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Eight Common Mistakes Pediatricians Should Avoid that Hinder Antimicrobial Immune Defenses: Strategies for Boosting Protective Immunity

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ABSTRACT

Antimicrobials and vaccinations are vital tools in the fight against infections and in supporting the immune system. Over recent years, significant improvements in life expectancy have been attributed to better access to antimicrobials. However, the increasing threat of antimicrobial resistance has become one of the leading causes of death globally. Vaccinations remain the cornerstone of preventive strategies. In addition to them, other preventive measures, such as handwashing, mask use, physical distancing, and proper nutrition, play crucial roles in reducing infection spread. Nutritional interventions that offer immunomodulatory and antioxidant effects should also be considered in conjunction with these strategies to enhance immune defenses further.

This paper aims to highlight common mistakes pediatricians should avoid that may hinder immune defenses and exacerbate the risk of viral and bacterial infections. By identifying and correcting these errors, pediatricians can improve patient outcomes, reduce the burden of disease, and promote more robust immune development in children.

Impact statement: This article aims to underline the crucial role of pediatricians in preventing recurrent respiratory infections in children and their sequelae, through diet and lifestyle suggestions, pollution prevention, vaccines and conscious use of antitussives, antipyretics and inhaled steroids.

Key words: *immunity; infections; children; prevention; lifestyle.*

Introduction

Antimicrobials and vaccinations are vital tools in the fight against infections and in supporting the immune system. Over recent years, significant improvements in life expectancy have been attributed to better access to antimicrobials, particularly in low -and middle- income countries[1]. However, the increasing threat of antimicrobial resistance jeopardizes these gains, as it has become one of the leading causes of death globally, with the highest burden in low-resource settings. Immunizations, which remain the cornerstone of preventive strategies, have successfully utilized diverse technologies such as inactivated, attenuated, nucleic acid, and viral vector-based vaccines[2]. These innovations have led to the development of highly effective and safe products. For instance, during the COVID-19 pandemic, vaccinations are estimated to have prevented around 14.4 million deaths globally[3].

Despite these advances, vaccine-preventable diseases still affect millions of individuals, particularly in regions like Europe[4].

In addition to vaccines, other preventive measures -such as handwashing, mask use, physical distancing, and proper nutrition- play crucial roles in reducing infection spread[5]. These measures gained widespread recognition during the COVID-19 pandemic, as they demonstrated their efficacy in mitigating viral transmission[6]. Nutritional interventions that offer immunomodulatory and antioxidant effects should also be considered in conjunction with these strategies to enhance immune defenses further.

This paper aims to highlight common mistakes pediatricians should avoid that may hinder immune defenses and exacerbate the risk of viral and bacterial infections. By identifying and correcting these errors, pediatricians can improve patient outcomes, reduce the burden of disease, and promote stronger immune development in children.

Multi-systemic and prolonged consequences of airway infections

Viral and bacterial infections of the airways that occur during childhood pose a relevant individual and social burden, and may impair health across the lifespan. Recurrent respiratory infections during the early years of life may have potential adverse effects both on the nervous and the respiratory systems. For instance, infants who suffer from bronchiolitis and, in the following months, from recurrent wheezing may experience early cognitive deficits. It has been shown that the cognitive status of children at the age of 3 years, assessed with the Bayley Mental Development Index (MDI), was inversely correlated with the number of wheezing days experienced during the first 24 months of life ($r = -0.13$, $p = 0.007$). Compared to healthy children, those who suffered from wheezing during the first year of life showed a 2-point MDI deficit (beta coeff. = -2.31, 95% CI: -4.63 to 0.02), and those with persistent wheezing (both first and second year) even had a 4-point deficit (beta coeff. = -4.41, 95% CI: -8.27 to -0.55)[7].

Cognitive impairment may be related to decreased respiratory function, leading to fluctuating oxygen delivery and consequent oxidative stress[8], which can be worsened by exposure to passive smoking[7] and the possible use of paracetamol for concomitant febrile respiratory infections[9]. These co-existing factors may impair brain development during its rapid growth phase. Interestingly, optimal selenium levels favor adequate cognitive function at 18 months of age during pregnancy[10], while recurrent episodes of virus-induced wheezing in the first years of life are associated with selenium and zinc deficiency[11], and low vitamin D levels[12]. Pneumonia-related hypoxia[13] and uncontrolled inflammation[14] can activate microglial cells, contributing to subsequent cognitive impairment and dementia[15].

In adults as well as in the elderly, a respiratory problem, such as pneumonia requiring hospitalization, is associated with a 53% higher incidence of cognitive impairment and

dementia compared with the general population (adjusted hazard ratio (aHR) 1.53, CI 95% 1.46-1.61) The highest risk was observed within the first year after hospitalization (aHR 1.89, 95% CI 1.75-2.05), and the effect was stronger in individuals aged 45-60 years (aHR 2.10, 95% CI 1.56-2.82)[16]. Surprisingly, the risk was lower for subjects over 80 years old (aHR 1.67, CI 95% 1.43-1.95). Still, is known that healthy aging is associated with a more remarkable ability to defend against oxidative stress and a well-balanced immune system response[17].

In addition to potential adverse effects on the nervous system, recurrent respiratory infections during the first years of life can both damage the airways and contribute to the development of chronic respiratory disease. A prospective study of 5197 children demonstrated that respiratory tract infections in the first three years of life are associated with an increased risk of asthma development by age 10 years (OR 1.79, 95% CI 1.19 - 2.59)[18].

Furthermore, a dose-response effect has been proven in children with nine or more ARIs/year that had a higher risk of asthma by the age of 7 years compared to infants from 0 to 23 months with fewer than five acute respiratory infections (ARIs)/year, (aOR 7.20; CI 95% 2.49-20.88). In children with subsequent asthma development, the mean duration of ARIs was longer, and the severity was higher compared to controls[19], thus reflecting a more unbalanced immune response. Although this may partly be attributed to airflow limitation with intermittent hypoxia, it is noteworthy that in the same study most ARIs occurred without wheezing[19]. Indeed, in another cohort of children followed from birth to 7 years of age, the frequent referral for major respiratory problems in the first three years of life was more predictive of asthma development at seven years of age ($p < 0.0001$) rather than the finding of wheezing at medical evaluation ($p = 0.05$)[20]. However, it is essential to remember that detecting wheezing by clinical examination seems insufficiently accurate[21]. Consequently, relying solely on this sign, without objective assessment of flow limitation[22], could result in medical undertreatment, of both bronchial obstruction and the pathogenetic mechanisms underpinning asthma, such as inflammation and oxidative stress[23]. It has been demonstrated that early airway infections are associated to changes in endothelial cell physiology, such as increased vascular permeability, thereby causing bronchial wall edema[24]. These changes contribute to bronchial hyperresponsiveness and reduced lung function, and could be ascribed to increased inflammatory responses[25] and oxidative stress.

A longitudinal study of the "British Cohort"[26] - 17.198 infants born in a specific week of the year 1946 in England, Scotland, and Wales, followed until adult age -provided evidence that participants who had experienced a lower respiratory tract infection during early childhood had a higher risk of dying from respiratory disease before they turned 73, compared to control (HR 1-93, 95% CI 1-10- 3-37; $p = 0.021$)[27], regardless of socioeconomic position, childhood household overcrowding, birth weight, gender, and adult cigarette smoking. These deaths represented one-fifth of all deaths in this cohort[27]. Impaired lung function is likely to link early childhood infections and respiratory mortality in adults and should be a clear reminder for pediatricians of their own essential role in prevention[28]. Identifying young children affected by lower airway infections, actively optimizing their health, and protecting airway development could be a way to disrupt the tracking of respiratory health impairment in childhood until adulthood. Remarkably, being born with smaller airways represents both a risk factor for the onset of bronchiolitis, recurrent wheezing during viral respiratory infections[29-31], as well as for the development of asthma in children and chronic obstructive bronchitis in adults[32]. Moreover, reduced respiratory function in adults is associated with increased mortality. This stresses the importance of adopting preventive measures in the early years of life, during pregnancy[33], and perhaps even before conception[34,35], and is a further reminder that prevention should be started but should not be limited to pediatric age.

Eight mistakes to avoid:

1. **Ignoring Environmental Impacts**
   Air pollution causes millions of deaths annually[36], contributing to adverse respiratory outcomes like asthma, reduced lung function, and COPD[37]. Children are particularly vulnerable to the detrimental effects of air pollution. Due to various physiological-behavioral factors, they run a higher risk of outcomes such as acute respiratory infections, asthma, and reduced lung function. The risk varies in different geographical regions, depending on the source of air pollution, the duration of exposure, and the concentration of pollutants[38]. Factors such as prenatal and childhood exposure to parental smoking can exacerbate these outcomes[39,40]. Emerging pollutants like microplastics are also harmful, leading to inflammation and other adverse effects on the respiratory system[41-43].

2. **Using a Presumptive Approach for Vaccinations**
   A participatory approach in discussing vaccinations, especially during pregnancy and early infancy, reduces vaccine hesitancy[44]. To promote adherence to vaccinations against diseases like pertussis, influenza, and RSV infection during pregnancy and early life is crucial, and necessitates of a close collaboration between pediatricians, neonatologists and obstetricians[45].

3. **Not Promoting Breastfeeding**
   Breastfeeding reduces the severity of RSV bronchiolitis, hospitalization duration, and the risk of SARS-CoV-2 infection in infants. Encouraging exclusive breastfeeding is essential for infant health[46,47].

4. **Neglecting Maternal Diet**
   A diet rich in fruits and vegetables during pregnancy and breastfeeding promotes early acceptance of these foods in infants[48]. This contributes to reduced risks of food allergies, atopic dermatitis, asthma, and improved lung and immune system development in children[49-51].

5. **Failing to Warn Against Smoking During Pregnancy.**
   Maternal smoking, including vaping, is a leading cause of abnormal lung development, resulting in increased respiratory diseases like asthma in children. Nicotine is harmful to fetal lung development, and exposure to secondhand smoke should be strongly discouraged[52-54].

6. **Suppressing the cough reflex.**
   Cough is a natural defense mechanism, and suppressing it can be harmful, especially in cases of infection[55]. While cough suppressants act on neural pathways, they do not address underlying inflammation[56]. Natural anti-inflammatory substances should be preferred[57].

7. **Overuse of paracetamol for fever**
   Fever is a critical defense mechanism against infections[58,59]. Overuse of paracetamol, especially during pregnancy and infancy, has been linked to the development of asthma[60,61]. The summary of evidence linking, with a causality ratio[60], the use of paracetamol with the onset of asthma is summarized in Table 1 **(Table**

1)[61]. Paracetamol depletes antioxidants and disrupts immune balance, prolonging infections[62] and increasing allergy risks[63,64].

8. **Over-reliance on steroids a panacea**
   Although effective for certain respiratory conditions, steroids are often overprescribed for treating cough and infections[65]. Moreover, they do not address the root causes of diseases like asthma and can worsen oxidative stress[66], leading to diminished efficacy and increased reliance on higher doses, thus contributing to long-term health risks.

Conclusions

Respiratory infections in early life and childhood, if recurrent and/or particularly severe, can have repercussions on the nervous system, ranging from a slight reduction in cognitive abilities in children to dementia in the elderly. The pathogenesis of these diseases can be attributed to oxidative stress and uncontrolled inflammatory response. Other consequences of early respiratory infections, including the development of asthma and allergies at a young age and COPD in the elderly, may recognize the same pathogenetic mechanism. Prevention should begin before conception and continue during pregnancy and in the early years of life through a diet rich in antioxidants and anti-inflammatory substances and by avoiding common mistakes that may hinder antimicrobial immune defenses.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests

The Authors have no conflict of interests relevant to this article to disclose.

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Author contributions

VH, CB and GF: conceptualized the study, drafted the initial manuscript, reviewed the literature and critically revised the final manuscript.
MP, GF, LT, GP and LP actively participated in critically reviewing the manuscript.
All Authors read and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Ethical approval

Human studies and subjects
N/A.

Animal studies
N/A.

***Table 1**. Summary of evidence identifying a causal relationship between the use of paracetamol and the development of asthma according to Bradford Hill criteria[61].*

Effect strength	Increased risk of asthma up to 2.1 (exposure to paracetamol in utero) Up to 7,3 (use of paracetamol in infancy or childhood) And up to 2,9 (use of paracetamol in adults)
Dose-response	Described for exposure to paracetamol in utero, childhood and adults
Coherence/coherence	Consistency between different studies in various age groups and populations worldwide Moderate consistency with some studies reporting a lack of effects, biases and/or confounders
Exposure before response	Observed in studies on exposure to paracetamol in utero And in adulthood
Biological plausibility	Increased oxidant-induced inflammation, potentially increased Th2 response, and stimulation of the transient receptor ankyrin 1 (TRPA-1)
Removal of exposure prevents the disease	Not yet reviewed
Specificity	No increased risk of asthma associated with aspirin or other nonsteroidal anti-inflammatory drugs
Temporal association	International trends of increasing use of paracetamol and increasing prevalence of asthma

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