

The following information resources have been selected by the National Health Library and Knowledge Service Evidence Virtual Team in response to your question. The resources are listed in our estimated order of relevance to practicing healthcare professionals confronted with this scenario in an Irish context. In respect of the evolving global situation and rapidly changing evidence base, it is advised to use hyperlinked sources in this document to ensure that the information you are disseminating to the public or applying in clinical practice is the most current, valid and accurate. For further information on the methodology used in the compilation of this document—including a complete list of sources consulted—please see our <u>National Health Library and Knowledge Service Summary of Evidence Protocol.</u>

## **YOUR QUESTION**

What characterizes atypical clinical presentation of COVID-19 in older patients [age 65+]?

### **IN A NUTSHELL**

Older people with COVID-19 often present with atypical clinical symptoms.

The HSPC<sup>1</sup> states: "It is important to remember that elderly people often present atypically with symptoms such as: lethargy; increased confusion; change in baseline condition; loss of appetite."

The WHO<sup>3</sup> and CDC<sup>4</sup> designate anorexia, malaise, muscle pain, sore throat, dyspnea, nasal congestion, headache, confusion, rhinorrhea, hemoptysis, vomiting and diarrhea as atypical or less common symptoms. BMJ Best Practice<sup>5</sup> and UptoDate<sup>6</sup> both describe common and atypical clinical presentations of COVID-19; less common symptoms include headache, sore throat, chest pain, haemoptysis, dizziness, confusion, nasal congestion, gastrointestinal disorders, anorexia, smell and taste disorders, and skin disorders. Canadian guidance<sup>2</sup> also lists atypical symptoms including delirium, functional decline, weakness, malaise, abdominal pain, unexplained tachycardia, anosmia, functional decline, conjunctivitis, falls, diarrhoea and decrease in blood pressure.

The international literature describes a variety of atypical presentations from patients who presented with symptoms of acute ischaemic stroke<sup>8</sup>; to altered mental status<sup>21</sup>, dizziness and syncope <sup>17,18</sup>; confusion and lethargy<sup>23</sup>. Other atypical symptoms mentioned in the literature include chills, malaise, sore throat, confusion, myalgia, headache, nausea, rash, back pain, gastrointestinal disorders, tremor and tachycardia<sup>7-23</sup>.



#### **IRISH AND INTERNATIONAL GUIDANCE**

#### What does the Health Protection Surveillance Centre say?

Health Protection Surveillance Centre (04 May 2020) Interim Public Health and Infection Prevention Control Guidelines on the Prevention and Management of COVID-19 Cases and Outbreaks in Residential Care Facilities and Similar Units. Version 4<sup>1</sup> Section 3.4 Clinical Features of COVID-19 The most common signs and symptoms include:

- fever [though this may be absent in the elderly]
- dry cough

Other symptoms can include:

- shortness of breath
- sputum production
- fatigue

Less common symptoms include:

- sore throat
- headache
- myalgia/arthralgia
- chills
- nausea or vomiting
- nasal congestion
- diarrhoea
- haemoptysis
- conjunctival congestion

"It is important to remember that elderly people often present atypically with symptoms such as: lethargy; increased confusion; change in baseline condition; loss of appetite."



### Regional Geriatric Programme of Toronto (2020) COVID-19 Resources: COVID-19 in Older Adults<sup>2</sup>

Atypical COVID 19 Presentations in Frail Older Adults

Typical symptoms of COVID-19 such as fever, cough and dyspnea may be absent in older adults despite respiratory disease. Only 20-30% of geriatric patients with infection present with fever. Atypical COVID-19 symptoms include delirium, falls, generalized weakness, malaise, functional decline, conjunctivitis, anorexia, increased sputum production, dizziness, headache, rhinorrhea, chest pain, hemoptysis, diarrhea, nausea or vomiting, abdominal pain, nasal congestion and anosmia. Tachypnea, delirium, unexplained tachycardia, or decrease in blood pressure may be the presenting clinical presentation in older adults.

Threshold for diagnosing fever should be lower [ie 37.5°C] or an increase of >1.5°C from usual temperature.

Atypical presentation may be due to several factors including physiologic changes with age, comorbidities and inability to provide an accurate history. Older age, frailty and increasing number of comorbidities increase the probability of an atypical presentation. Older adults may present with mild symptoms that are disproportionate to the severity of their illness. Consider COVID-19 as the cause of delirium [ie perform a COVID-19 swab and initiate isolation precautions] if any of the following are present:

- symptoms are suggestive even if only mild of ILI or low grade temperature are present
- history of COVID-19 exposure or exposure to others with ILI symptoms
- hypoxia otherwise unexplained even if mild

#### What does the World Health Organization say?

#### <u>World Health Organization (13 March 2020). Clinical management of</u> <u>severe acute respiratory infection when COVID-19 is suspected: interim</u> <u>guidance<sup>3</sup></u>

Clinical Syndromes Associated with COVID-19

Patients with uncomplicated upper respiratory tract viral infection may have non-specific symptoms such as fever, fatigue, cough—with or without sputum production—anorexia, malaise, muscle pain, sore throat, dyspnea, nasal congestion or headache. Rarely, patients may also present with



diarrhoea, nausea and vomiting. The elderly and immunosuppressed may present with atypical symptoms.

# What do the Centers for Disease Control and Prevention (United States) say?

<u>Centers for Disease Control and Prevention (2020). Interim Clinical</u> <u>Guidance for Management of Patients with Confirmed Coronavirus</u> <u>Disease (COVID-19)<sup>4</sup></u>

**Clinical Presentation** 

The signs and symptoms of COVID-19 present at illness onset vary; however, over the course of the disease most persons with COVID-19 will experience the following:

- fever [83%–99%}
- cough [59%-82%}
- fatigue [44%–70%]
- anorexia [40%–84%]
- shortness of breath [31%–40%}
- sputum production [28%–33%]
- myalgias [11%-35%]

Atypical presentations have been described, and older adults and persons with medical comorbidities may have delayed presentation of fever and respiratory symptoms. In one study of 1,099 hospitalized patients, fever was present in only 44% at hospital admission but later developed in 89% during hospitalization. Headache, confusion, rhinorrhea, sore throat, hemoptysis, vomiting and diarrhea have been reported but are less common [<10%].

## POINT-OF-CARE TOOLS

## What does BMJ Best Practice say?

Coronavirus disease 2019 (COVID-19)<sup>5</sup>

**Clinical Presentation** 

The clinical presentation resembles viral pneumonia and the severity of illness ranges from mild to severe. Severe illness is associated with older age



and the presence of underlying health conditions. Older patients and/or those with comorbidities may present with mild symptoms but have a high risk of deterioration. Atypical presentations may occur, especially in older patients or patients who are immunocompromised. The most common symptoms are:

- fever
- cough
- dyspnoea
- myalgia
- fatigue
- anosmia/dysgeusia

Less common symptoms include:

- anorexia
- sputum production
- conjunctivitis
- gastrointestinal symptoms
- sore throat
- confusion
- dizziness
- headache
- chest pain
- haemoptysis
- cutaneous manifestations

Patients may have gastrointestinal symptoms. The most common diagnosis in patients with severe COVID-19 is severe pneumonia. Initial impressions from cases in the US note that the clinical presentation may be broader than that observed in China and Italy, with chest pain, headaches, altered mental status, and gastrointestinal symptoms all observed on initial presentation. Severe hepatic and renal dysfunction that spares the lungs has also been observed.



#### What does UpToDate say?

## Coronavirus disease 2019 (COVID-19): Epidemiology, virology, clinical features, diagnosis, and prevention<sup>6</sup>

#### **Clinical Manifestations**

Initial presentation: pneumonia appears to be the most frequent serious manifestation of infection, characterized primarily by fever, cough, dyspnea, and bilateral infiltrates on chest imaging.

In addition to respiratory symptoms, gastrointestinal symptoms such as nausea and diarrhea have also been reported; and, in some patients, may be the presenting complaint. In a systematic review of studies reporting on gastrointestinal symptoms in patients with confirmed COVID-19, the pooled prevalence was 18 percent overall, with diarrhea, nausea/vomiting, or abdominal pain reported in 13%, 10% and 9% respectively.

Other reported symptoms have included headache, sore throat and rhinorrhea. Conjunctivitis has also been described. Dermatologic findings in patients with COVID-19 are not well characterized. There have been reports of maculopapular, urticarial and vesicular eruptions and transient livedo reticularis. Reddish-purple nodules on the distal digits similar in appearance to pernio (chilblains) have also been described, mainly in children and young adults with documented or suspected COVID-19.

#### INTERNATIONAL LITERATURE

#### What does the international literature say?

#### <u>D'Adamo et al (2020) Coronavirus Disease 2019 in Geriatrics and Long-</u> <u>Term Care: The ABCDs of COVID-19<sup>7</sup></u>

Typical clinical presentations for patients with COVID-19 are fever, cough and dyspnea. Older adults especially older people who are frail with chronic conditions may be afebrile and not present with cough, respiratory or sputum production.

Tachypnea, altered mental status or delirium, and unexplained tachycardia or a decrease in blood pressure may be the presenting clinical manifestations. Informal reports from US physicians who have cared for older patients with COVID-19 indicate that the most common presentation of infection began with malaise, muscle pains, low-grade fever and cough that



progressed to respiratory difficulty in the second week of illness; fever was not prominent in several cases.

#### Avula et al (2020) COVID-19 presenting as stroke<sup>8</sup>

The authors report on a series of four patients aged over 65 who presented with symptoms of acute ischemic stroke and elucidate the clinical characteristics, imaging findings and clinical course.

### <u>Aprahimian et al (2020) Geriatric Syndromes and SARS-CoV-2: More Than</u> <u>Just Being Old<sup>9</sup></u>

Clinically, older adults present similar symptoms of SARS-CoV-2 compared with younger individuals. Fever is usually one of the first symptoms, followed by cough and shortness of breath. Nevertheless, frail older adults can present atypical symptoms as is seen in normal routine for other conditions. Inflammatory biomarker levels tend to be lower or do not show major differences from those reported in younger adults. At the same time, older individuals are more likely to present with higher pneumonia severity index, more acute respiratory distress syndrome and acute organ dysfunction. Furthermore, lung lesions usually appear particularly severe in older adults. Tomographic findings show a more extensive bilateral ground-glass pattern of lung involvement, peripheric ground-glass opacity and consolidation, and interlobular septal, subpleural line and pleural thickening. Alveolar and interstitial involvement are two times more intense than in younger adults.

## Boccardi et al (2020) [Editorial] COVID-19: A Geriatric Emergency<sup>10</sup>

Geriatricians have already faced these difficulties in managing older patients during the seasonal flu peaks, but now there is one substantial difference in the management of older adults with COVID-19 infection: the need for the early recognition of atypical symptoms and signs that are so common at this age when their clinical expression is what we define as geriatric syndromes. The activation of already well established multi-domain interventions provided in a timely and tailored fashion might have a dramatic impact on a positive outcome. Geriatricians are ready to share their expertise and clinical management skills to fight the multisystemic derangements triggered by COVID-19. They have experimented and learned how important holistic and comprehensive patient management is, taking into consideration drug interactions, water balance, oxygenation, nutrition, pain control and early mobilization. The multidimensional evaluation is critical for fighting COVID-19



infection in the old age, but too often, the traditional clinical approach is still prevalent. In frail old persons, where immunosenescence confuses the clinical presentation, an expression of classical pathognomonic symptoms such as fever, cough and dyspnea cannot be expected.

### Lian et al (2020) Analysis of Epidemiological and Clinical Features in Older Patients with Corona Virus Disease 2019 (COVID-19) out of Wuhan<sup>11</sup>

A retrospective study in Zhejang Province comparing epidemiological, clinical and treatment data between older patients >60 and younger patients <60. 788 patients were included. The symptoms of cough, hemoptysis, sore throat, nasal obstruction, muscle ache, fatigue and gastrointestinal were similar between the two age groups. Shortness of breath and heart injury was higher in the older group.

#### <u>Kimball et al (2020) Asymptomatic and Presymptomatic SARS-CoV-2</u> <u>Infections in Residents of a Long-Term Care Skilled Nursing Facility [in]</u> <u>King County, Washington, March 2020<sup>12</sup></u>

Report from MMWR on a COVID-19 outbreak in a long term care facility in Washington. Sixteen days after first case, testing identified a 30.3% prevalence of infection among residents, indicating very rapid spread, despite early adoption of infection prevention and control measures. Approximately half of all residents with positive test results did not have any symptoms at the time of testing, suggesting that transmission from asymptomatic and presymptomatic residents, who were not recognized as having SARS-CoV-2 infection and therefore not isolated, might have contributed to further spread.

The report also includes a table showing typical and atypical symptoms. Typical symptoms: fever, cough, shortness of breath.

Atypical symptoms: chills, malaise, sore throat, increased confusion, rhinorrhea or nasal congestion, myalgia, dizziness, headache, nausea and diarrhea.

#### Landi et al (2020) The New Challenge of Geriatrics: Saving Frail Older People from the SARS-CoV-2 Pandemic Infection<sup>13</sup>

The aim of this review is primarily to analyze the epidemiology of COVID-19 in the older population, the clinical manifestation and diagnosis, the potential therapeutic strategies and the role of the geriatrician in managing this infection emergency.



The range of clinical presentations of COVID-19 disease have been described varying from asymptomatic infection to severe respiratory failure. The common clinical manifestations include fever, cough, fatigue, myalgia, shortness of breath, sore throat and headache. In addition, patients may also have gastrointestinal symptoms with diarrhea and vomiting. Some patients may have taste and smell disturbances. While interstitial pneumonia is present in most COVID-19 disease patients, pleuritic chest pain is present in only a few cases.

Based on the severity of symptoms, laboratory parameters and radiologic characteristics, patients are classified as mild, severe and critical types. Mild patients had non pneumonia or mild pneumonia with moderate signs and symptoms. Severe patients had numerous clinical symptoms including fever and cough, blood oxygen saturation less than 94%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio less than 300, respiratory frequency of 30 or more acts per minute and/or lung infiltrates more than 50%. Finally, critical patients had severe conditions, such respiratory failure, septic shock, and/or multiple organ dysfunction or failure.

#### Steardo et al (2020) Neuroinfection may contribute to pathophysiology and clinical manifestations of COVID-19<sup>14</sup>

Elderly patients recovering from pneumonia often exhibit delirium or deficits in attention and memory that persist over time and require treatment, which is frequently remarkably demanding. Delirium is commonly provoked by peripheral infection associated with systemic inflammation. Elevated concentrations of serum pro-interleukins and S100B have been observed during delirium in elderly patients. Neuroinflammation appears as an almost obligatory component in neurodegenerative disorders and has been implicated in psychiatric pathologies from acute psychosis to schizophrenia, autism spectrum disorder and affective disorders. There is a strong association between systemic inflammation and depressive syndromes with infections rising the risk of depressive episodes by ~60%.

#### <u>Fu et al (2020) Clinical characteristics of coronavirus disease 2019</u> (COVID-19) in China: a systematic review and meta-analysis<sup>15</sup>

The review included 43 studies with a total of 3,600 patients. The metaanalysis showed prevalence of 16 clinical symptoms among COVID-19 patients. Most common were fever [83%], cough [60%], fatigue [38%], then increased sputum production [3%], shortness of breath [3%] and myalgia [3%]. Other symptoms include chest pain, chills, headache, sore throat,



dizziness, diarrohea, rinnohea, nausea, nasal congestion, hemoptysis, and no obvious symptoms.

# Mills et al (2020) COVID-19 in older adults: clinical, psychosocial and public health considerations<sup>16</sup>

COVID-19 is a respiratory illness that commonly causes fever, cough, fatigue, shortness of breath, myalgias, sore throat, headache and chills. Nasal congestion and diarrhea also occur infrequently. Shortness of breath appears to be a more common complaint among older adults [12% for patients > 60 years vs 3% for patients < 60 years]. While 89% of patients experienced a fever during their hospitalization in one study, only 44% were febrile at the time of admission. Common laboratory abnormalities include lymphopenia and thrombocytopenia. Higher rates of lymphopenia and anemia, lower albumin and higher aspartate transaminase (AST) and C-reactive protein (CRP) are found in older adults compared to younger patients.

# Norman et al (2020) Typically Atypical: COVID-19 Presenting as a Fall in an Older Adult (Letter)<sup>17</sup>

The authors describe a case from Mount Sinai Hospital Toronto about an 82 year old whose initial symptom was vague dizziness.

The authors state that atypical presentation of illness is common in older adults. Symptoms, when present, may be non-specific, with presentations including falls, delirium or functional decline. Symptoms of chronic conditions may mask acute illness and sensory or cognitive impairment may limit an older adult's ability to perceive or report symptoms. Signs such as fever may be diminished or absent. There is already evidence that screening based on typical symptoms alone, which failed in this case, is insufficient to identify COVID-19 in older adults.

#### Tapé et al (2020) [Case Report] COVID-19 in a Patient Presenting with Syncope and a Normal Chest X-ray<sup>18</sup>

We describe a 79-year-old patient presenting with syncope along with a normal chest radiograph. Additionally, our patient had no recent travel, which suggests that she became infected via community transmission. At the time of presentation, she was neither hypoxic nor febrile. Although this may be an atypical presentation, this patient ultimately tested positive for SARS-CoV-2. Maximum isolation precautions were not put in place until approximately 12 hours after the patient's arrival in the Emergency



Department. A normal chest radiograph and atypical signs of infection such as syncope should not rule out COVID-19. It is important to keep COVID-19 in mind so as not to delay timely initiation of isolation precautions.

# Tay et al (2020) [Case Report] Atypical presentation of COVID-19 in a frail older person<sup>19</sup>

The authors report on a 94-year-old with controlled schizoaffective disorder and who presented with non-specific symptoms of delirium, low-grade pyrexia and abdominal pain.

**Key Points** 

Clinicians must be aware of the possibility of COVID-19 presenting nonspecifically, including with low-grade fever or delirium. This has implications for the screening and streaming of frail older people to COVID-specific facilities.There is potential for high risk of spread among healthcare professionals and other patients.

### Li et al (2020) [Case Report] Atypical presentation of SARS-CoV-2 infection: a case report<sup>20</sup>

A 74-year-old female patient complained of severe diarrhea. She did not have fever, coughing, or breathing difficulties. A physical examination revealed no obvious positive signs. The patient had been hypertensive for more than 10 years. Her blood pressure was well controlled. On January 9, 2020, the patient's son visited a colleague who was later confirmed positive for SARS-CoV-2 and his first close contact with our patient was on January 17. The patient was first diagnosed with gastrointestinal dysfunction. SARS-CoV-2-infected patients rarely show intestinal symptoms such as diarrhea while lacking respiratory signs or symptoms, whereas about 20%-25% of patients infected with MERS-CoV or SARS-CoV have diarrhea. According to current reports, COVID-19 has different clinical manifestations, such as fever, cough, fatigue and breathing difficulties. A small proportion of patients have sore muscles, headache and a sore throat. In rare cases, patients have no typical symptoms and can only be confirmed by nucleic acid testing and/or a CT scan. Therefore, clinicians should be aware of the atypical characteristics of SARS-CoV-2 infection, especially in patients with epidemic contact history.



### Singhania et al (2020) [Case Report] An Atypical Presentation of Novel Coronavirus Disease 2019 (COVID-19)<sup>21</sup>

The authors report on a 71-year-old admitted after initial presentation to ED with syncope but no fever, cough or chest pain. Three days later the patient was admitted again with altered mental status, but again no fever, chills, chest pain or shortness of breath. Negative procalcitonin, presence of lymphopenia and chest imaging raised suspicion of COVID-19 because the patient did not have any classic symptoms of fever and cough. The authors conclude that altered mental status in an elderly patient can be an atypical presentation of COVID-19.

# Pazgan-Simon et al (2020) [Case Report] Gastrointestinal symptoms as the first, atypical indication of SARS-CoV-2 infection<sup>22</sup>

A 66-year-old female presented with abdominal and back pain, loss of appetite, taste and nausea, no diarrhoea, fever or cough. CT results showed the presence of interstitial consolidations in the lower lobes in both lungs. The patient was transferred to the Infectious Disease Ward and had positive diagnosis of SARS-Cov-2.

#### Jansen et al (2020) [Case Report] A novel presentation of COVID-19 via community acquired infection<sup>23</sup>

A 76-year-old man presented with altered mental status and lethargy. The patient's wife said he had not been himself for about 3 days and had experienced some confusion. He did not have a fever or cough and had no known history of pulmonary disease. He was admitted for tests. CXR obtained showed nonspecific bibasilar airspace disease. Of note, the patient's D-dimer was elevated to 2574 and CT imaging was ordered to evaluate for pulmonary embolism. CTA of the chest with PE protocol revealed bibasilar opacities. He was positively diagnosed with COVID-19.

#### OTHER

#### British Geriatrics Society (14 April 2020) [Blog] Atypical COVID-19 presentations in older people – the need for continued vigilance<sup>24</sup>

Geriatric medicine has always recognised that older people may not present with typical symptoms and it is apparent that this is the case with COVID-19. Furthermore, older people have also been recognised has having a greater



risk of infection and death from COVID-19. While there is little research data, frontline experience both in the UK and in other countries suggests that many older people may present atypically and therefore slip through the triaging net. These patients are likely to be admitted to a general medical or a Care of Older People's ward; it is therefore important that staff on these wards are aware of the atypical patients and remain vigilant to the risk of infection.

COVID-19 results in a massive cytokine storm which results in a variety of symptoms including fever, fatigue, loss of appetite, myalgia and arthralgia, nausea, vomiting, diarrhoea, rash, tachypnoea, tachycardia seizures, headache, delirium, tremor and loss of coordination. On the basis of the pathophysiology of COVID-19 infection it is clear that its manifestations may be legion.

# [Clinical Trial] ReportAge-COVID Project: Clinical and Biological Predictors of COVID-19 Disease in Older Patients

First received on April 10, 2020. Last updated on April 14, 2020. NCT04348396

## Purpose

The project is an observational, prospective study. Its aim is to deepen our understanding of COVID-19 in older patients hospitalized and diagnosed with COVID-19. In particular, socioeconomic, diagnostic, biological, functional, therapy data will be collected at the patients' admission, during hospital stay, at the discharge and 1, 3, 6, 12 months after discharge. Results and findings will help support changes in clinical practice and decision making, with the aim to reduce the use of healthcare services and the healthcare expenditure.

### [Clinical Trial] Clinical-Epidemiological Characterization of COVID-19 Disease in Hospitalized Older Adults

First received on April 22, 2020. Last updated on April 23, 2020. NCT04362943

Purpose

A retrospective clinical-epidemiological study aimed at characterizing COVID-19 disease in adults older than 70 years, hospitalized in the "Perpetuo Socorro" Hospital of Albacete, Spain, from 09/03/2020 until 20/04/2020. Secondary objectives will be to analyze clinical-epidemiological characteristics of COVID-19 patients treated with Baricitinib or Anakinra, and to describe the efficacy and secondary effects of those drugs. MICRONIC REALERS

Produced by the members of the National Health Library and Knowledge Service Evidence Team<sup>†</sup>. Current as at 06 May 2020. This evidence summary collates the best available evidence at the time of writing and **does not replace clinical judgement or guidance**. Emerging literature or subsequent developments in respect of COVID-19 may require amendment to the information or sources listed in the document. Although all reasonable care has been taken in the compilation of content, the National Health Library and Knowledge Service Evidence Team makes no representations or warranties expressed or implied as to the accuracy or suitability of the information or sources listed in the document. This evidence summary is the property of the National Health Library and Knowledge Service and subsequent re-use or distribution in whole or in part should include acknowledgement of the service.

The following PICO(T) was used as a basis for the evidence summary:

Population person perso	OLDER PATIENTS [>65] WITH COVID-19
Intervention length location	ATYPICAL CLINICAL PRESENTATIONS
Comparison another intervention	
Outcome	

The following search strategy was used:

#1 2019-ncov or 2019ncov or covid-19 or sars-cov-2 or ((wuhan and coronavirus) and 2019/12[pdat]:2030[pdat] #2 aged (mh) #3 (aged or older or elderly or senior) #4 (#2 or #3) #5 (#1 AND #4)

\* Margaret Morgan, Librarian, Regional Hospital Mullingar [Author]; Dympna Lynch, Librarian. Cavan General Hospital [Author]; Brendan Leen, Regional Librarian, HSE South, St. Luke's General Hospital, Kilkenny [Editor]



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https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novelcoronavirus-(ncov)-infection-is-suspected [Accessed 5 May 2020]

<sup>4</sup> Centers for Disease Control and Prevention (2020) Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19) Revised April 3 2020 <u>https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html</u> [Accessed 5 May 2020]

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<sup>6</sup> UpToDate (2020) Coronavirus disease 2019 (COVID-19): Epidemiology, virology, clinical features, diagnosis, and prevention <u>https://www.uptodate.com</u> [Accessed 5 May 2020]

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