

## Research Article

# Improving the Primary Care Management of Preschool Children with Recurrent Acute Respiratory Tract Infections in the Czech Republic: Prompt Use of Erdosteine Can Reduce Antibiotic Prescribing

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### ABSTRACT

Acute Respiratory Tract Infections (RTIs) are very common in children and, although they are predominantly viral in origin and self-limiting, are a major cause of inappropriate antibiotic prescribing in primary care. Numerous strategies and interventions are being developed to optimize antibiotic prescribing for acute RTIs. In this article, we review the evidence that early use of erdosteine in children with acute RTIs of viral origin may reduce unnecessary antibiotic prescribing in the primary care setting. Erdosteine is an oral mucolytic agent that also has antibacterial and anti-inflammatory effects which are relevant for the treatment of respiratory diseases. Several randomised clinical studies in children with acute lower RTIs have shown that combined treatment with erdosteine and an antibiotic enables a more rapid improvement in symptoms, particularly cough, than antibiotic therapy alone. We describe the ERICA study, a non-interventional, observational, multicentre study performed in routine general

practice in the Czech Republic over the 2014–2015 winter season in 342 children with a history of recurrent RTIs ( $\geq 2$ ) treated with antibiotics in the previous winter season. During the monitored season, all children were prescribed erdosteine at initial presentation for an acute viral RTI, but only 21 (4.4%) of the 473 RTIs resulted in an antibiotic prescription. The mean number of antibiotics used was 0.06 versus 2.32 in the previous season ( $p < 0.001$ ). Also, 73.4% experienced only one RTI during the season. This is the first real-world primary care study to show that prompt use of erdosteine at the initial signs of an acute RTI of presumed viral origin results in a large reduction in antibiotic use and fewer respiratory infections in children with a history of recurrent RTI, many of whom were preschool age and had allergic disorders. Further studies with erdosteine are needed to confirm these findings.

**2. Key words:** Respiratory tract infections; Antibiotics; Child; Czech Republic; Erdosteine

### How This Fits in with Quality in Primary Care

#### What do we know?

- Antibiotics are over-prescribed in children presenting to primary care physicians with acute respiratory tract infections (RTIs) that are mainly caused by viruses and are self-limiting.
- Strategies/interventions that facilitate rational antibiotic prescribing are needed.
- Erdosteine has multiple mechanisms of action that are relevant for the treatment of respiratory diseases.

#### What does this paper add?

- Prompt use of erdosteine in children presenting with acute RTIs of viral origin reduces both antibiotic prescribing and the total number of respiratory infections experienced over a winter season.

### Introduction

Preschool children (aged  $< 5$  years) may experience up to 11 respiratory tract infections (RTIs) per year [1], and

such infections are the most common reason for paediatric consultations in primary care. Acute RTIs are usually treated empirically because the causative pathogen is unknown when treatment is initiated. Antibiotics are commonly prescribed

for acute RTIs and preschool children receive more than half of all antibiotics prescribed each year [2]. However, most acute RTIs do not require an antibiotic because they are predominantly caused by one of the >200 different strains of virus (e.g., rhinoviruses, respiratory syncytial virus, influenza or parainfluenza virus, adenoviruses or enteroviruses), are typically self-limiting and the risk of complications is small. In otherwise healthy children, antibiotics do not shorten the time to recovery from an RTI [3]. Nevertheless, it has been estimated that antibiotics are prescribed in up to 50% of patients with acute RTIs of presumed viral origin, most commonly for acute bronchitis [4]. Such inappropriate and high use of antibiotics in primary care has contributed to the development of antibacterial resistance [5], which is a serious and growing public health problem worldwide [6]. Antibiotics also negatively change the gut microbiome of a developing child and, thus, influence the maturation of the immune system. There is a clear need to improve antibiotic prescribing practices, particularly for children presenting in primary care with acute RTIs.

In the Czech Republic, a survey conducted in 2001 estimated that antibiotics were prescribed inappropriately in 42% of cases of acute RTI in children, most frequently for acute bronchitis and laryngotracheitis, which tend to be caused by viruses [7]. Despite these cautionary data, there has been little change among primary care paediatricians in the practice of antibiotic prescribing for children. Therefore, in 2014, the Czech Medical Association provided educational activities to improve antibiotic prescribing practices among primary care paediatricians and introduced a national antibiotic policy [8].

In 2005, the surveillance and reporting system for acute respiratory infections and influenza-like illness changed in the Czech Republic, so that data is collected weekly, analysed nationally and provided to the European Centre for Disease Prevention and Control (ECDC) and the World Health Organisation (WHO) [9]. In 2009, a national roundtable meeting was held to increase awareness of antibiotic resistance and to find ways of supporting rational antibiotic prescribing [10]. At that time, overall outpatient consumption of antibiotics in the Czech Republic was comparable to other European countries, with low levels of antibiotic resistance to the main bacterial causes of respiratory disease (*Streptococcus pneumoniae* and *Haemophilus influenzae*) but increasing resistance to macrolide antibiotics among *Streptococcus pyogenes*, a known bacterial cause of tonsillitis [10]. Antibiotic resistance rates for the major respiratory bacterial pathogens remain relatively low [11], but antibiotic consumption in the community increased between 2012 and 2015 from 17.5 to 19.5 defined daily dose (DDD) per 1000 inhabitants per day in the Czech Republic [12].

These findings suggest that primary care physician knowledge and prescribing behaviour still needs to be improved and that additional strategies/interventions should be developed to reduce inappropriate antibiotic prescribing for acute RTIs in the Czech Republic. Paediatric populations are an important target because RTIs in children can be transmitted rapidly in the close-contact environment of day care facilities and schools, and acute RTIs are usually managed in the primary care setting.

The purpose of this article is to review the evidence that early use of erdosteine in children may influence the development and severity of RTI symptoms. Erdosteine therapy may contribute to improved prescribing practice and facilitate rational use of antibiotics in children presenting with acute RTIs in primary care.

### Erdosteine

Erdosteine is an oral drug with multiple mechanisms of action that are relevant for the treatment of respiratory diseases.<sup>13</sup> It has been available since 1995 as a treatment for chronic bronchitis and chronic obstructive pulmonary disease (COPD), is marketed in nearly 40 countries worldwide, is well-tolerated and has a well-established safety profile. Erdosteine was originally developed as a mucolytic agent that acts by breaking the disulphide bonds of mucus glycoproteins, altering the physical properties of the mucus and leading to improved mucus clearance [13,14]. Importantly, erdosteine also displays antibacterial activity by reducing the ability of bacteria to adhere to mucosal cells and can potentiate the anti-adhesive effect of antibiotics [13]. The synergistic effects of erdosteine and antibiotics when used in combination has been confirmed with several different antibiotics in clinical studies of patients with acute exacerbations of chronic bronchitis or COPD, which are frequently caused by RTIs [13,15]. Furthermore, erdosteine has anti-inflammatory effects that may play a role in its therapeutic effects, especially when used in combination with antibiotics [13]. Moreover, a prospective post-authorisation pilot study in the Czech Republic found that erdosteine either alone or in combination with a topical corticosteroid was effective in the treatment of chronic rhinosinusitis with nasal polyposis [16]. There is also some evidence that erdosteine has antitussive effects, which may be related to improved mucociliary clearance and reduced release of chemokines from epithelial cells [14].

Several paediatric randomized controlled clinical studies have demonstrated that erdosteine is effective when used in combination with antibiotics in the treatment of children with acute lower RTIs (Table 1): erdosteine use results in a more rapid improvement in symptoms, especially cough [17-19]. Additionally, a small open-label study in Brazil reported that erdosteine was effective in 30 children with upper RTIs [20]. However, a randomized placebo-controlled study conducted in Turkey found no significant clinical benefit of erdosteine in the treatment of 92 children (aged 3–12 years) with acute rhinosinusitis [21].

Based on the results of these clinical studies, we postulated that prompt use of erdosteine in children presenting with acute RTIs of viral origin may reduce the severity and duration of symptoms, reduce/prevent bacterial colonization of the respiratory tract and the subsequent development of secondary bacterial infections or local bacterial complications, thereby reducing the need to use antibiotics.

### ERICA study

ERICA (Erdosteine in acute Respiratory Infections in Children – could we rationalise the Antibiotic treatment?) was a non-

**Table 1: Summary table of clinical studies investigating erdosteine and antibiotics administered in combination to children with acute lower respiratory tract infections.**

Ref	Study design	Main results/conclusions
<b>Bechara et al., [20]</b>	64 children (aged 2–12 years) with bronchitis were randomised to treatment with amoxicillin alone or amoxicillin plus erdosteine, both administered twice daily for 10 days	Amoxicillin plus erdosteine for 10 days was more effective than amoxicillin alone in improving clinical symptoms of odynophagia, rales, productive cough, morning and night coughing. No difference between groups in other symptoms
<b>Titti et al., [21]</b>	Multicentre, randomised, double-blind, parallel group study of erdosteine plus ampicillin vs ampicillin alone (100 mg/kg/day) for 5–9 days in 200 children with acute febrile lower RTI (acute bronchitis, asthmatic bronchitis, trachea-bronchitis, bronchoalveolitis). Erdosteine was administered as a syrup 3.5% to children age 2–4 years and in sachet form to children aged 5–10 years.	Combination of erdosteine plus ampicillin allowed a more rapid and definite amelioration of symptoms (especially cough [primary efficacy parameter]) compared with ampicillin alone
<b>Balli et al., [22]</b>	Multicentre, randomised, double-blind, placebo-controlled study in 158 children (aged 2–12 years) with acute lower RTI treated with amoxicillin alone or amoxicillin plus erdosteine for mean duration of 7.28 days.	Erdosteine in combination with amoxicillin produced a more rapid improvement in clinical symptoms (cough, rales) than amoxicillin alone.

interventional, observational, multicentre study conducted in outpatient general practice in the Czech Republic to investigate the efficacy and safety of erdosteine in the treatment of children with recurrent acute RTIs [22]. As the viruses responsible for acute RTIs typically have a seasonal occurrence, with higher levels during the winter months, the study was conducted over the winter season of 2014–2015 (i.e., from October 2014 to March 2015). The study included children (age <18 years) who had experienced at least two RTIs that had been treated with antibiotics in the previous winter season (2013–2014), and who presented in the monitored season (2014–2015) with a new RTI that was considered a viral infection according to the simple test for C-reactive protein (CRP  $\leq$  40 mg/L). Patients with primary bacterial infections indicated for antibiotic therapy were excluded from the study. Patients were enrolled during routine clinical practice and the decision to use erdosteine was based solely on the judgement of the attending doctor. Erdosteine was prescribed to all study participants at the initial consultation either as a suspension (5 ml of peroral suspension contains 175 mg of erdosteinum) (76% of cases) or a sachet of granules for preparing a solution (24% of cases) at the doses- according to body weight and age of children - 15–20 kg (3–6 years) 2.5 ml twice a day, 21–30 kg (7–12 years) 5 ml twice a day and over 30 kg (over 12 years) 5 ml 3 times a day (maintenance dosage is 4 to 8 mg/kg/day) - recommended in the SmPC [23].

The results of the ERICA study have been reported previously in the Czech language [22]. Of the 342 children monitored over the 2014–2015 season, 56.7% were male, the largest proportion (49.4%) were aged 3–6 years, and they experienced a total of 473 RTIs. All 342 children experienced an RTI during the monitored season: 251 (73.4%) experienced only one RTI, 57 (16.7%) had two RTIs, 28 (8.2%) had three RTIs and 6 (1.8%) had four RTIs. Of these infections, the most common diagnoses were acute bronchitis (40.0%), acute tracheobronchitis (18.6%), acute laryngopharyngitis (18.2%), and acute laryngitis and

tracheitis (14.2%). The main symptoms of these infections were cough (99.4%), rhinitis (61.7%) and fever (58.4%). In addition, 44.6% of the patients were reported to have atopy or allergies and 19.0% had asthma (Figure 1). The main finding of the study was that during the monitored season, only 21 (4.4%) of the 473 RTIs resulted in an antibiotic prescription (Figure 2). In comparison, all children had been prescribed antibiotics during the previous season: 77.5% had received 2 antibiotics, 17.0% had received 3 antibiotics, and 5.5% had received  $\geq$ 4 antibiotics. The mean number of antibiotics used during the monitored season was 0.06 (95% CI: 0.04; 0.09) versus 2.32 (95% CI: 2.24; 2.39) in the previous season;  $p < 0.001$  Wilcoxon's test. During the monitored season, the most frequently administered antibiotics were clarithromycin (52.4%) and amoxicillin/clavulanic acid (19.0%).

At follow-up, patients/parents reported the efficacy of treatment based on the number of infections as “very good” (79.9%), “satisfactory” (15.6%), and “not effective” (4.4%). Similarly, patient-reported tolerability of treatment was “very good” (90.7%), “good” (8.7%), and “poor” (0.6%).

## Discussion

Inappropriate antibiotic prescribing for the treatment of viral RTIs is a widespread and ongoing problem in primary care practice, emphasising the need to implement strategies that improve rational antibiotic prescribing. The ERICA study conducted in general paediatric practice in the Czech Republic is the first study to show that prompt use of erdosteine at the initial signs of an acute RTI of presumed viral origin results in a large reduction in antibiotic use and fewer respiratory infections in children with a history of recurrent acute RTIs, many of whom have allergic disorders. These results in the real-world primary care setting extend previously reported clinical trials findings of the efficacy of erdosteine when used in combination with antibiotics in children with acute RTIs [17–19].

## Selected patient characteristics

N of patients=342

SEX	N of patients		Characteristics	median (25., 75. kvantil)
Male	N=194	56,7%	Allergy	126 (26,6%)
Female	N=148	43,3%	Atopy	85 (18,0%)
			Asthma	90 (19,0%)

Figure 1: ERICA study: selected patient characteristics.

## RTI – antibiotic prescriptions

N of infections=473 [one patient could have more infections]

Season 2013/2014 – all patients were prescribed ATB

Season 2014/2015 – ATB prescription:

YES	N=21	4,4%
NO	N=452	95,6%

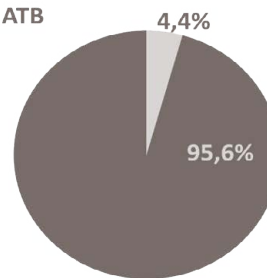


Figure 2: ERICA study: antibiotic prescriptions in monitored season versus previous season.

Research has identified many factors that may contribute to inappropriate antibiotic prescribing for acute RTIs in primary care, including diagnostic or prognostic uncertainty, lack of physician knowledge, physician time constraints, parent/patient expectations of receiving antibiotics, physician expectations of what parents/patients want/patient satisfaction, and poor doctor-patient communication [24,25]. Symptom severity is often used in general practice to inform decision-making and primary care physicians report taking the safer course of action “just in case”; they prescribe antibiotics to prevent secondary bacterial infections or severe complications that could lead to hospitalisation and because they have a fear of litigation if they do not prescribe antibiotics [26]. It is difficult to distinguish bacterial from viral RTIs based on clinical signs and symptoms [27], and co-infections with respiratory viruses and bacterial respiratory pathogens are common in children, especially during the winter season. Although the “watch and wait” approach requires subsequent re-consultation to check the patient’s clinical status, it is preferable to the immediate provision of an antibiotic prescription. Current evidence does not support the above-stated reasons for prescribing antibiotics in young children with uncomplicated acute RTIs [28]. Antibiotics can interfere with the development of both the microbiome and immune system during childhood, which may increase the risk of developing allergic disease and asthma as well as antibacterial resistance [29]. In addition, interactions between the respiratory microbiome and the immune system may alter the immune response during an acute RTI and modulate the clinical outcome.

Research efforts have been directed towards developing interventions that reduce or improve antibiotic prescribing

without causing adverse clinical consequences [24,29]. These include educational interventions for clinicians and parents/patients [30,31], shared decision making [32], delayed antibiotic prescribing [33], decision support tools, and rapid point-of-care testing (including CRP testing) to guide antibiotic prescribing, as well as providing reassurance about the safety of reducing antibiotic prescriptions for acute RTIs [34]. However, parents continue to have misconceptions about antibiotics for RTIs [35]; some do not distinguish between antipyretics and antibiotics or consider that symptomatic treatment is insufficient.

There is also increased interest in non-antibiotic therapies for the treatment of RTIs. In the ERICA study, we examined the effectiveness of erdosteine in the treatment of children with acute RTIs of viral origin for which antibiotic therapy was not indicated. Even though all the children had a history of repeated RTIs treated with antibiotics in the previous winter season, the majority did not require antibiotics and had fewer RTIs during the monitored winter season when they received erdosteine. These findings suggest that erdosteine could be considered an agent reducing the risk of bacterial superinfection in RTIs. The underlying mechanism may be a reduction in the inflammatory response resulting in decreased mucus secretion and bronchial oedema, thereby maintaining the airway diameter and minimising symptom severity. It is not known whether other mucolytic agents reduce antibiotic use in patients with acute viral RTIs, but N-acetylcysteine and carbocysteine have shown limited efficacy in reducing symptoms of acute RTIs in children. However, N-acetylcysteine has demonstrated antibacterial properties and the ability to interfere with biofilm formation and to disrupt biofilms, which play an important role in RTIs [36].



Importantly, 44.6% of children in the ERICA study had atopy or allergy and 19% had asthma. This indicates that children with allergic inflammatory diseases are prone to experiencing recurrent acute viral RTIs, which is supported by the frequent episodes of airway inflammation and symptoms reported by parents of children with allergic disease in the Czech Republic [37]. Viral respiratory infections have been associated with the development and exacerbation of asthma in children. Viral infection generally precedes bacterial infection of the airways and the virus-bacteria interaction worsens the severity of the illness and increases the risk of asthma exacerbation [38]. How a viral infection increases bacterial colonization and density in the airways is not well understood but may involve multiple mechanisms, including disruption of the airway epithelium, increased mucus production and an enhanced nutrient environment for bacterial growth. Given these observations, the anti-inflammatory effects of erdosteine probably have clinical relevance, especially in children with inflammatory airway disorders who not only have physiologically narrow airways but also can experience problems due to the oedema caused by the inflammatory response.

In the ERICA study, acute bronchitis was the most common diagnosis (40%) and clarithromycin was the most frequently prescribed antibiotic in children with acute RTIs of viral origin. Use of macrolides is surprising because they are not the first-choice antibiotics recommended in the Czech guidelines [8], and there is no evidence that they have a clinically meaningful benefit for patients with acute bronchitis or any other presumed viral acute RTI [4]. Thus, inappropriate prescribing of a suboptimal type of antibiotic continues in the Czech Republic. Other countries, including the United States, have reported increasing use of broad-spectrum antibiotics (e.g. amoxicillin-clavulanate, cephalosporins and macrolides) for respiratory infections where no antibiotic is indicated or when a narrow-spectrum antibiotic (e.g. penicillin, amoxicillin) would be more appropriate and likely cause fewer drug-related adverse events [39].

### Strengths and limitations of ERICA study

ERICA was the first study to investigate whether the prompt use of erdosteine could reduce antibiotic prescribing for acute RTIs of viral origin in primary care over a winter season, thereby reducing inappropriate prescribing. ERICA was an observational study that included outpatient general practitioners and provided real-world data for a cohort of children from 12 regions in the Czech Republic. Another strength of the study was the use of CRP tests to distinguish between the viral and bacterial aetiology of the RTI evaluated together with symptoms in the monitored season. Moreover, the study increased awareness of the national antibiotic policy among paediatricians, was managed in cooperation with the Association for Primary Paediatric Care in the Czech Republic, and the study results were presented during regional seminars across the whole country.

The ERICA study has several limitations that should be considered when interpreting the findings. First, it did not include a control group and all patients included in the analysis

received erdosteine. Second, because viral aetiology of RTIs in the previous season was not confirmed, we cannot determine how many of the antibiotic prescriptions during that season were inappropriate. Third, as the types of respiratory virus in circulation vary every winter season, comparisons between seasons are difficult even within a given patient population. Finally, although we postulated that erdosteine may reduce the severity and duration of RTI symptoms, we did not measure these outcomes directly.

### Implications for primary care practice

The findings of the ERICA study have several implications for routine general practice. First, prompt use of erdosteine in children presenting with acute RTIs of viral origin has the potential to reduce inappropriate antibiotic prescribing in primary care as the ERICA study showed that antibiotic use was much reduced in such cases. A reduction in antibiotic use among children with acute RTIs may not only decrease the spread of antibiotic resistance but also reduce unnecessary health care costs and adverse events associated with antibiotics. Moreover, the cost of erdosteine is lower than antibiotic treatment and erdosteine has a well-documented safety profile. Second, erdosteine was effective in children at the highest risk of acute RTIs; i.e. preschool children and those with allergic disorders. Third, as parent expectations/demand for antibiotics is a major factor influencing antibiotic prescribing in children, more widespread use of point-of-care CRP tests in the primary care setting may help to identify patients who probably have a viral cause of their infection, which will allow physicians to discuss more appropriate treatment options and manage parent expectations for antibiotics. Such diagnostic tests can also inform and improve appropriate prescribing of antibiotics: a meta-analysis of primary care studies has shown that point-of-care CRP testing reduces antibiotic prescribing for acute RTIs [40].

### Conclusion

There is much potential to improve rational antibiotic prescribing in the management of acute RTIs in children in primary care in the Czech Republic and other countries. Continuing education programs on the diagnosis and management of acute RTIs are needed together with other interventions that reduce unnecessary antibiotic prescribing. Novel therapeutic approaches may also be needed and the promising results from the ERICA study suggest that prompt use of erdosteine in the treatment of acute viral RTIs may contribute to optimizing antibiotic use in primary care practice although further studies with this drug are needed.

### Ethical Approval

The ERICA study was conducted in accordance with legal and ethical requirements (Czech State Institute for Drug Control [SUKL] identification number 1410020003).

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## Conflicts of Interest

The authors state that there are no conflicts of interest regarding the publication of this article.

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