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Guide to Leading a Patient with Symptoms of an Acute Respiratory Infection during a Coronavirus Pandemic (COVID-19)

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Abstract

BACKGROUND: Over 500 viruses and bacteria primarily cause respiratory infections. During COVID-19 pandemic, these respiratory infections remain; i.e., COVID-19 has no ability to suppress these infections from the circulation. Therefore, it is very important to differentiate respiratory infections from COVID-19. Proving the presence of COVID-19 with polymerase chain reaction (PCR) is not evidence that the disease was caused by this virus. Possible options are: First, a random encounter of the virus in the patient's upper respiratory tract; second, further possible colonization with a coronavirus (or with COVID-19); the third option is to have an infection; and the fourth possibility is to have a disease or COVID-19 upper respiratory infection. Unfortunately, the method with PCR, although it is with high sensitivity and specificity, does not help us to distinguish which of these four possibilities are in question.

AIM: We aimed to present a guide to leading a patient with symptoms of an acute respiratory infection during a coronavirus pandemic (COVID-19).

RESULTS: A pandemic of COVID-19 shows that many patients get primary viral pneumonia, but people with normal immune system have no problem recovering. People with reduced immunity die from COVID-19, as opposed to the pandemic influenza virus. It is indirectly concluded that COVID-19 in itself is not very virulent, but it weakens the immunity of those infected who already have some condition and impaired immunity. The available scientific papers show that there is no strong cytokine response, patients have leukopenia and lymphopenia, some patients have a decrease in CD4 T-lymphocytes. From the results of the autopsies available so far, it is clear that there are very few inflammatory cells in the lungs and a lot of fluid domination. Hence, SARS-Cov-2 only somehow speeds up the decline in immunity. The previously published radiographic findings of COVID-19 patients, gave a characteristic findings of the presence of multifocal nodules, described as milky glass, very often localized in the periphery of the lung. Whether it is typical pneumonia, atypical, viral, mixed-type pneumonia, or mycotic pneumonia, it can progress to severe pneumonia. The pneumonia becomes severe when breathing is over 30/min; diastolic pressure below 60 mmHg; low partial oxygen pressure in the blood (PaO_2/FiO_2 <250 mmHg) (1 mmHg = 0.133 kPa); massive pneumonia, bilateral or multilayered lung X-ray; desorientation; leukopenia; and increased urea.

CONCLUSION: Patients with COVID-19 placed in intensive care units should be led by a team of anesthesiologists with an infectious disease specialist or an anesthesiologist with a pulmonologist. Critical respiratory parameters should be peripheral oxygen saturation <90%, PaO_2/FiO_2 ratio 100 or <100, tachycardia above 110/min.

Introduction

Acute respiratory infections are the most common infections in humans. As many as, two-thirds of all infections are thought to be respiratory infections. Over 500 viruses and bacteria primarily cause respiratory infections. Adults have a respiratory infection 3–5 times a year. At children, that number is much higher. Upper respiratory infections (rhinitis, sinusitis, tonsillopharyngitis, angina, gingivostomatitis, and laryngitis) are much more common than lower respiratory (tracheitis, bronchitis, bronchiolitis, alveolitis, and pneumonia). During COVID-19 pandemic, these respiratory infections remain, i.e., SARS-Cov-2 has no ability to suppress these infections from the circulation. Therefore, it is very important to differentiate respiratory infections from COVID-19. A good demarcation will increase the effectiveness of treating respiratory infections. We are very successful in treating bacterial infections. There are good antiviral drugs for the flu or influenza virus. We must consider about mycotic respiratory infections, and there are effective antifungal drugs for them.

Laboratory biochemical analyzes give us great help in distinguishing viral from bacterial infection and acting correctly in the decision to give an antibiotic. Thus, high sedimentation, leukocytosis with neutrophilia, high C-reactive protein (CRP), and elevated procalcitonin values are in addition to bacterial infection. Normal erythrocyte sedimentation rate, peripheral lymphocyte dominance (blood count), and normal CRP are in addition to viral infection.

Acute rhinitis (cold) – upper respiratory infection that from the 1st day goes with catarrhal symptoms (runny nose, sneezing, burning eyes, and tearing) with signs of general infectious syndrome and temperature up to 37.5°C to be treated as a common

cold syndrome (acute rhinitis). The most common causes are rhinoviruses, coronaviruses, influenza type C, parainfluenza, and respiratory syncytial virus (RSV).

Flu – if the patient had a high fever for 2–3 days (37.5–39.5), severe infectious syndrome (headaches, myalgias, arthralgias, bone pain, malaise, and drowsiness), there are no catarrhal signs, and the same occur after 2–3 days, then these patients have the flu and need to seek serological confirmation of influenza virus.

Catarrhus febrilis respiratorius – if the patient has a high fever from the 1st day, accompanied by symptoms of the general infectious syndrome, but from the 1st day, there are catarrhal symptoms (sneezing, runny nose, burning in the eyes, and tearing), then it is a so-called catarrhal febrile respiratory syndrome. This syndrome is most commonly caused by so-called atypical (intracellular) bacteria, primarily *Mycoplasma pneumoniae, Legionella pneumophila, Chlamydia pneumoniae,* and adenoviruses from viruses with this clinical picture [1], [2], [3].

Laboratory biochemical analysis will be very helpful in differentiating whether it is a bacterial or a viral infection. Thus, leukocytosis, with a predominance of polymorphonuclear in the peripheral smear, together with high CRP values (above 100 mg/L) and accelerated erythrocyte sedimentation rate (above 20 mm/1 h) goes in favor of bacterial upper respiratory infection and those patients regardless. The obtained microbiological and serological results should be treated with antibiotics and corona infections should be separated. Moderately elevated or normal values of leukocytes, elevated CRP but with values below 50 mg/l, moderately elevated erythrocyte sedimentation rate (10–20 mm/1 h), and clinical picture of catarrhus febrilis respiratorius (1st day temperature and catarrhal signs) atypical bacterial infection (*M. pneumoniae*, so-called Pontiac fever caused by *L. pneumophila* and *C. pneumoniae*) and should be treated with macrolide antibiotics or tetracyclines. If we have a predominance of lymphocytes (regardless of the values of leukocytes), the sedimentation of erythrocytes in normal values 5–10 mm/1 h, and CRP is with normal values of 1–10 mg/l or slightly elevated; then, it is a viral upper respiratory infection, called rhinitis syndrome. Possible causes are rhinoviruses, influenza type C, parainfluenza, and coronaviruses in adults, and in children, the most common causes are RSV, rhinoviruses, influenza type C, parainfluenza, and coronaviruses. If the epidemiological situation in the region goes with the confirmation of many cases with the confirmed presence of COVID-19, then the most likely upper respiratory infection is with a coronavirus. Proving the presence of SARS-Cov-2 with polymerase chain reaction (PCR) is not evidence that the disease was caused by this virus. Possible options are: First, a random encounter of the virus in the patient's upper respiratory tract; second, possible colonization with a coronavirus (or with COVID-19); the third option is to have an infection; and the fourth possibility is to have a disease or COVID-19 upper respiratory infection. Unfortunately, the method with PCR, although it is with high sensitivity and specificity, does not help us to distinguish which of these four possibilities are in question. The infection does not cause any clinical problems, but can be proven by serological tests. Proof of the presence of IgM antibodies to SARS-Cov-2 by serological test is reliable and acceptable evidence that it is an upper respiratory infection caused by COVID-19. Regardless of the etiological cause of rhinitis, or even an upper respiratory infection is with COVID-19, treatment should be symptomatic, i.e., the patient should rest, use more fluids through the mouth (teas, juices), Vitamin C (in high doses), and nothing else. Antibiotics and corticosteroids are contraindicated, and analgesics, antipyretics, immunoglobulins, immunomodulators, etc., may cause harm. Patients with upper respiratory tract infection with COVID-19 should be treated at home [1], [3], [4], [5], [6], [7], [8].

From the epidemiological data so far, about 15% of all COVID-19 patients develop lower respiratory tract infections. These primary viral pneumonias should be treated in a hospital. To increase treatment efficacy, and to reduce mortality, it is necessary to properly differentiate primary viral pneumonia with COVID-19 from other pneumonia. Pneumonia is a serious disease with high mortality. They are the 10th leading cause of death in the world, and in the age group of 65, they are the sixth leading cause of death. There are several divisions of pneumonia, but the most appropriate is the division of hospital-acquired pneumonia and community-acquired pneumonia.

Hospital-acquired pneumonias are common conditions, especially in patients who have been placed on a respirator or have had a diagnostic procedure on the respiratory tract (bronchoscopy and biopsy). Of all intrahospital infections, 13%–18% have nosocomial pneumonia. These pneumonias are sent with a high mortality rate of 33%–50% depending on the cause: *Streptococcus pneumoniae, Staphylococcus aureus, P. aeruginosa, Klebsiella*, and *Acinetobacter* species.

Community-acquired pneumonia – The best results in practice are given by the division of typical and atypical pneumonia. Typical pneumonias have a rich auscultatory finding, the presence of small moist bronchial murmurs (crepitations), and/or impaired breathing in a particular region. This auscultatory finding is confirmed by a rich rentgenogram. Atypical auscultation pneumonia has a normal finding because the inflammation is in the interstitium and the airways are free. However, the X-ray has a rich finding and diagnoses pneumonia. Depending on the size of the lesion, both typical and atypical pneumonias may have small inflammatory foci (bronchopneumonia), segmental, lobular, or occupy multiple lobes, i.e., be multilobar/massive unilateral or bilateral pneumonia. The advantage of this division into typical and atypical is that this division helps for proper antibiotic treatment. Pneumonia mortality is reduced if appropriate

antibiotic treatment is started within the first 4–6 h. Typical pneumonia is most commonly caused by pneumococcus (*S. pneumoniae*), *S. aureus,* and *Haemophilus influenzae*. The good part is that all these causes are susceptible to the same groups of antibiotics. Our drug of choice is the third-generation cephalosporin for parenteral use, ceftriaxone in doses of 30–50 mg/kg/bw [1], [3], [8], [9], [10].

Atypical pneumonia is caused by viruses and so-called atypical intracellular causes (*M. pneumoniae, L. pneumophila, Chlamydia pneumoniae,* and *Coxiella burnetii*). The good side is that these intracellular bacteria are sensitive to macrolide antibiotics and tetracyclines. Unlike viral atypical pneumonia, we have a moderate increase in erythrocyte sedimentation rate of 15–30 mm/1h, and moderately elevated CRP, in addition to possible leukocytosis. The drug of choice during pandemic with COVID-19 should be azithromycin 5 mg/kg/bw, preferably intravenously [1].

Another division of community-acquired pneumonia is primary and secondary. Primary pneumonia involves pneumonia caused by any infectious agent and is caused by a primary infection of the same cause. Secondary pneumonia is pneumonia caused by another upper respiratory infection, usually viral. This viral infection is thought to damage the respiratory epithelium, disrupting the defense mechanisms of the respiratory tract, and a secondary bacterial pneumonia develops within a few days to 2 months of the virus infection. These secondary bacterial pneumonias usually present with clinical and etiological presentation of typical pneumonia. Secondary pneumonia is also of fungal etiology (*Cryptococcus neoformans,* Pneumocystis jiroveci*, Histoplasmosis,* and *Candida* spp.). Fungal pneumonia occurs after a serious decline in immunity due to malignancy, severe chronic disease, starvation, treatment with cytostatics, and long-term treatment with antibiotics. These pneumonias are much more common than we think and diagnose and are often the cause of death.

Primary pneumonia can be caused by any cause. Primary pneumonia is usually caused by a bacterium. Viruses rarely give rise to primary pneumonia. Primary viral pneumonia occurs when the virus is highly virulent. As a rule, primary viral pneumonia is difficult to treat and ends in death. Such primary viral pneumonias give many viruses (RSV, varicella, measles, and SARS-Cov-1). Influenza virus does not cause primary viral pneumonia during epidemics. However, during pandemics that occur after major, so-called shift antigenic changes, and when there is a population that will first encounter a new subtype of influenza virus, primary viral pneumonia is a common and significant cause of death. During the 1918–1920 pandemic caused by the H1N1 subtype of Influenza A virus, such primary viral pneumonias were given only to people born after 1890, as most of the elderly had contact with the H1N1 subtype that had circulated before. Hence, young people with good and enhanced immunity died of primary viral pneumonia. The autopsy finding is up to 2 L of non-fibrinous fluid in the lungs. Coronaviruses typically present with a mild clinical picture of upper respiratory infection, followed by bacterial secondary pneumonia. No matter how and when the mutation occurred and COVID-19 occurred, it is evident that now in this COVID-19 pandemic, most of the deaths are due to the development of primary viral pneumonia and acute respiratory distress syndrome. During pandemics with influenza pneumonia with high mortality, young people have a good immune response, and the development of pneumonia is due to the virulence of the causative agent itself. A pandemic of COVID-19 shows that many patients get primary viral pneumonia, but people with normal immune system have no problem recovering. People with reduced immunity die from COVID-19, as opposed to the pandemic influenza virus. It is indirectly concluded that COVID-19 in itself is not very virulent, but it weakens the immunity of those infected who already have some condition and impaired immunity. The available scientific papers show that there is no strong cytokine response, patients have leukopenia and lymphopenia, some patients have a decrease in CD4 T-lymphocytes. From the results of the autopsies available so far, it is clear that there are very few inflammatory cells in the lungs and a lot of fluid domination. Hence, COVID-19 only somehow speeds up the decline in immunity [1], [3], [8], [10], [11], [12].

It is necessary to strictly distinguish which patients have developed primary viral pneumonia from COVID-19, from patients who are positive for COVID-19, but for some other reason develop ARDS. These causes may be: The COVID-19 virus itself; other viruses; other infectious agents; holding patients on the respirator for more than 12 h; long-term oxygen delivery; hemodynamic disturbances; and alveolar capillary shunts, some internist notches [1], [3], [8].

X-ray Characteristics of Pneumonia

Lung X-rays certainly confirm the existence of a process in the lungs, but they rarely have specifics that will point us to the etiological cause. However, lobar pleuropneumonia suggests a possible pneumococcal etiology, cotton-like shadows (pneumatocele) of staphylococcal pneumonia, and a clearly limited round shadow of possible coxiellosis. The description of changes in the interstitium suggests that we have atypical bacterial pneumonia or interstitial viral pneumonia. The previously published radiographic findings of COVID-19 patients, gave a characteristic findings of the presence of multifocal nodules, described as milky glass, very often localized in the periphery of the lung. It is this kind of finding of peripheral nodules such as milky glass that has been pathognomonic to Chinese radiologists who have only begun to diagnose primary viral pneumonia

with COVID-19 based on this finding. This finding in 80–85% coincided with the positivity of SARS-Cov-2 with PCR [9], [12], [13].

Specialist infectious disease specialists outside the pandemic successfully treat acute respiratory infections. However, during a pandemic due to a large number of patients, general practitioners and physicians with other specialties will be involved in the treatment of patients with COVID-19. A doctrinal approach in the treatment of patients with COVID-19 will give the best results, and there will be the smallest percentage of deaths.

Guide for the Treatment of Patients with Pneumonia

Pneumonia should be treated by an infectious disease specialist or pulmonologist. In conditions of increased number of pneumonias (larger than hospital capacities), the easier forms can be treated by a family doctor or internist.

Typical Pneumonia

If the pneumonia is characterized by typical pneumonia (rich auscultatory findings, radiographic confirmation, and laboratory biochemical analysis in addition to bacterial infection) to be treated doctrinally with third-generation cephalosporin for parenteral use, ceftriaxone 30–50 mg/kg/bw/i.v, once a day if up to 2 g, twice a day if given a maximum dose of 2 g ×2.0 g. The treatment should be in hospital. Mild forms can be treated on an outpatient basis. Intravenous fluids should be kept to a minimum. Do not include oxygen therapy. If the patient is treated on an outpatient basis, see the vital parameters at least once a day and follow the auscultatory findings. This therapy should be given a chance to work for at least 4 days. If there is a withdrawal of the auscultatory finding, a decrease in CRP values, a decrease erythrocyte sedimentation rate, regardless of the values of leukocytes in the blood, continue therapy for 10–12 days. After that control, lung graphics and a set of laboratory biochemical analyze. If after 4 days, there is a worsening of the pulmonary auscultatory finding, and/or a worsening of the condition, the patient should be treated exclusively in hospital. Replacing ceftriaxone with moxifloxacin 400 mg daily/iv (streptococcal pneumonia, the most common cause of typical pneumonia, is most sensitive to moxifloxacin, has a good effect on staphylococcal and anaerobic bacteria), and atypical intracellular bacteria. If there is a good assumption (a valid finding on lung X-ray, furunculosis…) that it is MRSA instead of moxifloxacin, immediately go with vancomycin 25–60 mg/kg/day. If it is assumed that aspiration and/or mixed pneumonia are possible, metronidazole 30 mg/kg/day should be added in two daily doses (clindamycin is a good choice 10–30 mg/kg/day/i.m. or i.v. in two doses). Continue intravenous fluid delivery to a minimum. Oxygen should not be given as support. Avoid expectorants. Give antitussives if there is a persistent irritating cough. Moxifloxacin should be given a chance to be effective again for at least 4 days. If there is no withdrawal of the finding or the patient's condition worsens, after 4 days of moxifloxacin therapy, replace with vancomycin [1], [14].

Atypical Bacterial Pneumonia

Atypical bacterial pneumonia can go into epidemic forms (*M. pneumoniae*, *C. pneumoniae,* and *L. pneumophila*) and can be easily transmitted from person to person. Due to the similar clinical picture and uncharacteristic laboratory biochemical parameters, they make serious differential diagnostic difficulties, i.e., we can hardly distinguish them from atypical pneumonia of viral origin. The drug of choice for atypical bacterial pneumonia (during COVID-19 pandemic) should be azithromycin 5 mg/kg/bw preferably intravenously. Treatment with other macrolide antibiotics or tetracyclines may not work because of the resistance of the primarily *L. pneumophila* to them. Treating these bacterial atypical pneumonias with cephalosporins or other beta-lactam antibiotics is without effect [1], [14].

Primary Viral Pneumonia

Many viruses can cause primary viral pneumonia, but the most common are influenza A virus, influenza B virus, RSV, human metapneumovirus, and adenovirus types 4 and 7. Influenza A viruses are statistically the most common primary pneumonia virus, but this occurs when there is a large shift antigenic change in hemagglutinin and neuraminidase and the appearance of a new circulatory subtype (H2N2). Some variants of circulating influenza subtype H1N1 know how to obtain many virulent features and give primary viral pneumonia. Because the epidemiological situation in the world regarding influenza A virus is calm (there is no new subtype, the variants that are now circulating are not so virulent), in a pandemic with COVID-19, it is expected that most of the primary viral pneumonia will be caused by COVID-19. Leukopenia, a weak immune response, a decrease in CD4 T-lymphocytes in some patients, and a characteristic radiographic finding of

peripheral nodules and/or changes described as an opaque glass suggest primary viral pneumonia with COVID-19 [8], [10], [11], [13], [15], [16], [17].

Recommendations for Therapy

Do not do more than possible. It should be borne in mind that in many papers in these patients were given various antiviral drugs, although it is known that they do not act on the virus. Even if there is a presumption that viral pneumonia may be caused by influenza viruses, it is not justified to give oseltamivir which is effective only if therapy is started within the first 36 h of illness (pneumonia occurs secondary after 8 days). Antiretroviral drugs do not work either. Giving such antiviral drugs is only an alibi without scientifically proven support. Giving corticosteroids to most patients (according to studies published in scientific journals) can only reduce the immune response, that is already weak [4], [6], [11], [13], [15], [17], [18]. Giving chloroquine and other and other antiparasitic drugs justified is only if we want to achieve a reduction in the anti-inflammatory response. Because the majority of patients with such primary viral pneumonia with COVID-19 have no problem recovering regardless of the size of the pathological process, it is best to leave the patient's immunity to fight alone. Provide suppurative therapy, give Vitamin C (in high doses), and avoid intravenous fluids. Giving a drug without confirmed scientific proof that the drug is effective only, will do harm regardless of the doctor's intention to do something.

Mycotic Pneumonia

Mycotic pneumonia is a possible etiological cause as a secondary infection in patients with COVID-19. Therefore, in massive bilateral pneumonias with a characteristic X-ray finding for COVID-19 (peripheral nodules and milk glass findings) in which there are medium values of inflammatory markers in the blood (CRP, procalcitonin, and erythrocyte sedimentation rate), antimycotic replacement should be considered for antiparasitic and antiviral drugs that do not act on the COVID-19 [1], [9], [19].

Severe Pneumonia

Whether it is typical pneumonia, atypical, viral, mixed-type pneumonia, or mycotic pneumonia, it can progress to severe pneumonia. The pneumonia becomes severe, when breathing is over 30/min; diastolic pressure below 60 mmHg; low partial oxygen pressure in the blood (PaO_2/FiO_2 <250 mmHg) (1 mmHg = 0.133 kPa); massive pneumonia, bilateral or multilayered lung X-ray; desorientation; leukopenia; and increased urea. When a pneumonia progresses and becomes severe pneumonia, the patient should be transferred to an intensive care unit. (Note: Peripheral oxygen saturation of up to 90% and tachycardia up to 110/min are not in themselves indicative of intensive care treatment). Switching to an intensive care unit does not mean immediately putting the patient on a respirator. Patients with COVID-19 placed in intensive care units should be led by a team of anesthesiologists with an infectious disease specialist or an anesthesiologist with a pulmonologist. Critical respiratory parameters should be peripheral oxygen saturation <90%, PaO_2/FiO_2 ratio 100 or <100, and tachycardia above 110/min. Severe acidosis itself may also be an indication for respiratory placement. Before setting up a respirator, make an operational plan, i.e., clearly set a goal of which parameters will be improved and for how long. Reduce the risks of getting ARDS from the respirator itself, and the risks of getting secondary pneumonia from a respirator [1], [6], [9], [10], [12], [20].

Conclusion

Distinguishing between typical and atypical bacterial pneumonia from atypical viral pneumonia is very important during a pandemic with COVID-19. Distinguishing primary viral pneumonia from secondary bacterial or fungal pneumonia is also important and will yield good results in successfully treating and reducing the percentage of deaths during pandemic with COVID-19. When we separate pneumonia with COVID-19, from other pneumonia, we will be able to analyze them much better and get much more accurate results. This will make it much easier and faster for us to come up with scientific explanations of what is happening to us and how to successfully oppose COVID-19.

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