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CHRONIC COUGH IN CHILDHOOD: A CLINICAL AND THERAPEUTIC APPROACH (PART II)

Doina Pleşca[1],Victoria Hurduc[1], Iulia Ioan[1],Anca Bădărău[2]

[1.] Pediatrics and Pediatric Neurology Department, [2]Dr. Victor Gomoiu[2] Clinical Hospital for Children, UMF "Carol Davila", Bucharest
[2.] Department of Physiology, UMF "Carol Davila", Bucharest

Abstract. The article is divided of two parts. In the first part, the authors discuss about the chronic cough, a subject of a great interest in pediatric practice. Physiopathology, the most important etiologic categories, clinical and paraclinical data, principles of therapy of chronic cough are reviewed.
The authors underline the importance of the history of the disease, in establishing the cause of chronic cough in children. A cough that worsens at night may be caused by sinusitis, asthma, or gastroesophageal reflux. The cough that disappears during sleep, suggests a psychogenic cause.
Clinical examination has to be thorough, complete and repeated, focused on ENT segment, chest, respiratory and cardio-vascular system. When clinical data and history cannot establish the cause of chronic cough, paraclinical evaluation is necessary. Any child with chronic cough, no matter the age, must have chest X-Ray examination to eliminate aspiration of foreign body or another severe disease (congenital anomaly, cystic fibrosis, bronchiectasis, cardiomegaly, mediastinal mass).
In the second part, the authors present the main clinical entities (cough variant asthma and eosinophilic bronchitis, cough during and after respiratory infections, allergic rhinitis, chronic sinusitis and rhinoadenoiditis, passive smoking, gastroesophageal reflux, bronchiectasis, aspiration syndrome / foreign body aspiration, deglutition difficulties, vocal cords dysfunction, compression syndrome, psychogenic cough, otogenic causes - Arnold ear – cough reflex, cough as a side effect of the medication) and the etiologic treatment. The indications of an etiologic treatment have to be influenced by a detailed history of the disease and by clinical examination. In the absence of an etiologic factor, the patient will receive symptomatic treatment only if the cough is responsible for awakeness, vomiting and fatigue. Tolerability of cough is the element that determines the indications for inhibitors of cough.
Keywords: algorithmic approach to the diagnosis; chronic cough, child

5. Particular etiologies

5.1. Cough variant asthma and eosinophilic bronchitis

In the industrialized countries, asthma represents the main cause of pediatric chronic cough, at any age. Many surveys in school-age children showed a prevalence varying between 6-10%. Cough represented the most frequent symptom (92-96%); wheezing episodes were present in 75-86% of the cases, and expiratory dyspnea in 25-79% of the cases. The cough is dry, nocturnal, exasperating and voluntary triggered by exercise, during daytime. The medical history of these children often includes trigger factors (animal contact, pollutants etc) and yearly periodicity (wind, pollen season etc).

Asthma is a chronic inflammatory disorder of the small airways characterized by airflow limitation due to bronchospasm, edema and mucosa destruction causing a particular respiratory symptomatology,

Prof. Dr. Doina Pleşca, MD, PhD
Pediatrics and Pediatric Neurology Department,
"Dr. Victor Gomoiu" Clinical Hospital for Children,
21, Basarabiei Blvd, sect.2, Bucharest
Phone: 021.323.22.30; 021.321.20.42

mainly expiratory dyspnea and wheezing.

Cough variant asthma is associated with the same physiopathologic process and clinical signs, but wheezing is absent while cough is the most obvious clinical sign.

In 1979, Caorrao reported 6 adults with asthma whose unique symptom was chronic cough. In 1981, Cloutier and Loughlin showed there is a connection between asthma and isolated chronic cough in children, noticing an improvement after administration of theophylline retard. Ever since, several studies have brought arguments in favor of the presence of an association between chronic cough and asthma in children.

Ninan & colleagues (1995) showed that a medical history of atopy (eczema, allergic rhinitis) is much more frequent in cough associated with wheezing, and does not significantly correlate to isolated chronic cough. Association between eczema, allergic rhinitis and home moisture may be predictive for chronic cough equivalent of asthma. Wright & colleagues (1996) found that the male gender, the presence of allergic rhinitis in mother, the medical history of bronchiolitis and a high level of IgE helped to differentiate the children with cough from the asymptomatic ones. The same authors have noticed that skin tests for allergy are more frequently positive in children with cough variant asthma than in children with isolated cough. Preterm birth also is preferentially associated with chronic cough variant asthma. Tabel VI presents the risk factors for chronic cough in children.

Cough variant asthma	Cough not suggesting asthma
• associated with wheezing • nonproductive • triggered by exercise • frequently repeated • nocturnal • preterm birth • medical history of bronchiolitis • high level of total IgE • positive skin tests • eczema • allergic rhinitis + eczema + home moisture • obstructive syndrome in pulmonary function testing or demonstrated bronchial hyperreactivity	• associated to passive smoking • productive and in the morning • productive and male gender • associated with frequent otitis • signs evoking another etiology
Factors whose predictive value has not been formally demonstrated	
• male gender • maternal atopy • parental asthma • home moisture • onset age • cough severity • response to inhaled therapy included beta-sympathomimetic*s*	

Table VI. The risk factors for chronic cough in children (adaptation from Marguet C., Coudec L., 2001)

There have been attempts of determining a characteristic profile for cough variant asthma. In this case, cough is most frequently nocturnal, nonproductive, triggered by exercise and may be associated with risk factors for asthma.

Performing pulmonary function testing, demonstrating the bronchial hyperreactivity and establishing clinical response to salbutamol administration are mandatory for finding the chronic cough's etiology.

In 2002, Gibson PG and Fujimura M. have reported a number of patients with chronic cough, but with no clinical signs, evoking asthma or bronchial hyperreactivity, but whose sputum contained eosinophils and metachromatic cells in proportions similar to those from asthmatic patients. This disorder was named eosinophilic bronchitis. Its causes, mechanisms and therapeutic management

are similar to those of asthma. Its prognosis is unknown, the authors suggesting that eosinophilic bronchitis is a "precursor" of asthma.

5.2. Cough during and after respiratory infections

During childhood, the respiratory infections' incidence in a year varies between six and eight episodes (5–8 episodes in children under 4 years of age and 2.4–5 episodes in children of 10–14 years of age). This number may increase in children who go to nursery school, kindergarten or school or in children with big families. Repeated respiratory infections during cold season may induce chronic cough. The most frequent microorganisms that produce these disorders are various: *syncytial respiratory virus* (RSV), *Cytomegalovirus, Mycoplasma pneumoniae, Chlamydia trahomatis, Pneumocystis carinii, Bordetella pertussis.*

The postinfectious chronic cough pathogenesis is unknown, although a transient bronchial hyperreactivity may be described in some cases. Postinfectious cough usually spontaneously resolves in weeks or months; it has the possibility of recurrence with new infections.

Cough during daytime and/or nighttime and wheezing paroxysms (bronchial obstructive syndrome) are clinical elements of viral induced bronchiolitis.

Mycoplasma pneumoniae infection is common during childhood, frequently producing an upper respiratory infection. Nevertheless, this etiology represents the most frequent cause of pneumonia in children aged 5 to 15 years. Cough appears a few days after the onset of the disease, it progressively aggravates, with coughing fits. It can last for weeks or months. The cough is productive and frequently associated with hemoptoic sputum. In 40% of cases, acute infection is associated with wheezing. After this infection, the patient may have a lasting bronchial hyperreactivity (for weeks, months or years) (Milgrom H., 1998).

Whooping cough represents a cause of chronic cough par excellence and is currently in recrudescence (7796 reported cases by CDC in 2006). Causes are multiple: increase of the frequency of contacts (nursery school, kindergarten, school), incomplete efficacy of vaccination and decrease of the post-vaccination immunity over time, paucisymptomatic contacts (adults), decrease of the frequency of prescription for certain antibiotics (macrolides). The classic form of the disease is found in non-vaccinated children and it is characterized by dry, irritating cough which evolves into coughing fits, ended with an inspiratory "whoop" sound or vomiting; the previously vaccinated children have a nonspecific symptomatology with isolated cough. A whooping cough is suspected especially during periods of low postvaccination immunity, particularly before booster doses or when those have not been made. Epidemiologic data show that the carriage of *Bordetella pertussis* in adults and older children is so big that it represents a real natural reservoir with a potential to contaminate the younger children. The presence of lymphocytosis (> 10000/ mm^3) is inconstant and nonspecific. The usual diagnostic methods (cultures, serology) are more or less expensive, cover long periods of time and have less sensitivity. Adenylate-cyclase semiquantitative radio-immunologic dosage of nasal secretion smear is a sensitive and simple test that can provide a result within a few hours. PCR identification also has a good positive predictive value.

In conclusion, it is good to suspect whooping cough in a patient presenting chronic cough unexplained by other etiologies. The treatment with macrolides is at choice; it limits the disease's contagiousness and it also treats the symptoms, in spite of the unanimously accepted clinical inefficacy.

5.3. Allergic rhinitis, chronic sinusitis and rhinoadenoiditis

Allergic rhinitis and chronic sinusitis present cough due to secretion of post nasal drip which irritates the larynx. Chronic sinusitis may be an early manifestation of an immunodeficiency syndrome or of a ciliary dysfunction. The symptoms of these disorders are nasal obstruction and rhinorrhea along with cough.

During the chronic upper airway obstruction syndrome, the nocturnal respiratory symptoms (cough, snoring, many awakenings, obstructive apnea) are often associated with failure to thrive (not gaining height and/or weight), and sometimes with a chronic pulmonary heart syndrome (thoracic deformation, right ventricular hypertrophy, pulmonary arterial hypertension).

Irwin RS. and Madison JM.(2000) appreciate that the most frequent cause of chronic cough in children is chronic rhinorrhea.

5.4. Passive smoking

Passive smoking in children is a common reason for visiting the pediatric pneumologist. The latest studies from many developing countries show that at least one parent from a three members family is a smoker. Moreover, some American surveys showed

the presence of nicotine in the urine of 9 out of 10 children. Unfortunately, the severity of this public health problem is systematically underestimated.

Symptoms due to tobacco impregnation vary from one child to another: ENT disorders, bronchitis, asthma, isolated cough, cephalea, digestive problems, school difficulties ("Monday morning" syndrome). The respiratory symptoms are as serious as the child's native respiratory fragility (asthma, mucoviscidosis, repeated episodes of viral bronchiolitis, bronchopulmonary dysplasia). Passive smoking diagnosis is based on medical history and questions about the environment in which the child lives. The cigars consumption is evaluated by the number of cigars smoked by entourage. Maternal smoking appears to best correlate to the child tobacco impregnation. The only efficient treatment against smoking is represented by a serious discussion with the parents and their monitoring. In case of diagnosis doubts, the dosage of cotinine or nicotine from the hair can be performed.

Exposure to smoke from gas heaters (stoves, cookers) leads to increasing in prevalence of cough associated to respiratory infections as an effect exposure–response. Exposure to other environmental pollutants (nitrogen dioxide, gas from cookers, etc.) is also associated with an increased incidence of pediatric cough.

5.5. Gastroesophageal reflux

It is one of the most common causes of childhood chronic cough and a cause of infant apnea, in the absence of aspiration syndrome. The cough occurs by stimulation of the vagus nerve, and also by gastric content aspiration.

The gastroesophageal reflux was found in approximately 50% of adult patients with chronic cough, being very common in children, too (McGeady S., 1999). Although most infants presenting reflux are asymptomatic, in some cases they may have chronic cough, dyspnea paroxysms, wheezing or stridor.

In adults, it has been shown that gastroesophageal reflux may be the reason for persistent cough and cough may also provoke gastroesophageal reflux episodes; data on cough itself causing GER in adults is unavailable in children. As cough is a very common symptom in children and respiratory symptoms may exacerbate the gastroesophageal reflux, it is difficult to differentiate cause and effect. Infants commonly present regurgitations, however there are few healthy infants presented with cough related to these episodes. The effects of the surgical intervention (Nissen fundoplication) on cough and other respiratory symptoms are inconsistent. One prospective study about the etiology of chronic cough in children (Holinger LD, 1986) found only one child with gastroesophageal reflux disease out of a series of 38. A more recent retrospective study found coexistent GER in 4 of 49 children. In contrast to data in children, the studies in adults show that gastroesophageal reflux is a frequent cause of chronic cough (Irwin RS, 2002).

The management of this problem is different in preschool children. The cough and the gastroesophageal reflux are common symptoms in children over one year and a half of age, so that it is mandatory to assess if there is a connection or not between the respiratory symptoms and the gastroesophageal reflux. The diagnosis of cough (or asthma or recurrent respiratory problems) related to gastroesophageal reflux is extremely difficult. The medical history is important especially if during the neonatal period the child presented vomiting, regurgitations, postural cough, resolution of cough with proton pump inhibitors and antireflux therapy and its reappearance after stopping the therapy, and symptoms (cough, sibilant rales, polypnea) related to gastroesophageal reflux during pH monitoring.

Chest X-ray shows recurrent pneumonia, consequence of the airways' segmental collapse during exhalation. Chest radioscopy shows airways' caliber variations from normal to significant decrease, depending on the respiratory phase. Atelectatic images are found most of the time.

5.6. Bronchiectasis

Bronchiectasis and similar disorders (chronic bronchitis in children) represent rare causes of isolated chronic cough in children. The presence of chronic cough, failure to thrive (in weight and height), diarrhea with a chronic evolution represent only a few of the clinical signs which are indications for performing sweat test to confirm the suspicion of cystic fibrosis. In infants, this disorder is clinically similar to "whooping cough".

The suspicion of chronic pulmonary suppuration may arise when a patient presents with chronic bronchorrhea, thoracic deformation, digital clubbing, persistent radiological anomalies from one X-ray to another. Bronchoscopy is useful in assessing bronchorrhea, allowing in the same time an airways' anatomic exam and culture assay.

5.7 Aspiration syndrome / foreign body aspiration

Aspiration pneumonia represents a common

disorder in infants and young children and it is often mistaken for a nonspecific respiratory infection. Aspiration pneumonia in infants occurs following the aspiration of milk, as a result of a sucking reflex disorder or a tracheoesophageal fistula. The diagnosis of this disease is based on clinical examination (cough, faint voice, sucking and deglutition disorders), X-ray (the thickening of perihilar and peribronchovascular interstitium, areas with small segmental or lobar opacities), esophageal pH monitoring and bronchoscopy.

In general, foreign body aspiration determines an acutely installed clinical picture although there are situations when a patient may present chronic cough if the foreign body aspiration has not been previously diagnosed. A normal pulmonary X-ray does not exclude foreign body aspiration.

Foreign body aspiration is frequent especially in children of 9 to 39 months of age; the most frequent localizations are – hypopharynx, larynx, trachea, bronchi, esophagus. Foreign body aspiration in airways may determine wheezing (45% of cases), chronic cough (70% of cases), stridor, and a diminished vesicular murmur in pulmonary auscultation (53% of cases). The positive diagnosis is suggested by the persistent radiological signs (atelectasy, unilateral emphysema) and by bronchoscopy.

5.8.Deglutition difficulties

Deglutition disorders in infants are suspected when there is coughing during breastfeeding. Some infants and children have not developed the cough reflex yet, that is why they present excessive chronic bronchial secretions and recurrent respiratory infections. Bronchoscopy, mainly examining the crossover area between the respiratory tract and the digestive tract, is essential in this case, allowing the discovery of false ways (spontaneously saliva inhalation). This investigation also aids in establishing the cause (functional incoordination, laryngomalacia, bronchomalacia, abnormal aerodigestive ways, etc.).

5.9 Vocal cords dysfunction

Vocal cords dysfunction is a functional disorder of the upper airway characterized by a paradoxical adduction of vocal cords during the inspiratory phase and occasionally during the expiratory phase. So, the vocal cords adduct and produce shortening of breath, harsh, "brassy" cough and stridor.

The cough is presented most frequently during effort, which imposes investigating in order to differentiate effort asthma from vocal cords dysfunction.

5.10 Compression syndrome

Tracheomalacia or bronchomalacia are conditions characterized by flaccidity due to incomplete maturation or congenital absence of the supporting tracheal or broncheal cartilage. Although most infants with this condition are asymptomatic, some may present chronic cough, paroxistic dyspnea, wheezing and stridor. These children may have recurrent pneumonia or ventilation disorders (atelectasis) as consequence of the collapse of certain airway segments.

In some situations, the trachea may be partially obstructed by a right aortic arch, a double aortic arch, a patent ductus arteriosus or the left carotid artery. These anomalies are all labeled as vascular rings. Typical symptoms include inspiratory stridor, expiratory wheezing and "barking" cough. A vascular ring will be suspected in any infant presenting stridor. Gormley and colleagues (1999) found that 75% of children with tracheomalacia secondary to congenital vascular anomalies presented persistent cough. Airway malacia does not permit normal mucociliary clearance and it is obvious that chronic cough in these children is due to the bronchitic process distal of this lesion.

5. 11. Psychogenic cough

There are three types of cough with functional or psychogenic overlay: habit cough, tic cough and psychogenic cough. The distinctions between these categories may be unclear and may reflect a spectrum of severity.

In some cases, complete assessment of chronic cough may require searching the psychosocial factors which influence its origin, evolution, duration and eventual exacerbations. Some children transform coughing in a game to draw attention to themselves or to stimulate the affective behavior of parents. This type of cough occurs exclusively during daytime, completely disappears during sleep, is sometimes impressive and determines parents' anxiety. Psychogenic cough is a diagnosis of exclusion. Some authors recommend that teenagers presenting isolated cough which disappears during sleep should undergo no investigations. Psychotherapy and sedative medicines are often inefficient in these patients. The recommended treatment is ortophonic reeducation. In case of failure, hypnotherapy may be a choice.

5.12. Otogenic causes: Arnold Ear – Cough Reflex

The auricular branch of the vagus nerve is

present in approximately 2.3 to 4.2 % of people. In these people, the Arnold ear – cough reflex can be elicited (with bilateral occurrence in 0.3 to 2 % of people). The reflex can be elicited by palpation of the posteroinferior wall and rarely by palpation of the anteroinferior wall of the external acoustic meatus (ear canal). Case reports of chronic cough associated with ear canal stimulation from wax impaction, cholesteatoma, and acquired aberrant sensory referral post-cardiac transplant have been reported. In children, the significance of the ear reflex and cough was described as early as 1963. It is a very rare cause of childhood chronic cough.

5.13. Medication and adverse reactions.

It has been reported that chronic cough is part of the side effects of the treatment with conversion enzyme inhibitors and with antiasthmatic medication immediate to the inhaling. It is presumed that cough appeared due to chronic vagus stimulation.

Treatment principles

In cough management, the clinician must have knowledge of certain general problems:

1. Normal children occasionally cough. This symptom does not have to be treated. Its treatment leads to unnecessary medical product delivery and services. Cough in this situation is termed "expected cough".

2. In older children, cough is also subject to psychological influences because, as in adults, cough is cortically modulated. Rietveld SV and colleagues (2000) showed that children were more likely to cough under certain psychological settings.

3. The subjective perception of cough severity is dependent on the population that is being studied. The reporting of childhood respiratory symptoms is biased, and parental perceptions of childhood cough play an important role.

4. Cough is subject to the period effect (i.e., the spontaneous resolution of cough). The therapeutic benefit of placebo treatment for cough has been reported to be as high as 85%. The results of nonplacebo controlled intervention studies must be interpreted with caution.

The indications of an etiologic treatment have to be influenced by a detailed history of the disease and by clinical examination. In the absence of an etiologic factor, the patient will receive symptomatic treatment only if the cough is responsible for awakeness, vomiting and fatigue.

Tolerability of cough is the essential factor that determines the indications for inhibitors of cough. The administration of cough medicine will last maximum one week; at the end of this week, the child has to be reexamined.

Cough medicines act on different levels of the reflex arch, namely: receptors (local anesthetics), afferent pathways (opiates and dextrometorphane) and cough centers. There are several types of cough medications; they are classified in opiates, non-opiates and others.

Opiate medicines are classified in two classes, namely phenanthrene derivatives which do not suppress respiration (*Dextrometorphane, Noscapine*) and phenanthrene derivatives which do suppress respiratory centers (*Morphine, Methadone, Codeine, Ethylmorphine, Pholcadine*).

Non-opiate medicines do or do not have antihistamine effect. For example, a non-opiate medicine without antihistamine effect is *Clobutinol* which has an antitussive effect similar to that of Codeine's, but with no respiratory suppression effect. Phenothiazine derivatives and pimetixene are non-opiate medicines with antihistamine effect. A great number of cough medicines contain these two substances alone or in association.

Cough medicines are not indicated in children with respiratory distress, mucoviscidosis, bronchiectasis. They are not efficient in patients with asthma whose cough is ameliorated by bronchodilator administration.

The American Academy of Pediatrics Recommendations (2006) affirms there are no controlled studies regarding the efficacy of cough medicine administration in children. The indications of this therapy have not been precisely established. In most respiratory infections, cough suppression is hazardous and not indicated. Plus, the use of antitussive remedies was associated to a significant morbidity and even mortality. Accidental intoxication with cough medicines is common in children under 5 years of age. Cough secondary to viral infections is of short duration and must be treated with mucolitic medicines and exposure to humidified air.

The antihistamines' efficacy in suppressing pediatric cough is minimal. The evaluation of the antihistamines' effects alone or associated with nasal decongestants in acute cough treatment showed that these medicines were comparable with placebo in resolving this syndrome. However, until now there is no study about their effect on chronic cough.

In treating chronic cough other medicines were used namely: *inhaled corticosteroids, bronchodilators.*

A meta-analysis made by Smueny JJ and Flynn CS, 2001 showed "there is no proof to use the β2-agonists for treating acute cough in children without proofs of airway obstruction". There is also no proof for the use of anticholinergic agents for the treatment of nonspecific cough in children.

The use of corticosteroids in treating pediatric chronic cough has lead to many polemics. Studies made by Chang AB and colleagues (1998) showed that pediatric chronic cough treatment with inhaled corticosteroids has to be of short duration, carefully administered. There is no study regarding the oral corticosteroids' use in children with nonspecific cough. The use of dexamethasone has had no significant benefit in ameliorating cough related to pertussis. The oral corticosteroid treatment introduced on parental pressure had no benefit, even in wheezing presenting children (Oommen A, Lambert PC, 2003), but in exchange it was associated with a significant increase in hospitalization (p = 0,058).

Guidelines for evaluating and treating chronic cough in pediatrics made by the American College of Chest Physicians in 2006, recommend:

1. Children with chronic cough require careful evaluation for the presence of specific diagnostic indicators (level of evidence E/A)
2. Children with chronic cough should undergo a chest radiograph and spirometry (level of evidence E/A).
3. In children with specific cough, further investigations may be warranted, except when asthma is the etiologic factor (level of evidence E/B).
4. Children with chronic productive cough should be investigated to document the presence or absence of bronchiectasis and to identify underlying causes (cystic fibrosis, immune deficiency) (level of evidence B).
5. In children with chronic cough, the etiology should be defined and treatment should be etiologically based (level of evidence E/A).
6. In children with nonspecific cough, cough may spontaneously resolve, but children should be reevaluated for the emergence of specific etiologic pointers (level of evidence B)
7. In children with nonspecific cough and risk factors for asthma, a short trial of 2 to 4 weeks with beclomethasone, 400 μg/day, or the equivalent dosage with other inhaled corticoid may be warranted. However, it should be noted that most children with nonspecific cough do not have asthma. These children should be reevaluated in 2 to 4 weeks after the therapy started (level of evidence B).
8. In children who have started therapy with a medication, if the cough does not resolve during the medication trial within the expected response time, the medication should be withdrawn and other diagnoses considered (level of evidence C).
9. Cough suppressants and other OTC cough medicines should not be used as patients, especially young children, may experience significant morbidity and mortality (level of evidence C).
10. In all children with chronic cough, exacerbating factors (exposure to tobacco smoke) should be determined and interventional options for the cessation of exposure advised (level of evidence B).
11. Children should be managed according to the specific guidelines for children because etiologic factors and treatments in children are different from those in adults (level of evidence B).
12. In children less than 14 years of age with chronic cough, when pediatric–specific cough recommendations are unavailable, adult recommendations should be used with caution.

Conclusions

Children with chronic cough must be investigated according to children specific guidelines, which are distinct from those for adults, as are the etiologic factors and treatment. In children, cough is a very frequent symptom, and in most cases, it is associated to respiratory infections. However, cough may be a symptom of a serious disorder, too, so that every child with chronic cough has to be thoroughly investigated in order to identify a possible serious respiratory and / or systemic disease.

Pediatric cough must be strictly treated according to its etiology, and there is not enough evidence for the use of cough medicines (for the symptomatic relief of cough). If cough medicines are used, the child has to be carefully observed and the medication has to be stopped if it has no effect within the expected response time. It is very important to evaluate the response time.

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