NOAH Evidence Summary

In the United Kingdom, the standard management of suspected early-onset neonatal infection (EOI) requires a minimum of 36 hours of intravenous (IV) antibiotic administration. Discontinuation of antibiotics is recommended if the neonate remains clinically stable, C-reactive protein (CRP) trends and levels are reassuring, and all microbiological cultures return negative. However, in cases where infection concerns persist, IV antibiotic therapy may be extended up to seven days (NICE guidelines).

The administration of prolonged courses of IV antibiotics presents challenges, including extended hospital admissions, separation of families, repeated attempts at intravenous cannulation, costs to the health system and the potential nephro- and oto- toxic impacts of repeated doses of Gentamicin.

The NOAH project aligns with recently released UK Health Security agency guidelines which suggest that, in children and young people (including newborns), intravenous-to-oral switch should be considered within 48 hours of the first dose of intravenous (IV) antimicrobial being administered. The guidance recognises that neonates may require special consideration.

Neonatal Oral Antibiotics at Home (NOAH) is a clinical management strategy for eligible neonates with suspected early-onset bacterial infection, enabling a switch from prolonged hospital-based intravenous (IV) antibiotics to home-based oral antibiotic therapy. It aims to provide a safe, effective alternative to hospitalization, ensuring that eligible neonates can complete their antibiotic course at home under appropriate monitoring and follow-up.

Historically, IV antibiotics have been the preference for the treatment of neonates with suspected infection. This is due to concerns about absorption and metabolism of oral preparations potentially not achieving sufficient efficacy to treat bacterial infections in neonates. In low resource settings, oral antibiotics are used and are advocated by the World Health Organisation (2) for babies with suspected early onset infection, however, the quality of evidence is low and findings cannot be extrapolated to high income settings. As is pointed out by Keij et al, evidence is emerging to suggest that adequate therapeutic serum concentrations of antibiotics can be reached via the oral route in neonates.

Two studies in particular have examined the pharmacokinetics of oral antibiotics in neonates. Autret et al. found that amoxicillin levels were comparable between IV and oral routes, except immediately after dosing, at which point serum concentration was higher following IV antibiotic. Oral amoxicillin peaked at 2–6 hours and remained above the minimum inhibitory concentration (MIC) for neonatal pathogens in most cases. Gras-le-Guen et al assessed switching full-term neonates with early-onset group B Streptococcal (GBS) disease from IV to oral amoxicillin after 48 hours of IV therapy. Among 222 neonates, all maintained effective serum amoxicillin concentrations on oral therapy (≥5 mg/L), with good gastrointestinal tolerance. Most were discharged by day five without complications or readmissions. Both authors conclude that antibiotic serum concentration can be maintained in the theraeputic range through the oral delivery route in neonates.

The most compelling evidence to support the use of oral antibiotics for the treatment of suspected early onset infection in neonates comes from the RAIN trial (Keij et al). In a multicentre, randomised, open-label, non-inferiority trial conducted across 17 hospitals in the Netherlands, the efficacy and safety of an early switch from intravenous (IV) to oral amoxicillin–clavulanic acid were compared with a full course of IV antibiotics in neonates (≥35 weeks postmenstrual age, 0–28 days postnatal age, ≥2 kg) with probable bacterial infection requiring prolonged treatment. Among 504 neonates included in the intention-to-treat analysis, the cumulative reinfection rate 28 days post-treatment was <1% in both

groups, confirming non-inferiority (between-group difference 0% [95% CI –1.9 to 1.9]). No significant differences in adverse events were observed (50% vs 45%; p=0.247). Neonates in the oral antibiotic group had a significantly shorter median hospital stay (3.4 vs 6.8 days; p<0.0001). The findings indicate that an early IV-to-oral switch with amoxicillin is a safe and effective alternative to prolonged IV therapy, reducing hospitalisation duration without increasing adverse outcomes.

Carlsen et al further evaluated the safety and efficacy of switching term-born neonates with EOI from IV antibiotics to oral amoxicillin in clinical practice. Conducted in Eastern Denmark from 2018 to 2020, the prospective cohort included 835 neonates treated for suspected EOI, of which 90% of eligible cases transitioned to oral therapy after initial IV treatment. The oral switch therapy, initiated 36–48 hours after IV antibiotics in stable neonates, resulted in a significant reduction in hospital stays from a median of 7.4 days to 3.0 days, with no observed readmissions due to infections. The authors conclude that switching to oral antibiotic therapy in clinically stable term-born neonates with probable EOI was safe and enabled earlier discharge to home. The results support the standard use of intravenous-to-oral switch therapy in neonates with probable EOI.

There two further relevant studies although both are small. Gyllensvärd et al. implemented a quality improvement initiative that used C-reactive protein levels and clinical symptoms to guide shorter courses of IV antibiotic therapy, with a switch to oral antibiotics after 72 hours for eligible babies. The authors conclude that their new pathway reduced hospital stays and led to decreases in both antibiotic duration and hospital costs without affecting safety. Similarly, Manzoni et al. explored a switch to oral antibiotics in full-term neonates, combining initial intravenous antibiotics with a transition to oral therapy after three days if clinical and laboratory data indicated infection resolution. Again, they reported shortened hospital stays, but also increased breastfeeding rates and maintained clinical safety.

In a recently published rapid evidence review, Gifford et al posed the question ‘In the setting of high-income countries, is it safe to switch intravenous antibiotics to the oral route in term neonates with culture-negative early-onset infection (EOI) who are clinically improving and tolerating oral feeds?’ The authors concluded that switching from intravenous to oral antibiotic therapy appears safe for term neonates with probable early-onset infection, provided they are clinically stable and feeding well, however outpatient monitoring should be in place to ensure patient safety after discharge.

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