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Acute Respiratory Infections in Children during Coronavirus Disease 2019: Without Reverse Transcriptase-Polymerase Chain Reaction Test and With Risk of Over-Prescription of Antibiotics, the Perfect Storm

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Abstract

Preliminary evidence suggests that children are as likely as adults to become infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that produces coronavirus disease 2019 (COVID-19), with a frequency of cases of 1.7% to 2%, and with more benign symptomatology. Most children present with fever and cough, with infections in the upper respiratory tract, and they not likely to require hospitalization. Thus, COVID-19 disease is frequently presented to the pediatrician or general practitioner as an Acute Respiratory Infection (ARI), which is the most common type of infection in the world. So, at present, the SARS-CoV-2 virus is one more aetiological agent of ARI. At present, and as with adults, a confirmed case of COVID-19 in children requires a positive reverse transcriptase-polymerase chain reaction test for SARS-CoV-2. However, the reality is that there is a lack or limited capacity of tests in many places. Thus, the doctor may feel the urge to prescribe antibiotics for ARI in children, without sufficiently considering the consequences of inappropriate treatments. Despite antibiotics are not recommended for treating uncomplicated ARI, antibiotic prescribing is widespread. Also, telemedicine visits that are frequent during COVID-19 outbreak, may Increase even more antibiotic overprescribing. COVID-19 antibiotics are reserved for patients suspected of having concomitant bacterial or fungal infections. But, in practice, Azithromycin (AZM) tends to be empirically prescribed, since among other effects it seems to inhibit viral replication, and is subject to studies. However, there is still little scientific evidence to support its administration, and the consequences of inadequate prescription of antibiotics should be considered. In paediatrics patients, prudent and judicious use of antibiotics, including AZM, for ARI, is even more necessary during the COVID-19 pandemic.

Keywords: Children; COVID-19; SARS-CoV-2; General practice; Pediatrician; Antibiotics; Azithromycin; Acute respiratory infections

Introduction

In December 2019, a cluster of pneumonia cases emerged in Wuhan City, Hubei Province, China. The coronavirus disease 2019 (COVID-19) is caused by the SARS-coronavirus-2 (SARS-CoV-2), a virus primarily zoonotic. WHO has declared COVID-19 a global pandemic and a public health emergency. The spread of the COVID-19 epidemic is unprecedented and it continues to spread affecting many countries and territories around the world [1-3]. Its figures are rapidly changing, and when this is written, as of May 8, 2020, the pandemic has infected more than 3,800,000 people and killed more than 260,000 worldwide; The United States has more than 1,200,000 cases, followed by more than 220,000 in Spain, and more than 215,000 in Italy [4]. Presentations of COVID-19 have ranged from asymptomatic/mild symptoms to severe illness and mortality. Common symptoms have included fever, cough, and shortness of breath. Other symptoms, such as malaise and respiratory distress, have also been described [5].

Children (persons aged <18-19 years) are not the face of this pandemic; but they risk being among its biggest victims. While they have thankfully been largely spared from the direct health effects of COVID-19 (at least to date), the crisis is having a profound effect on their wellbeing [6]. While clinical data available to date are based largely on the disease experience in China, Europe, and the United States, the paediatric literature on COVID-19 is still in its infancy and will undoubtedly evolve. Children with COVID-19 are underrepresented in case counts, especially missing data on younger babies [7,8].

But, to date it seems that the involvement in children is less, with much milder symptomatology. It is admitted that the percentage of total COVID-19 cases in children is between 1.7% to 2%, with a median pediatric age of 11 years, with 57% males, and they are associated with much lower case fatality rates. Preliminary evidence suggests that children are just as likely as adults to be infected with SARS-CoV-2, but less likely to develop symptoms or develop severe symptoms. COVID-19 is mainly a respiratory tract infection with a predominantly mild clinical disease trajectory in most children [7-11].

Fever, dry cough, and fatigue, as well as nasal congestion and runny nose, were the most commonly reported

symptoms; gastrointestinal symptoms are observed in infants. Similar to the adult findings, radiographic findings include bronchial thickening, ground-glass opacity, and evidence of pneumonia [12]. But, less frequent classic signs and symptoms among children vs adults [7,9,10]: Fever, cough, or shortness of breath: 73% of children vs 93% of adults; Fever: 56% vs. 71%; Cough: 54% vs. 80%; Shortness of breath: 13% vs. 43%; Myalgia: 23% vs. 61%.

Usually, most children presenting with fever and cough, and there are more SARS-CoV-2 infections in the upper respiratory tract than in the lower respiratory tract [7,13,14]. Further, it is not being likely hospitalization or intensive care is require (5%-20% cases get to be hospitalized) [12], so they can often be attended by primary care professionals (paediatricians and general practitioners/family doctors).

Antibiotics are reserved for patients suspected of having concomitant bacterial or fungal infections. Immunosuppressed patients are at high risk of secondary infection. Paediatrics cases of COVID-19 infection are typically mild, but underlying co-infection may be more common in children than in adults. This finding may suggest that routine antibacterial treatment could be considered in paediatrics patients. But, in children, their young immune systems, ACE2 receptor levels, and even exposure to other coronaviruses might play a role in their resilience [15-17].

Despite the lower frequency of respiratory symptoms in children compared to adults, COVID-19 is often presented to the paediatrician or general practitioner (GP) as an Acute Respiratory Infection (ARI). ARI is a group of diseases that occur in the respiratory system, caused by different microorganisms such as viruses and bacteria, which start suddenly. It is the most frequent infection in the world and represents an important public health issue. The respiratory viruses involved in ARIs are the respiratory syncytial virus, influenza, parainfluenza, and adenoviruses. The main symptoms are fever, malaise, stuffy and runny nose, cough, sore throat, expectoration, and difficulty breathing [18,19]. Consequently, the SARS-CoV-2 virus causing the current outbreak of COVID-19 [20,21] is one more etiological agent of the ARI.

In this scenario, this article, which is a personal vision, based on an unsystematic or opportunistic search for information and the author's experience, aims to summarize and reflect on the possible impact of the outbreak of COVID-19 and telecare on the prescription of antibiotics in AIR in children in places where it is not possible to carry out diagnostic tests.

Discussion

At present, and as with adults, a confirmed case of COVID-19 in children requires a positive reverse transcriptase-polymerase chain reaction (RT-PCR) test for SARS-CoV-2, based on nasopharyngeal or throat swab. WHO is urging governments to conduct more tests for COVID-19 due to concerns about the failure to report cases in many countries around the world; As more and more nations have introduced stringent measures to try to delay the spread of the virus, the WHO cautions that evaluating the impact of these measures will only be possible with accurate data on the disease. It also warns that a lack of data on how many people have the disease could undermine containment and mitigation efforts in many countries [22].

However, the reality is that there is a lack of diagnostic tests or that in many places Health Authorities have a limited ability to test, so the criteria of many countries such as Spain, or the CDC in the United States, to determine who is tested remain extremely strict, at least during March and April 2020: only people who had recently traveled or had contact with someone who had the virus, or people with a clinical picture of acute respiratory infection admitted to the hospital, or respiratory infection of any degree in health personnel; and similarly, routine diagnostic tests are not performed on contacts [17,23].

In this scenario, without a definitive diagnosis, where children and minors are a risk group for IRA (for COVID-19, respiratory syncytial virus, etc.), everything conspires so that the healthcare professional Primary (paediatrician, GP) feel the urge to prescribe antibiotics (perhaps even more so than before) in ARI in children, without sufficiently considering the consequences of these inadequate treatments

Most cases of COVID-19 in children are mild, and treatment consists of supportive care. While there are several studies underway, no medications or biologics have yet been shown to be effective in the prevention or treatment of COVID-19, and there is currently no vaccine available. IRA is a common presentation in general practice and is linked to high rates of inappropriate antibiotic prescription [23-26]. Inappropriate prescribing of antibiotics is a major public health problem, as it contributes to antibiotic resistance. In the US, medical providers often incorrectly prescribe antibiotics for acute viral respiratory infections, especially during peak influenza season. Antimicrobial therapy is extremely common in US ambulatory care settings and other countries [27,28].

Antibiotics are not recommended for treating uncomplicated IRA, despite this, antibiotic prescribing for IRA is widespread. Paediatricians and GPs report parental pressure and fear of losing patients if they do not prescribe antibiotics, however, parental views on antibiotics for ARI are unclear [29]. Studies about patients 'level of knowledge about antibiotic use converge on the view that it is quite poor, and, in particular, that the erroneous belief that antibiotics are indicated in cases of viral infections has been widespread [30]. Patient demand is the most common reason given by physicians as a cause for prescription of antibiotics. The related factors motivated the use of clinically unnecessary antibiotics in the face of perceived patient demand are:

Physicians want their patients to consider clinical visits as valuable and believe that an antibiotic prescription demonstrates value

Doctors want to avoid the negative repercussions of denying antibiotics

Physicians believe that certain patients are impossible to satisfy without a prescription for antibiotics and consider that efforts to convince such patients is a waste of time [31,32]. Currently a lot of patients are rightly being assessed remotely and this healthcare mode could favor the prescription of antibiotics. Kids with cold symptoms seen via telemedicine visits were far more likely to be prescribed antibiotics than those who went to a doctor's office or clinic, and a higher proportion of those prescriptions disregarded medical guidelines [33,34]

The GP or paediatrician may suspect that some mothers/fathers value the quality of their medical care for their child for the number of pharmacological prescriptions they receive. And it seems that the patients/parents who receive antibiotic prescriptions are the most satisfied. It should also be borne in mind that some doctors need to master the art of persuading patients that they do not need unnecessary medications, which can be an interview, without a doubt, more difficult than prescribing drugs [35].

One of the most common antibiotics prescribed, and more in telecare, is azithromycin (AZM) [34]. Furthermore, AZM is an antibiotic that tends to be empirically prescribed in COVID-19. It has been the subject of some experimental treatments for coronavirus patients [36] (as well as for severe respiratory syncytial virus infection in young children as it could reduce hospital stay and endotracheal markers for viral replication) [37]. AZM is a classic antibiotic in the treatment of respiratory infections of bacterial origin. But its use in COVID-19 is being analyzed due to the high risk of associated bacterial infections and the anti-inflammatory effect of this antibiotic. AZM kills senescent cells; in addition, normal healthy cells thrived in the presence of AZM. The new interpretation is that the antibiotic is likely to kill "inflammatory" fibroblasts, which could be useful as a preventive treatment for older people, as well as a treatment for people who already have the virus [38,39]. on the other hand, since AZM (and doxycycline) are commonly used antibiotics that inhibit viral replication, this could be considered as having a side effect because of functionally inhibits the synthesis of cellular proteins, and this would explain why have been reported to inhibit viral replication (so, these antibiotics behave as anti-viral agents), which could be useful for the treatment and prevention of COVID-19. In addition, AZM is an immune modulator that has been reported to provide clinical benefit in inflammatory airway diseases [37,40].

Of course, the full effects of SARS-CoV-2 in children, such as its milder symptoms, its role as vectors of the disease, or paediatric multisystemic inflammatory syndrome, which may include persistent fever and characteristics, are not well understood at present [41]. But it must be remembered that worldwide, therapeutic management of COVID-19 has been largely supportive, and to date, no specific therapy has been scientifically proven to reduce mortality. Doctors treat patients, using medications such as chloroquine, hydroxychloroquine, azithromycin, lopinavir-ritonavir, and interleukin-6 inhibitors outside of their stated, approved uses, and without study protocols, with little scientific evidence to support their administration, beyond *in vitro* studies [42].

Likewise, it is necessary to take into account the consequences of inappropriate prescription of antibiotics: resistance, adverse drug events, and effects on the microbiome. Thus, the reduced prescription of antibiotics in children is proposed. In this subject progress has been made: antibiotic prescription rates in the US for children, they decreased by 13% between 2011 and 2015, while rates among adults remained stable. Improvement in paediatric antibiotic prescription is likely to be the result of several factors, including the introduction of the pneumococcal conjugate vaccine, efforts public health to educate parents and health professionals, and doctors' efforts to change behavior [43,44].

Conclusion

In summary, children represent a small fraction of confirmed COVID-19 cases, and pediatric cases of COVID-19 infection are typically mild, but underlying co-infection may be more common in children than in adults. In the absence of a PCR test, probably many COVID-19 cases present as ARI indifferent from other aetiologies. This situation of uncertainty and anguish for the doctor may suggest him or her that routine antibacterial treatment should be considered in paediatric patients, without taking into account the general advice against it, or accepting antibacterial treatment in uncritically way or with incomplete results studies; or as a method to reduce doctor anxiety, or at the request of parents. Also, telemedicine visits that are frequent during COVID-19 outbreak, may Increase even more antibiotic overprescribing.

The expression perfect storm was popularized by a movie based on real events: those suffered by swordfish fishermen surprised by the conjunction of two large storms, one with continental cold air and the other with hot air on Sable Island. The collision or the fusion of both caused great misfortunes. The expression is applied to the sum of negative circumstances that are capable of creating situations of maximum tension. The high frequency of ARI, the over-prescription of antibiotics in ARI, the COVID-19 outbreak, the absence of PCR tests for its diagnosis, the anxiety generated in doctors and patients, the non-face-to-face consultations through telecare, and the anecdotal or preliminary data on the use of antibiotics like AZM in COVID-19, form a perfect storm for the misuse of antibiotics in children. So, prudent and judicious use of antibiotics in ARI in children is even more necessary during the COVID-19 pandemic time.

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