# A systematic review of the efficacy of antibiotics switch therapy in neonates

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## ABSTRACT

**Aim:** The Switch from intravenous antibiotic treatment to oral antibiotic therapy for neonates is not currently common in high-income regions, primarily due to concerns regarding safety and adequate exposure. The objective of this systematic review is to evaluate the effectiveness and safety of early transitioning from intravenous to oral antibiotics in neonates with suspected bacterial infections, as compared to a complete course of intravenous antibiotics. **Material and Methods:** A search was carried out using different terms i.e. switch therapy, antibiotics in neonates, iv to oral switch to find the related articles. A total of 9 studies were used that described antibiotic switch therapy in neonates**. Results:** The findings from selected studies indicated that transitioning to antibiotic switch therapy had a notable impact on decreasing the length of hospital stays and the recurrence of infections in neonates. **Discussion:** Oral switch therapy is not a widespread practice in neonates yet. Antibiotic therapy is started immediately in case of maternal factors-based or clinical symptoms-based suspicion of infection. Antibiotic therapy can be stopped 36-48 hours after the disappearance of symptoms, reassurance of inflammatory parameters, and negative cultures in the best-case scenario.

**Keywords:** intravenous, neonates, effectiveness, bacterial infection

## INTRODUCTION

Proved bacterial infection in the first 72 hours of life, also known as early-onset sepsis, has a ratio of 1 in 1000 live births which further increases in low birth weight and premature infants [1]. Infection is the main cause of mortality and morbidity in newborns [2].Forty-five percent of childhood deaths under 5 years of age occur in neonatal age and the main cause of death in this group (22%) is neonatal bacterial infection [3]. Non-specific clinical symptoms and laboratory findings make early diagnosis challenging in this group [4]. IV antibiotics are prescribed for at least 7 days when there is a provenor probable bacterial infection [5]. Parent-child bonding is affected by prolonged hospital stay which is necessary for IV antibiotic therapy and there is an increased risk of hospital-related infections and costs of treatment are also increased [6]. Once the patient is clinically well, switch to oral antibiotics within the course of treatment also known as, oral switch therapy, is now a part of standard practice in older children and it has been proven to be safe and effective for several infections and indications [7]. The choice of antibiotic

is based on a probabilistic approach and those drugs are considered which are active against most of the common bacteria cultured in infected neonates, as well as have better safety and tolerability, as there is no availability of microbiological data and also there is increased risk of rapidly worsening bacterial diseases[8]. To reach therapeutic serum levels quickly and prevent the development of complicated and more severe infections, antibiotics are administered intravenously in newborns with suspected bacterial infections [9]. According to NICEguidelines, IV route of antibiotic administration is recommended for the treatment of severe infections like hospital-acquired pneumonia especially in those patients who are at high risk of antimicrobial resistance (Available at:www.nice.org.uk/guidance/ng139). Infection, increased risk of phlebitis, excess administration of sodium and fluid, high cost of treatment, and longer stay at the hospital are important disadvantages of prolonged IV administration of antibiotics [10]. Common barriers preventing clinicians from an early IV to oral switch have been investigated in multiple studies [11]. There may be circumstances where reliable achievement of therapeutic concentrations of antibiotic after oral administration is uncertain due to gastrointestinal irregularities influencing drug absorption, nausea/vomiting, swallowing dysfunction, and non-compliance in adhering to oral regimen due to altered mental state as in dementia and decreased consciousness, and multiple other factors [12]. The misconception of clinician that IV administered antibiotic is stronger and more effective in obtaining therapeutic concentration and has better tissue penetration as compared to orally given antibiotic is another inappropriatereason [11]. When administration of antibiotics is decided in severe infections, it is better to start with IV antibiotics(Available at:www.nice.org.uk/guidance/ng139). The achievement of effective antibiotic concentration rapidly after IV administration makes this approach justified. A switch from IV to oral therapy should be considered in patients with good clinical response and normal functioning of the gastrointestinal tract after initial IV treatment for 48 to 72 hours as there is an increasing amount of recent evidence in this favor(Available at:www.nice.org.uk/guidance/ng139).To our knowledge, there have been limited systematic reviews conducted to assess the utilization of oral antibiotics in neonates. Given the uncertainties surrounding oral absorption during the initial weeks of life, the absence of substantial evidence could be a potential explanation for the non-standardization of oral switch therapy in neonatal care. Consequently, the objective of this systematic review is to assess the existing body of evidence regarding the safety and effectiveness of transitioning from intravenous (IV) to oral therapy in neonates.

**Material and Methods**

**Search strategy:**We conducted a comprehensive literature search following the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Available at: http://www.prisma-statement.org/). Our search encompassed various reputable databases, including PubMed, Medline, ScienceDirect, Embase.com, Web of Science, Cochrane Central, and Google Scholar. Initially, we screened titles and abstracts, and subsequently, three independent reviewers thoroughly examined the full texts of potentially relevant articles. Any disagreements were resolved through discussion or consultation with a third investigator. Additionally, we screened congress abstracts, reference lists, and review articles for potential studies.

**Inclusion and exclusion criteria:**Our inclusion criteria were limited to research involving human subjects, including randomized controlled trials (RCTs), intervention studies, and retrospective studies that explored the use of oral antibiotics, including oral switch therapy, as well as pharmacological investigations in neonates.Articles written other than in the English language were not included in this systematic review.

**Data extraction:**Two authors independently extracted the following data from selected articles i.e. Author name, study type, sample size, intervention, antibiotics used, and outcomes.

## RESULTS

A total of 253 studies from all the databases were identified. After the removal of duplicates, we reviewed the full text of 92 potential articles.Those studies excluded who answered the focus questions. Further assessment was performed by the author. Finally, 35 articles were chosen for full reading. A total of 7 articles were selected after reading by all the authors independently. Figure 1 shows the selection process. Additionally, 2 articles were selected through screening of reference lists, leading to 9 selected publications for this review. The characteristics of the included studies are described in Table 1.

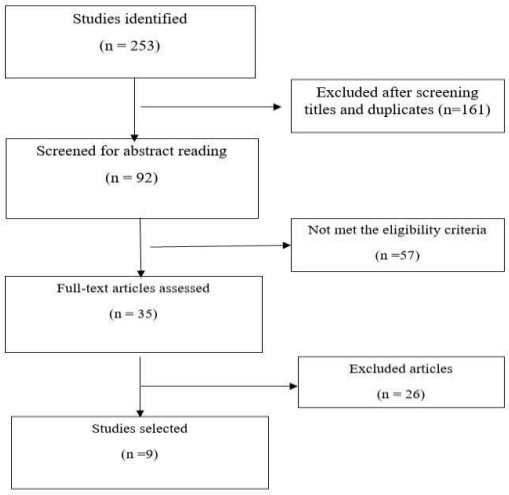


**Fig: 1.** Flow diagram detailing the search strategy

In a multicenter, randomized clinical trial, the effectiveness of oral therapy versus initial intravenous treatment was assessed in a group of 306 children aged 1 to 24 months. These children were divided into two groups: one received oral cefixime for a duration of 14 days (with a double dose on the first day), while the other group received initial intravenous cefotaxime treatment for 3 days, followed by oral cefixime for the subsequent 11 days. Our findings suggest that oral cefixime can be considered a safe and efficacious treatment option for children presenting with fever and urinary tract infections. The use of cefixime has the potential to result in significant reductions in healthcare costs [13].

An uncontrolled iv-to-oral switch trial was performed in 222term neonates with probable or proven group B-

streptococcal (GBS) sepsis. Subjects switched to oral amoxicillin (300mg/kg/day q6h) after 48 h of IV amoxicillin (100mg/kg per day). Serum levels were all above the minimal inhibitory concentration (MIC) for GBS. Moreover, therapy was well tolerated without any side effects or reinfections, and a reduction of 5 days in hospital admission was seen [14]. Another retrospective study evaluated the efficacy of iv to oral switch therapy in 172 newborns with a UTI. In total, 119 patients switched to oral amoxicillin/clavulanic acid as continuation therapy. None of the orally treated newborns experienced similar signs and symptomsin the 6months after treatment [15].Manzoni et al. (2009) performed antibiotic switch therapy from IV to oral in 36 term neonates with a probable or proven bacterial infection. After 72 h of IV treatment (Ampicillin/sulbactamAmikacin), patients who were asymptomatic switched to oral cefpodoxime (10mg/kg/day), a third-generation cephalosporin. Seventy-two matched controls continued on IV therapy. Admission duration was significantly lower and breastfeeding rate was significantly higher among neonates with an oral switch [16].In a randomized trial study switch therapy (IM to oral) was done on 82 neonates with bacterial infection and showed no significant effect as compared to the control group (only IM) [17].In a prospective study evaluating the efficacy of antibiotic switch therapy in pneumonia patients, participants were randomly allocated into two groups: Group I received intravenous ampicillin at a dose of 200 mg/Kg/day every 6 hours, while Group II switched to oral amoxicillin at a dose of 40 mg/Kg/day every 8 hours after two days of intravenous ampicillin treatment at the same dose as Group I. The hospital stay duration for children who underwent the switch to oral antibiotics was significantly reduced. Additionally, there was a notable decrease in complications, including edema/extravasation, inflammation, and abscess formation at the cannula site, among children who switched to oral antibiotics [18]. Keij et al. (2019) performed a multicenter randomized control trial involving 550 neonates with probable bacterial infection in which one group continued on IV treatment (penicillin and gentamicin) while the other group was switched from IV to oral (Amoxicillin/clavulanic acid). It reduced the risks of hospital-related complications such as nosocomial infections andimprovement in quality of life (QOL) and better mother-child bonding was observed [19]. The study assessed the efficacy of switching 478 clinically stable neonates with early onset infection from intravenous to oral antibiotics. None of the neonates required readmission due to infection. The median hospitalization duration was 3.0 days (IQR 2.5-3.5) for the switch group and 7.4 days (IQR 7.0-7.5) for the intravenous therapy group. Despite the convenience of oral administration, the adoption of switch therapy did not lead to a higher overall antibiotic usage [20].

**Table 1: Efficacy of switch therapy in neonates**

| Reference | Study design | Size | Age | Type of infection | Intervention group | Antibiotic | Results |
|---|---|---|---|---|---|---|---|
| Hoberman et al 1999 [13] | Randomized clinical trial | 306 | 1 to 24 months | UTI and fever | Group I= Oral Group II= Switch IV to oral | Oral=Cefixime IV= Cefotaxime | Oral cefixime was effective treatment to reduce UTI and reduction in hospital expenditure |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Gras le Guen et al 2007 [14] | Cohort study | 222 | Newborns 2 days | Early onset GBS sepsis | Switch to oral after 48 hours of iv antibiotics | Amoxicillin | 1 No re-infection within 3 months 2 serum level above MIC for GBS 3 Well tolerated 4 Reduction of 5 days in hospital stay |
| Magin et al 2007 [15] | Retrospecti ve study | 172 | PNA 7-31 dys | UTI | N=119, iv-to-oral switch | Amoxicillin/Cl avulanic acid | No relapse within 6 months of treatment |
| Manzoni et al 2009 [16] | Case control study | 108 | Full term newborn | Presumed/ proven bacterial infection | N=36, Iv-to-oral antibiotic switch N=72, completely iv | Cefpodoxime | 1 reduction in hospital stay 2 significantly higher breastfeeding |
| Abdullah baqui et al 2015 [17] | Randomize d trial study | 82 | 0-6 days | Bacterial infection with one or more clinical signs | Im-to-oral switch | Benzyl penicillin and gentamicin for 2 days Amoxicillin for 5 days | Results were same for control group and switch from im-to-oral group |
| Sharma D et al 2016 [18] | Prospective and observation al | 40 | 2-to-59 months | Pneumoni a | Group I=IV ampicillin Group II=Switch to oral amoxicillin after 2 days of IV ampicillin | Ampicillin and Amoxicillin | 1 Significant reduction of hospital stay in group II 2 Reduction in edema, inflammation, extravasation and abscess at site of cannula in group II |
| Keij et al., 2019 [19] | multicentre randomised controlled trial | 550 | 0-28 days | Probable bacterial infection | Group I= IV for 7 days Group II= switched to oral after 48 hours of iv | IV= penicillin and gentamicin Oral= Amoxicillin/cla vulanic acid | reduce the risks of hospital-related complications such as nosocomial infections and improvement in QOL and better mother-child bonding |
| Carlsen et al 2023 [20] | Cohort study | 478 | All term born neonates | Early onset infection | IV-to-oral switch | Amoxicillin | 1 No readmission due to infection 2 Reduction in hospital stay |
| Mohamme d Abdalhad y et al 2023 [21] | Randomise d open-label, non-inferiority trial | 510 | 0-to-28 days | Probable bacterial infection | Group I= IV Amoxicillin/clav ulanic acid Group II=IV-to-oral switch | Amoxicillin/cla vulanic acid | No Bacterial reinfection within 28 days |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Carlsen et al 2023 [22] | Cohort study | 478 | All term born neonates | Early onset infection | IV-to-oral switch | Amoxicillin | 1 No readmission due to infection 2 Reduction in hospital stay |
| Mohammed Abdalhady et al 2023 [23] | Randomised open-label, non-inferiority trial | 510 | 0-to-28 days | Probable bacterial infection | Group I= IV Amoxicillin/clavulanic acid Group II=IV-to-oral switch | Amoxicillin/clavulanic acid | No Bacterial reinfection within 28 days |

randomly assigned to either switch to oral antibiotics after 48–72 hours (intervention group) or continue intravenous antibiotics (control group). Both groups

In a randomized open-label non-inferiority trial, 510 infants aged 0 to 28 days, receiving a 7-day course of antibiotics for suspected bacterial infection, were received treatment for 7 days, and no bacterial reinfections were reported within 28 days [21].

**DISCUSSION**

Many advantages including a reduction in hospital stay and a reduction in associated health costs are obtained from the early intravenous-to-oral antibiotic switch which is described in several current guidelines [22]. However, oral switch therapy is not a widespread practice in neonates yet. Antibiotic therapy is started immediately in case of maternal factors-based or clinical symptoms-based suspicion of infection. Antibiotic therapy can be stopped 36-48 hours after the disappearance of symptoms, reassurance of inflammatory parameters, and negative cultures in the best-case scenario [23]. Special value and importance should be given to the culture of “prolonged antibiotic therapy is not safe at all” [24,25].Switching from IV to oral antibiotics in pediatric patients is according to general proposed principles about the need and time of switch in a number of different infections [26,27]. Generally, there is no recommendation for IV-to-oral switch in neonates aged less than 28 days, however, it is shown in an open-label, randomized, multicenter, non-inferiority trial that an early IV-to-oral switch with amoxicillin-clavulanic acid is non-inferior to IV course in probable neonatal bacterial infection [28]. Early IV-to-oral switch in infants aged less than 90 days with bacteremic and non-bacteremic urinary tract infections has a growing body of evidence in a recent review [29]. It is confirmed by these findings that the possibility of switch therapy can be used by all neonatologists who aim to avoid unnecessary pain and other harmful effects in full-term neonates. Oral antibiotics used should be effective against suspected bacteria causing infection and also they should be well tolerated and safe. Furthermore, there should be a minimal effect of the pharmacokinetics of antibiotics on their absorption from intestines in the first days of life when administered to neonates. It is a known fact that physiological factors like gastric pH, intestinal absorption, gastric emptying time, the composition of meals, frequency of food intake, and bacterial composition of the gut may have negative effects on the pharmacokinetics of antibiotics in neonates [30,31].

**CONCLUSION**

Encouraging the transition from intravenous to oral antimicrobial therapy management can enhance patient convenience and reduce costs. It's important to note that while this switch is beneficial in many cases, it may not be suitable for all infections. Further clinical studies are

necessary to establish its applicability across various infection types and patient profiles, where evidence remains limited.

While the concept of transitioning has been discussed and successfully implemented at numerous institutions over decades, there's an urgency to adopt it on a broader scale globally. This can be achieved through various strategies, including:

1. Direct Sequential Therapy: Switching from intravenous to oral administration of the same drug at the same dose.
2. Switch Drug Therapy: Transitioning from one oral drug to another within the same class, having similar antimicrobial MIC potency, protein binding, and related properties.
3. Step-Down Therapy: Adjusting the dose size and/or frequency of oral dosing, with the switch occurring either within the same class or between different classes of drugs.

**Scientific Responsibility Statement**

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

**Animal and human rights statement**

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors of this article.

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**Conflict of interest**

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