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The role of erythromycin in the management of constipation in children: A systematic review

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Abstract
Constipation is a prevalent gastrointestinal disorder among children, affecting approximately 10-30% of the pediatric population worldwide. It is associated with significant morbidity, including abdominal discomfort, fecal incontinence, and emotional distress, often leading to repeated healthcare visits and reduced quality of life. Although first-line management typically involves dietary modifications, behavioral interventions, and the use of osmotic or stimulant laxatives, a subset of patients fails to respond adequately to these conventional therapies. In such cases-particularly those involving delayed gastric emptying, functional constipation refractory to standard treatment, or neurogenic bowel dysfunction-alternative therapeutic strategies are required.

Erythromycin, a macrolide antibiotic with potent prokinetic properties mediated through stimulation of motilin receptors in the gastrointestinal tract, has been increasingly investigated as an adjunctive treatment for constipation in both adult and pediatric populations. Its ability to enhance gastrointestinal motility at low doses makes it a potentially attractive option in managing dysmotility-related constipation. However, its dual role as an antimicrobial agent raises concerns regarding the development of bacterial resistance when used chronically for non-infectious indications.

This systematic review summarizes the evidence base for erythromycin in the treatment of paediatric constipation. A thorough search was conducted across PubMed, Embase, Scopus and the Cochrane Library for relevant trials, observational studies and case series published from 2000 to 2024. The focus of this review was threefold with the primary outcome measuring frequency of bowel movements along with decreased symptoms of constipation and a global improvement in clinical outcomes. The secondary measures analysed the safety, adverse effects, tachyphylaxis and antibiotic resistance.

The review results found that erythromycin may be able to improve bowel frequency and reduce the symptoms of constipation on a short term basis with select children that is with documented motility disturbances. However long term effects remain unknown, possible diminishing therapeutic effect over time was contributed as ironically making its usage infrequent due to the risk of antibiotic resistance. Adverse effects were mainly mild contributing but in some cases were associated to gastrointestinal discomfort and rarec cases of arrhythmia due to QT prolongation.

We conclude that though some potential exists for erythromycin as a second line prokinetic agent in children who fail to respond to conventional treatments for constipation, it should only be specified for certain types of children in specific clinical situations and under medical supervision. Further need for quality RCT of adequate size with longer follow-up and standard assessment of outcomes need to be undertaken to identify what it place as a possible treatment, or aid in understanding what longer term side effect may exist on paediatrics.

Keywords: Erythromycin, constipation, pediatrics, prokinetic agents, gastrointestinal motility, antimicrobial resistance, systematic review.

1. Introduction

Constipation is one of the most common gastrointestinal complaints seen in everyday pediatric clinical practice and affects about 10-30% of children worldwide [1-4]. Constipation is defined in the Rome IV criteria as a functional gastrointestinal disorder that can present with infrequent bowel movements, hard or lumpy stools, painful defecation, and/or a sense of incomplete evacuation. Constipation must persist for at least 2 months prior to diagnosis [5]. Despite its high prevalence, constipation continues to be relatively complex and multifactorial, adversely impacting a child's quality of life, leading to emotional distress, and increasing repeated visits to the healthcare provider [6].

Most clinicians provide therapy to children with constipation in a stepped approach, starting with diet changes, behavioral interventions, along with non-polymeric and sending systemic agents, such as osmotic and stimulant laxatives [7]. The most common systemic agents used to treat constipation, whether for disimpaction or maintenance therapy, are polyethylene glycol (PEG), lactulose, or mineral oil [8]. A unique cohort of patients will not achieve full response with conventional first line therapy, especially patients with underlying motility disorders, neurogenic bowel dysfunction, or functional constipation; these patients will either worsen or remain unchanged with acute therapy or maintenance therapy [9, 10].

For these patients, clinicians may consider other therapeutic options, such as prokinetic agents. Prokinetics can increase gastrointestinal motility through several pharmacological mechanisms, and has been documented in the literature for the treatment of delayed gastric emptying, gastroparesis, and chronic constipation [11]. Erythromycin is a macrolide antibiotic, which has been used effectively for bacterial infections, but has become more" popular" for its potent prokinetic effects in humans, through the activation of motilin receptors in the gastrointestinal tract [12].

Motilin, a hormone released during fasting, is responsible for stimulating phase III of the migrating motor complex (MMC) for peristalsis and improved gastric emptying [13]. Erythromycin stimulates motilin receptors and elicits virtually the same physiological effects at low doses well below antimicrobial concentrations [14]. These two class features antibiotic and prokinetic makes erythromycin an attractive off label treatment option for gastrointestinal dysmotility disorders, especially in children, whose treatment options continue to be limited [15].

Although there are multiple observational studies and small clinical trials that have demonstrated justifiable results when using erythromycin to improve stool frequency and decrease gastrointestinal-related constipation symptoms in children [16-18], there are still concerns about long-term efficacy, tachyphylaxis development, side effects, and the potential impact on antibiotic resistant bacteria [19, 20]. Therefore, more thorough review is needed of existing literature to define erythromycin as a treatment option in pediatric constipation.

This systematic review will evaluate the current findings about erythromycin for constipation in children, including considerations regarding clinical efficacy, dosing regimens, safety, and culture of antimicrobial stewardship. We will aim to consolidate existing findings from clinical trials, observational studies, and case reports, with the goal of providing clinicians with a clearer understanding of how and when to consider erythromycin as a part of a more expansive treatment plan in children with constipation.

2. Mechanism of Action

Erythromycin is a 14-membered ring macrolide antibiotic that is best recognized for its antimicrobial activity by it through binding to the 50S ribosomal subunit of target bacteria, where it inhibits protein synthesis [1]. Erythromycin, in addition to its antibacterial activity, is noted for its prokinetic effects due to its stimulation of motilin receptors in the GI tract [21].

2.1 Motilin and Gastrointestinal motility

Motilin is a peptide hormone with 22 amino acids secreted by endocrine M-cells in mucosa of the upper small intestine, particularly the duodenum and jejunum [22]. Motilin is important for regulating the migrating motor complex (MMC)-a cyclic pattern of electrical activity and contractile activity in a fasting state that clears residual food and bacteria from the stomach and small intestine [23].

The MMC has four phases:

- **Phase I:** Electrical and motor quiescence lasting approximately 40-60 minutes.
- **Phase II:** Irregular, low amplitude contractions that gradually becoming greater in low amplitude over the course of 10-20 minutes.
- **Phase III:** Regular, high amplitude contractions occurring at intervals of approximately every 90-120 minutes that enhances peristalsis and propulsion of luminal contents.
- **Phase IV:** A short transitional phase that returns it back to Phase I.

Before the beginning of Phase III, Motilin increases indicating its role in regulating the onset of this dramatic contractile activity [24].

2.2 Erythromycin as a Motilin Receptor Agonist

Erythromycin has a similar chemical structure to motilin and is able to bind the same type of motilin receptor, motilin receptor type 1 (MLNR), on smooth muscle cells and enteric neurons in the GI tract [25]. Erythromycin binding to MLNR activates a complex network of signaling events, resulting in increased release of acetylcholine from myenteric neurons, and consequently increasing gastric and intestinal motility [26].

Unlike other prokinetic agents (e.g., metoclopramide and domperidone), which act through dopaminergic pathways, the stimulation of motilin receptors by erythromycin does not cross the blood-brain barrier, and can therefore minimize potential central nervous system side effects (e.g., extrapyramidal symptoms) [27].

Furthermore, the prokinetic effect of erythromycin can occur using very low doses, typically between 3-10 mg/kg/day, divided into 2 or 3 daily doses on an empty stomach [28]. At these doses, serum concentrations remain below those necessary to elicit a bactericidal effect, which reduces selective pressure for antimicrobial resistance [29].

However, after prolonged use of erythromycin (even at low doses), tachyphylaxis could occur in which the prokinetic response decreases, likely due to downregulation of motilin receptors, or desensitization of signaling pathways [30].

3. Clinical Evidence in Pediatric Constipation

Erythromycin has been assessed as a prokinetic agent in the management of pediatric constipation in observational reports, case series, and a very limited number of randomized controlled trials (RCTs).Much of the initial evidence supporting erythromycin for use in pediatric constipation comes from observational data. Observational studies as well as case series may be small in number and often involve retrospective chart review but can provide real-world evidence for clinical use.

- Asaleem *et al.* (2015) performed a case series and retrospective study involving 42 children, ages ranging from 2-12 years, with refractory functional constipation who were treated with low-dose erythromycin (3-5 mg/kg/day) for a minimum of four weeks [31]. The authors noted a significant increase in spontaneous bowel movements per week (1.8 to 4.5-mean) and a decrease in fecal impaction; no serious adverse effects noted during treatment.
- A different retrospective analysis by El-Chammas *et al.* (2009), focussing on 30 children with neurogenic bowel dysfunction due to myelomeningocele, noted that 6 weeks

of erythromycin improved stool frequency and abdominal distension in about 67% of patients [32]. This indicates that erythromycin may be particularly beneficial in patients with an underlying motility impairment.

- A smaller case series by Kalach and Cadranel (2007) reported favorable outcomes in 5 children with chronic idiopathic constipation who had failed treatment with standard laxatives [33]. All 5 children had improved bowel regularity within two weeks of starting erythromycin therapy, though two children needed dose adjustments due to mild GI adverse effects.

A potential association between erythromycin and improved bowel function in selected pediatric populations, particularly in the context of delayed transit times and neurogenic causes of constipation may exist; observational studies has methodological limitations to directly support this conclusion.

3.2 Randomized Controlled Trials (RCTs)

Although limited in number, RCTs provide higher-level evidence regarding the efficacy and safety of erythromycin in pediatric constipation.

- Owais *et al*. (2011) conducted a double-blind, placebo-controlled trial involving 60 children aged 2-12 years diagnosed with functional constipation according to Rome III criteria [34]. Participants received either erythromycin (5 mg/kg twice daily) or placebo for 4 weeks. The erythromycin group demonstrated a statistically significant increase in the number of weekly bowel movements compared to the placebo group (mean: 4.6 vs. 2.3, $p < 0.05$). However, the therapeutic effect appeared to diminish within 2 weeks after discontinuation of the medication, indicating possible development of tachyphylaxis.
- Another RCT by Zafar *et al*. (2017) compared erythromycin with domperidone in 80 children with chronic constipation [35]. Both groups showed improvements in stool frequency and consistency, but the erythromycin group experienced more frequent adverse effects, including diarrhea (15%), abdominal cramping (10%), and decreased appetite (8%). Despite these findings, the authors concluded that erythromycin could be considered as an alternative when first-line prokinetics are ineffective or not tolerated.

Despite methodological limitations such as small sample sizes and short follow-up periods, these RCTs support the potential role of erythromycin in managing constipation in children, particularly in those who do not respond adequately to conventional therapies.

4. Safety and Side Effects

Although erythromycin is generally well tolerated in the short term, its use especially for prolonged periods-raises concerns regarding safety, tolerability, and long-term consequences. As both an antibiotic and a prokinetic agent, it carries risks related to gastrointestinal side effects, tachyphylaxis, cardiac toxicity, and antimicrobial resistance [36].

4.1 Common Adverse Effects

The most frequently reported adverse effects of erythromycin in pediatric patients are gastrointestinal in nature, these include:

- Nausea and vomiting.
- Abdominal cramps and pain.
- Diarrhea or loose stools.
- Decreased appetite.

These symptoms are often dose-dependent and may be mitigated by administering the drug in lower doses, dividing the daily dose into multiple smaller administrations, or using enteric-coated formulations [37]. In clinical trials evaluating erythromycin for constipation, up to 20-30% of children experienced mild gastrointestinal discomfort that did not require discontinuation of therapy [35].

4.2 Cardiac Toxicity and QT Prolongation

One of the more serious but relatively rare complications associated with erythromycin use is QT interval prolongation, which can lead to potentially life-threatening arrhythmias such as torsades de pointes [38]. This effect appears to be mediated through blockade of cardiac potassium channels (hERG) and is more likely to occur in patients with:

- Pre-existing cardiac conditions
- Electrolyte imbalances (e.g., hypokalemia, hypomagnesemia)
- Concomitant use of other QT-prolonging medications
- Genetic predisposition

A U.S. Food and Drug Administration (FDA) drug safety communication warned about this risk, particularly when erythromycin is used in high doses or intravenously [39]. While oral low-dose regimens for prokinetic purposes are less likely to cause significant cardiac effects, clinicians should exercise caution in at-risk populations and consider baseline electrocardiographic (ECG) screening when appropriate.

4.3 Tachyphylaxis and Loss of Efficacy

Tachyphylaxis-defined as a rapid decrease in drug response after repeated administration-is a well-documented phenomenon with erythromycin when used as a prokinetic agent [40]. Several studies have shown that the beneficial effects on bowel frequency and motility tend to diminish after several weeks of continuous use, likely due to downregulation of motilin receptors or desensitization of signaling pathways [41].

In a placebo-controlled trial by Owais *et al*. (2011), while initial improvements were observed during the 4-week treatment period, these benefits rapidly declined after discontinuation, indicating limited sustainability of the therapeutic effect [34].

4.4 Antimicrobial Resistance

Perhaps the most significant concern surrounding the off-label use of erythromycin in non-infectious indications is the potential contribution to antimicrobial resistance [42]. Even at low doses, subtherapeutic exposure to macrolides may exert selective pressure on gut and respiratory flora, promoting the emergence of resistant strains such as macrolide-resistant *Streptococcus pneumoniae* and Group A, *Streptococcus* [43].

This issue has important implications for public health, especially considering the global rise in antibiotic resistance and the increasing emphasis on antimicrobial stewardship programs. Therefore, the use of erythromycin for chronic constipation must be carefully weighed against alternative prokinetic agents that do not carry antimicrobial activity [44].

5. Comparison with Other Prokinetic Agents

While erythromycin has demonstrated some efficacy in managing constipation in children, it is important to compare its profile with other available prokinetic agents to guide clinical decision-making. Several alternative medications are used in

pediatric gastrointestinal motility disorders, each with distinct mechanisms of action, safety profiles, and regulatory considerations.

5.1 Metoclopramide

Mechanism

Metoclopramide is a dopamine D2 receptor antagonist that enhances upper gastrointestinal motility by increasing acetylcholine release through central and peripheral effects.

Advantages

- Rapid onset of action (within 30 minutes)
- Available in oral, intravenous, and rectal formulations
- Well-established use in gastroparesis and delayed gastric emptying

Disadvantages

- Risk of extrapyramidal side effects (e.g., dystonia, tardive dyskinesia), especially in children
- Potential for central nervous system depression
- Limited long-term use due to neurologic risks [45].

5.2 Domperidone

Mechanism

Domperidone is also a dopamine receptor antagonist but does not cross the blood-brain barrier significantly, thereby reducing the risk of central nervous system side effects.

Advantages

- Lower incidence of neurological side effects compared to metoclopramide
- Effective in improving gastric emptying and bowel frequency
- May be used off-label in children under medical supervision

Disadvantages:-

- Risk of QT prolongation and cardiac arrhythmias (FDA has not approved domperidone for general use in the U.S.)
- Requires careful monitoring in patients with electrolyte disturbances or underlying heart disease [46].

5.3 Prucalopride

Mechanism

Prucalopride is a selective serotonin (5-HT_4) receptor agonist that enhances colonic motility without affecting dopamine or motilin receptors.

Advantages

- High efficacy in adult studies for chronic constipation
- Once-daily dosing
- No antimicrobial activity or risk of resistance

Disadvantages

- Limited data on safety and efficacy in children
- Not currently approved for use in patients under 18 years of age
- Expensive and not widely available in many countries [47].

5.4 Erythromycin

Mechanism

As previously discussed, erythromycin acts as a motilin receptor agonist, enhancing gastrointestinal motility at low doses without reaching bactericidal levels.

Advantages

- Oral administration with rapid onset of effect
- Can be effective in patients with delayed gastric emptying or neurogenic bowel dysfunction
- Readily available and cost-effective

Disadvantages:

- Development of tachyphylaxis after prolonged use
- Gastrointestinal side effects (nausea, diarrhea, abdominal cramping)
- Risk of QT prolongation
- Concerns about antimicrobial resistance with long-term use [48].

Table 1: Comparative Overview of Prokinetic Agents in Pediatric Constipation

Agent	Mechanism	Onset of Action	Administration Route	Advantages	Disadvantages
Erythromycin	Motilin receptor agonist	1-2 weeks	Oral	Low cost, available, short-term efficacy	Tachyphylaxis, GI side effects, antimicrobial resistance
Metoclopramide	Dopamine antagonist	<30 min	Oral, IV, PR	Fast-acting, well studied	Extrapyramidal symptoms, CNS effects
Domperidone	Dopamine antagonist	1-2 weeks	Oral	Fewer CNS side effects	Cardiac toxicity, limited approval
Prucalopride	5-HT_4 agonist	1-2 weeks	Oral	High efficacy in adults	Limited pediatric data, expensive

6. Current guidelines and recommendations

In accordance with the emerging interest in the use of erythromycin as a prokinetic in the management of children with constipation, current international guidelines do not recommend the use of erythromycin as a first-line treatment. Current international clinical practice guidelines recommend a stepwise approach to management of childhood constipation, including the use of disimpaction, maintenance with laxatives, dietary interventions and behavioural therapy. While there may be use of prokinetics in the management of constipation, especially when there is delayed gastric emptying or in cases of refractory constipation, erythromycin has not been specifically mentioned as an option due to limited evidence and the implications of antimicrobial resistance and tachyphylaxis in recent studies.

If prokinetics such as erythromycin are used, NASPGHAN has advised to start erythromycin for 14 days, and to stop the medication if there has been no evidence of benefit over 2-4 weeks.

6.2 Recommendations from the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)

ESPGHAN recommendations for the management of childhood functional constipation similarly indicate that there is not enough evidence to recommend regular use of prokinetic agents in children, as a routine treatment [51]. In particular, ESPGHAN recommends that while there are some studies showing erythromycin benefits in bowel frequency and motility, the results varied widely across patient groups. Additionally, there was lack of long-term safety data.

However, ESPGHAN was cautious about the possible contribution of chronic, low-dose macrolides to antimicrobial resistance from chronic non-infectious uses in children. [52].

6.3 Other National and Regional Guidelines

- In the United Kingdom, the National Institute for Health and Care Excellence (NICE) does not include erythromycin in its guidance for managing constipation in children, focusing instead on lifestyle modification, laxative therapy, and specialist referral when necessary [53].
- In Japan, where macrolide antibiotics are more commonly used for non-antimicrobial purposes, erythromycin is occasionally prescribed off-label for gastrointestinal dysmotility; however, this practice is increasingly scrutinized due to rising rates of macrolide resistance [54].

6.4 Expert Consensus and Clinical Practice

In clinical practice, many pediatric gastroenterologists consider erythromycin as a second-line or adjunctive option in managing constipation, particularly in:

- Children with documented delayed gastric emptying
- Patients with neurogenic bowel dysfunction (e.g., myelomeningocele)
- Those who fail to respond to standard laxative therapy

Use is typically limited to short-term trials (4-8 weeks), with close monitoring for efficacy, side effects, and signs of diminishing response due to tachyphylaxis [55].

7. Future Directions

Despite the existing body of literature on the use of erythromycin in pediatric constipation, several critical knowledge gaps remain. Addressing these through future research will help clarify its role in clinical practice and guide evidence-based decision-making.

7.1 Need for High-Quality Randomized Controlled Trials (RCTs)

To date, most studies evaluating erythromycin in children with constipation have been small-scale observational studies or short-term RCTs with limited follow-up periods. Larger, multicenter RCTs are needed to:

- Confirm the efficacy of erythromycin in specific pediatric subpopulations (e.g., neurogenic bowel dysfunction, delayed gastric emptying).
- Assess long-term outcomes, including sustained improvement in bowel function and quality of life.
- Evaluate the impact of different dosing regimens on efficacy and safety.

Future trials should also incorporate standardized outcome measures such as:

- Weekly bowel movement frequency
- Stool consistency (e.g., Bristol Stool Scale)
- Symptom severity scores
- Use of rescue medications or hospitalizations

7.2 Biomarkers and Predictors of Response

Identifying clinical or biological predictors of response could help personalize treatment decisions. Potential areas of investigation include:

- Genetic polymorphisms affecting motilin receptor expression or function
- Gastric emptying studies to identify responders
- Gut microbiota composition before and after treatment

Such biomarkers may allow clinicians to select patients most likely to benefit from erythromycin while avoiding unnecessary exposure in non-responders.

7.3 Impact on Antimicrobial Resistance

Given the growing concern about antimicrobial resistance, future research must evaluate the consequences of low-dose, long-term erythromycin use in children. Studies should assess:

- Changes in gut and respiratory flora
- Emergence of macrolide-resistant pathogens
- Cross-resistance with other antibiotic classes

These data would support antimicrobial stewardship efforts and inform risk-benefit analyses when considering erythromycin for prokinetic use.

7.4 Exploration of Novel Motilin Receptor Agonists

Research into newer motilin receptor agonists that lack antimicrobial activity is ongoing. These agents could offer the prokinetic benefits of erythromycin without contributing to antibiotic resistance. Clinical development and testing in pediatric populations are essential steps toward expanding safe and effective treatment options.

8. Conclusion

Erythromycin demonstrates modest prokinetic effects in children with refractory constipation and may offer short-term benefits in select clinical scenarios, particularly in those with documented delayed gastric emptying, neurogenic bowel dysfunction, or functional constipation unresponsive to conventional laxative therapy. Its mechanism as a motilin receptor agonist allows for enhanced gastrointestinal motility at low doses, avoiding systemic antimicrobial activity. However, its dual role as an antibiotic raises significant concerns regarding antimicrobial resistance, especially when used chronically for non-infectious indications.

While observational studies and limited randomized controlled trials suggest that erythromycin can improve bowel movement frequency and reduce symptoms of constipation in some pediatric patients, several limitations remain:

- Small sample sizes
- Short follow-up durations
- Heterogeneity in patient populations and dosing regimens
- Lack of validated outcome measures

Moreover, adverse effects such as gastrointestinal discomfort, QT prolongation, and the development of tachyphylaxis further limit its long-term utility. Compared to other prokinetic agents like metoclopramide, domperidone, and prucalopride, erythromycin offers advantages in availability and cost but lacks consistent evidence supporting sustained efficacy and safety.

Current international guidelines from NASPGHAN and ESPGHAN do not recommend erythromycin as a first-line agent for pediatric constipation. Instead, they advocate for its use only in specific, well-defined cases under close monitoring. Future research should focus on conducting large-scale RCTs with extended follow-up periods, identifying biomarkers of response, assessing antimicrobial resistance patterns, and exploring novel motilin receptor agonists without antimicrobial properties.

In summary, while erythromycin holds promise as a second-line

prokinetic option in the management of refractory constipation in children, its use must be carefully considered within the broader context of antimicrobial stewardship and individualized patient care.

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