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INFECTIONS AND DRUG THERAPIES: THEIR EFFECTS ON ADOLESCENT GROWTH AND SEXUAL MATURATION

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Abstract: INTRODUCTION The introduction discusses the intricate processes of puberty and growth, emphasizing their regulation by hormonal, genetic, and environmental factors. It highlights how infections, such as HIV and tuberculosis, and chronic illnesses can interfere with these processes, leading to significant delays in growth and sexual maturation. The introduction also covers the impact of various medications, including antibiotics, antivirals, corticosteroids, and chemotherapy, on growth patterns. The importance of understanding these interferences for public health and clinical practice is underscored. **OBJETIVE** To explore the impact of infections and medications on puberty, growth, and sexual development in children and adolescents **METHODS** This is a narrative review which included studies in the MEDLINE – PubMed (National Library of Medicine, National Institutes of Health), COCHRANE, EMBASE and Google Scholar databases, using as descriptors: "Puberty and growth" AND "Infections" AND "Medications" AND "Sexual development" AND "Endocrine disruption" in the last years. **RESULTS AND DISCUSSION** The results and discussion section delves into the detailed analysis of how specific infections and medications impact growth and puberty. It presents data showing that infections like HIV and tuberculosis lead to delayed puberty and stunted growth due to chronic inflammation, immune system impairment, and nutritional deficiencies. The section also examines the role of medications, such as antiretrovirals and corticosteroids, in exacerbating these growth delays. The discussion highlights the complex interactions between infections and medications and the need for a multidisciplinary approach to manage these issues effectively. It also addresses the psychosocial impacts of delayed puberty and the importance of tailored interventions to support affected children and adolescents. **CONCLUSION** The conclusion emphasizes the multifaceted nature of growth interference due to infections and medications, calling for comprehensive public health strategies and clinical management approaches. It underscores the need for early detection, effective treatment, and ongoing support to mitigate the impact of these factors on development. The conclusion also highlights the importance of further research and global collaboration to enhance our understanding and develop innovative strategies for managing growth delays in children and adolescents.

Keywords: Growth interference**;** Chronic infections**;** Antiretroviral therapy**;** Pediatric endocrinology**;** Delayed puberty.

INTRODUCTION

The interference of infections and medications in puberty, growth, and sexual development presents a critical area of research due to its profound implications on pediatric health[1]. Puberty and growth are complex processes regulated by a finely tuned interplay of hormonal, genetic, and environmental factors. Puberty is characterized by the maturation of the hypothalamic-pituitary-gonadal axis, leading to increased production of sex steroids and the development of secondary sexual characteristics[2]. Growth, particularly during adolescence, involves not only hormonal regulation but also genetic predisposition, nutrition, and overall health status. Disruptions in these processes can have long-lasting effects, impacting physical development, psychological well-being, and future health outcomes[3].

Infections can significantly impact growth and development, particularly when they occur during critical periods such as infancy and adolescence[4]. Common infections that have been documented to interfere with growth include HIV, tuberculosis, and

chronic infections[4]. HIV, for instance, can delay puberty and impair growth through its direct effects on the immune system and the secondary effects of chronic illness and malnutrition[5]. Tuberculosis, a chronic bacterial infection, can similarly stunt growth and delay puberty, particularly in cases of prolonged illness or inadequate treatment. Viral infections like Epstein-Barr virus have also been associated with delayed growth and puberty due to their impact on the immune system and overall health[6].

Bacterial and fungal infections further complicate the picture, as they can lead to chronic inflammation and a prolonged immune response, both of which are detrimental to normal growth patterns[7]. Chronic infections, by their very nature, exert a persistent stress on the body, often leading to malnutrition, delayed development, and other systemic effects that impair growth and sexual maturation[8]. The interplay between chronic infections and the body's hormonal milieu is complex and multifaceted, often necessitating a multidisciplinary approach to management[9].

Medications, particularly those used in the treatment of chronic illnesses and infections, can also interfere with growth and development[10]. Antibiotics, while lifesaving, can disrupt the gut microbiota, which is increasingly recognized for its role in growth and development[11]. Prolonged use of antibiotics has been associated with growth suppression and other developmental issues. Antiviral and antiretroviral medications, essential for managing viral infections like HIV, can also have side effects that impact growth and sexual maturation[11]. These medications often require long-term use, further compounding their impact on development[12].

Corticosteroids, commonly used for their anti-inflammatory and immunosuppressive effects, are known to delay growth and puberty when used over prolonged periods[13]. These effects are due to the steroids' interference with the hypothalamic-pituitary-adrenal axis, leading to suppressed growth hormone secretion and other hormonal imbalances[13]. Similarly, anabolic steroids, though sometimes used illicitly for their muscle-building properties, can have profound effects on puberty and growth, often leading to early closure of growth plates and stunted final adult height[14].

Chemotherapy drugs, used in the treatment of pediatric cancers, are another class of medications that can significantly impact growth and development[14]. These drugs often target rapidly dividing cells, a characteristic shared by both cancer cells and normal growth cells, leading to growth delays and other developmental issues[15]. The impact of these medications is often compounded by the physical and emotional toll of cancer and its treatment, further highlighting the need for comprehensive management strategies[16].

Endocrine disruptors, a broad category of chemicals that interfere with hormonal function, also play a significant role in affecting puberty and growth[17]. Medications that act as endocrine disruptors can lead to early or delayed puberty, growth disturbances, and other developmental anomalies[18]. The mechanisms by which these disruptions occur are complex and involve alterations in hormonal signaling pathways critical for normal development[19].

The interaction between infections and medications is another crucial aspect to consider[20]. In many cases, children and adolescents may be dealing with both chronic infections and the side effects of long-term medication use, leading to compounded effects on growth and development[20]. This intersection necessitates a careful balance in treatment strategies to manage the infection effectively while minimizing negative impacts on growth. Psychosocial factors also play a significant role in puberty and growth delays

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due to infections and medications[21]. Chronic illness and the side effects of treatment can lead to psychological stress, social isolation, and other issues that further impact development. Understanding the psychosocial dimensions of these delays is crucial for developing comprehensive care strategies that address both physical and emotional health[21].

The public health significance of understanding how infections and medications interfere with puberty, growth, and sexual development cannot be overstated[20]. These interferences can lead to significant long-term health issues, including reduced adult height, delayed sexual maturity, and increased risk of chronic diseases[21]. Public health strategies must therefore focus on early detection, effective management, and comprehensive support systems to mitigate these impacts and promote healthy development[21].

OBJETIVES

To examine the physiological mechanisms by which these factors interfere with normal developmental processes.

SECUNDARY OBJETIVES

To provide an overview of the public health significance and clinical management strategies for growth delays caused by infections and medications.

To analyze specific infections (e.g., HIV, tuberculosis) and their effects on growth patterns and puberty onset.

To assess the role of various medications, including antibiotics, antivirals, corticosteroids, and chemotherapy, in disrupting growth and sexual maturation.

To highlight the psychosocial and long-term health outcomes of growth delays and propose comprehensive management approaches.

METHODS

This is a narrative review, in which the main aspects of physiological mechanisms by which these factors interfere with normal developmental processes in recent years were analyzed. The beginning of the study was carried out with theoretical training using the following databases: PubMed, sciELO and Medline, using as descriptors: "Puberty and growth" AND "Infections" AND "Medications" AND "Sexual development" AND "Endocrine disruption" in the last years. As it is a narrative review, this study does not have any risks.

Databases: This review included studies in the MEDLINE – PubMed (National Library of Medicine, National Institutes of Health), COCHRANE, EMBASE and Google Scholar databases.

The inclusion criteria applied in the analytical review were human intervention studies, experimental studies, cohort studies, case-control studies, cross-sectional studies and literature reviews, editorials, case reports, and poster presentations. Also, only studies writing in English and Portuguese were included.

RESULTS AND DISCUSSION

The analysis of growth patterns in children and adolescents infected with HIV reveals a clear delay in puberty onset and overall growth. Studies have shown that HIV-infected children often exhibit stunted growth and delayed sexual maturation compared to their uninfected peers[22]. The mechanisms behind this include the direct impact of the virus on the immune system, chronic inflammation, and the nutritional deficiencies often associated with HIV[23]. Additionally, the side effects of antiretroviral therapy (ART), while essential for managing HIV, can further compound growth delays. Research indicates that while ART can improve overall health and prolong life, it may not fully normalize growth

patterns in children with HIV, necessitating ongoing monitoring and intervention[24].

Tuberculosis (TB) is another infection with significant implications for growth and development[25]. Chronic TB infection, particularly when inadequately treated, can lead to prolonged periods of illness and malnutrition, both of which are detrimental to normal growth trajectories[25]. The inflammatory response to TB, along with the stress of chronic illness, can suppress the growth hormone axis and delay puberty. Studies have shown that children with TB often exhibit growth retardation and delayed sexual development, highlighting the need for aggressive treatment and nutritional support to mitigate these effects. Chronic infections, in general, pose a substantial risk to normal growth and development[26]. Infections such as chronic hepatitis, recurrent respiratory infections, and other long-standing illnesses can lead to persistent inflammation, immune activation, and malnutrition, all of which interfere with the body's normal growth processes. The cumulative impact of these infections on long-term growth outcomes can be profound, leading to reduced adult height and delayed sexual maturation. Addressing these infections early and effectively is crucial for minimizing their long-term impact on development[27].

The prolonged use of antibiotics, while necessary for treating bacterial infections, can also have unintended consequences on growth and development[27]. Antibiotics can disrupt the gut microbiota, which plays a crucial role in nutrient absorption and immune function[27]. Prolonged antibiotic use has been associated with growth suppression and altered development, likely due to these disruptions in the gut microbiota and subsequent nutritional deficiencies. Studies have highlighted the need for careful antibiotic stewardship and the use of probiotics to mitigate these effects[28].

Antiviral medications, particularly those used to treat chronic viral infections like HIV and hepatitis, can also impact growth and sexual maturation. [28] These medications often have side effects that include growth suppression and delayed puberty[28]. For example, protease inhibitors used in ART regimens have been associated with altered lipid metabolism and insulin resistance, which can impact growth. The long-term use of these medications requires careful monitoring and management to balance the benefits of viral suppression with the potential for growth delays[28,29].

The use of corticosteroids, while beneficial for their anti-inflammatory properties, is well-documented to cause growth suppression and delayed puberty[30]. Corticosteroids interfere with the hypothalamic-pituitary-adrenal axis, reducing growth hormone secretion and altering normal hormonal balances necessary for growth and development. Studies have shown that children on long-term corticosteroid therapy, for conditions such as asthma or autoimmune diseases, often exhibit significant growth delays[30]. Strategies to mitigate these effects include using the lowest effective dose, alternate-day dosing, and adjunct therapies to support growth[31].

Chemotherapy, used in the treatment of pediatric cancers, presents another significant challenge to normal growth and development[32]. These drugs target rapidly dividing cells, a characteristic shared by both cancer cells and normal growth cells. As a result, children undergoing chemotherapy often experience growth delays, delayed puberty, and other developmental issues[32]. The impact of chemotherapy is further compounded by the physical and emotional stress of cancer and its treatment. Long-term follow-up and supportive care are essential for managing these effects and promoting healthy development post-treatment[32].

Endocrine disruptors, which include a variety of chemicals and medications, interfere with the body's hormonal signaling pathways critical for growth and sexual development[33]. Medications that act as endocrine disruptors can lead to early or delayed puberty, growth disturbances, and other developmental anomalies[33]. The mechanisms by which these disruptions occur involve alterations in the hypothalamic-pituitary-gonadal axis and other hormonal pathways. Studies have shown that exposure to endocrine disruptors during critical periods of development can have lasting effects, necessitating careful consideration of these substances in pediatric care[34].

The interaction between infections and medications is particularly complex, as both can independently and synergistically impact growth and development[35]. Children dealing with chronic infections often require long-term medication, leading to compounded effects on growth[35]. For instance, a child with HIV may experience growth delays due to the infection itself and the side effects of ART. Similarly, a child with chronic asthma may face growth suppression from both the chronic inflammatory state and the long-term use of corticosteroids[36]. These interactions highlight the need for a comprehensive, individualized approach to managing pediatric patients with chronic conditions[36].

Case studies provide valuable insights into the real-world impacts of infections and medications on growth and development[37]. For example, a longitudinal study of children with HIV demonstrated significant improvements in growth following the initiation of ART, but many still did not achieve normal growth patterns, indicating the need for additional interventions[37]. Another case study of a child with chronic TB highlighted the importance of aggressive treatment and nutritional support in mitigating growth delays[38]. These case studies underscore the importance of personalized care and ongoing monitoring to address the multifaceted impacts of infections and medications on development[38].

Long-term outcomes of growth interference due to infections and medications can include reduced adult height, delayed sexual maturity, and increased risk of chronic diseases[39]. Studies have shown that children who experience growth delays often continue to face health challenges into adulthood, including increased susceptibility to metabolic disorders, cardiovascular diseases, and osteoporosis[39]. The lifelong impact of disrupted growth and puberty underscores the need for early intervention and comprehensive management strategies[40]. Addressing these challenges requires a multidisciplinary approach, incorporating endocrinologists, infectious disease specialists, pediatricians, and nutritionists to provide holistic care[40].

Hormonal changes induced by infections significantly impact growth and sexual maturation[41]. Chronic infections like HIV and tuberculosis disrupt the normal secretion of growth hormone and sex steroids, leading to delays in puberty and growth[41]. The inflammatory cytokines released during chronic infections can inhibit the hypothalamic-pituitary-gonadal axis, reducing the secretion of gonadotropins and subsequently sex steroids, which are critical for normal pubertal development[42]. This hormonal disruption necessitates interventions that not only address the infection but also support the endocrine system to promote normal development[42].

Metabolic effects of infections and medications are another critical area of concern. Infections like HIV can induce insulin resistance and dyslipidemia, further complicating growth and development[42]. Medications, particularly antiretrovirals, can exacerbate these metabolic disturbances.

Studies have shown that children on long-term ART often develop metabolic syndromes, including insulin resistance and lipid abnormalities, which can impact growth[42]. Managing these metabolic effects requires a comprehensive approach that includes dietary interventions, physical activity, and careful monitoring of metabolic parameters.Nutritional deficiencies are common in children with chronic infections and those on long-term medications, further impairing growth. Infections can lead to malabsorption of nutrients, while medications like antiretrovirals and corticosteroids can alter metabolism and nutrient utilization[43]. Ensuring adequate nutrition through dietary support and supplementation is crucial for promoting normal growth and development. Studies have highlighted the importance of a balanced diet rich in essential nutrients to counteract the negative effects of infections and medications on growth[43].

The psychosocial impact of delayed puberty due to infections and medications cannot be overlooked[42,43]. Children experiencing delayed growth and puberty often face psychological stress, social isolation, and reduced self-esteem, which can impact their overall well-being. Addressing these psychosocial factors is critical for promoting healthy development. Interventions should include psychological support, counseling, and social integration programs to help children cope with the challenges of delayed development[44]. Comparative analysis of different infections reveals varying impacts on growth and puberty. For instance, while HIV and tuberculosis have profound effects on growth, other infections like Epstein-Barr virus may have more transient impacts[44]. Understanding these differences is crucial for tailoring interventions to the specific needs of children with different infections[44]. Regional variations in infection rates and healthcare access also play a significant role in growth interference, highlighting the need for context-specific public health strategies[42,43].

Preventive strategies are essential for mitigating the impact of infections and medications on growth and development[45]. These strategies include early detection and treatment of infections, judicious use of medications, and regular monitoring of growth parameters[45]. Public health policies should emphasize the importance of preventive care, vaccination, and nutritional support to promote healthy growth[45]. Clinical management of growth delays should involve a comprehensive approach, incorporating medical, nutritional, and psychosocial interventions to address the multifaceted impacts of infections and medications[45].

The role of pediatric endocrinologists is pivotal in managing growth interference in children. These specialists are equipped to address hormonal imbalances and provide targeted therapies to support normal development[46]. Collaboration between endocrinologists and other healthcare providers is essential for developing effective treatment plans that address the root causes of growth delays[44,46]. Public health policies should support the integration of endocrinology services into routine pediatric care to ensure early intervention and comprehensive management[40]. Global health perspectives provide valuable insights into effective strategies for combating growth delays caused by infections and medications[41]. International collaborations and knowledge exchange can help identify best practices and innovative approaches to managing these challenges. For instance, successful interventions in one region can be adapted and implemented in other regions with similar challenges, fostering a global effort to promote healthy growth and development[44,46].

Educational interventions are crucial for healthcare providers to understand the impact of infections and medications on growth[47]. Continuing medical education programs should include modules on the latest research and best practices for managing growth delays. Additionally, family education and support are vital for helping parents understand the importance of treatment adherence, nutritional support, and psychosocial interventions[47]. Providing resources and support to families can empower them to actively participate in their child's care and promote positive health outcomes. A multidisciplinary approach is essential for managing growth interference in children[48]. This approach involves collaboration between various healthcare providers, including pediatricians, endocrinologists, infectious disease specialists, nutritionists, and psychologists[48]. By working together, these professionals can develop comprehensive care plans that address the medical, nutritional, and psychosocial needs of children experiencing growth delays. This holistic approach ensures that all aspects of a child's development are considered and addressed[48].

Identifying research gaps is crucial for advancing our understanding of the interference of infections and medications in puberty and growth[49]. Current research often focuses on individual infections or medications, but there is a need for more comprehensive studies that examine the combined effects of multiple factors. Future research should explore the long-term outcomes of growth interference, the mechanisms underlying these effects, and the most effective interventions for promoting normal development[49]. Ethical considerations are paramount in treating children with infections and medications that impact growth. Informed consent, respect for the child's autonomy, and consideration of the long-term effects of treatment are critical ethical principles that should guide clinical practice[50]. Healthcare providers must balance the need for effective treatment with the potential risks to growth and development, ensuring that decisions are made in the best interest of the child[50].

CONCLUSION

The interference of infections and medications in puberty, growth, and sexual development is a complex and multifaceted issue that requires a comprehensive and multidisciplinary approach. Early detection, effective management, and ongoing support are essential for mitigating the impact of these factors on development. By addressing the biological, social, and healthcare dimensions of growth interference, we can promote healthy development and improve long-term health outcomes for children affected by chronic infections and long-term medication use. Further research and global collaboration are needed to enhance our understanding and develop innovative strategies for managing these challenges. Healthcare providers, policymakers, and families all have critical roles to play in supporting the growth and development of children facing these complex health issues.

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