infants in North America was about one per 1,800 livebirths, and not materially different from older pediatric age groups.⁴ Bacterial sepsis occurs most commonly as late-onset in preterm neonates or early-onset in term and

preterm neonates⁵. However, it is uncommon in febrile neonates who seek medical care after discharge home⁶. Therefore, we question whether the systematic, immediate use of antibiotics in these situations remains justified. We realize that this practice is supported by expert guidelines,⁷ and speculate that it is heavily influenced by historical perspectives. We believe that the growing issue of AMR mandates revisiting this approach.

The situation in resource-poor settings requires additional consideration. Scarce epidemiological data in these places complicate the application of knowledge.^{8,9} Co-morbidities including prematurity, malnutrition, micronutrient deficiencies and maternal HIV infection, can compromise post-natal immunological adaptation and thus increase the risk of sepsis.¹⁰ Yet one study in South Asia suggested that most cases of sepsis in young children could have had non-bacterial causes, although these findings require confirmation.¹¹ Although we cannot reject that the benefits of prescribing antibiotics to treat “redolent of sepsis” in these settings could outweigh the risks, we are open to the possibility that the opposite may be true and this is worthy of investigation. Moreover, diagnostic tests are often unavailable and thus antibiotics can be started without measures to inform cessation of therapy. Non-resilient health systems typically don’t have the safety net for advance care of the critically ill patients, which creates an overreliance on antibiotics.

We call for a more judicious use of antibiotics in neonates, discouraging their systematic empiric use when sepsis is only a remote possibility. In line with 2018 North American recommendations,¹² models of care should be adapted to facilitate serial clinical and laboratory assessments rather than immediate treatment in low-risk infants. Clinical decision algorithms should evaluate the effectiveness and safety of withholding antibiotics in specific subgroups,¹³ which could include those who are well-appearing at the time of assessment or who only have a low grade fever.¹⁴ Efforts should also focus on educating health workers in recognizing early danger signs.¹⁵ Research is needed to develop pragmatic, severity-based definitions for neonatal sepsis. In low resource settings, there is an urgent need for a universal application of measures that have proven effective in reducing infant mortality over the past century in resource-rich countries,¹⁶ including improving sanitary conditions at birth, access to health care and in early infancy, safe milk and vaccination. Robust actions are needed to bolster resilience of health systems to prevent, diagnose and to treat the ill neonate, including local access to neonatal expertise. Finally, access to existing laboratory tests (e.g. procalcitonin, c-reactive protein) need to be facilitated, and next-generation diagnostic tests that are fast, reliable and widely accessible also need to be developed to address the limitations of the current reference standard, ‘blood culture’, which is both insensitive and prone to contamination, especially in resource-poor settings.

Ultimately, considerable research will be needed to counteract entrenched and traditional thinking, and support practice changes. However, actions should be consistent with the recognition that promoting widespread antibiotic use without addressing the fundamental sanitary and operational health system issues raised above fuels AMR and will eventually render their use obsolete for those who truly need these drugs.¹⁷ Changes need to be deliberate and include consideration of the present understanding of pathophysiology and the local context. These daunting must be addressed to ensure that improvements in neonatal health are sustainable across nations.

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