Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

10th March 2021

COVID-19 KCE CONTRIBUTION AMBULATORY CARE

INTENSIFIED HOME-MANAGEMENT FOR WORRISOME COVID-19 ADULT PATIENTS

PASCALE JONCKHEER, JEAN-LUC BELCHE, DIEGO CASTANARES-ZAPATERO, GILLES HENRARD, VICKY JESPERS, CHRIS DE LAET, PATRIEK MISTIAEN, MAXIME MOUILLET, THOMAS ORBAN, CÉLINE RICOUR, DOMINIQUE ROBERFROID

This document is a rapid review of scientific literature retrieved from several publicly funded COVID-19 resource collections. The literature included in these repositories is not always peer-reviewed or externally validated. KCE synthesised the evidence in short time frames to respond to urgent questions and could therefore not follow its regular methodological procedures. Moreover between search date and publication date there is a very good chance that newer publications came available but they cannot be taken into account.This work is used to inform guidance of other governmental agencies (like Sciensano, CSS/HGR, AFMPS/FAGG and SPF/FOD).

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AA	Ambiant Air
ABG	Arterial Blood Gaz
ACHG	Academisch Centrum HuisartsGeneeskunde
AINS	Anti-Inflammatoire Non Stéroïdien
APB	Algemene Pharmaceutische Bond / Association Pharmaceutique Belge
ARMS	Accuracy Root Mean Square
BCFI	Belgisch Centrum voor Farmacotherapeutische Informatie
BVIKM	Belgische Vereniging voor Infectiologie en Klinische Microbiologie
BMI	Body Mass Index
BSTH	Belgian Society on Thrombosis and Haemostasis
BTS	British Thoracic Society
CBIP	Centre Belge d'Information Pharmacothérapeutique
CDC	Centers for Disease Control and prevention
CEBM	Centre for Evidence-Based Medecine
CHOC	Corona High Oxygen Care
CI	Confidence Interval
CMG	Collège de Médecine Générale
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	COronaVIrus Disease 2019
CPAP	Continuous Positive Airway Pressure
CSS	Conseil Supérieur de la Santé
DOAC	Direct Oral AntiCoagulant
ECDC	European Center for Disease, prevention and Control
ECG	Electrocardiogram
EHR	Electronic Health Record
EMR	Electronic Medical Record
FDA	Food and Drug Administration
GI	Gastro-instestinal
GP	General Practitioner
HAS	Haute Autorité de Santé
Hb	Hemoglobin
HbCO	Carboxyhemoglobin
HBP	High Blood Pressure
HCQ	Hydroxychloroquine
HCSP	Haut Conseil de la Santé Publique
HFNO	High Flow Nasal Oxygen
HGR	Hoge Gezondheidsraad

HTSC	Hospital and Transport Surge Capacity
ICMS	Incident & Crisis Management System
ICU	Intensive Care Unit
IDSA	Infectious Disease Society of America
INAMI	Institut National d'Assurance Maladie-Invalidité
INR	International Normalised Ratio
LFNC	Low Flow Nasal Canula
LMWH	Low Molecular Weight Heparin
Min.	Minute
NEMJ	New England Journal of Medecine
NEWS	National Early Warning Score
NHG	Nederlands Huisartsen Genootschap
NHS	National Health Survey
NICE	National Institute for health and Care Excellence
NIH	National Institute for Health
NPV	Negative Predictive Value
NSAID	NonSteroid Anti-Inflammatory Drug
OD	Once Daily
OR	Odds Ratio
OSA	Obstructive Sleep Apnoea
OST-Liège	Outbreak Support Team in Liège
PPI	Proton Pump Inhibitor
PPV	Positive Predictive Value
PSI	Pneumonia Severity Score
RCT	Randomised Controlled Trial
RIZIV	RijksInstituut voor Ziekte- en Invaliditeits Verzekering
RMSD	Root Mean Square Deviation
RMSE	Root Mean Square Error
RN	Research Nurse
SARS-CoV	Severe Acute Respiratory Syndrome-CoronaVirus
SBIMC	Société Belge d'infectiologie et de Microbiologie Clinique
SC	Subcutaneous
SD	Standard Deviation
SFMV	Société Française de Médecine Vasculaire
SpO2	Oxygen Saturation of Hemoglobin measured by pulse Oximetry
SR	Systematic Review
SWAB	Stichting Werkgroep Antibiotica Beleid
UFH	Unfractionated Heparin
UK	United Kingdom

VACU	Virtual Acute Care Unit
VKA	Vitamin K Antagonist
VTE	Venous ThromboEmbolism
WHO	World Health Organisation

1 INTRODUCTION

1.1 Context

In many countries facing the COronaVIrus Disease 2019 (COVID-19) outbreak, the healthcare system was progressively stretched to capacity, emergency departments were overwhelmed and a lack of hospitalbeds threatened to occur.[1, 2]

Belgium was no exception and the hospital admissions due to COVID-19 peaked a first time in early April 2020, followed by a second even higher peak in early November 2020. During this second wave of the COVID-19 epidemic, the overstretched capacity of the Intensive Care Units (ICU) was a matter of concern. Patients from some overburdened hospitals had to be transferred to other hospitals within Belgium and even abroad.

In order to relieve hospital overloading and save intensive care beds for the most severe cases, the option to treat highly selected patients at home with intensified monitoring and therapy emerged. A decision-aid tool for the home-based management of COVID-19 adult patients was elaborated by the Outbreak Support Team in Liège (OST-Liège) (see Figure 1, version as of 01/11/2020). It aims at helping the General Practitioners (GPs) with a number of crucial considerations to decide which patient with a (confirmed or highly suspected) COVID-19, is eligible for intensified home-based care (monitoring and treatment) in the context of hospital saturation.

Such an approach is in line with the WHO interim guidance on home care[3] which recommends that:

- COVID-19 care pathways be established at local, regional and national levels**.** COVID-19 care pathways are for persons with suspected or confirmed COVID-19.
- Hospitals and health systems at local, regional, national and global level plan and be ready to surge clinical care capacity (staff, structure, supplies and systems) in order to be able to provide appropriate care of all COVID-19 patients and maintain essential health services.
- Each institution should establish a plan for what to do in situations of resource scarcity to cover the allocation or access to critical medical interventions (such as oxygen, intensive care beds and/or ventilators). Such a plan should establish a clear overall aim.

The OST-Liège decision-aid tool was inspired by other existing algorithms/tools and was discussed with emergency teams and hospital physicians in four hospitals in Liège. A first diffusion towards the French-speaking GPs was performed in November 2020 in a webinar[a].

At the end of October 2020, the Collège de Médecine Générale (CMG) and the Cellule d'Appui Scientifique Universitaire (CASU) asked KCE to validate the various components of this decision-aid tool.

1.2 Objective

The aim of this document is to present the review of the OST-Liège decision-aid tool supporting general practitioners in the home care based management (monitoring and treatment) of worrisome COVID-19 patients (see Figure 1). This review was performed in a tight time frame (between early November and end-December 2020) because of a possible risk of a third wave of COVID-19.

A new version of the decision-aid tool is presented at the end of this document focusing on **intensified home-based care in a context of hospital saturation for COVID-19 patients with signs of pneumonia** (see definition below) **presenting an oxygen saturation (SpO_2) ≤94% or a respiratory rate ≥25/minute but no red flags**.

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[a] https://www.youtube.com/watch?v=-nX1WHSHb-g&feature=youtu.be&ab_channel=Sant%C3%A9Ardenne (from minute 16)

Figure 1 – Original decision-aid tool from OST-Liège

1.3 Research questions

Within this context of relative urgency, KCE established a list of potential research questions (based on the content of the drafted decision-aid tool of the OST-Liège) and discussed them with representatives of the CMG and the CASU. The proposed research questions were also disseminated to several French- and Dutch-speaking representatives of general practitioners and adapted afterwards. The final version includes 12 questions in three categories: clinical appraisal; context aspects and treatment (Table 1). Two questions were excluded for the reasons explained in Table 2.

Table 1 – Included research questions

Clinical appraisal of confirmed or highly suspected COVID 19 patients managed at home
1. What are the **criteria** defining need for **home-based intensified care**?
2. What are the **clinical signs** indicating that an urgent hospitalization is required (‘**red-flags**’)?
3. What are the **personal risk factors for negative outcomes of COVID-19?**
Contextual aspects for the home care management of worrisome COVID 19 patients
4. What are the **environmental and organizational factors enhancing home-based management** of those patients?
5. How can the provision of **oxygen** be ensured?
6. Do all pulse oximeters (saturometers) currently available on the market provide accurate measurement of SpO_2?
7. What is the added value of **telemonitoring** health parameters of COVID-19 patients staying at home?
Treatment components for worrisome COVID 19 patients managed at home
8. What are the recommendations for the **prophylaxis of thromboembolic events**?
9. Are **corticosteroids** indicated, even in patients who do not need oxygen at home?
10. Should **proton pump inhibitors (PPIs)** be prescribed to COVID-19 patients receiving corticosteroids, and under which conditions?
11. Which protocols have to be used for providing **oxygen at home** for COVID-19 patients?
12. Are there **other medications** to be recommended? • Hydroxychloroquine (HCQ): Does the recent non peer-reviewed systematic review by Ladapo et al. 2020 (Randomized Controlled Trials of Early Ambulatory Hydroxychloroquine in the Prevention of COVID-19, Hospitalization, and Death: Meta-Analysis; http://doi.org/10.1101/2020.09.30.20204693) provide new elements in favor of using hydroxychloroquine in patients with COVID-19 treated at home? • Antibiotics (AB): Are antibiotics useful in COVID-19 patients?

Table 2 – Excluded research questions

1. Which measures are useful in the home setting to **limit the spread of the virus** towards family members and care providers and is the necessary material available for this? This research question was excluded because it is largely covered by Sciensano[b].
2. Which **additional therapeutic measures** (such as vitamin D, zinc, N-acetylcysteine, acetylsalicylic acid, Montelukast…) can be taken to reduce the risk of hospitalization? This additional research question was proposed by a general practitioner but we decided to exclude it because it cannot be answered in a few weeks and should make the object of a separate research on preventive actions (several trials are currently carried out on this topic).

[b] Sciensano: communication. in French (https://covid-19.sciensano.be/fr/covid-19-outils-de-communication) or in Dutch (https://covid-19.sciensano.be/nl/covid-19-communicatiemateriaal)

1.4 General consideration on methods

The context of this research was particular at different levels:

- Validating the various components of a decision-aid tool implying several **research questions**
- Addressing these research questions in a **very limited time** (5-6 weeks) given the urgency of the situation
- **Anticipating a crisis situation,** i.e. intensified home-based treatment of worrisome COVID-19 patients in case of saturated hospital capacity: the scientific literature on this specific putative topic is likely to be rare.
- Working in a context of **uncertainties about the validity, reliability and durability** of current scientific publications on some COVID-19 topics since they are carried out in very short time and new evidence is accumulating every day.[4]

Given these elements, we decided to set up rapid pragmatic reviews (i.e. no systematic reviews) and use innovative methods of validation, e.g. pragmatic collection of existing guidelines, decision trees/algorithm and systematic reviews for a comparative approach.

AFMPS/FAGG provided support for questions relating to drug therapy following the same principles. Methods used were adapted for each research question and are described in the corresponding chapters. Based on our findings, we proposed modifications in the OST-Liège decision-aid tool. We assessed the face-validity of our recommendations by organizing a continuous consultation of a panel of general practitioners.

1.5 Definition

We refer through this document to several concepts which needed to be clearly defined:

- '**Home-based** care/treatment/management': any care delivered in the domiciliary setting of the patient, i.e. the place where he/she lives (whatever it is at home or in a nursing home).
- '**COVID-19 patient':** any patient with a suspected or confirmed SARS-CoV2 related disease.
- '**Moderate COVID-19':** the second severity level of the SARS-CoV2 related disease as defined by the WHO, i.e adolescent or adult with clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) but no signs of severe pneumonia (see details of all categories in Chapter 2).
- '**Worrisome COVID-19'**: a subcategory of the moderate COVID-19 level of the disease which includes the **patients with signs of pneumonia** (see definition above) **presenting an oxygen saturation (SpO_2) ≤94% or a respiratory rate ≥25/minute** (for details, see Chapter 2) but **no red flags** (see Chapter 3). This subcategory of patients is the target population considered in this document.
- '**Intensified home-based care':** a higher level of care for an acute infection than usually (i.e. before the pandemic) delivered by medical and paramedical staff in the domiciliary setting, for example, close clinical monitoring/telemonitoring and/or acute oxygen therapy. This type of care is the target intervention considered in this document.
- '**Hospital saturation':** the situation where a lack of hospital beds occurs because of a peak in the incidence of COVID-19 cases (pandemic wave). This exceptional situation is the only context in which the content of this document can be used.

2 CRITERIA DEFINING NEED FOR INTENSIFIED CARE FOR PATIENTS WITH COVID-19 AT HOME

2.1 Summary

- **There are currently several categorizations of COVID-19 severity in adult patients and the terms "severe" or "moderate" illness can have different significations according to the source. However, we decided to favor the severity scale of the WHO which offers an international standard.**
- **In this report, we define a new subcategory of patients: the worrisome COVID-19 patient. This subcategory concerns patients with a moderate COVID-19 level according to the WHO severity scale but requiring intensified home-based care because they present with or near to hypoxemia (critical lowered blood oxygen saturation levels).**
- **The criteria determining the need of intensified home-based management consist of a $SpO_2 \leq 94\%$ or a respiratory rate (RR) ≥ 25 /min in any patient with no red flags (see Chapter 3) and with at least one sign of pneumonia: fever, cough, dyspnoea or fast breathing (RR≥ 21/min).**
- **Few changes are needed in the OST-Liège decision-aid tool.**

2.2 Background

Not considering the situation of hospital saturation due to the SARS-CoV2 pandemic wave, the usual care for patients needing oxygen therapy and close monitoring because of acute respiratory distress is provided at the hospital level (except in the respect of advanced care planning e.g. terminally ill patients).

However, the SARS-CoV2 pandemic changed some principles. As explained in the WHO report on home care for patients with suspected or confirmed COVID-19, *"home care may be considered for an adult or child with confirmed or suspected COVID-19 when inpatient care is unavailable or unsafe (e.g. when capacity is insufficient to meet the demand for health-care services)".[3]*

Thus in the case of hospital saturation, a new type of care has to be considered, **the home-based intensified care** (see definition in section 1.5). This new type of care must be exclusively reserved to the situation of hospital saturation, and for highly selected patients only in precise domiciliary situations.

Indeed, the WHO mentions that decision for isolating and caring COVID-19 patients at home should be based on 3 types of factors: the clinical evaluation, the assessment of the home setting and the ability by healthcare workers and caregivers to monitor the patient at home (see Appendix 18.1). The current chapter focuses on the clinical criteria (symptoms and signs) which allow to select the patients eligible for intensified care at home while the criteria related to the environment are addressed in the chapter 5.

2.3 Research question

The research question "*What are the criteria defining need for home-based intensified care for a patient with COVID-19?*" to which this chapter aims to answer, is based on the upper box of the preliminary version of the OST-Liège decision-aid tool (see Figure 1). The criteria identified in the preliminary version define a quite severe form of COVID-19 for which the implementation of home-based intensified care is required. Those criteria were the followings: "breathing difficulties" AND "<94% of blood O_2 saturation in room air OR respiratory rate (RR) > 24/minute".

2.4 Methods

A narrative review was performed to describe the physiological and pathophysiological aspects of blood oxygenation and respiratory variables.

A pragmatic review of the scientific literature in Medline was made followed by a search in Google for retrieval of the grey literature. The key words were (i) COVID AND oxygen saturation AND

("primary care" OR "ambulatory care"); and (ii) COVID AND respiratory rate AND ("primary care" OR "ambulatory care").

For the definition, range and cut-off, we did a search for identifying consensus-based guidelines on 'home-based care of COVID-19 patients' in international or foreign national health agencies, followed by a snowballing approach to retrieve further documents. As such, data sources identified by other KCE experts were also collected and analyzed.

2.5 Results

We found five sources of information, useful to establish home-based care criteria, in international, national or regional institutions: World Health Organization (WHO)[5], National Health Service (NHS)[6], National Institute of Health (NIH)[7], Haute Autorité de Santé (HAS)[8] and Domus Medica - Academisch Centrum Huisarts Geneeskunde (ACHG).[9, 10] Two in-scope publications from the scientific literature were identified during the grey literature search: a publication from Blazey-Martin et al.[11] and a publication from Greenhalgh et al.[12] both concerning the primary care setting.

Therefore, a total of 7 sources were analyzed. The results, an overview of the relevant criteria to identify the COVID-19 level of severity for which an intensified home-based care is required, are presented in Table 3. None of the identified sources described guidance specific for the situation of hospital saturation.

2.5.1 Severity levels of illness and parameters used

Several institutions propose a categorization for describing the severity of COVID-19.

Word Health Organization (WHO)

Since May 2020, the WHO proposes 4 categories of COVID-19 severity in the interim clinical guidance: mild, moderate, severe and critical disease[5]:

- *Mild disease is defined by symptomatic patients meeting the case definition for COVID-19 without evidence of viral pneumonia or hypoxia.*
- *Moderate disease is defined by clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) but no signs of severe pneumonia.*
- *Severe disease is defined by clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) plus one of the following: respiratory rate >30 breaths/minute; severe respiratory distress; or SpO_2 <90% on room air.*
- *Critical disease concerns life-threatening stage of COVID-19, which are cared in ICU.*

This categorization provides a first interesting way to identify the group of patients which should benefit from home-based intensified care i.e. patients with moderate disease. Indeed, the lower level, i.e. the mild disease level, concerns the usual target patient population in ambulatory care outside a situation of hospital saturation, while higher levels of severity, i.e. patients in the severe and critical disease level, include patients too unstable to be cared at home (except in case of advanced care planning). **Clinical signs of pneumonia, respiratory rate and SpO_2** are the parameters used to define the different categories.

Domus Medica - ACHG in Belgium

The ACHG made a synthesis of evidence on the follow-up and care for COVID-19 patients at home. This note was published on the Domus Medica website.[9] They also performed several BestBET studies in March 2020.[10] One study by Oversteyns et al.[13] analyzed 15 publications at the beginning of the pandemic (March 2020). It focused on teleconsultation by the general practitioner and searched to identify the clinical situations which must lead to an at home clinical visit instead of a remote evaluation. This BestBET work[13] concludes that, in the Belgian context, patients can be subdivided, on the basis of a telephone anamnesis, in 4 categories for further remote or on-site follow-up in primary care:

- *Mild cases with mild symptoms and no suspicion of pneumonia. These patients should not be seen clinically. Information with attention to alarm signals and advice on isolation in the home environment is sufficient.*

- *Mild symptoms in people at increased risk of complications. These patients should be clinically examined.*
- *Moderate cases with complaints such as fever, coughing and shortness of breath, with suspicion of pneumonia. These patients need further clinical examination.*
- *Severe cases with severe shortness of breath and tachypnea (>30/min), thoracic pain and possible hemoptysis. These patients need to be urgently referred to the emergencies for further investigation*.

The categories slightly differ from those of the WHO by defining an extra subcategory including people at increased risk of complications. The severe category includes thoracic pain and hemoptysis as extra warning clinical signs. Applying this classification system, patients who require a home-care intensified management fit either to the moderate category or to the mild category if they have increased risk of complications (see chapter 4).

Also Wouters et al.[14] and Michielsen et al.[15] performed a BestBET work. Their systematical review of publications available at the beginning of the pandemic (March 2020) concluded that the **respiratory rate, SpO_2, decrease in SpO_2 and oxygen need** are important parameters to evaluate the severity of the patient's condition.

National Health Service in England (NHS)

A UK document named "Pulse oximetry to detect early deterioration of patients with COVID-19 in primary and community care settings" revised in January 2021, proposes 3 categories of COVID-19 (see details in Appendix 18.2).[6]

- *The Mild Disease category is defined by a 0_2 oximetry saturation ≥ 95% OR any of respiratory rate inferior to 20 or a heart rate inferior to 90 or a new confusion within the NEWS2 score of 0-2 OR if an 0_2 oximetry saturation decrease of less than 3 % as usual in patient with hypoxemic chronic comorbidity.*
- *The Moderate Disease category is defined by a 0_2 oximetry saturation of 93-94% OR any of a respiratory rate of 21-24/min or a heart rate of 91-130/min or a new confusion within a NEWS2 score of 3-4 OR if an 0_2 oximetry saturation decrease of less than 5 % as usual in case of hypoxemic chronic comorbidity.*
- *The Severe Disease category is defined by a 0_2 oximetry saturation equal or of less than 92% OR any of a respiratory rate superior to 25/min or a heart rate superior to 131/min or a new confusion within a NEWS2 score superior to 5 OR if an 0_2 oximetry saturation decrease of more than 4% as usual in case of hypoxemic chronic comorbidity.*

The parameters used in the NHS categorization are **respiratory rate, SpO_2, decrease in SpO_2 but also heart rate and confusion.**

National Institute of Health in US (NIH)

In the document "Clinical Presentation of People with SARS-CoV-2 Infection" last updated 7 October 2020, the NIH proposes 5 categories of COVID-19 severity[7]:

- *Asymptomatic or Presymptomatic Infection: Individuals who test positive for SARS-CoV-2 using a virologic test (i.e., a nucleic acid amplification test or an antigen test), but who have no symptoms that are consistent with COVID-19.*
- *Mild Illness: Individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnea, or abnormal chest imaging.*
- *Moderate Illness: Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have saturation of oxygen (SpO2) ≥94% on room air at sea level.*
- *Severe Illness: Individuals who have SpO2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mmHg, respiratory frequency >30 breaths per minute, or lung infiltrates >50%. The NIH specify that: "For severe*

illness, oxygen therapy should be administered immediately using a nasal cannula or a high-flow oxygen device".

- *Critical Illness: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.*

The NIH adds: *"The definitions for the severity of illness categories listed above also apply to pregnant patients but the threshold for certain interventions may be different for pregnant patients and non-pregnant patients. For example, oxygen supplementation is recommended for pregnant patients when SpO_2 falls below 95% on room air at sea level, to accommodate physiologic changes in oxygen demand during pregnancy and to assure adequate oxygen delivery to the fetus."*

Moreover, the NIH highlights that if "*In general, adults with SARS-CoV-2 infection can be grouped into the severity of illness categories, the criteria for each category may overlap or vary across clinical guidelines and clinical trials, and a patient's clinical status may change over time*".

The parameters used by the NIH for distinguishing the different categories are **clinical signs** of COVID-19 infection, **SpO_2, respiratory rate but also the ratio PaO2/FiO2 or presence of lung infiltrate** which are two parameters unavailable for home-care**.**

2.5.2 Physiological and pathophysiological aspects of blood oxygenation

Because the hypoxemia is a crucial severity sign in COVID-19 patients, a brief reminder of physiological and pathological aspect of blood oxygenation is presented in this chapter.

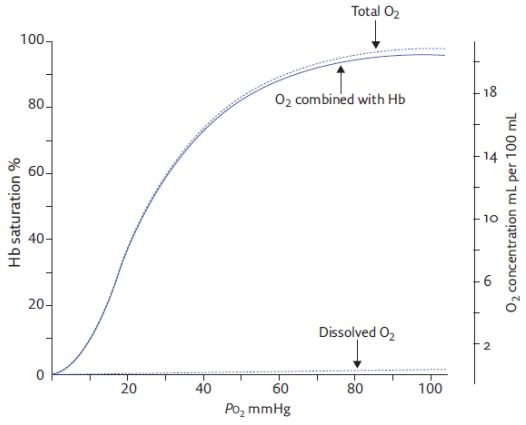
Oxygen pressure and saturation

The pressure of oxygen in the blood (PaO_2) corresponds to the amount of oxygen dissolved in blood plasma. Oxygen saturation (SaO_2) reflects the oxygen in blood bound to the hemoglobin and corresponds to the percentage of hemoglobin loaded with oxygen.

The healthy level of arterial blood hemoglobin oxygen saturation ranges between 95 and 100%. It diminishes slightly with age and lower saturation can still be normal in elderly patients. Moreover, patients with chronic respiratory disease can chronically present moderately decreased oxygen saturation levels (ranging between 88-94%).

The relationship between oxygen pressure and saturation describes a sigmoidal curve relationship as shown in Figure 2. The curve has two portions. When oxygen pressure is high, the curve has a flat shape whereas it becomes steeper when oxygen pressure falls. The flat portion indicates that hemoglobin can load a large amount of oxygen even though oxygen in the blood decreases. The steep portion corresponds to a disproportionate fall in oxygen saturation, facilitating an unbinding of oxygen from hemoglobin in order to be delivered to tissues. Blood oxygen saturation (SaO_2) can be measured at home by pulse oximetry (SpO_2) (see chapter 7 on pulse oximetry).

Figure 2 – Oxygen dissociation curve in a healthy subject with a normal hemoglobin concentration (15 g/dL).[16]

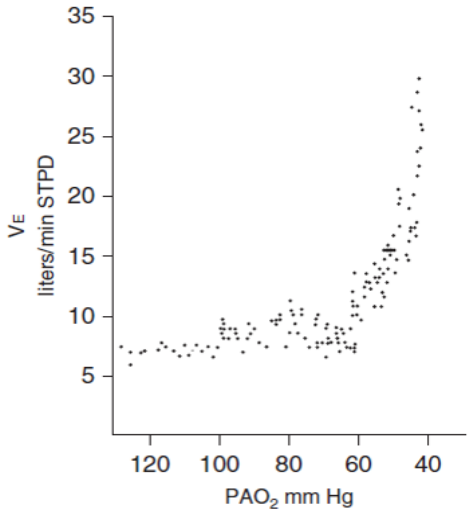


Hypoxemia is defined as a decrease of oxygen pressure below 80 mmHg or arterial blood hemoglobin saturation of less than 95%.[17] Hypoxemia is the most often secondary to a pulmonary disease.

Hypoxemia and respiratory rate

Respiratory rate is generally included in the severity scores to assess pneumonia. Since minute-ventilation is increased in response to hypoxemia, the respiratory rate is also a good warning sign of hypoxemia (see Figure 3).

Figure 3 – Ventilator response to progressive isocapnic hypoxia in healthy subject (PAO_2: alveolar oxygen pressure; VE: minute-ventilation; STPD: Standard Temperature and Pressure Dry)[23]



2.5.3 Tools for detecting hypoxemia

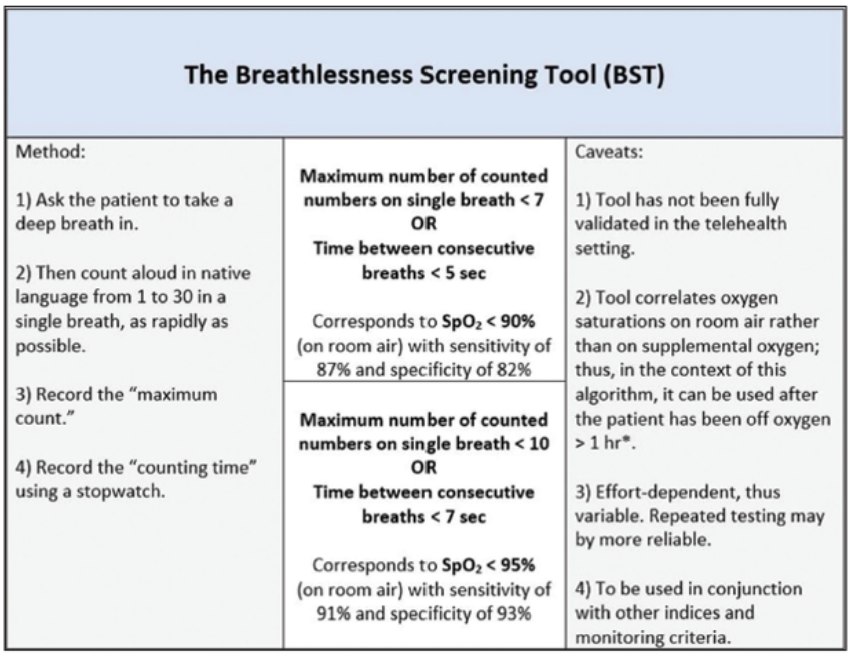
Two means were identified in the collected data to measure or estimate hemoglobin oxygen saturation: the pulse oximetry and the breathlessness screening tool.

Before the COVID-19 outbreak, pulse oximetry in outpatient settings was mainly used in various chronic respiratory condition such as chronic obstructive pulmonary disease (COPD) patients requiring oxygen at home or for detecting hypoxemia in patients with pneumonia.[18]

Oximetry is now widely used in COVID-19 patients and appears to an easy option to evaluate the level of hypoxemia at the primary care level although some concerns are evoked (see chapter 7 on pulse oximetry).

In a study published by Sardesai et al., it has also been proposed to apply a breathlessness screening tool to detect hypoxemia. This tool consists of observing the fall of oxygen saturation after counting from 1 to 30 in a single breath (see Figure 4).[19] This test has been previously shown to correlate with the severity of dyspnoea and the importance of oxygen desaturation.[20] It has not been validated in primary care and the UK Centre for Evidence Based Medicine has raised concern about it as it may lead to false reassurance when used remotely.[21]

Figure 4 – The Breathelessness Screening Tool.[19]



The Breathlessness Screening Tool (BST)		
Method: 1) Ask the patient to take a deep breath in. 2) Then count aloud in native language from 1 to 30 in a single breath, as rapidly as possible. 3) Record the "maximum count." 4) Record the "counting time" using a stopwatch.	**Maximum number of counted numbers on single breath < 7 OR Time between consecutive breaths < 5 sec** Corresponds to **SpO_2 < 90%** (on room air) with sensitivity of 87% and specificity of 82% **Maximum number of counted numbers on single breath < 10 OR Time between consecutive breaths < 7 sec** Corresponds to **SpO_2 < 95%** (on room air) with sensitivity of 91% and specificity of 93%	Caveats: 1) Tool has not been fully validated in the telehealth setting. 2) Tool correlates oxygen saturations on room air rather than on supplemental oxygen; thus, in the context of this algorithm, it can be used after the patient has been off oxygen > 1 hr*. 3) Effort-dependent, thus variable. Repeated testing may by more reliable. 4) To be used in conjunction with other indices and monitoring criteria.

SpO2 = Peripheral capillary oxygen saturation, * = an arbitrary time interval, which can be modified by decision of home oxygen team

2.5.4 Particular clinical presentation of hypoxemia in COVID-19

When respiratory deterioration occurs, it is frequently one week after the first symptoms of COVID-19.[22] One characteristic of the respiratory impairment observed, is that patients can have hypoxemia without significant dyspnoea.[23, 24] This phenomenon of asymptomatic hypoxemia is thought to be responsible for the phenomenon of rapid clinical deterioration and mortality and is frequently associated with a delayed escalation of care.[25]. Due to this atypical silent clinical presentation (lack of dyspnoea), it can easily be overlooked. However, such respiratory worsening can be identified by pulse oximetry.

2.5.5 Criteria (range and cut-off) defining worrisome COVID-19 patients

Different criteria (i.e. range or cut-off of parameters) are used for referring COVID-19 patients to hospital. These are presented in the Table 3. In most cases the need for oxygen therapy is an important reason justifying hospitalization. However, none of the identified references consider the context of hospital saturation.

According to **WHO**[5]**,** hospitalization is required for the severe category of COVID-19 which is defined by **clinical signs of pneumonia** (fever, cough, dyspnoea, fast breathing) plus one of the following: **respiratory rate >30 breaths/minute, severe respiratory distress, or SpO_2 <90%** in ambient air. Thus, as intensified home care concerns moderate disease, patients presenting with signs above the cut-offs (RR >30 or or SpO_2 <90%) cannot be cared for at home and must be hospitalized.

In Belgium, the **BestBET** performed by Wouters et al.[14] addressed the question about criteria for hospitalizations of patients in the primary care setting and globally concluded in agreement with the National Early Warning Score (NEWS) used in hospitals and home care in the UK. The criteria used in this tool are **high temperature, respiratory rate >24 breaths/minute and oxygen saturation <90%, systolic blood pressure <90 mmHg or >220 mmHg and a decreased level of consciousness**. However, evidence that these criteria can identify a more severe COVID-19 course are limited. Another BestBET by Oversteyns et al.[13] analyzed the clinical situations leading to an home visit instead of a remote (e.g. telephone) evaluation by the GP. The results showed that **tachypnea (RR >24 breaths/minute)** is one of the triggers for a home visit.

In the UK, to decide on care at home for mild and moderate stages (**0_2 oximetry saturation ≥93%** OR any of **respiratory rate inferior to 25 breaths/minute** or a **heart rate inferior to 130/minute** or a new confusion within the **NEWS2 score of 0-4** OR if an **0_2 oximetry saturation decrease of less than 5%** as usual in patient with hypoxemic chronic comorbidity), the **NHS** takes one additional precaution: "*the patient must do effort test: 40 steps walk or 1 minute sit to stand test. After this test, if the **O_2 oximetry saturation drops for more than 2%,** the patient should be admitted into hospital".* The criteria used by the NHS are more cautious than those from the WHO, reflecting the **ambulatory context** in which the criteria were established, and not taking into account the COVID-19 hospital saturation situation. In this line, home-based oxygen therapy is not considered in this UK report.

In the US, the **NIH** proposed oxygen therapy for the severe illness category which is defined as patients having a **SpO_2 <94% in ambulant air at sea level, a respiratory rate >30 breaths/minute, PaO_2/FiO_2 <300 mmHg, or lung infiltrates >50%.**[7]

In France, the **HAS** published in November 2020 rapid responses regarding home care for non (or not anymore)-hospitalized patients with COVID-19 requiring oxygen therapy.[8] In this document, the HAS suggests four criteria related to the patient: (i) **autonomy** (e.g. Katz > 3/6), (ii) **SpO_2 between 90 and 92%,** (iii) no other **sign of severe COVID-19** and (iv) no **exclusion criteria**. Two kinds of exclusion criteria are defined: the major criteria and the minor criteria. The presence of 1 major criterion or 2 minor criteria is sufficient to exclude a patient from home-based oxygen therapy (more details are available in Appendix 18.3. Inclusion and exclusion criteria are checked by the GP and the medical hospital referent. This report also concerns patients dismissed from hospital.

The publication of **Blasey-Martin et al** described the successful use of an algorithm in a large urban academic medical centre of primary care practice in Boston, USA. In this algorithm, **SpO_2<95% and respiratory rate>25 breaths/minute** were the cut-offs chosen as criteria of an increased concern leading to doubling the monitoring frequency (more details are available in Appendix 18.4).[11]

The study of **Greenhagh et al.** aimed to develop an early warning score for patients with suspected COVID-19 who need escalation to a next level of care. The study was based in UK primary health care. The tool is composed of 10 items to which 0, 1, 2 or 3 points are attributed. If the total of the points is less than 4, the risk is evaluated as low. If the score is between 4 and 6, the risk is moderate and if the score is bigger than 6, the risk is high. A high score leads to a referral to the emergency room, a moderate score leads to a home visit, and a low score leads to a remote follow-up. The item **SpO_2** is scored as follows: a SpO_2 of 96% or above = 0 point, a SpO_2 of 95% = 1 point, a SpO_2 of 94% = 2 points and a SpO_2 of 93% or less = 3 points. The item **respiratory rate** is scored as follows: range 12-20/min gives 0 point, range 21 to 24 gives 1 points, range 25-29 gives 2 points and 30 breath/min or more gives 3 points (more details are available in Appendix 18.5).[12]

Table 3 – Overview of criteria identifying COVID-19 patients requiring home-based intensified care

Source	WHO	Domus ACHG	NHS	NIH	HAS	Blazey Martin et al	Greenhalgh et al.
Title of the report / publication	Clinical management of COVID-19: interim guidance 27 may 2020	Which factor can help clinicians when to hospitalize patients infected with COVID-19	Pulse oximetry to detect early deterioration of patients with COVID-19 in primary and community care settings	Clinical Spectrum of SARS-CoV-2 Infection	Réponses rapides dans le cadre de la Covid-19 – Prise en charge à domicile des patients atteints de la Covid-19 et requérant une oxygénothérapie	Primary Care Population Management for COVID-19 Patients	What items should be included in an early warning score for remote assessment of suspected COVID-19? Qualitative and Delphi study

Main topic	Definition of severity level of COVID-19	Criteria triggering hospitalization	Primary care assessment pathway	Definition of severity level of COVID-19	Inclusion and exclusion criteria to oxygen therapy	Remote identification of COVID-19 patients needing additional medical support	Proxy extracted from the score table
Cut-off for	Hospitalization	Hospitalization	Possible hospitalization	O_2 therapy	O_2 therapy	Intense monitoring	Next level of care
O_2 oximetry saturation	<90% at rest and AA	<90%	93-94% at rest and AA	<94% on room air at sea level	90 to 92%	<95%	94-95%
Respiratory rate	≤30/min	>24/min	21-24/min	>30/min		22-25/min	21-29/min 9-11/min

AA: ambient air

2.6 Discussion

2.6.1 Appropriate parameters for defining worrisome patients

The choice made by the OST-Liège team on items defining the target population for their decision-aid tool (SpO_2, RR and a respiratory symptom) was very much alike the items proposed by WHO to determine COVID-19 severity level. Other institutions (NHS, NIH, and HAS) also used similar items to define COVID-19 patients' categories (sometimes with other additional criteria).

The presence of pneumonia symptoms is linked by WHO to the moderate level of the disease. However, not all patients with one or more sign(s) of non-severe pneumonia will require intensified care but only the worrisome patients. In the identified sources, two clinical signs converge to guide the decision of closer monitoring and of the potential rapid need for oxygen therapy: the saturation in oxygen estimated by pulse oxymetry (SpO_2) and the respiratory rate (RR). As explained in the NHS report, patients most at risk of poor outcomes are best identified by oxygen levels. Besides, as the respiratory rate is increased in response to hypoxemia, an increased respiratory rate can be the first sign of the respiratory condition worsening. Physiologically, the combination of SpO_2 and RR allows to detect the silent hypoxemia which is the most at risk situation for a negative outcome in COVID-19 illness.

2.6.2 Criteria (range and cut-off) of the appropriate parameters

According to the literature, it is clear that patients with severe COVID-19 cannot be cared for at home (see red flags in chapter 3) and patients with mild level of illness without any signs of pneumonia do not require intensified care (except a closer monitoring in case of accumulation of risk factors, see discussion of Chapter 4). So, the target population of patients eligible for home-based intensified care is situated between those two levels of the COVID-19 illness, i.e. the presence of at least a sign of (non-severe) pneumonia: fever, cough, dyspnea or fast breathing (defining as breathing faster than usual, i.e. a RR ≥ 21/min).

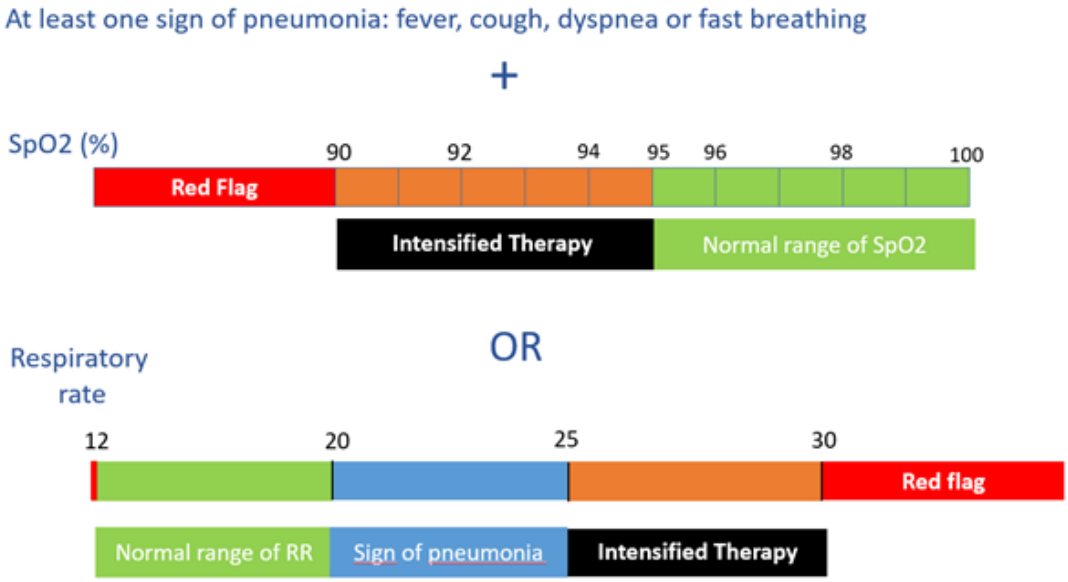
The normal SpO_2 for an adult ranges from 95% to 100%. Most of the identified sources use SpO_2 as parameters but cut-offs differ according to the context. The NIH considers oxygen therapy when the SpO_2 is <94%[7] and the HAS set up a lower threshold (SpO_2 between 90 and 92%) to select patients for oxygen therapy at home in a situation of hospital saturation.[8] The WHO and the BestBET of Wouters et al. suggest a threshold of 90% for hospitalization.[14] The NHS algorithm (see Figure 11) advices to perform a more careful assessment of patients with SpO_2 of 93-94% and to send any patient with a SpO_2 below 93% detected in primary care to the emergency department.[6] Similarly, the algorithm used by the primary care center described by Blazey-Martin et al. advices to perform a more profound assessment of patients with SpO_2 <95%.[11] In the cumulative score of Greenhalgh et al., 0, 1, 2 or 3 points is/are attributed to patients with a SpO_2 ≥ 96%, equal to 95%, equal to 94% or ≤ 93%. In this score, a SpO_2 of 95% or less is considered concerning.[12]

In summary, the information from the sources converges towards the conclusion that **the first cut-off** which allows to identify the patient eligible for home-based intensified care in case of hospital saturation is a **SpO_2<95% (94% or less).**

The data collected in Table 3, outside hospital saturation, shows that the cut-offs chosen by each institution or author for the respiratory rate (RR) threshold vary a lot, within a range between 21 to 29 according to the setting and the intervention addressed. As a reminder, the normal RR ranges from 12/min to 20/min. An increase of the RR is indeed an indirect sign of respiratory distress but is not an issue itself. However, patients with a respiratory rate ≥25/min should be selected for "intensified home care" since those patients can rapidly worsen and display a fall in SpO_2. The British Thoracic Society guidelines suggest to closely monitor the oxygen saturation in this case as it can potentially and rapidly decrease.[26] So, we decide that the **second cut-off** chosen to identify patients needing intensified home-care should be a **RR ≥ 25/min**.

A visual summary is given in Figure 5.

Figure 5 – Clinical criteria defining the need for home-based intensified care



2.7 Conclusion

Based on the above considerations and in accordance with the results collected and summarized in Table 3, we suggest the following cut-offs to identify the patient eligible for home-based intensified care in case of hospital saturation: a SpO_2 ≤94%(i.e. any desaturation) or a respiratory rate ≥25/min. Those clinical criteria should be followed-up particularly in patients who present at least one symptom of pneumonia: fever, cough, dyspnoea or fast breathing (RR ≥21/min).

These two cutt-off criteria and the symptoms for pneumonia define the subcategory of worrisome COVID-19 patients who could benefit from an intensified home-care management. This clincial information determines the target population of the decision-aid tool, therefore it is placed at the beginning of the tool as the entry point.

The level of minimal SpO_2 inducing the need of an oxygen therapy is discussed in the chapter 6.

2.8 Proposed changes in the OST-Liège decision-aid tool

We suggest to replace "breathing difficulties" by "any of the following symptoms of pneumonia: fever, cough, dyspnea or fast breathing (RR ≥21/min)".

We suggest to change the cut-off of the saturation in O_2 from < 94% to ≤94% i.e. any desaturation.

We suggest to keep the cut-off of ≥25/min for the RR.

3 RED FLAGS REQUIRING EMERGENCY HOSPITALIZATION FOR PATIENTS WITH COVID-19

3.1 Summary

- **Most of the publications relative to 'red-flags' in COVID-19 patients focus on respiratory conditions. The other clinical variables quoted in several algorithms have been less documented in the scientific literature.**
- **Identified red flags are:**
  - **Oxygen saturation at rest :**
    - **SpO_2 < 90%**
    - **SpO_2 < 88% if chronic hypoxemic lung disease**
    - **SpO_2 ≤ 92% with an oxygen flow max 4L/min**
  - **Respiratory rate ≥ 30/min at rest or respiratory rate < 12/min**
  - **Hemodynamic impairment: systolic hypotension < 100 mmHg OR tachycardia > 120/min OR bradycardia < 45/min**
  - **Altered consciousness**
  - **Clinical signs of dehydration and/or hypovolemia**
  - **No improvement of health status after 72 hours of intensified home-based management**
- **Several changes are proposed in the OST-Liège decision-aid tool.**

3.2 Background

A strategy involving primary care in case of hospital saturation could relieve hospitals overloading and allow them to save inpatients beds for the most severe patients. In the previous chapter, criteria allowing to identify COVID-19 patients deserving a close monitoring at home were presented.

However, by now, it is well recognized that the condition of patients with Covid-19 can unexpectedly and rapidly worsen and that dyspnea is not a reliable sign as it can be absent in patients with severe hypoxia.[27] So, other clinical signs have to be closely monitored to identify patients requiring an immediate hospitalization. Red flags is the name given to those clinical signs which alert the healthcare provider to the urgent need to hospitalize the patient. Each provider, but also patients and informal caregivers should be able to quickly detect those "red flags".

3.3 Research question

In this chapter, the studied research question is "*What are the clinical signs indicating that an urgent hospitalization is required ('red-flags')?* In the preliminary version of the OST-Liège decision-aid tool, this topic was addressed in the red box (see Figure 1). The red flags listed in that box were: altered consciousness, dehydration, blood pressure<100mmHg, RR>30/min or bradypnea, and SpO2<90% in ambient air.

3.4 Methods

A review of the literature for "red flags" was carried out in MEDLINE (PubMed). The key words were used as follows: COVID AND oxygen saturation AND ("primary care" OR "ambulatory care"), COVID AND oxygen AND ("primary care" OR "ambulatory care"), COVID AND hypotension AND ("primary care" OR "ambulatory care"), COVID AND ("acute kidney injury" OR "renal failure") AND ("primary care" OR "ambulatory care"), COVID AND consciousness AND ("primary care" OR "ambulatory care"). This search was completed by a retrieval of grey literature in Google.

Studies were included if they assessed the red flags conditions in hospitalized or non-hospitalized COVID-19 patients. Given the paucity of studies in primary care for worrisome COVID-19 patients, we considered, with the limits that this entails, that scientific sources including patients who were discharged at home after an evaluation in the emergency department can be applied to patients fully treated at home in case of hospital saturation.

Besides, we retrieved information from guidelines from foreign national health agencies (NHS, HAS) published on the same topic. We also compared our work with a synthesis note published by Domus Medica - ACHG.[9]

3.5 Results

In our review on 'red-flags', we predominantly retrieved articles related to the respiratory conditions. We classified our results in a first part including the respiratory-related 'red flags', on one hand, and brought together the other 'red flags', on the other hand.

3.5.1 Respiratory-related red-flags

Oxygen saturation: from hypoxemia to hypoxia

Hypoxia, i.e. a reduced level of tissue and organ oxygenation, is most often secondary to a pulmonary disease. It occurres when the oxygen pressure in the blood falls below 60 mmHg (vs 80mmhg for hypoxemia) and corresponds to an oxygen saturation of 90%. A SpO_2 <90% put the patient on the "steep" area of the oxygen–hemoglobin dissociation curve, where small changes in PaO_2 cause large changes in SpO_2 and a rapid clinical deterioration (see Figure 2 in chapter 2).

However the range of SpO_2 values used to guide the decision for hospitalizing ambulatory hypoxemic patients varies and is controversial. Indeed, it has been mainly studied in hospital and critical care settings, with uncertainty around its application in outpatient settings. First, guidelines for community pneumonia by American Thoracic Society (ATS) and Infectious Disease Society of America (IDSA) are based on measures that cannot be calculated in a home setting context since they consider the ratio between blood arterial oxygen pressure and the amount of oxygen given (PaO_2/FiO_2) inferior to 250, as a major criteria for severity and subsequent need for hospitalization.[28] Second, guidelines for oxygen home therapy published before the pandemic are exclusively made for patients with chronic pulmonary diseases and cannot be applied in the current context.[29]. Finally, regarding patients with COVID-19, there is no study at the time of writing this document on the best SpO_2 target in an outpatient setting receiving supplemental oxygen.

Facing those constraints, studies analysing the correlation between SpO_2 and severe outcomes were identified in the aim to extrapolate the data about the SpO_2 level which absolutely indicates the need of an urgent hospital admission. Based on this assumption, six studies were identified (Table 4).

In a cohort of patients presenting (Non COVID-19) pneumonia and discharged home after assessment in an emergency department, an initial SpO_2 below 90% has been shown to be associated with an excess of mortality at 30 days or a need for hospitalization.[30]

Besides, a prospective cohort study aiming at assessing the role of pulse oximetry in (non COVID-19) patients referred from the primary care, determined that SpO_2 <90% could predict worse outcome. This association was maintained after adjustment for disease severity through the use of the CRB-65 score[c] including confusion, increased respiratory rate, hypotension and age.[31]

In the same line, regarding patients with SARS-CoV2 infection, it has been shown that, in patients discharged home after being assessed in emergency unit, pulse oximetry monitoring was useful to estimate the need of being retransferred to the hospital.[32] Ambulatory measurement of SpO_2 <92% was associated with an increased likelihood of hospitalization, intensive care admission, acute respiratory distress syndrome, and septic shock.

In COVID-19 patients requiring oxygen therapy in emergency department, SpO_2 below 90.5% has been shown to be associated with mortality.[33]

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[c] The CRB-65 score is a clinical prediction rule that grades the severity of community-acquired pneumonia in terms of 30-day mortality. (https://bjgp.org/content/60/579/e423)

Two other cohort studies determined that values of SpO2 ≤93% were correlated with hospital (re)admissions in patients with COVID-19.[34](Blair pre-print[35])

Table 4 – Studies on oxygen saturation threshold and outcome

Author	Design	N	Settings	SpO_2	Outcome
Majmudar[30] 2011	Population based-cohort study	2923	**Pneumonia**	<90%	30-days mortality/ hospitalization: adjusted OR: 1.7 [1.1-2.8]
			ED assessment and discharged home	<92%	30-days mortality/ hospitalization: adjusted OR: 1.1 [0.8-1.7]
Bewick[31] 2010	Prospective cohort study	467	**Pneumonia** Patients referred from primary care to ED and hospitalized	<90%	30-days mortality/ICU admission OR: 1.09 [1.05-1.14] per unit decrease of SpO_2
Shah[32] 2020	Prospective non-controlled	77	**COVID-19 patients** ED assessment and discharged home Hospitalization: 29% *NB: SpO_2 measured at home*	<92%	RR for hospitalization: 7 [3.4-14.5] RR for ICU admission: 9.8 [2.2-44.8] RR for ARDS: 8.8 [1.7-38.7] RR for septic shock: 6.6 [1.3-32.9]
Akhavan[34] 2020	Retrospective cohort study	519	**COVID-19 patients** ED assessment and discharged home	Various cut-offs	ED re-admission within 10 days: higher proportion of readmitted patients in lower SpO_2 at first assessment (no OR available)
Xie[33] 2020	Retrospective cohort study	140	**COVID-19 patients (moderate and severe)** First SpO_2 early after O2 beginning (in ED)	≤90%	Median survival (IQR): 8 (4-20) days (≤90% group) vs 16 (9-31) days in Kaplan Meier analysis (p=0.001). Adjusted HR: 47.41 [6.29-357.8] (adjusted for age and sex)
Blair[35] 2020	Prospective cohort study	118	**COVID-19 patients** Outpatient setting	≤93%	Decrease in SpO_2 is associated with increased risk of hospitalization. SpO_2 values ≤93%: high specificity (92%) for hospitalization

N: number of patients; OR: Odds ratio; RR: Relative Risk; IQR: Interquartile Ratio; HR: Hazard Ratio; ED: Emergency Department; ICU: Intensive Care Unit; ARDS: Acute Respiratory Distress Syndrome; O_2: oxygen.

Besides scientific publications, some international and foreign national health agencies have also tried to identify the best cut-off to use as red flags to shift from primary care to hospital. Differently to us, they have not automatically designed their model or criteria according to a hospital saturation situation. As shown in the chapter 2, the WHO defines the severe form of COVID-19 disease using a SpO_2 below 90% but they mention that this threshold has been arbitrary defined.[5] The National Health Service (NHS) in UK proposes, in this remote assessment monitoring algorithm, a threshold of SpO_2 ≤94% to decide a hospitalization in patients with initially moderate symptoms of COVID-19 without chronic pulmonary disease (Figure 12 in Appendix 18.2). This algorithm does not consider the domiciliary administration of supplemental oxygen.[6]

A consensus in a French study considered that SpO_2 ≤94% while breathing normal room air is a contraindication for staying at home.[36] However, experts participating to this consensus guidelines did not consider home-based oxygen therapy. Besides, the 'Haute Autorité de Santé' (HAS) considers a threshold of 92% at room air to start oxygen therapy at home in case of of hospital saturation[8] but only in absence of recognized risk factors for negative outcome (see Chapter 4). Those guidelines consider that amount of oxygen has to be lower or equal than 4L/min. They proposed a SpO_2 below 90% as red flag (or the necessity to deliver more than 4L/min of oxygen).

In Belgium, Domus Medica - ACHG emphasized that oxygen saturation is an important tool in the management of COVID-19. Although there is no consensus on the optimal threshold, a SpO_2 below 90% is proposed as a 'red flag'.[14]

Regarding patients with chronic respiratory disease, the value of SpO_2 should cautiously be interpreted since they can chronically have decreased value of SpO_2 (ranging between 88-94%). and because they are at high risk of CO_2 accumulation when oxygen is administered.[37] According to the British Guidelines for emergency oxygen use, the threshold value SpO_2 below 88% is a red flag requiring an hospital assessment [21] (see paragraphe 2.5.2). The value of SpO_2 should always be interpreted in the light of the clinical condition (increasing dyspnea or other signs of clinical deterioration).

Respiratory rate

Respiratory rate is usually included in the scores assessing the severity of pneumonia. We identified 5 studies on this topics as shown in Table 5.

One of the first studies aiming at classifying the risk of death and adverse outcomes in non COVID-19 patients considered a respiratory rate above 30/min to upgrade the level of severity through the Pneumonia Severity Score (PSI).[38] The CURB-65 score (including the variables confusion, blood urea, respiratory rate, blood pressure and age) has been used from 2003 to evaluate the risk of mortality in case of pneumonia and considers also the respiratory frequency above 30/min as severe.[39]

The ATS (American Thorax Society) recommends to use PSI rather than the CURB-65 score [40] to determine the need for hospitalization because PSI identifies larger proportions of low risk patients and has a higher discriminative power in predicting mortality.[41] Guidelines warns that this prognosis score may underestimate the severity in younger patients and that PSI should be used in conjunction with clinical judgment. Interestingly, in the SMART-COP score predicting the need for intensive respiratory support, the respiratory frequency is adapted to the patient age in order to discriminate signs of severity in younger patients: >25/min if younger than 50 years old and >30/min if older.[42]

In the specificity of COVID-19 pneumonia, although the respiratory rate has been recognized as independent risk factor for in-hospital death[43], there is no consensus nor study determining the threshold to guide hospitalization.

In contrast, in one of the first reported paper on COVID-19[22], non-survivor patients had a respiratory rate higher than 24/min. In the same way, Bahl *et al*. observed the same trend with survivors having a median respiratory rate of 21/min *versus* 24/min in non-survivors.[43] This threshold of 25/min has been adopted as a tool for hospitalization decisions in a consensus meeting between French and Belgian experts.[36] However, this consensus did not consider the possibility of transient ambulatory oxygen supplementation. The same result is presented in the Belgian BestBET from Domus Medica – ACHG.[10] In this publication, the clinical signs suggestive of worsening proposed by the NEWS score used in the UK were reviewed and the conclusion mentioned that several studies have shown that a respiratory rate >24/min was associated with worse outcome. However, evidence is limited and the studies did not consider home oxygen therapy.[14]

Before the SARS-CoV-2 pandemic, the National Early Warning Score (NEWS) was used in UK for determining the degree of illness of a patient and the need for prompt urgent care intervention. NEWS considered the RR threshold of 25/min as the most severe in their scale.[44] This score has been shown to predict medium-term outcomes (14-day transfer to ICU or death) among COVID-19 patients.[45]

In the same vein, a new severity prediction tool has specifically been developed for the remote assessment of COVID-19 patients (RECAP: REmote COVID-19 Assessment in Primary Care). In this grading tool in which a score is attributed according to the level of impairment of each variable, a respiratory rate >25/min is considered as moderate risk raising awareness for potential worsening. If it exceeds 30/min, it is considered as a 'red-flag' for urgently referring the patient to hospital.[12] The World Health Organization indicates also that a resting respiratory rate >30 breaths/min is a critical sign for the diagnosis of severe COVID-19.[5]

Table 5 – Studies on respiratory rate threshold and outcome

Author	Design	N	Settings	RR	Outcome
38	Pneumonia severity score	14199	Hospital	>30/min	Risk of death
39	CURB-65 score	1068	Emergency -Hospital	>30/min	Risk of death
41	Prospective comparison of PSI, CURB and CURB-65	3181	Emergency -Hospital	>30/min	Risk of death
42	SMART-COP	882	Emergency	>25/min if ≤ 50 years >30/min if >50 years	Need for intensive respiratory and hemodynamic support
43	Predictor scoring system on COVID-19 patients	1629	Hospital	>24/min in non-survivors	Risk of death

3.5.2 Other vital variables

Hemodynamic impairment, signs of renal dysfunction and alteration of consciousness are part of other variables analyzed in the literature and quoted in some algorithms. Nevertheless, those topics have less frequently been research subjects for the time being.

Alteration of hemodynamics indicated by arterial hypotension and/or tachycardia are 'red flags' and have to be managed according to the guidelines of critically-ill patients with shock. The NIH[46] recommends to refer to the Sepsis surviving Campaign Recommendations adapted for Covid-19 pandemic.[47] Shock occurs most frequently in patients with severe form of infection who need to be admitted in the intensive care unit (ICU). Cardiac injury secondary to the hypoxia or myocarditis and arythmia have also been reported.[48, 49] In primary care, arterial hypotension below 100 mmHg and heart rate above 110 beats/min have been proposed as 'red-flag' thresholds.[126] The National Early Warning Score 2 (NEWS 2) used for the clinical assessment of patients in UK includes heart rate and blood pressure to evaluate the risk of clinical deterioration. Thresholds vary and scores are attributed according to the severity of impairment (e.g. 2 points are attributed if systolic blood pressure < 100 mmHg whereas 3 points are attributed below 90 mmHg; heart rate > 110/min and ≥131/min get 2 and 3 points, respectively).[44] [50]

Renal function has been studied in hospitalized patients. Patients hospitalized with COVID-19 are at a significant risk of acute kidney injury. About one fifth of patients with acute kidney injury will require extra-renal replacement therapy.[51, 52] Since clinical signs of dehydration and/or hypovolemia can lead to renal failure, they have to be considered as a 'red-flag'.

Alteration of consciousness in Covid-19 patients has been reported and can be ascribed to many causes such as encephalitis, cerebrovascular disorders like stroke, or as a consequence of the overall severity (hemodynamics impairment or secondary to accumulation of CO_2 causing respiratory acidosis, for example).[53]

3.6 Discussion

3.6.1 Respiratory-related red-flags

No study has been run to specifically identify, in a patient evaluated at home, the cut-off value of **SpO_2** below which he should be transferred to hospital (=SpO_2 red flag). Even the threshold of SpO_2 below 90% used by the WHO for defining the severe level of COVID-19 has been arbitrary chosen.[5] However, there is a link in several studies between a SpO2 <90% and mortality. Pathophysiological data highly suggest that hypoxia can favour organ failure [54] and worsen systemic inflammation.[55] Because a SpO_2 <90% put the patient on the “steep” area of the oxygen–hemoglobin dissociation curve, the risk of rapid clinical deterioration is present at this time and the patient can rapidly worsen, with a significant risk for urgent tracheal intubation and cardiac arrest. Seeing the associated mortality and morbidity, we recommended that this threshold must lead to hospitalize the patient. This is also the value proposed as a red flag by the Domus Medica - ACHG BestBET.[14]

As mentioned above, for patients with **chronic lung diseases** having decreased oxygen saturation, the value of SpO_2 should be interpreted in the light of the usual values (drop $\geq$ 3-4%) and the clinical condition (increasing dyspnoea or other signs of clinical deterioration) [19] Since patients with chronic respiratory diseases such as chronic obstructive pulmonary disease are more vulnerable and at higher risk for worsening, SpO_2 below 88% is a red flag in this kind of patients.[56] In addition, awareness should be raised about signs of CO_2 accumulation and respiratory acidosis (drowsiness, flushed face, sweating, headache, flapping tremor) that indicate the need for a transfer to a hospital setting for non-invasive or invasive ventilation.

The interpretation of saturation values according to the amount/flow of oxygen delivered can be a way to interpret the patient condition and to detect a worsening. However, the markers (SaO_2/FiO_2, PaO_2/FiO_2) evaluating this characteristic have mainly been studied in hospitalized patients with severe hypoxemia and cannot be applied in ambulatory setting.[57, 58] Furthermore, the exact amount of delivered oxygen obtained with nasal cannula vary in a wide range[59] and cannot be used to calculate such ratio. According to the data collected by the some public health institution, a **flow of oxygen need** which exceed 4 L/minute or which do not lead to reach an improvement of the SpO_2 (i.e SpO_2 >92%) can also serve as a red flag.

Regarding the respiratory rate, the proposed threshold is most often >30 breaths/minute. However all the above-mentioned prognosis scores have been evaluated in emergency departments or inpatient settings and not in an outpatient setting. They often require biological values not immediately available in general practice. The CURB-65 score has been adapted for primary care without the necessity of biological values determination but is not sufficiently validated.[60] Some authors proposed to adapt the CURB-65 score in a SCRB-60 score that does not need to measure the level of blood urea.[19] The result of the score is included in the algorithm determining the severity and to authorize a remote follow-up *versus* an hospitalization. In this SCRB-60 score, respiratory threshold is also 30/min. On the other side, in case of low respiratory frequency, authors proposed a minimal acceptable respiratory frequency limit of 12/minute.[19]

Moreover, it is important to highlight that caregivers should always interpret both oximetry and respiratory rate values according to their clinical judgment that overrides any proposed algorithm.

3.6.2 Other vital variables

Other red-flags are quoted in the literature although they appear to be less frequently studied (or published). They concerns logically hemodynamic impairment, signs of renal dysfunction and alteration of consciousness.

In addition, if the patients does not show any sign of clinical improvement within 72 hours of intensified home-based management, it is highly recommended to consider this evolution as a red flag and to organize hospital transfer. Such an evolution presumably reflects a worsening respiratory impairment requiring other types of respiratory supports.

Discussion with some general practitioners underline the need of some precisions regarding the signs of renal dysfunction. To be consistent with a list of clinical red flags, we proposed to translate the renal dysfunction on clinical signs of dehydration and of hypovolemia as following:

[3] **Clinical signs of dehydration**: weight loss ≥ 5% (severe if >10%), positive skin fold, thirst, dry mouth, possible confusion and decrease of urine flow.[61],[62]

[4] **Clinical signs of hypovolemia**: arterial hypotension, tachycardia, cold and marbled extremities and decrease of urine flow.[62]

3.7 Conclusion

Several red flags can be identified in the literature, mostly related to the respiratory variables and a list of them can be inserted in the decision-aid tool. This list aims to exclude COVID-19 patients from the intensified home-care strategy and has to lead the general practitioner to refer the patient for a hospitalization.

- In the absence of chronic lung disease, a SpO_2 below 90% must lead to hospitalize the patient (red flag).
- In patients with chronic pulmonary disease, SpO_2 below 88% is a red-flag.
- Because SpO_2 has to be interpreted according to the amount of oxygen delivered and since the need of increased oxygen requirements is a sign of clinical worsening, we suggest an oxygen flow of maximum 4 L/minute
- The respiratory rate should not be equal or superior to 30 breaths/minute at rest or respiratory rate <12/min
- Other red flags are hemodynamic impairment, alteration of consciousness and signs of dehydration and/or hypovolemia.
- No improvement of health status after 72 hours of home-based management is also proposed as a red flags.

Although several triage algorithms and assessment scores exist they cannot be currently recommended because they need to be validated. In the expectation of highly validated triage strategies, the clinical judgment of each caregiver should always take precedence and may override the suggested decision–aid tool.

3.8 Proposed changes in the OST-Liège decision-aid tool

We suggest to specify different levels of oxygen saturation at rest according to the context (SpO_2 <90%; SpO_2 <88% if chronic hypoxaemic lung disease; $SpO_2 \leq 92\%$ with an oxygen flow max 4L/min)

The respiratory rate has to be changed from “>30/min” to ≥ 30/min at rest or respiratory rate <12/min

We propose to keep “Altered consciousness”, to change “Tension systolique<100 mmHg” by “Hemodynamic impairment: systolic hypotension < 100 mmHg OR tachycardia > 120/min OR bradycardia < 45/min” and to change “Etat de déshydratation: oligo-anurie” by “Clinical signs of dehydration and/or hypovolemia”

Finally, we propose to add the red flag: “No improvement of health status after 72 hours of home-based management”.

4 RISK FACTORS FOR NEGATIVE OUTCOMES OF COVID-19

4.1 Summary

- **Many public health and knowledge institutions propose a list of factors predisposing to negative outcomes in case of COVID-19. The description of the methodology and the date of the last update vary between them.**
- **Risk factors are often presented in 2 categories: 'established' and 'may be' risk factors. In both cases, the category should not be considered definitive as evidence on COVID-19 is rapidly accumulating.**
- **We propose the following risk factors for identifying COVID-19 patients requiring a careful monitoring at home: :**
  - **Age: >65 years old with, in a footnote, "For patients over 75 years old that are residents in an institution, please refer to the therapeutic protocol for COVID-19: in French http://docs.toubipbip.be/docs/d574edb2e8fce1a0.pdf."**
  - **Obesity: BMI ≥ 30**
  - **Diabetes: type 1 and 2**
  - **Chronic heart condition (with the following diseases in footnote: "heart failure, coronary disease, cardiomyopathies and pulmonary hypertension")**
  - **Chronic lung disease**
  - **Chronic kidney insufficiency (stage 3a to 5)**
  - **Chronic liver diseases**
  - **Malignant hemopathy or active cancer**
  - **Severe immunosuppression with, in footnote, a non-exhaustive list of condition: "ongoing chemotherapy, severe inhered immunodeficiency, transplant,… See CBIP in French (https://www.cbip.be/fr/chapters/12?frag=8900094) or in Dutch (https://www.bcfi.be/nl/chapters/12?frag=8900094)."**
  - **Neurological conditions or major psychiatric disorders requiring anti-psychotics with, in footnote, a non-exhaustive list of neurological conditions: "dementia, Down syndrome, cerebral palsy,…"**
  - **Homozygous sickle cell disease**
- **This list on risk factors implies several changes in the OST-Liège decision-aid tool.**
- **Moreovere, one note has to be added related to the title of the box in order to emphasize the cumulative risk with several factors: "The presence of one of the risk factors is a warning sign which should trigger, according to your clinical judgement, a twice more frequent home-based monitoring or, if not possible, an indication for a hospital admission (except when in contradiction with the advanced care planning). Be aware that each additional age year after 65 years and each accumulation of risk factors induces a higher risk.**

4.2 Background

In addition to the clinical signs leading to consider the intensified home care therapy (see chapter 2) or to the need of urgent hospitalization (see chapter 3), other factors related to the patient's history and clinical profile can have an impact on the set-up of those care. Indeed, risk factors for negative outcomes related to comorbidities or to the age can have a role in the assessment of the eligibility to access home-based intensified care or in the frequency and intensity of the monitoring. In this chapter, we try to identify and list the main risk factors of negative outcomes in COVID-19 patients.

4.3 Research question

The initial question was "*What are the risk factors of aggravation for patients with COVID-19 at home?*" In the OST-Liège decision-aid tool, the preliminary list included age >65 years, obesity, diabetes type 2 (and cardiovascular comorbidity), high blood pressure (HBP), severe renal, liver, heart or respiratory failure, and immunosuppression. Because the logistical and environmental factors are analyzed in the chapter 5 and because the symptomatic factors (i.e. red flags) are analyzed in the chapter 3, we have changed this question in "*What are patients characteristics (age, comorbidities) predisposing COVID-19 patients to negative outcomes (hospitalization, ICU admission, death)*?"

4.4 Methods

In order to provide a response in a very short time, we mainly searched public health and knowledge institutions websites for data summaries and reports on risk factors to negative outcomes to COVID-19, notably by a simple google search on the following key words 'risk factors for severe covid-19'; 'facteurs de risque covid-19 sévère'; and 'risicofactoren covid-19 ernstig'. We then did a systematic screening of the URL which popped out in the three first google pages.

The following institutions were identified: Sciensano, Centers for disease control and prevention (CDC), Haute Autorité de Santé (HAS), Haut Conseil de la Santé Publique (HCSP), World Health Organisation (WHO), BMJ open, UK government, Royal College of General Practice, European Centre for Disease Prevention and Control (ECDC), Medscape, Up-To-Date, Mayo Clinic, Johns Hopkins Medicine, Alberta Health Service, Rijks Instituut voor volksgezondheid en milieu (RIVM), Universiteit Ziekenhuis Leuven, Domus Medica and the Academisch Centrum HuisartsGeneeskunde (Domus Medica - ACHG), Nederlands Huisartsen Genootschap (NHG) and Norwegian Institute of public Health.

Only the institutions for which the list of risk factors was accompanied, in open access, by scientific references were further analyzed. So the following identified sources were not described in this document: UK Government, Royal College of General Practice, Up-to-date, Nederlands Huisartsen Genootschap and John Hopkins Medicine. As recommendations in the HAS report about risk factors were based on the HCSP reports, we analyzed rather the reports of the HCSP.

Only two sources precisely described their methodology in including evidence table: Domus Medica - ACHG and Alberta Health Service. Others gave a summary of their methodology: Sciensano, HCSP, CDC, WHO and the Norwegian Institute of Public Health. Those who remains only gave a list of references: BMJ Open, ECDC, Medscape, Mayo Clinic and Rijksinstituut voor Volksgezondheid en milieu.

It is important to note that the date of publication differed according to the source. Domus Medica - ACHG published a list of factors predisposing to severe COVID-19 at the beginning of the first wave (March 2020); Sciensano, WHO, Medscape, Mayo Clinic, Alberta Health Service, and Rijksinstituut voor Volksgezondheid en Milieu published their list before the second wave in Europe (May to August 2020); and only HCSP, CDC, BMJ Open, ECDC and Norwegian Institute of public health had updated their results with more recent data published during the second wave (October to December 2020)

Finally, the Belgian data collected and analyzed through a multivariate logistic regression by Sciensano[63] on the request of the Conseil supérieur de la santé (CSS) / Hoge Gezondheidsraad (HGR) was used to illustrate the findings from the grey literature. Only the data on the adjusted odds ratio for death in the all patients cohort[64] was presented in the Appendix 18.6.

4.5 Results

As described in the methodology, many institutions have already carried out a fairly extensive analysis of the factors predisposing to negative outcomes following SARS-CoV-2 infection.

We presented in the Table 5, the identified institutions and the URL link as verified on January 26Th 2021.

Table 6 – Overview of the selected data sources and their URL

Data source	URL
Domus Medica - ACHG[65]	https://www.domusmedica.be/actueel/achg-synthese-nota-thuisopvolging-en-behandeling-van-covid-19-patienten https://www.domusmedica.be/richtlijnen/coronavirus/wetenschappelijk/welke-patientengroepen-lopen-een-hoger-risico-op https://www.achg.be/covid-19-01/vraag-en-antwoord https://cdn.nimbu.io/s/1kphvhi/assets/1585662407756/16_Evidence%20tabel%20Risk%20complications%20finale%20versie.pdf
Sciensano and CSS/HGR[66]	https://covid-19.sciensano.be/fr/covid-19-informations-generales https://www.health.belgium.be/sites/default/files/uploads/fields/fpshealth_theme_file/201030_css-9597_9611_vaccination_strategy_covid_19_vweb.pdf
WHO[3]	https://www.who.int/publications/i/item/home-care-for-patients-with-suspected-novel-coronavirus-(ncov)-infection-presenting-with-mild-symptoms-and-management-of-contacts
Medscape[67]	https://emedicine.medscape.com/article/2500122-overview#a4
Mayo Clinic[68]	https://www.mayoclinic.org/diseases-conditions/coronavirus/in-depth/coronavirus-who-is-at-risk/art-20483301
Alberta Health Service[69]	https://www.albertahealthservices.ca/assets/info/ppih/if-ppih-covid-19-sag-risk-factors-for-severe-covid-19-outcomes-rapid-review.pdf
Rijksinstituut voor Volksgezondheid en Milieu (RIVM)[70]	https://lci.rivm.nl/richtlijnen/covid-19
HCSP[71]	https://www.hcsp.fr/Explore.cgi/avisrapportsdomaine?clefr=942
CDC[72]	https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fneed-extra-precautions%2Fgroups-at-higher-risk.html
BMJ Open[73]	https://bestpractice.bmj.com/topics/en-gb/3000201/epidemiology
ECDC[74]	https://www.ecdc.europa.eu/en/covid-19/latest-evidence/epidemiology
Norwegian Institute of public health[75]	https://www.fhi.no/en/publ/2020/COVID19-and-risk-factors-for-hospital-admission-severe-disease-and-death-3rd_update/

Primary publications of epidemiological studies are numerous (3979 hits in Pubmed on the 3rd of December), as well as systematic reviews and meta-analyses (92 hits in Pubmed on the 3rd of December). And data continues to flow regularly into databases, requiring frequent updates, done by the majority of the institutions mentioned above.

The two aspects which are important to take into account in order to properly identify SARS-CoV-2 positive patients at risk of developing a severe form of COVID-19 were, on the one hand, the strength of the scientific evidence and, on the other hand, the strength of the association between the two variables. So, risk factors are usually classified in two different levels: the 'established' level or the 'may be' level. In both cases, the attributed category should not be considered as definitive as new publications may change conclusions all the time in this COVID period.

4.5.1 Age

According to the Alberta Health Service systematic review (SR) which did the most evidence-based analysis of the literature on risk factors identified in this research, *"there is consistent evidence that increasing age has a consistent and* ***high strength association*** *with hospitalization and death from*

COVID-19". The association is the strongest in people older than 65 years and is enhanced in the presence of additional comorbidities.[69] This risk factor emerged since the beginning of the pandemic (Domus Medica[76] - ACHG[77])[65] and the 3rd update done by the Norwegian Institute of Public Health confirms that **older people** are the most at risk of negative outcomes of COVID-19: "*Increasing age was found to be **the strongest predictor of death** due to COVID-19*".[75] However, age cut-offs vary from institution to institution: 60 for the WHO[3], 65 for Sciensano and CSS/HGR [66], the HCSP[71], the BMJ Open[73] and the Alberta Health Service[69]. The RIVM[70] chooses a cut-off of 70 in insisting on the importance of the vulnerability. And the last report of the HCSP highlights the important risk for people aged of 70 or more (HR>5).[71] The other institutions do not specify any age cut-off. In the Belgian Sciensano cohort, an OR of 1.97 (95%CI 1.90-2.04) for death is found for 10 year-increase of age[64] and in the report of the CSS/HGR, data shows that "*50% of the people admitted in ICU for COVID-19 and more than 90% of the people dying from COVID-19 were older than 65 years*".[66]

4.5.2 Diabetes

According to the Alberta Health Service SR, *"diabetes has a consistent **moderate strength association** with hospitalization from COVID-19. Of note, the literature did not often distinguish between type 1 and type 2 diabetes"*[69] This factor popped out since the beginning of the pandemic[65] and the 3rd update done by the Norwegian Institute of Public Health confirms that "*diabetes mellitus type I and II was associated with increased risk for severe COVID-19 and is a **strong predictors** of COVID-19 related death (OR/HR >=3)*".[75] However, some variation occur between institutions: (i) the HCSP and the RIVM insist on unbalanced diabetes with complications; and (ii) the CDC[72], the BMJ Open, Mayo Clinic[68] and Medscape[67] stipulate that type II diabetes is an 'established' risk factor while type I diabetes is categorised as a 'may be' risk factor. All the other institutions agree with no distinction or stage of the diabetes. In the Belgian Sciensano cohort, an OR of 1.21 (95%CI 1.11-1.32) for death is found in patients with diabetes.[64]

4.5.3 Obesity

Obesity popped out as a risk factor since the beginning of the pandemic[65]. According to the Alberta Health Service SR*, "obesity is **consistently associated** with severe outcomes of COVID-19. Risk of hospitalization has a low strength association with obesity; however, risk of ICU admission/intubation is consistently associated with increasing body mass index (BMI), with a high strength association between BMI >35 and ICU admission or intubation. Risk of mortality had low strength association with obesity*.[69]

The 3rd update done by the Norwegian Institute of Public Health explains that "*two recent studies report an increased risk of hospital admission with increasing body mass index (BMI) and that morbid obesity (BMI>40) was associated with increased risk for severe COVID-19"*.[75] Most of the institutions point to obesity as a predisposing factor when the BMI is above 30 but the RIVM chooses a cut-off of 40. Only Sciensano fact sheet does not describe obesity as a risk factor and the ECDC[74] qualifies obesity as a potential ("may be") factors. But in the Belgian Sciensano cohort, an OR of 1.28 (95%CI 1.13-1.44) for death is found in obese patients.[64]

4.5.4 Cardiovascular disease

According to the Alberta Health Service SR, "*cardiovascular disease is poorly defined in the literature and has an inconsistent association with severe COVID-19 outcomes. […] large studies looking specifically at chronic heart failure, and meta-analyses of cardiovascular disease showed a stronger association with severe COVID-19 outcomes than small hospital-based studies. More research is needed to clearly determine the risk posed by different chronic cardiovascular conditions*."[69] For precision purpose, the cardiovascular disease was then sometimes analyzed by more specific conditions (severe heart disease, high blood pressure, cerebrovascular disease) but some institutions kept using this global terminology (HCSP, WHO, BMJ Open and Domus Medica - ACHG). In the Belgian Sciensano cohort, the term cardiovascular disease is used but it does not include high blood pressure (HBP). The analyse of this cohort shows that an OR of 1.21 (95%CI 1.21-1.31) for death is found for patients with cardiovascular disease.[64]

4.5.4.1 Severe chronic heart disease including heart failure

Sciensano and the WHO[3] used the naming of severe chronic heart disease to target a part of the cardiovascular risk factor of negative COVID-19 outcomes. The HCSP defines differently and more precisely heart conditions predisposing to severe COVID: coronary disease, history of cardiac surgery and heart failure in stadium III or IV of the New York Heart Association (NYHA) functional classification.[71] The CDC, the BMJ Open and Medscape agree partly with the HCSP but includes also cardiomyopathies in the list without including the history of cardiac surgery. The Mayo Clinic includes two additional conditions within the appellation 'serious heart disease': pulmonary hypertension and congenital heart disease. Finally three institutions only focus on heart failure: the Alberta Health Service says that "*chronic heart failure **may have an association** with worse outcomes"* [69]*;* the Norwegian Institute for Public Health described that *"one recent study reports increasing risk by heart failure which stand out with a greater associated risk of hospital admission (OR/HR >=3) and was associated with increased risk for severe COVID-19"* [75]*;* and the RIVM explains that any chronic disorder of the heart function which qualifies for the flu vaccine is a risk factor.[70]

4.5.4.2 High blood pressure

According to the Alberta Health Service, "*hypertension alone does not have a consistent association with severe COVID-19 outcomes; at best, the association is **low strength**. The association with severe COVID-19 outcomes increases when hypertension, diabetes, and obesity are co-occurring; however, it is unclear if this relationship is additive or synergistic"*.[69] This factor popped out since the beginning of the pandemic [65] but has lost strength of its association with severe COVID-19 overtime. While CDC, BMJ Open and the Mayo Clinic consider high blood pressure as a "may be' risk factor, Sciensano, ECDC, Medscape, RIVM and Norwegian Institute of Public Health do not mention it. The HCSP stipulates that the HBP should be complicated by cardiac, renal or cerebrovascular conditions to be considered as a risk factor.[71] In the cohort of Sciensano, HBP is not associated with the risk of death (OR of 0.97 (95%CI 0.90-1.05).[64]

4.5.4.3 Cerebrovascular disease

This factor appears quite recently in risk factors lists of institutions. It is only mentions by HCSP, WHO, CDC, BMJ Open and Medscape. The first two institutions include it in the "established" risk factors with a position of a much higher risk by the HCSP (HR>5), while the next three included it in the "may be" category.

4.5.5 Serious chronic lung disease

According to the Alberta Health Service SR, *"pulmonary disease is poorly defined in the literature, although most included studies used chronic obstructive pulmonary disease (COPD) or asthma in their models. […] Notably, large studies and meta-analyses showed a stronger association with severe COVID-19 outcomes than small hospital-based studies. More research is needed to clearly determine the risk posed by different pulmonary conditions."*[69] In an aim of precision, pulmonary disease was further analyzed by more specific conditions (COPD, asthma, cystic fibrosis and pulmonary fibrosis) although some institutions may still use the global terminology (Sciensano, WHO, ECDC, RIVM). For example, the RIVM says that "*chronic abnormalities and dysfunctions of the respiratory tract and lungs which, because of their severity, are under the treatment of a pulmonologist*" defines the pulmonary conditions which are risk factors. In the same line, the HCSP suggests to consider a pulmonary condition as a risk factor if the pulmonary function is at risk of decompensation in case of a viral infection and further listing COPD, severe asthma, pulmonary fibrosis, cystic fibrosis and sleep apnoea syndrome.[71] In the cohort of Sciensano, an OR of 1.31 (95%CI 1.19-1.44) for death is found for patients with chronic lung disease.[64]

4.5.5.1 COPD

According to the Alberta Health Service SR, "*COPD appears to have a **low strength** association with severe COVID-19 outcomes (on balance, less than 2X increased odds of severity)"*.[69] The CDC, the WHO, Medscape, the Mayo clinic, Domus Medica - ACHG and the BMJ Open consider COPD as an "established" risk factor.

4.5.5.2 Asthma

It is considered by the CDC, the BMJ Open, Medscape and the Mayo Clinic as a "may be" risk factor. But according to the Alberta Health Service SR, *"asthma appears to have **no significant risk** of severe COVID-19 (on balance)".[69]*

4.5.5.3 Cystic fibrosis and pulmonary fibrosis

Cystic and pulmonary fibrosis are considered by the CDC, Medscape and the Mayo Clinic as a "may be" risk factor. But according to the Alberta Health Service SR, *"there is **little to no data** for patients with rare conditions that are thought to confer higher risk of severe COVID-19 outcomes (e.g. lung transplant patients, cystic fibrosis), presumably because these patients may have been extremely diligent in public health precautions and are not represented within study samples. Moreover, it is unlikely that robust data will be available to quantify the risks to patients with these rare conditions. Patient-specific judgment, with extrapolation from other conditions, will likely be required to mitigate risk to these individuals."[69]*

4.5.6 Smoking

Except Medscape which identify smoking as a "may be" factor, 4 other institutions which stipulate smoking in their list, consider it as an "established" factor. However this factor was not listed by the other institutions: Sciensano, HCSP, ECDC, RIVM, Mayo Clinic and the Norwegian institute of public Health.

4.5.7 Chronic kidney disease

According to the Alberta Health Service SR, *"kidney disease was poorly defined in the literature. The association between chronic kidney disease (CKD) and severe outcomes of COVID-19 is consistent but varies by outcome. On balance, the odds or risk of death from COVID-19 associated with CKD appears to be **low strength**. The risk of hospitalization is higher - studies report a moderate strength association between CKD and hospitalization or ICU admission."*[69] This risk factor was not identified at the beginning of the pandemic.[65] Except the BMJ Open, all the other institutions consider CKD as an 'established' risk factors. The 3rd update by the Norwegian Institute of Public health confirms that *"one recent study reports increasing risk by severe kidney disease which stand out with a greater associated risk of hospital admission (OR/HR >=3) and was reported as a strong predictors of COVID-19 related death (OR/HR >=3)."*[75] The last report of the HCSP highlights that patients with CKD at the 5th state are at much higher risk (HR>5).[71] In the cohort of Sciensano, an OR of 1.23 (95%CI 1.22-1.36) for death is found for patients with chronic renal disease.[64]

4.5.8 Chronic liver disease

Few institutions include liver disease in the list of risk factors and if they do, it is in the 'may be' category. Still, the HCSP and the RIVM stipulate severe cirrhosis (Child Pugh B or C) as a risk factors, but those data seem based on experts' opinions rather than on scientific studies. However, in the cohort of Sciensano, an OR of 1.64 (95%CI 1.33-2.02) for death is found for patients with chronic liver disease.[64]

4.5.9 Immunodeficiency

Some institutions make a difference according to the cause of the immune depression (CDC, BMJ Open, Medscape and the Mayo Clinic). Others do not (Sciensano, HCSP, WHO, ECDC, RIVM and the Norwegian Institute of Public Health). When the cause is taking into account, immunosuppression induced by solid organ transplant are considered as an "established' risk factor while other causes like blood or bone marrow transplant, inherited immune deficiencies, HIV, use of corticosteroids, or use of other immune weakening medicines, are considered as 'may be' risk factors. Where the term 'immunodeficiency' includes all types of causes, it is considered as an 'established' risk factor. This last position is confirmed by the 3rd update made recently by the Norwegian Institute of Public Health which shows that "*one recent study reports increasing risk by ongoing chemotherapy and severe immunodeficiency which stand out with a greater associated risk of hospital admission (OR/HR >=3) and that ongoing chemotherapy, organ transplant patients, severe immunodeficiency, were reported as **strong predictors of COVID-19 related death** (OR/HR >=3)."*[75] The last report of the HCSP highlights that patients who have received a stem cell transplant or a grade B or C chemotherapy

are at much higher risk (HR>5).[71] In the cohort of Sciensano, an OR of 1.64 (95%CI 1.25-2.16) for death is found for immunocompromised patients.[64]

4.5.10 Cancer

According to the Alberta Health Service SR, *"most included studies considers cancer as a covariate (defined as "cancer" or "malignancy"). Cancer appears to have a **low strength association** with severe COVID-19 on its own, but is a synergistic factor with age, sex, and other comorbidities."*[69] This risk factor was not identified at the beginning of the pandemic[65] but now the majority of the selected institutions stipulates it in their list of risk factors as an 'established' risk factor. And two institutions precise the importance of the active state of the cancer: Sciensano and the HCSP. In the cohort of Sciensano, an OR of 1.42 (95%CI 1.27-1.59) for death is found for patients with solid cancer while an OR of 2.15 (95%CI 1.72-2.69) for death is found for patients with hematological cancer.[64]

4.5.11 Sickle cell disease and thalassemia

Four institutions introduce sickle cell disease in their list as an 'established' risk factor: CDC, BMJ Open, Medscape and Mayo Clinic, all are related to Anglo-Saxons countries. Thalassemia was introduced by the CDC, Medscape and the Mayo Clinic, from the same publication environment. The BMJ open notices that the evidence about thalassemia is limited.

4.5.12 Neurologic conditions

Five institutions introduced recently this group of conditions in their list and in particular dementia as a 'may be' risk factor. Moreover, the recent update by the Norwegian Institute of Public Health mentions that *"dementia was reported as a strong predictors of COVID-19 related death (OR/HR >=3)".* This institution also highlights other neurologic condition like *"major psychiatric disorder with antipsychotics, cerebral palsy and Down syndrome (one study)* which *were reported as strong predictors of COVID-19 related death (OR/HR >=3)."*[75] The last report of the HCSP highlights that patients with Down syndrome, dementia or stroke are at much higher risk (HR>5).[71] In the cohort of Sciensano, an OR of 1.27 (95%CI 1.13-2.02) for death is found for patients with chronic neurological disease and an OR of 1.50 (95%CI 1.36-1.66) for death is found for demented patients.[64]

4.5.13 Pregnancy

According to the Alberta Health Service SR, *"evidence regarding pregnancy and COVID-19 outcomes is limited. Compared to non-pregnant women, pregnant women **may be at higher risk** of ICU admission. There is conflicting data on the risk of mortality among pregnant women, with the absolute risk of mortality among pregnant women less than 1% in all published studies (till June). These findings should be interpreted with caution as there are few studies with small sample sizes, limiting the reliability of the estimates of absolute and relative risk."*[69] However, this particular condition was the object of numerous update in institutions' risk factors list in the previous three month but still controversial. For the RIVM, on the basis of available data till October 2020, there is so far no evidence that getting COVID-19 during pregnancy increases the risk of a serious course in the pregnant woman herself. But this position is not taken by the CDC and the BMJ Open which consider since October that pregnancy is an 'established' risk factor.

4.6 Discussion

Based on the data at hand, the **elderly** are clearly the main group at risk of hospital admission, severe illness, and death if infected by COVID-19. Most **comorbidities** appear to increase risk and an increasing number and severity of comorbidities contribute to a further increase in the overall risk. [75]

It is important to note that a certainty on the risk factors list cannot be reached for at least four reasons:

1. In a same document (e.g. "Clinical management of COVID-19" by the WHO[5]), the way to name the same type of risk factor for severe COVID-19 can vary from one section to another; this example illustrates the difficulty of naming these factors precisely at the present time.

2. Only summaries of data have been analyzed here. In order to get a much more accurate picture of the situation, a systematic review of the data by risk factors is essential but not feasible in the time frame.
3. The evidence base is rapidly evolving. Each time new primary studies or systematic reviews and meta-analysis are published, updates are required. Therefore, the overview given in this document should be updated regularly.
4. Data analyses of the Sciensano cohort are a snapshot of an ongoing situation and only data on death odds ratio are taken into account. An overall analyses of all negative outcomes as defined in this document (hospitalization, ICU admission and death) would have been of added-value but are not reachable in the given time frame.[64]

Because the first precaution is "*primum non nocere*", **uncertainties** lead to be cautious in the interpretation of the results. In this way, some 'may be' risk factors only recently added to institutions' list but with higher OR/HR, were included in the risk factors list of the decision-aid. And all potential risk factors evoked in this document but not included in the current list should also be kept in mind in the aim to regularly update the list by new literature search (see warning in the last box and in the footnotes of the decision-aid).

Recently, some institutions have tried to introduce a **severity rate in risk factors lists**. For example, in its report of the 29th of October, the HCSP described a list of factors with a ranking according to Hazard Ratio.[71] Also in the HCSP report, several risk factors are listed in a much more detailed manner: for example, the age factor is split in two categories (60-69 and 70+), each corresponding to a different level of risk, depending of the strength of the association with negative outcome (see details in Appendix 18.7). Based on that report, the HAS has recently (November 2020) defined the criteria which would allow French GPs to carry out acute oxygen therapy at home to COVID-19 patients.[8] Some of these criteria are personal risk factors; others are of symptomatic, logistical or environmental nature. Although these lists are of utmost interest, the lack of methodology behind their set-up encourages a prudent use of it as is. Indeed, the weight from expert and the weight from evidence retrieval behind the list is not known.

Also, some clinical and epidemiological research teams are trying to develop **global risk scores** where each predisposing factor is assigned a number of points or a certain weight. Those tools are currently not yet sufficiently validated to make widespread use of them, but they will certainly be very useful in the future.

Moreover, questions about the impact of risk factors identification still exist: **Which role should be given to risk factors:** the role of a danger sign stimulating the physician to monitor closer the patient or the role of exclusion criteria to benefit from home-based intensified care ? The 'Haute Autorité de Santé' (HAS) in France[8] has chosen recently to use risk factors as exclusion factors to oxygen therapy at home (see also Chapters 2, 4 and 6).

In the sources identified in chapter 2, some data have highlighted the role that risk factors can play. The WHO[3] stipulates, in its interim guidance on home care, that moderate disease without risk factors for poor outcome may not require emergency interventions or hospitalization *and that patients with one or more of these risk factors should be monitored closely for deterioration*". Domus Medica - ACHG stipulates that risk factors such as age and possible comorbidities should be taken into account when deciding a hospitalization and the BestBET of Oversteyns et al. which analyzed 15 publications at the beginning of the pandemic, concludes that even if patient presents only mild symptoms, the presence of risk factors should trigger an on-site clinical visit by the GPs instead of a remote follow-up.[13] The table score of Greenhalgh et al. takes also into account the presence of comorbidities in the evaluation of the need for an escalation to next level of care (e.g. it gives one point in case of 1 or 2 comorbid risk factors and 2 points in case of 3 or more comorbid risk factors).[12] Also, algorithms developed by researchers use list of risk factors to determine a certain type of close monitoring. For example, in the algorithm used in a large urban academic medical centre primary care practice in Boston the presence of a risk factor induces a closer monitoring than for patient without risk factors (call twice a day instead of call once a day) (see Chapter 2).[11]

So according to those sources, risk factors should rather have a role of danger sign potentially triggering a closer monitoring.

However, no one knows which type of close monitoring is adapted to each risk factor or to a combination of them.

4.7 Proposed changes in the OST-Liège decision-aid tool

We suggest the following changes:

- Age: keep cut-off of 65 with, in a footnote, “For patients over 75 years old that are residents in an institution, please refer to the therapeutic protocol for COVID-19: in French http://docs.toubipbip.be/docs/d574edb2e8fce1a0.pdf
- Obesity: add the cut-off of BMI ≥ 30
- Diabetes: add type 1 and 2; do not precise the required presence of cardiovascular comorbidities
- A category 'chronic heart condition' should be added, with the following diseases in footnote: heart failure, coronary disease, cardiomyopathies and pulmonary hypertension.
- A category 'chronic lung disease' should be added
- A category 'chronic kidney disease' should be added with between brackets 'stage 3a to 5
- A category 'chronic liver disease' should be added
- A category 'malignant hemopathy or active cancer' should be added
- Severe immunosuppression should be added with, in footnote, a non-exhaustive list of condition: ongoing chemotherapy, severe inhered immunodeficiency, transplant… (or see list in CBIP)
- A category 'major psychiatric disorder requiring anti-psychotic and neurological condition' could be added with, in footnote, a non-exhaustive list of neurological conditions: dementia, Down syndrome, cerebral palsy,…
- Homozygous sickle cell disease

A warning note should be added: “New data are published every day. Therefore, the snapshot given here should be updated regularly (last update: 01-12-2020).”

5 ENVIRONMENTAL AND ORGANIZATIONAL FACTORS ENHANCING HOME-BASED MANAGEMENT

5.1 Summary

- **There is a paucity of quality studies on this topic.**
- **Three main elements enhancing a sustained home-based management of patients with COVID-19 were retrieved in the literature:**
  1. **The frequent telemonitoring (at least 2-3 times a day) of health parameters (through various means, e.g. phone line or video) either done by the patient, the informal caregivers and/or the health care professionals is the most cited one. This allows to detect health deteriorations rapidly and take necessary actions by the coordinating GP or in some instance by the hospital staff (see chapter 8).**
  2. **The capacity to self-care safely at home must be met. The patient and/or his/her caregiver can be trained either to use appropriately oxygen therapy or pulse oximeter, or to identify red flags in order to prompt quick reaction and call the nearest hospital. A telephone number that can be reached 24/7 can be useful.**
  3. **A multi-disciplinary team of health care providers is required. Such team can include a coordinating GP, nurses, physiotherapists and a reference hospital team, sharing communication channels, information and a common workflow. Such a team allows integrated care with the consultation of all parties including the patient and his/her caregivers. Therapeutic options should be duly discussed with the patients.**
- **A recent guidelines from the Haute Autorité de Santé (HAS) translates these principles in a set of criteria to decide if a patient is eligible for home-based treatment (see text). None of them contradict fundamentally the preliminary version of the OST Liège decision-aid tool but some criteria could be useful.**
- **Several changes are proposed in the OST-Liège decision-aid tool.**

5.2 Background

Clinical signs are not the only parameters to be taken into account for proposing an intensified home-care to worrisome COVID-19 patients. The WHO underlines in this interim guidance ""Home care for patients with COVID-19 presenting with mild symptoms and management of their contacts" [3] that the decision as to whether to isolate and care for an infected person at home depends on three factors: clinical evaluation of the patient, home setting and ability to monitor the patient at home (see Appendix 18.1). In the 3 previous chapters, we have considered the clinical assessment of the patients, including red flags (see Chapter 3) and risk factors of negative outcomes (see Chapter 4). This chapter focuses on the environmental (home setting) and the organisational factors (patient/informal caregivers/health care professional abilities) also needed.

5.3 Research question

The research question is formulated as: "*What are the environmental and organizational factors enhancing home-based management of* ***worrisome COVID-19 patients***?" In the OST-Liège decision-aid tool, several factors were listed in four categories: care capacity, home care capacity, concertation with hospital/specialist, concertation with patient/caregiver).

This is a challenging research question for literature review. First, scientific papers specifically reporting on these aspects are likely to be rare. Relevant information may be reported incidentally in the body of papers with a more general scope. This hampers performing a rapid literature review, whereas such approach is indicated taking into account the short time frame allowed. We adapted the search for evidence subsequently, i.e. we performed a pragmatic rapid literature review. Second, environmental and organizational facilitators are highly context-dependent and the extrapolation to the Belgian context might turn out to be challenging or inappropriate. Therefore, it is also important to consider field-rooted experiences of health professionals.

5.4 Methods

A search was performed in MEDLINE (Pubmed) using the following keywords: COVID* AND (moderate OR severe) AND ("ambulatory care" OR "ambulatory treatment" OR "ambulatory management" OR "home-based care" OR "home-based treatment" OR "home-based management" OR "home treatment" OR "home care" OR "home management"). Specificity of the search was put forward instead of sensitivity. The same string was applied in Google for retrieving grey literature.

Inclusion criteria were:

1. Patients with moderate to severe clinical presentation of COVID-19 were considered.
2. Home-based treatment of patients was implemented. Studies on patients discharged from hospital who remained at moderate to high risk for decompensation and re-admission were also eligible. We made the assumption that recommendation draw from these studies could also apply to patients treated at home without having been hospitalized first.
3. Pragmatic conditions (either at the health care team level or at the patient level) for a successful home-based treatment were reported and possibly tested.
4. The study was carried out in a Western country.

The screening of retrieved references was done only on title and abstract.

Results from the literature review were discussed with an ad hoc panel of GPs (co-authors: JLB, GH, TO) for adaptation to the Belgian context.

5.5 Results

The search in MEDLINE yielded 417 hits. Most of the references were out of scope, i.e. they were focused on home-based management of vulnerable patients or mild cases of COVID-19. One study was excluded after assessment of the full text because only a small fraction of the patients needed oxygen therapy.[78] We included 3 peer-reviewed documents, of which only one was a primary study focusing on home-based management of patients discharged from hospital (see Table 7).[79] In the grey literature category, we included one recent guidelines produced by the Haute Autorité de Santé (HAS) in France.[8]

None of the peer-reviewed papers provided very explicit documentation or recommendation on the elements facilitating the home-based management of worrisome COVID-19 patients. In two papers, a care algorithm was described.[79, 80] Main elements mentioned as facilitators are the regular telemonitoring of patient health status (1-3 times a day) and the involvement of nurses for care delivery, i.e. developing a partnership with various provider types.[79, 80] The process for establishing telehealth services requires aligning distinct team members, including clinicians, office staff, billers, coders, audio/visual technologists, administrative support, as well as patients.[80] Thus it is important to elaborate a workflow for each aspect of the patient visit for distributing responsibilities in the most efficient way.[80]

One of the study insisted on the ability to self-care safely at home and the training of the patient (e.g. for using pulse oximeter).[79] Two of the studies evaluated the outcomes of implementing a care algorithm in which some categories of COVID-19 patients could be treated at home.[79, 80] The cohort study by Borgen et al. reported satisfactory results in terms of absence of safety issue (3.5% admitted to hospital, i.e. not more than in the comparison group) and number of days of hospitalization avoided (482 hospital patient days avoided for 78 patients).[79]

Table 7 – Factors enhancing home-based management

Author/ Study type	Patients concerned	Capability of health care team	Environmental aspects
Borgen[79] Cohort study	• 192 patients home-managed* vs. 593 in hospital • Confirmed or suspected cases of COVID-19 • Medically stable to be discharged home with supportive care • Oxygen saturation ranging from 90% to 93%	• Provision of oxygen concentrator and/or pulse oximeter. Case manager provided education about and demonstration with an oxygen concentrator and/or pulse oximeter (depending on the O_2 levels) using the teach-back method to ensure the patients understood the instructions. • Daily telemedicine visits with primary care provider • Daily home care telenursing that included at a minimum, oxygen saturation levels, temperature, and intake and output	• Availability of a caregiver • Ability to self-care safely at home • Access to a computer, tablet, or a phone with video capabilities
Sagar[80] Case series	• Homebound • Under care of a physician • In need of intermittent skilled nursing care	• Ability to treat mild hypoxia at home • A clinical registered nurse (RN) providing regular telehealth visits to enrol patients, identify home needs, review temperatures and pulse oximetry readings, and report back to the primary provider • Engaging in partnerships with other care provider types	• Video capacity allowing a more detailed assessment of general appearance and breathing status
Sartor[81] Narrative review	NA	• Counseling patients on supportive care measures and precautions for return to hospital in case of disease worsening • Telephone or telehealth appointments at appropriate intervals based on clinical disease severity and risk factors for complications	• Patient stay isolated • Self-care measures • Measures including use of facemasks by all parties and scrupulous hand hygiene strictly observed

**: all patients were first evaluated in hospital*

The guidelines published by the HAS[8] was elaborated on the basis of a narrative literature review, national and international recommendations and a stakeholder consultation. It was validated by the College of the HAS on November 5th 2020. The algorithm to keep patients at home is similar to the Belgian one. A favourable psycho-social environment is one of the criteria listed. Recommendations concern three areas of eligibility: the patient environment, the patient capability, and the health care providers. At the patient level, a differentiation is made between patients discharged from hospital with oxygen therapy and patients with no prior hospitalization.

According to the HAS, a patient is eligible for home-based treatment (after discharge from hospital) if the elements hereunder are met. All footnotes are comments from KCE.

1. At the environment level:
    - The patient lives in a permanent and healthy home

- An informal caregiver is present all the time (24h/24h, 7 days/7 days)d.
- There is a reliable phone line. A telemonitoring application is recommended.
- There is a hospital with an ED at less than 30 minutes
- The patient can be isolated in a room of the house.

2. At the patient level:

2.1. For patients discharged from hospital with oxygenotherapy:

- Autonomous (e.g. Katz scale >3/6)
- Informed on red flags and how to contact the reference hospital team
- Weaning from oxygen therapy with a need of oxygen < 4L/min to maintain a SpO2>92% at rest
- Does not present exclusion criteria (either one major criteria or at least two minor criteria; for the list of criteria please see Appendix 18.3)

2.2. For patients with no prior hospitalization:

- Autonomous (e.g. Katz scale >3)
- Informed on red flags and how to contact the reference hospital team
- Presenting a SpO_2 <92% and >90% at rest
- No sign for a severe COVID-19
- Does not present exclusion criteria (either one major criteria or at least two minor criteria; for the list of criteria please see 18.3)

3. At the level of health care providers:

3.1. A multi-professional team ensuring a coordinated health pathway is available[e]:

- A GP coordinates the team and ensure the medical follow-up
- Registered nurses ensure the monitoring of health parameters, nursing, and provision of drugs. He/she ensures at least 2 visits per day (morning and evening) and preferably 3 visits per day
- A physiotherapist visits the patient at least once per day
- A home care provider (private service company or pharmacist) can start the oxygen therapy in less than 4 hours and can monitor the material 24/7
- A reference hospital team (pulmonologist, emergency physician, infectious disease specialist,…) is ready to intervene at the request of the coordinating GP. The patient has the contact information of the reference hospital team (24/7).
- The team will educate caregivers and patients (e.g. on the recognition of red flags, use of oxygen therapy).
- Telemonitoring of health parameters must be used when available
- …

3.2. Appropriate equipment must be available:

- Oxygen concentrator or liquid/gas oxygen

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[d] The reason of such an extensive presence of the caregivers is not explained by the HAS. It may stem from the consideration that such patients should be in principle followed up at the hospital level with a continuous monitoring to detect early any degradation of the health status.

[e] Task shifting (e.g. the physiotherapist, or even the caregiver, measuring the SpO2) is not considered by the HAS. A clear task description of each team member is necessary.

- Individual Protection Equipment. A FFP2 mask is recommended for caregivers and health care professionals[f]
- Saturometer
- Electronic blood pressure monitor which can be used by caregivers

Of note, Sciensano also provides regular updates of good practice guidelines:

- Procedures in private practice (in Dutch and in French):

  https://covid-19.sciensano.be/sites/default/files/Covid19/COVID19_procedure_out%20patients_NL.pdf & https://covid-19.sciensano.be/sites/default/files/Covid19/COVID19_procedure_out%20patients_FR.pdf

- Procedures for nurses at home (in Dutch and in French):

  https://covid-19.sciensano.be/sites/default/files/Covid19/COVID-19_procedure_nurses_NL.pdf & https://covid-19.sciensano.be/sites/default/files/Covid19/COVID-19_procedure_nurses_FR.pdf

Some of the recommendations can apply to patients treated at home:

- Ideally, the same one person of the household should care for the patient for limiting contagiousness. Other persons in the household with chronic health problems should temporarily stay at another place.
- Cleaning:
  - Ventilate the rooms regularly.
  - Clean all rooms at least daily. Bleach water can be added in the soaped water bucket to disinfect[g].
- Special attention must be paid for diabetes treatment as COVID-19 is a risk factor for glycemia dysregulation.

5.6 Discussion

Three main elements enhancing a sustained home-based management of patients with COVID-19 were retrieved in the included documents.

The frequent telemonitoring (1-3 times a day[79],[8]) of health parameters (through various means, e.g. phone line or video) either done by the patient, the caregivers and/or the health care professionals is the most cited one. This allows to detect health deteriorations rapidly and take necessary actions by the coordinating GP or in some instance by the hospital staff. The process for establishing telehealth services requires aligning distinct team members, including clinicians, office staff, billers, coders, audio/visual technologists, administrative support, as well as patients.[80] More details on this topic are available in the chapter 8.

Second, the capacity to self-care safely at home must be met. Two of the documents mentioned the need to train the patient either to use appropriately oxygen therapy or pulse oximeter, or to know red flags in order to prompt quick reaction and call the emergency department of the nearest hospital.[8, 79] Part of this self-care can also rely on the almost permanent presence of a caregiver.

Last but not least the added value of a multi-disciplinary team of health care providers is emphasized. Such team can include a coordinating general practitioner (GP), nurses, physiotherapists and a reference hospital team, sharing communication channels, information and a common workflow defining the role and responsibilities of each team members. Such a team allows global care together with the consultation of all parties including the patient and his/her caregivers. Therapeutic options should be duly discussed with the patients.

A recent guidelines from the Haute Autorité de Santé (HAS) proposed a comprehensive set of criteria to decide if a patient is eligible for home-based treatment.[8] These criteria include most of the elements cited above. The number of eligibility criteria to be met is not defined, and the final decision should be made based on the clinical judgement of the GP. Some of these criteria could be usefully

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[f] This is not in line with Belgian recommendations

[g] The solution should contain a concentration of 0.1% NaOCl.

introduced in the OST-Liège decision-aid tool. Of note, the list of exclusion criteria in the HAS guideline is extensive, and some of these should be weighted in situations where hospital capacity is overstretched and home-based management of some categories of patients is unavoidable.

The exact role of the environmental and organizational factors on the quality of care was specifically assessed in none of the references. Factors enhancing home-based management of COVID-19 patients were described quite superficially. For example, it was seldom obvious how much the patients contributed to the measurement of their own health parameters, or how the necessary increase of human resources to monitor such patients was met. However, recommendations that can be drawn from these documents make clinical sense, and no safety issues were reported. None of them contradict fundamentally the current structure of OST-Liège decision-aid tool. A second limitation is the non-systematic character of this review, imposed by a short timeline. This may have resulted in a selection bias. However, our objective was certainly not to achieve an exhaustive review but to identify experiences of home-based management of COVID-19 cases to draw lessons for the Belgian case, if possible.

5.7 Proposed changes in the OST-Liège decision-aid tool

We propose to change the initial boxes in the following groups of items:

- Patient autonomy, training, preferences (with explanations in 3 footnotes):
  - Patient autonomy for food, hydration, monitoring, ability to call for help, therapy.
  - Patient and/or his/her caregiver training to use appropriately oxygen therapy and pulse oximeter, or to identify red flags in order to react quickly and call the nearest hospital. A telephone number that can be reached 24/7 can be useful.
  - Importance of information and consultation with the patient, in particular on the level of intensity of care that the patient wants to receive, including admission to hospital in the event of an urgent medical situation (red flags).
- Informal caregivers 24/7
- Multi-disciplinary team of health care providers (with the footnote: This team can include a coordinating GP, nurses, physiotherapists and a reference hospital team, sharing information by the same communication channels, information; such a team allows integrated care with the consultation of all parties including the patient and his/her caregivers. Therapeutic options should be duly discussed with the patients).
- Personal Protection Equipment for formal/informal caregivers
- Reliable pulse oximeter
- Quickly available O_2
- Consignment of all information in the (electronical) medical record
- **Information & Concertation: patient, caregivers, healthcare team (including hospital reference specialist for COVID-19)**

6 PROVISION OF OXYGEN DEVICE AT HOME

6.1 Summary

- **Since a shortage of oxygen was noticed in Belgium in primary care setting during the first wave of the COVID-19 pandemic, different initiatives were taken by concerned authorities.**
- **Nevertheless a future shortage of oxygen devices at home cannot be excluded. In this context, the useless stock of oxygen has to be avoided. As the AFMPS/FAGG underlines: "*Empty oxygen cylinders and other used equipment have to be made available to suppliers as soon as possible".***
- **Some other supports of breathing are currently studied (as the use of CPAP) in COVID-19 pneumonia and further publications would be able to provide additional solutions.**
- **Finally, importance of safety measures, patient information and consent document is reminded and inserted in the OST-Liège decision-aid tool.**

6.2 Background

In the Chapter 5, the availibity of oxygen device is mentioned as an environnemental condition for proposing intensified home-care to worrisome COVID-19 patients. Oxygen delivery at home is a therapeutic option used from many years before the COVID-19 outbreak and the reimbursement conditions of oxygen at home is defined by the INAMI-RIZIV, whatever for chronic and for acute oxygen need (see Appendix 18.8).

Several systems of oxygen provision exists (Table 8) and some recommendations for their use are formulated in the guidelines "*Patients after hospital discharge and residents of nursery homes"* elaborated by the AFMPS / FAGG published on May, 15th 2020 (URL links in Table 8).[82, 83]

Table 8 – Description of types of oxygen devices (Sardesai et al.)[19]

Device	Characteristics
Oxygen concentrator	Electrically powered device which filters room air, removing nitrogen, to provide an oxygen-enriched gas mixture. Home concentrators require installation and regular maintenance by specialized vendors. **In the context of the current pandemic, this is not ideal as it potentially increases infectious exposure risk to both household members and the company personnel.**
ansportable and portable concentrators	Similar to home concentrators, but generally smaller in size and weight. In the context of the COVID-19 algorithm, it is the devices recommended by Sardesai et al, at flow rates of 4 L/min or less.
Cylinder oxygen (gaseous oxygen)	Reinforced metal container with compressed gas under high pressure which is safely and steadily released via its regulator
Liquid oxygen	Oxygen cooled such that it condenses from gaseous to liquid form and can be stored in appropriately insulated containers; however, this approach requires training to reduce problems with gas leakage and burns.

However during the first wave of this COVID-19 pandemic, since more and more patients needing oxygen were managed at home (and nursing home), a shortage of oxygen devices (cylinder oxygen) was notified by some general practitioners in Belgium leading to a crucial delay of several days before the patients' access to oxygen therapy. Moreover because hospitals have another system of oxygen delivery (liquid oxygen), availability of oxygen therapy was easier in this setting, which leads certain patients to be or stay hospitalized during the first wave mainly for oxygen need.

The availability/accessibility of oxygen is thus confirmed as a crucial condition to organize intensified home-care for worrisome COVID-19 patients and decrease the risk of hospital saturation.

6.3 Research questions

The initial research question of this chapter was formulated as "*How can the **provision of oxygen** be ensured for COVID-19 patients with intensified home-care*?"

However, it appeared that different initiatives are currently developed in Belgium regarding this question. For example, in November 2020, the Flemish medical news announced that the hospitals had been asked to prepare 'high oxygen care units'. https://www.mediquality.net/be-nl/topic/article/23233994/23233994.

Therefore, we decided to change the question on "Which are the Belgian agencies and authorities initiatives for improving oxygen delivery for COVID-19 patients?".

6.4 Methods

In order to describethe recent initiatives for ensuring oxygen delivery to COVID-19 patients in Belgium, we searched information from several key organizations: the federal agency for medications (AFMPS / FAGG), the Belgian pharmaceutical association (Algemene Pharmaceutische Bond / Association Pharmaceutique Belge (APB)), the federal service of public health in particular the Hospital & Transport Surge Capacity (HTSC) Comittee. We used documents published on the corresponding websites, minutes from some meetings, and interviews of key representatives of these federal organizations.

6.5 Results

We identified 3 initiatives developed in Belgium for oxygen provision in the context of COVID-19 pandemic.

6.5.1 Oxygen provision in the ambulatory setting

The Agence Fédérale des Médicaments et Produits de Santé (AFMPS) / Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten (FAGG) is the agency who manages the O_2 devices for ambulatory care in Belgium. During the COVID-19 pandemic, the AFMPS / FAGG elaborated different actions and communications about oxygen provision. The websites references of these actions are presented in Table 8.

In April 2020, a note was published with the following information[84, 85],

- *All forms of oxygen therapy are available in an ambulatory setting: oxygen concentrator, gaseous and liquid oxygen. Of course, indication, flow and material required should be taken into account.*
- *Reimbursement of liquid oxygen is provided by the RIZIV-INAMI, also via pharmacies open to the public. The RIZIV-INAMI has also ensured that a new supplier is authorized to deliver reimbursed oxygen concentrators from 10.04.2020.*
- *When a supplier has a stock of oxygen but cannot deliver it due to a lack of personnel, vehicles, drivers ... he can call on another supplier, the Ministry of Defense or the Civil Protection. This is particularly the case for deliveries to nursing and care homes where the nursing staff have the necessary experience to take care of the installation of oxygen.*
- *As a last resort and in an emergency, when oxygen cannot be provided, the patient should be hospitalized.*

A system of "*ticketing"* is also organized since April 2020 for facilitating the online order of oxygen by pharmacists.[86, 87] With this *Covid-oxygen.be* platform, pharmacists no longer have to call each supplier one after the other to see if they can meet oxygen request. As one order is entered in Covid-oxygen.be, it is recorded by the oxygen supplier who has oxygen availability and a confirmation ticket is sent to the pharmacist.

Besides, on November 2020, in a note on their website, the AFMPS / FAGG underlines the need of a rational use of oxygen device and formulates several advices (See Appendix 18.9):

- *No useless stock: Empty oxygen cylinders and other used equipment are made available to suppliers as soon as possible (to be disinfected, filled and distributed again).*
- *Rational use of oxygen, only under physician prescription*
- *Order by pharmacists only (and with the online ticketing system Covid-oxygen.be if possible)*

Table 9 – Websites references of Belgian actions regarding oxygen delivery for COVID-19 patients

Source	Website references (Url link)
	Guidelines for oxygen use in COVID-19 patients after hospital discharge and residents of nursery homes
AFMPS	https://covid-19.sciensano.be/sites/default/files/Covid19/COVID-19_Bonne_utilisation_oxygene_sortieHopital_et_MRS_FR.pdf
FAGG	https://covid-19.sciensano.be/sites/default/files/Covid19/COVID-19_Goed_gebruik_van_O2_ziekenhuisontslag_en_zorgcentra_NL.pdf
	Measures for ensuring oxygen supply
AFMPS	https://www.afmps.be/fr/news/coronavirus_mesures_prises_par_lafmps_et_les_partenaires_concernes_pour_continuer_a_garantir
FAGG	https://www.fagg.be/nl/news/coronavirus_maatregelen_van_het_fagg_en_de_betrokken_stakeholders_om_de_bevoorrading_van
	Recommendations and procedures for ensuring oxygen supply in COVID-19 patient
APB	https://www.apb.be/fr/corp/sante-publique/Info-Corona/Recommandations-questions-scientifiques/Pages/oxygene.aspx
APB	https://www.apb.be/nl/corp/volksgezondheid/Info-Corona/Wetenschappelijke-vragen-en-aanbevelingen/Pages/Zuurstof-maatregelen,-richtlijnen-en-communicatie.aspx
	Guidelines for respiratory management ofCOVID-19 patients in hospital
AFMPS	https://covid-19.sciensano.be/sites/default/files/Covid19/COVID-19_Traitements_respiratoires_hopitaux_FR.pdf
FAGG	https://covid-19.sciensano.be/sites/default/files/Covid19/COVID-19_Respiratoire_behandeling_ziekenhuizen_NL.pdf

6.5.2 Corona High Oxygen Care beds

In 2020, after the first wave of COVID-19 pandemic, the Belgian hospitals were asked by the Hospital & Transport Surge Capacity (HTSC) Committee, to create 'Corona High oxygen care" (CHOC) beds" (see Appendix 18.10).

These CHOC beds are proposed for High Flow Nasal Oxygen (HFNO) delivery in conventional care units. They aim to facilitate the **exit from ICU** for patients who still need oxygen and monitoring but no real intensive care. Each hospital must offer 15% of additional beds in these units. However because not all hospitals have the organizational ability to realize this objective, the 15% is aimed rather by network of hospitals. Therefore, there are hospitals without High Qxygen Care Units. Data on these units are gathered by Sciensano (number of patients in beds with high oxygen care/hospital) and by the Incident & Crisis Management System (ICMS) plateform (number of available beds with high oxygen care/site). Ideally, 299 beds with high oxygen care units should be created.

In order to support this development, the government purchased HFNO devices (Optiflow®) to increase the amount of available devices.

6.5.3 Intermediate centers (Schakelzorg centra / Structures intermédiaires)

The concept of “intermediate” centres aims to facilitate an **early exit from hospital (step down).** These centers can be managed in primary care by general practitioners and nurses. Normally they do not manage patient requiring oxygen therapy but, if needed, they can be supplied by O_2. Each Region can organize this offer and use different settings: old hospitals in Wallonia, rehabilitation centers (schakelzorgcentra) in Flanders. Financial support can be provided by INAMI/RIZIV. However the number of available intermediate centers appears to be currently low (e.g. 25 beds in an old hospital in Charleroi, some beds in Seraing, etc.). A step-up approach (i.e. center used by general practitioners for patients needing O_2 without possible hospitalization) is not foreseen.

6.6 Discussion

A shortage of oxygen was observed in Belgium during the first wave of COVID-19 pandemic and different agencies worked together to facilitate the oxygen provision in ambulatory setting.

However, despite these initiatives, it is not certain that a shortage can be avoided if a third wave occurs. It is why the importance of quickly returning unused devices to the circuit still makes sense and should be highlighted.

Moreover some prospects has not been explored here due to lack of time, but perhaps it should be the subject of further researchs such as the use of CPAP in primary care. CPAP and double trunk mask are used in hospital settings in Belgium.[88, 89] In the UK some CPAP devices were reprogrammed to serve in the COVID Crisis to assist breathing and their efficacy are currently studied (https://royalpapworth.nhs.uk/our-hospital/latest-news/cpap-treating-covid-19) but we have no idea if this proposition is feasible at home.

Finally, we have to remind the caution measures for using oxygen at home. The AFMPS / FAGG in these guidelines underlines the interdiction of smoking at home, not only because of the risk of explosion and fire, but also because COHb displaces O_2 from Hemoglobin which can compromise the goals of oxygen therapy, including correction of hypoxia. A regular and professional maintenance of the oxyconcentrators is also underlined in the AFMPS / FAGG guidelines).[82, 83] which specify that an obsolete device cannot be reused without prior inspection by the supplier.

Sardesai et al. highlight that oxygen therapy at home requires oxygen safety training and appropriate treatment consent documentation, with clearly documented risk-benefit-alternative discussion.[19] A table with safety measure proposed by Sardesai et al. in available in Appendix 18.11.

6.7 Proposed changes in the OST-Liège decision-aid tool

We propose to add two bullets in the box related to oxygen therapy:

- Respect safety measures
- Free the unused material (instead of “pensez à désescalade pour libérer le materiel”)

7 RELIABILITY OF PULSE OXIMETERS

7.1 Summary

- **There are different pulse oximeters available on the market with vairable reliability.**
- **Several recommendations regarding the use of pulse oxymeters can be formulated:**
  - **Use CE labelled oximeters (CE mark) and, if possible, those providing the ARMS (Accuracy root mean square)[h] as information to assess their reliability.**
  - **Use devices with a curve display or at least a pulse signal display and only accept values associated with a strong pulse signal.**
  - **When interpreting the results, be aware of possible hypoperfusion (hypotension, vasoconstrictor drugs and vascular patient). Cold extremities should be warmed up before measurement.**
  - **Perform measurements at rest, during silent breathing.**
  - **Use index or middle finger, clean the finger and remove nail polish if necessary (avoid toes or earlobes).**
  - **Stabilize the device to avoid motion and observe the readings for 30 to 60 seconds to identify the most current value.**
  - **In case of patient self-use, provide instructions on how to use the device.**
- **Acces to reliable pulse oximeter is a condition to be added in the OST-Liège decision-aid tool.**

7.2 Background

Because some COVID-19 patients do not display signs of decreased blood oxygen content and because polypnoea is often delayed in respiratory failure, it is important to define the oxygen status accurately (see chapters 2 and 3).

Oxygen saturation can basically be measured in two ways:

- arterial blood gas analysis through an arterial puncture
- non-invasive pulse oximetry (most commonly done at the finger)

Since pulse oximetry is a non-invasive technique, its performance and reliability compared to arterial blood gas analysis are of utmost importance. This chapter deals with those aspects.

7.3 Research questions

This chapter focuses on the reliability of pulse oximeters to answer the specific research questions:

"Do all pulse oximeters currently available on the market provide accurate measurement of SpO_2?"

7.4 Methods

This review is not a systematic review of the literature with structured clinical recommendations. It is expert opinion based on a narrative review of the literature with some methodology reported, as define by Faggion et al.[90]. The presentation of results is based on the "BestEvidenceTopics" (Best BET) framework.[i]

A search of information was performed as following:

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[h] From a mathematical point of view ARMS is a root mean square error, which is an assessment of the quality of an estimator.

[i] https://bestbets.org/background/evidence-based-medicine.php

- Consultation of clinical summaries Uptodate[91] and Dynamed[92] with exploration of the bibliographical lists.
- Consultation of Medline through Pubmed (see Appendix 18.12).
- Consultation of two websites in order to find out about the legal regulations concerning pulse oximeters:
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pulse-oximeters-premarket-notification-submissions-510ks-guidance-industry-and-food-and-drug
  - https://www.afmps.be/fr
- Contact with a notified body authorized to assess the conformity of medical devices (SGS S.A.[j]).

7.5 Results

Among the 22 studies found, seven were analyzed and used to answer to the research question (see evidence tables in Appendix 18.13). The national and European regulations on medical devices were also reviewed, as presented below.

7.5.1 National and European regulations

Pulse oximeters are medical devices as defined by the Royal Decree on medical devices of 18 March 1999. They fall within the scope of this provision which is a transposition into Belgian law of a European Directive: The Council directive 93/42/EEC of 14 June 1993 concerning medical devices, amended by regulation (EU) 2017/745 of the European parliament and of the council of 5 April 2017.

In this Council directive, we can read that “The accuracy, precision and stability of medical devices with a measuring function must be guaranteed on a scientific basis in order to be released on the European market and to be recognized as conform to the legislation (CE marking)” (Council directive annex 1 ch.2 15.1). In addition, the instructions for use must contain the degree of precision of the device (Council directive annex 1 ch.3 23.4 h). Manufacturers are obliged to carry out a clinical evaluation (Council directive Art.10 § 3) and to keep the technical documentation (Council directive Art.10 § 4) up to date in order to allow the evaluation and confirmation of conformity. In the case of devices with a measuring function, the technical documentation must specifically mention the methods used to ensure the accuracy of the devices (Council directive annex 2 6.2 f). The technical documentation is kept at the disposal of the competent authorities for a period of 10 years (Council directive Art. 10 § 8) but unfortunately not directly available for consultation in the context of this research.

Oximeters are class IIa medical devices, which means that CE marking is required through the approval of a notified body (SGS S.A. is such a notified body in Belgium).

In theory, **a device without CE marking cannot be marketed in the European Economic Area**. However, it is clear that **online commercial venders offer devices for sale with a minimal descripti**on, sometimes even without mentioning brand or model. Under these conditions, the evaluation of the conformity by consumers is impossible[k].

7.5.2 Inherent reliability

7.5.2.1 Information provided by manufacturers

As mentioned above, a user manual including information to assess the reliability of the measurement is delivered with pulse oximeters legally marketed in Belgium.

Three notions are important in order to be able to correctly use this information:

a. Accuracy: the closeness of the measured value to the true value;

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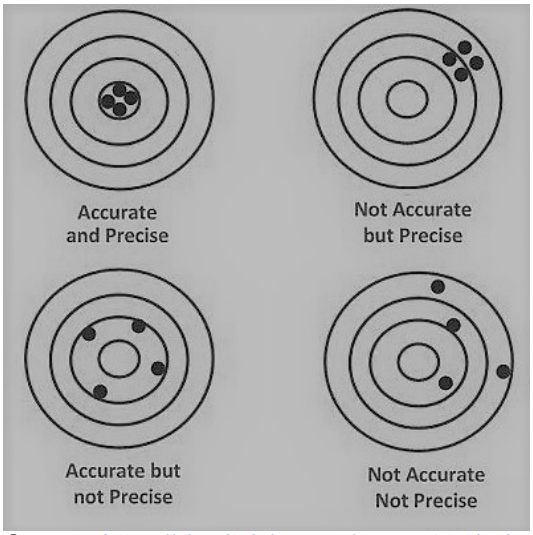
[j] SGS is the world's leading inspection, verification, testing and certification company.

[k] See for example : https://www.wish.com/search/oxygen%20saturation%20monitor

b. Precision: the closeness of the repeated measures to each other;

c. Bias: the difference between the average of the measurements and the true value (conceptual opposite of the accuracy).

Figure 6 – Accuracy vs Precision



Source : https://circuitglobe.com/wp-content/uploads/2016/09/accuracy-and-precision-compressor.jpg

Commonly, the information is provided for a range of saturation values with a margin of uncertainty of ± X% (e.g. 70-100%, ±2%). This notation can be misleading: it seems to indicate a perfect accuracy (bias = 0) and only gives information on the precision of the measurements. Historically, the precision given corresponds to only one standard deviation (SD) (i.e. 68.27% of the measurements within the interval), which means that in about 1/3 of the cases the measurement exceeds the given interval.[93] Thus, in 2013, the ARMS (Accuracy root mean square) or RMSE[l] (Root Mean Square Error) becomes required by the FDA as information to assess reliability because it reflects bias and precision. Moreover, the FDA recommend a ARMS ≤3% which corresponds approximately to an error of 4%.[m] This requirement does not seem to be applied to receive CE marking although some devices provide information on the ARMS in their instructions for use (MightySat® Rx, Onyx® Vantage 9590®).[n] In most cases, it is not clear whether the accuracy provided is the ARMS or the previous method of information (assumed zero bias and 1SD accuracy) such as for the MD300K2® or PO 60®.[o]

7.5.2.2 Absorbance and saturation estimation

A pulse oximeter does not directly measure oxygen saturation, but rather a ratio of absorbance during pulsatile blood flow (considered as the cumulative absorbance of arterial blood, venous blood, and surrounding tissue) to absorbance during non-pulsatile blood flow (considered the absorbance of venous blood and surrounding tissue). This ratio is converted to an estimation of saturation using an internal algorithm. The algorithms were developed through experiments on healthy people placed in a state of hypoxia. For ethical reasons the minimum oxygen saturation of 75% was never passed. Therefore, the estimation of the saturation through the algorithm is only a mathematical extrapolation. This is the reason why the manufacturers give an accuracy between 70 and 100% of the oxygen saturation. Therefore, the reliability of the measurement can decrease significantly for patients with

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[l] Root mean square error = $\sqrt{(\text{bias}2 + \text{precision}2)}$

[m] In February 2021, the FDA confirms this and mentions: “for example, a pulse oximeter saturation of 90% may represent an arterial blood saturation of 86-94%" https://www.fda.gov/medical-devices/safety-communications/pulse-oximeter-accuracy-and-limitations-fda-safety-communication

[n] Instructions of use: MightySat® Rx and Onyx® Vantage 9590

[o] Instructions of use : MD300K2® and PO 60®

severe hypoxemia. Finally, the use of algorithms, developed in experiments on healthy people, for patients with co-morbidities is questionable.[91],[93]

7.5.2.3 Non-compliant devices

As previously said, online commercial vendors propose the public to purchase finger oximeters whose compliance with regulation is impossible to assess. It is important to emphasize that these types of devices cannot be used reliably because of the potentially highly inaccurate measurements[95], especially in a situation where saturation ≤90%.[96] In recent years, a whole series of devices for the public has also appeared, monitoring various vital parameters (e.g. Zensorium Tinké®, Withings Pulse Ox® and other: see here and here). There is a lack of validation and evaluation of these devices. Those devices should be used very cautiously and their use should not replace the use of a proper medical device.[97] Regarding smartphones, although some of them show an apparent reliability of the measurements under normoxic conditions in healthy people[98], it is not currently recommended to use applications with the flash and the camera of the phone.[99]

7.5.3 External reliability

Regardless of the device used, there are various factors, related to the context, which have an impact on the reliability of saturation measurement.

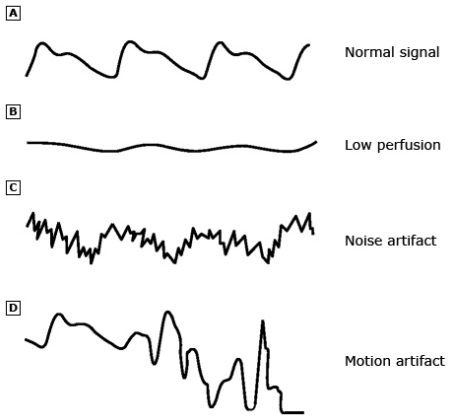
7.5.3.1 Hypoxemia and hemoglobin dissociation curve

As a reminder, the reliability of the measurement in case of severe hypoxemia (saturation ≤ 75%) is not guaranteed and the manufacturers do not even provide accuracy figure for values below 70% saturation. For recall, the oxygen saturation of hemoglobin depends on the partial pressure of oxygen in the blood (PaO_2) (see chapter 2 on threshold). For $PaO_2 \leq 60$mHg (corresponding to a saturation below 90%), the dissociation curve starts to correspond to a steep line which implies a greater variation of hemoglobin saturation for any variation of PaO_2. Thus, under these conditions, it is important not to stop at the first value provided by the oximeter but to take several minutes to identify the dominant values.[91],[92],[93]

7.5.3.2 Pulse signal strength and pattern

The normal shape of the pulse oximeter curve corresponds to a notched dicrotic wave.

Figure 7 – Shape of the pulse signal



Source:
https://www.uptodate.com/contents/image?imageKey=PULM/107547&topicKey=PULM%2F1612&search=oximeter&source=outline_link&selectedTitle=1%7E78

In case of loss of the dicrotic appearance, the shape is considered inadequate and no interpretation is possible.

The following situations can explain this phenomenon:

- Incorrect placement of the probes due to malposition or placement on the same side as a blood pressure cuff or arterial line.
- Motion artifacts (poor signal-to-noise ratio).
- Lack of pulsatility of blood flow (hypoperfusion), which may result from low blood pressure, from the use of vasoconstrictor drugs or from a peripheral vascular disease (diabetes, coronary artery disease, Raynaud's phenomenon, etc.).
- Hypothermia (via hypoperfusion by vasoconstriction and shivering with motion artifacts).

Thus, the display of a curve by the pulse oximeter represents an asset by allowing the estimation of the reliability of the measurement. At least a device that provides information on the strength of the pulse signal is recommended.[91],[92],[93],[100]

7.5.3.3 Dyshemoglobinemia

No distinction can be made between CO-complexed hemoglobin (carboxyhemoglobin or HbCO) and oxyhemoglobin (same absorbance), which can lead to an overestimation of actual hemoglobin saturation (especially in heavy smokers). Conversely, hemoglobin without its binding power (methemoglobin) can lead to an underestimation of the real oxygen saturation. Glycated hemoglobin in poorly controlled diabetic patients (HbA1c > 7%) can also cause an overestimation of the real hemoglobin saturation, which does not prevent the use of a pulse oximeter but may justify the use of arterial gas analysis in case of doubt. Most congenital hemoglobinopathies also have an impact on the reliability of saturation measurements by a pulse oximeter.[91],[92],[93]

7.5.3.4 Various

May also influence the measurement:

- Ambient light interference[93]
- Nail polish
- Increased skin pigmentation (especially when actual saturation is low).[91],[92],[93]

7.6 Conclusion

Based on the information gathered, various recommendations can be formulated:

- Use **CE marked oximeters** and, if possible, obtain the ARMS (Accuracy root mean square) as information to assess their reliability.
- Use devices with a curve display or at least a pulse signal display and **only accept values associated with a strong pulse signal**.
- When interpreting the results, be cautious of **possible hypoperfusion** (hypotension, vasoconstrictor drugs and vascular patient) and warm the cold extremities before measurement.
- Perform **measurements at rest**, during silent breathing.
- Use **index or middle finger**, clean the finger and remove nail polish if necessary (avoid measuring at toes or earlobes).
- **Stabilize the device** to avoid motion and **observe the readings for 30 to 60 seconds** to identify the most current value.
- In case of patient self-use, provide **instructions on how to use** the device.

7.7 Proposed changes in the OST-Liège decision-aid tool

This chapter confirms the need of adding “reliable pulse oximeter” in the evaluation of the environemental conditions of the new decision-aid tool (see chapter 5). A referral to the list of advises cited above should be foreseen.

8 TELEMONITORING FOR COVID-19 PATIENTS STAYING AT HOME

8.1 Summary

- **Telemonitoring has been applied in several projects with COVID-19 patients staying at home**
- **There is much heterogeneity in the telemonitoring interventions**
- **All studies with telemonitoring in COVID-19 patients are observational studies and no comparative trials have been performed so far**
- **Telemonitoring in COVID-19 patients seems to be feasible**
- **There is at current no evidence on the (cost)effectiveness of telemonitoring for COVID-19 patients staying at home**
- **Few changes are proposed in the OST-Liège decision-aid tool.**

8.2 Background

Telemonitoring has been used in the past decade for several patient groups, including patients with respiratory diseases and showed promising results (e.g.[101-108]). Therefore it could be argued that such remote monitoring strategies and devices could also be of use when applied to patients with COVID-19, staying at home or in a residential care setting, both in a pre-hospital and post-hospital admission phase. When the monitoring strategy early warns for deterioration and immediate action can be taken, potential hospital admissions could be avoided. Similarly it could be envisioned to discharge patients earlier from hospital, when adequate monitoring is provided. The use of telemonitoring and other digital health applications for COVID-19 patients has already been advocated by several authors [109-113].

8.3 Research question

In this chapter, we focuses on the following question: "*What is the added value of **telemonitoring** health parameters of COVID-19 patients staying at home?"*

8.4 Method

We performed a rapid search in PUBMED, MEDxRIV, CEBM and (Scholar) Google to find out if telemonitoring has been applied for COVID-patients with the aim to avoid hospital admissions and/or to discharge patients earlier from hospital and to see if this was feasible and effective (more information on search strategies can be found in Appendix 18.14).

8.5 Results

Several publications[111, 114, 115] list technologies and devices (smartphones, sensors) that could be used for remote monitoring of respiration rate, heart rate, temperature and oxygen saturation in COVID-19 patients; all conclude that these technologies and devices have **a lot of potential**. One publication[98] stated that smartphones can be a valuable tool to measure oxygen saturation, but this was contested by others[116-118] who conclude that smartphones lack accuracy in measurement to be safely used in COVID-19 patients (see also Chapter 7 on reliability of pulse oxymeters).

Telemonitoring has been applied in the past year in the care for patients with COVID-19 outside the hospital. Several projects and studies in several countries have been performed or are going on. In our searches, we identified 22 projects, located in Australia [119, 120], Belgium[121-127], Canada[128], Ireland[129], Italy[130], Spain[131], the Netherlands[132-135], United Kingdom[136, 137] and the USA[138-143]. All of them are **observational studies** or ongoing pilot-projects; **no randomized trial** could be identified. More details of these projects can be found in Appendix 18.15

Telemonitoring has been used in symptomatic and asymptomatic, confirmed and suspected COVID-19 patients in the period after testing and before hospital admission ("pre-admission models"), as well after hospital discharge ("step-down models") for patients staying at home, in intermediate care structure (e.g. adapted hotel) or in a residential care setting. Some telemonitoring projects have been led by secondary care while others are mainly based in primary care.

The concept of **telemonitoring has many appearances** and ways to deliver it, varying from simple telephone calls to patients at home, to smartphone apps that ask patients to fill out and submit symptom check lists, to smartphones build-in features that measure activity grade and some vital signs, to sophisticated wearable monitoring sensors for respiratory and cardiac functions. Collected data are then periodically or continuously transmitted to a healthcare provider/team in a remote location. Next to collecting data, most of the telemonitoring programs also contain active interaction between the patient and health care providers through telephone or videoconference. Most of the time, **telemonitoring is part of a broader multicomponent intervention** targeted at stabilizing and treating the SARS-Cov-2 infections, e.g. pharmaceutical treatment by anticoagulants and corticosteroids or oxygen therapy. So, there is a **lot of heterogeneity in what is generally called telemonitoring, prohibiting to make good comparisons and to draw overall conclusions.**

Based on the identified projects, all publications stated that their telemonitoring strategy was feasible, that patients and healthcare providers were satisfied, that it gave patients reassurance and that it might have helped to keep patients at home (both pre and post-hospital). But due to heterogeneity of the telemonitoring interventions and the larger context in which they were embedded, nothing can be said about the working component(s); and due to a lack of comparison groups, no conclusions can be drawn of the (cost)effectiveness of telemonitoring modalities.

The 22 identified examples overlap to some extent with the 17 ones identified in the review of Vindrola et al.[144], although they identified some we didn't and vice versa. However they made the same observations: large heterogeneity in interventions, all observational studies and no control groups.

> *The primary aim of the remote home monitoring models was the early identification of deterioration for patients self-managing COVID-19 symptoms at home. Most models were led by secondary care. Broad criteria for the eligible patient population were used and confirmation of COVID-19 was not required (in most cases). Monitoring was carried via online platforms, paper-based systems with telephone calls or (less frequently) through wearable sensors. We could not reach conclusions regarding patient safety and the identification of early deterioration due to lack of standardised reporting across articles and missing data. None of the articles reported any form of economic analysis, beyond how the resources were used. Conclusions: The review pointed to variability in the implementation of the models, in relation to healthcare sector, monitoring approach and selected outcome measures. Lack of standardisation on reporting prevented conclusions on the impact of remote home monitoring on patient safety or early escalation during COVID-19.[144]*

These findings are also in line with a survey[145, 146] in which project leaders of eight telemonitoring initiatives in the UK were interviewed. They found that some models have been led by secondary care while others are mainly based in primary care. Furthermore, some have been designed as pre-hospital models (admitting patients from the community or emergency department) while others have functioned as stepdown 'wards' (facilitating early discharge from hospital). The monitoring of patients remotely was perceived by staff as a safe way to ensure patients received the appropriate care at the right place. However, limited evidence was available to assess the effectiveness of the remote home monitoring models since no comparator data were available for the absence of remote home monitoring.

8.6 Conclusion

Telemonitoring has been applied in patients with COVID-19, both pre and post hospital and seem to be promising and feasible. However, there is a large variety within the telemonitoring systems (techniques, dose, devices, etc..) and therefore they cannot be evaluated as 1 homogenous group. Moreover, telemonitoring is only one part of a multicomponent intervention. Next to this, all research so far are observational studies lacking a (randomized) control group. Therefore there is no current evidence that telemonitoring is a (cost)effective strategy. Also accuracy of smartphones and wearable apps and patches still need to be demonstrated if they measure timely and accurate enough respiratory functions in COVID-19 patients.

8.7 Proposed changes in the OST-Liège decision-aid tool

In the original version of the OST-Liège decision-aid tool, there were two references to SafeLink® (a web application for the home-monitoring of COVID-19 patients).

Because this is not the only web application available in Belgium for COVID-19 patients, we suggest to remove this mention and to replace it by a footnote linked to the item of patients monitoring: "*Monitoring can be carried out by the patient, relatives or a health professional (general practitioner, nurse, physiotherapist etc.) BUT the medical decision remains the responsibility of the general practitioner.* ***Telemonitoring*** *appears feasible in COVID-19 patients even though there is currently no evidence on the (cost)effectiveness of telemonitoring for COVID-19 patients cared for at home*."

9 THROMBOPROPHYLAXIS FOR COVID-19 PATIENTS AT HOME

9.1 Summary

- **SARS-CoV-2 infection may predispose patients to thromboembolic events.**
- **The Belgian Society on Thrombosis and Haemostasis (BSTH) elaborated in May 2020 recommendations for anticoagulation management in non-hospitalized COVID-19 patients. The AFMPS / FAGG and the CBIP / BCFI endorse the same recommendations.**
- **Many RCTs on the thromboprophylaxis in COVID-19 patients are ongoing. Meanwhile, the BSTH can be considered as the reference.**
- **Based on these recommendations, some adaptations of the OST-Liège decision-aid tool are proposed.**

9.2 Background

SARS-CoV-2 infection may predispose patients to thrombotic disease, both in the venous and arterial circulations, due to excessive inflammation, platelet activation, endothelial dysfunction, and stasis.[147, 148] This may result in diffuse pulmonary microthrombosis leading to respiratory insufficiency, pulmonary embolism, deep venous thrombosis, arterial thrombosis, catheter thrombosis, and disseminated intravascular coagulopathy.[149] People with COVID-19 who develop thromboembolism have a worse vital prognosis.[147-149]

There are several drugs that can be used in the prophylaxis of thromboembolic events, such as heparinoids (unfractionated heparin (UFH) or low molecular-weight heparin (LMWH)), vitamin K antagonists (VKA) and direct anticoagulants (DOAC) as dabigatran, apixaban, édoxaban, rivaroxaban.[149] Guidance is needed on such prophylaxis during the home-based management of COVID-19 cases.

9.3 Research questions

In this chapter, the first question focuses on '*What are the recommendations for the prophylaxis of thromboembolic events in COVID-19 patients treated at home*?" In the OST-Liège decision-aid tool, a box focused on thromboprophylaxis, proposing Enoxeparine 4000 UI 1/day in 3 categories of indications: >75 years old or BMI>30; <75 years old and BMI <30 if confined in room of bedridden; <75 years old with a d-dimere rate 2 x superior to the age normal value.

A related question emerged during discussion with general practitioners and concerns the prophylaxis of thromboembolic events in such patients who already have a prior indication for anticoagulation, either by anticoagulant or antiaggregant (antiplatelet) drugs (e.g. clopidrogel).

9.4 Methods

We used as a primary source the guidance from the Belgian Society on Thrombosis and Haemostasis (BSTH) published in May 2020 for hospitalized and non-hospitalized COVID-19 patients.[148] The BSTH algorithms are based on current knowledge (as of May 2020) and the work was initiated after a fast review of the evidence was performed in April 2020 by KCE (https://kce.fgov.be/en/tromboprophylaxis). As stated by recent systematic reviews[150], robust evidence from ongoing clinical trials is still needed to determine the impact of thromboprophylaxis on thromboembolism and mortality risk of COVID-19.[149-151] For the above reasons, we made no attempt to update the BSTH guidance. The references provided by the AFMPS / FAGG and the CBIP / BCFI were used to verify some specific details not explained or mentioned by the BSTH (see Appendix 18.16 for details).

9.5 Results

The BSTH algorithm for the prevention of venous thromboembolism (VTE) in patients with COVID-19 treated at home is presented in Figure 8.[148]

The working group of the BSTH stresses that these recommendations should be regarded as guidelines that will be helpful in most patients but that in patients at high risk of bleeding (such as low platelet count, recent major bleeding, dialysis,…) risks and benefits of thromboprophylaxis should be weighed on an individual basis. We present below their recommendations in several categories: patients with no known VTE; patients with chronic anticoagulation treatment and pregnant women.

9.5.1 General considerations

- If the patient's condition allows it, mobilization should be encouraged to reduce VTE risk.
- Be aware for signs and symptoms of VTE. Systematic screening for VTE is not recommended but there should be an increased awareness for the possible development of VTE: for example look for clinical signs like swollen leg, and hypoxemia non-proportionate to the respiratory status.
- In case of suspected VTE, the patient should be referred for appropriate diagnostic testing. Initiation of therapeutic anticoagulation can be considered if clinical suspicion is high and bleeding risk is low, while awaiting results of diagnostic testing.
- If LMWH has to be administered at home, self-administration should be encouraged in order to avoid contact with healthcare workers.

9.5.2 Patients with SARS-CoV-2 infection who are severely ill[p] and who are immobilized (bedridden) at home with no known VTE or other indication for therapeutic anticoagulation

- With no additional risk factors for VTE, LMWH prophylaxis can be considered.[q]
- With risk factors for VTE, LMWH prophylaxis is **recommended**. These risk factors are:
  - known thrombophilia
  - personal or familial history of VTE
  - obesity (BMI>30)
  - heart failure
  - respiratory failure
  - age >70
  - active cancer
  - major surgery in the last 3 months
- The proposed medication by the BSTH is enoxaprine which is a LMWH. The dose advised in hospitalized patients is 50 IU anti-Xa/kg/OD for two weeks (after which the situation of the patient should be re-evaluated).[r]

9.5.3 Patients with chronic anticoagulation treatment

- In all cases, anticoagulation therapy should be continued (unless contraindicated). No additional anticoagulation (e.g. LMWH) is required. The BSTH does not specify if this also applies to patients with a chronic antiplatelet treatment. There is a paucity of evidence on thromboprophylaxis in COVID-19 patients treated at home. In principle, combining an

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[p] In patients with known SARS-CoV-2 infection who are asymptomatic or mildly symptomatic, BSTH recommends against prophylactic anticoagulation.

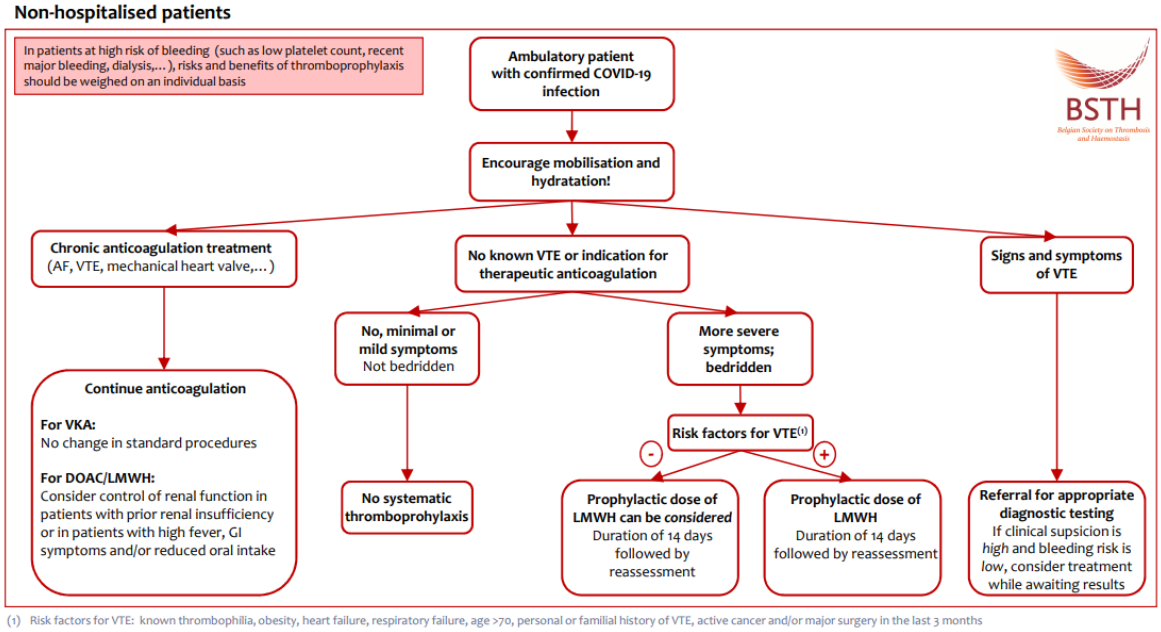
[q] For hospitalized patients, the BSTH recommends that LMWH prophylaxis should be considered which is a little bit stronger.

[r] The 4000 IU of enoxaprine refered in the OST-Liège decision-aid tool is thus appropriate for a patient averaging 80 kg.

anticoagulant and an antiplatelet is possible and effective, but it increases the risk of bleeding and risks and benefits should be weighted.

- In patients under chronic vitamin K-antagonists, the treatment should be continued as long as the patient has good oral intake and stable International Normalized Ratios (INRs).
- In patients under chronic direct oral anticoagulants (DOAC) or LMWH, control of renal function in patients with prior renal insufficiency or in patients with high fever, gastrointestinal symptoms and/or reduced intake should be considered.

Figure 8 – BSTH algorithm for the prevention of venous thromboembolism in patients with COVID-19 treated at home



Source: *https://www.bsth.be/application/files/9715/9111/2103/Anticoagulation_algorithm_2-_Non-hospitalized.pdf*

9.5.4 Pregnant women

The working group of the BSTH stresses that these guidelines do not change the standard anticoagulation management during pregnancy and post-partum. Pregnancy does not change the general recommendations as stated above (against thromboprophylaxis for non-hospitalized women with known SARS-CoV-2 infection without severe symptoms; recommended thromboprophylaxis for pregnant women with severe COVID-19 symptoms (high fever, immobilization…).

9.5.5 Duration of thromboprophylaxis

The BSTH mentions that "Duration of the prophylaxis in non-hospitalized patients (if no chronic anticoagulation required) is recommended for 14 days. After 14 days, the need for prophylaxis prolongation should be reassessed".

Only Nederlands Huisartsen Genootschap (NHG) states that thromboprophylaxis should last at least as long as the patient is bed bound.

9.5.6 Dosage of D-Dimers

Routinely adaptation of the anticoagulation regimen based on **D-dimers** levels is not recommended by the BSTH[s] as results may vary according to the assay used. Most guidelines (NHG, SFMV, NIH) also advises against it.

[s] However, for hospitalized patients increasing D-Dimer levels can be indicative of development of VTE and can guide the decision to perform imaging for VTE

9.6 Discussion

The BSTH algorithms are based on current knowledge (as of May 2020) and a limited level of evidence. Many clinical trials are ongoing to determine the impact of thromboprophylaxis on thromboembolism and mortality risk of COVID-19.[149-151] The paucity of evidence is even dire for patients treated at home. In the absence of clear evidence in support of changing the current protocol, a conservative approach applies. In particular, patients already receiving a chronic anticoagulation treatment (e.g. DOAC, VKA) should continue their treatment and not be prescribed LMWH on top of their chronic treatment. In patients already receiving a chronic antiplatelet treatment, risks and benefits of prescribing LMWH should be weighed on an individual basis.

The BSTH recommendations are in line with other international guidelines gathered by the AFMPS / FAGG (see Appendix 18.16.2), i.e. the guidelines by the Société Française de Médecine Vasculaire (SFMV)[152], by the Netherlands Huisartsen Genootschap (NHG)[153], and by the National Institute of health (NIH)[154].

Thus although the BSTH were elaborated in May 2020 on a limited level of evidence, it is reasonable to infer that are still valid in December 2020 (no new evidence available). Results of ongoing trials may modify the recommendations in the future.

9.7 Proposed changes in the OST-Liège decision-aid tool

Based on the recommendations of the BSTH, we proposed to:

- Add “Encourage mobilization & hydration in all patients
- Remove : Indications:
  - >75 years old OR BMI >30
  - <75 years old and BMI <30 but confined in room of bedridden
  - <75 years old but with with a d-dimere rate 2 x superior to the age normal value
- Change « Prophylactic enoxaparine (Clexane®) 4000 UI 1/ day in SC, during 14 days » by :

  Enoxaparine SC 50 UI kg/ day, during 14 days:
  - To be considered according to clinical judgement in all bedridden patients
  - Recommended in bedridden patients with risk factors for venous thromboembolism*
  - Not to be added to chronic anticoagulation treatment

* **Risk of venous thromboembolism**: known thrombophilia; personal or familial history of VTE ; obesity (BMI>30); heart failure; respiratory failure; age >70; active cancer; major surgery in the last 3 months.

10 OXYGEN THERAPY IN COVID-19 PATIENTS TREATED AT HOME

10.1 Summary

- **Evidence on oxygen therapy at home for patients with COVID-19 is very sparse.**
- **Decision to provide oxygen therapy has to be based on pulse oximetry (SpO2) and not only on clinical observations.**
- **AFMPS / FAGG recommendations for patients after hospital discharge and for residents of nursery homes specify that:**
  - **For oxygen flow rates ≤ 3 L / min, an oxygen concentrator is the most suitable source of oxygen.**
  - **For flow rates greater than 3 L / min, only oxygen cylinders or liquid oxygen can be used.**
  - **When oxygen therapy is stopped, the supplier of the installation should be immediately informed (in order to decrease the risk of devices shortage).**
  - **One guideline from the Netherlands provides recommendations for oxygen therapy at home for a selected group of patients. Among these recommendations, several are useful but some were modified.**
- **Propositions for oxygen therapy in worrisome COVID-19 patients at home are:**
  - **Preferably give oxygen through nasal cannula. A classical oxygen mask can be used in case of a congested nose.**
  - **Start oxygen when SpO2 ≤ 94%**
  - **Start at 2 L / min,**
  - **Target O_2 saturation > 92% (in patients with chronic hypoxaemic lung disease, target values are 88-92%).**
  - **Check saturation at rest at least 30 minutes after start. If necessary, increase the dosage with 1 L / min**
  - **Maximum O_2 administration via nasal cannula is 4 L / min.**
- **Several changes are needed in the proposed OST-Liège decision-aid tool.**

10.2 Background

On May, 15th 2020, a working group coordinated by the Agence Fédérale des Médicaments et Produits de Santé (AFMPS) / Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten (FAGG) has prepared guidelines for oxygen therapy in two specific situations refarding COVID-19 (for details see Appendix 18.17.1).

(1) Patients after hospital discharge and residents of nursery homes:
FR (https://covid-19.sciensano.be/sites/default/files/Covid19/COVID-19_Bonne_utilisation_oxygene_sortieHopital_et_MRS_FR.pdf),
NL (https://covid-19.sciensano.be/sites/default/files/Covid19/COVID-19_Goed_gebruik_van_O2_ziekenhuisontslag_en_zorgcentra_NL.pdf)
(2) Hospitalized patients:
FR (https://covid-19.sciensano.be/sites/default/files/Covid19/COVID-19_Traitements_respiratoires_hopitaux_FR.pdf),
NL (https://covid-19.sciensano.be/sites/default/files/Covid19/COVID-19_Respiratoire_behandeling_ziekenhuizen_NL.pdf

However, Belgian general practitioners (GPs) asked for additional guidance. Indeed COVID-19 patients not presenting with severe symptoms may sometimes require, transiently, some small

amount of oxygen. During the first two waves of the pandemics, these patients were usually transferred to a hospital for this purpose. But in case of hospital saturation (and in order to avoid this saturation), primary health care providers including a team combining GPs, nurses and physiotherapists could also manage hypoxaemic patients at home.

10.3 Research questions

In this chapter, we focus on the following research question: "*Which protocols have to be used for providing oxygen at home for COVID-19 patients?*" More specifically, this question tagets patients who slightly worsen but need to stay at home because of the lack of hospitals capacity. In the preliminary version of the OST-Liège decision-aid tool, a box focused on oxygen therapy, proposing to use nasal cannula, start with 2L/min, control after 30 minutes in order to exceed the saturation threshold of 90% (max 92% if COPD), steps of 0.5L-1L/min, max 5L/min.

10.4 Methods

A quick search was performed on December 11th, 2020 in Medline with the search terms: "COVID AND oxygen AND ("primary care" OR "ambulatory care")". We also analyzed guidelines from different key organisations' websites: National Institute for Health and Care Excellence (NICE), Nederlands Huisartsen Genootschap (NHG), National Institutes of health (NIH), Infectious Diseases Society of America (IDSA), World Health Organisation (WHO), Haute autorité de Santé (HAS) and British Thoracic Society (BTS). We also checked the New England Journal of Medicine (NEJM). The recommendations of the AFMPS / FAGG guidelines mentioned above are also included in the discussion.

10.5 Results

Oxygen therapy in COVID-19 patients at home is poorly described in the literature. Most often the described role in primary care is the diagnosis of the suspected patients, surveillance (telemedicine included, especially telephone calls) to detect warning signs in case of worsening and subsequent referral to the hospital.[155] The proposed management at home is mainly supportive.[156]

Several key institutions (NIH, WHO) reserve oxygen therapy for severe disease managed in a hospital setting[157],[5] (more details in Appendix 18.17.2 and 18.17.3). **NICE** in their "COVID-19 rapid guideline: managing symptoms (including at the end of life) in the community", mentions only *"when oxygen is available, consider a trial of oxygen therapy and assess whether breathlessness improves"* without any protocol for the delivery of oxygen[158] (more details in Appendix 18.17.4).

The **British Thoracic Society (BTS)** guidelines for oxygen use in adults provides some thresholds. [26] Those guidelines have been designed for the use of oxygen in various emergency settings secondary to many diseases such as pneumonia. They provide recommendations about oxygen administration and monitoring. They propose that oxygen should be prescribed in hypoxaemic patients to achieve a normal or near-normal oxygen saturation. As such, they recommend 94-98% as a goal.[26] That means that oxygen therapy should be administered below 94%. The same institution adapted this guidelines for the COVID-19 and proposes to start oxygen below SpO2 of 94% (more details in Appendix 18.17.5).

The **HAS** elaborated a rapid response on oxygen therapy at home for COVID-19 patients where 7 answers are formulated[8] (see Appendix 18.17.6). The first response is that the home-based care of patients with COVID-19 requiring oxygen therapy must be exceptional and reserved for the current epidemic context. Moreover, an organisational aspect is highlighted in this document: the need of a first-line multi-professional team in conjunction with a reference hospital team (pneumology, infectious diseases, critical care, etc.) and the urgent medical aid service.

The **NHG** addresses specifically the organisation of oxygen treatment at home for a selected group of COVID-19 patients and refers to a specific guideline '*Oxygen use at home for (suspected or proven) COVID-19 patients[159]* (more details in Appendix 18.17.7).

Three categories of patients are described in this guideline:

1. Patient with (suspected) COVID-19 for whom it has been decided not to refer to hospital and to receive home treatment based on co-morbidity and / or vulnerability and / or because home treatment is in line with the patient's goals and wishes;

2. Stable patient who is recovering from COVID-19 and leaving the hospital with need to continue O_2;
3. A dying patient with COVID-19.

Since the first category of patients is the closest to the patients targeted in this search, we reproduced here the content of the NHG guideline.

For the NHG," the goal of oxygen administration in this group of patients is to reduce the risk of organ damage from hypoxia and thus increase the patient's chance of enduring COVID-19". O_2 may also contribute to the comfort of the patient.

The following recommendations are proposed:

- Consider oxygen at home as supportive treatment in critically ill patients, at a saturation <90% and / or respiratory rate > 24 / min (also without complaints of dyspnoea and / or fatigue).
- Preferably give oxygen through nasal cannula. A mouth mask can be used in case of a congested nose.
- Start at 2 L / min,
- Check saturation at rest at a minimum 30 minutes after start.
- Target O_2 saturation ≥ 90% (in patients with COPD, target value of ≥ 90 and <92%).
- If necessary, increase the dosage with 1 L / min.
- Maximum meaningful O_2 administration via nasal cannula is 5 L / min.
- If the patient experiences dyspnoea, combine O_2 administration with morphine at a low threshold; In case of anxiety give a benzodiazepine if necessary (symptom control with COVID-19 in the home situation).

The role of general practitioner is described as:

- arranges O_2 at home;
- makes agreements with the community nurses (wijkverpleegkundigen) about monitoring[t];
- checks at least daily saturation, respiratory frequency, temperature, dyspnoea and exhaustion (on a scale of 0-10) (measured by patient / informal care / community nursing / general practitioner) and adjusts the O_2 dosage if necessary;
- makes agreements in a personal treatment plan with patient and family about supportive medication and about who can be called in which situation;
- makes an execution request (uitvoeringsverzoek) for the community nurses stating in which situation which medication can be given;
- decreases the O_2 when the patient's condition improves, based on saturation and comfort. If the patient deteriorates, see advice for "dying patient with COVID-19" (stervende patiënt met Covid-19).

However, in the general note of the NHG guideline, it is also highlighted the preference to manage this kind of patient not at home and the availability concern of O_2.

- Availability of O_2 is dependent on region and period.
- O_2 is administered at home with a concentrator, but in case of insufficient availability, O_2 cylinders could be used at home. The disadvantage of this is that they often have to be replaced (daily).

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[t] Coordinate who provides the necessary pulse oximeter and thermometer: the patient himself, general practitioner, hospitals. If it is not possible to arrange a oximeter at the patient's home, the community nurses can carry out checks with their own oximeter. NB. clean thoroughly before re-use on other patients or keep the oximeter clean using a plastic bag around it, the saturation is then measured through the plastic.

- In view of the user comfort, preference is given to administration by means of nasal cannula. With a congested nose, a mouth mask can be used
- If a patient is receiving O_2 at home, adequate informal care is required. If not available, consider referring the patient to a Corona unit / institution.
- Administration of O_2, via nasal cannula or mouth mask does not require an extension of the prescribed personal protective equipment
- Smoking / second-hand smoke / risk of carelessness with open fire are contraindications for O_2 at home in connection with risk of facial burns and explosion hazard
- Patients with COVID-19 with indication of O_2 and without restriction for hospital admission should not be treated at home. They can deteriorate so quickly that more intensive monitoring and higher O_2 administration should be possible. Refer these patients to hospital.
- For patients needing O_2 because of another pathology than COVID-19, recommendations are not different than before the Corona pandemic

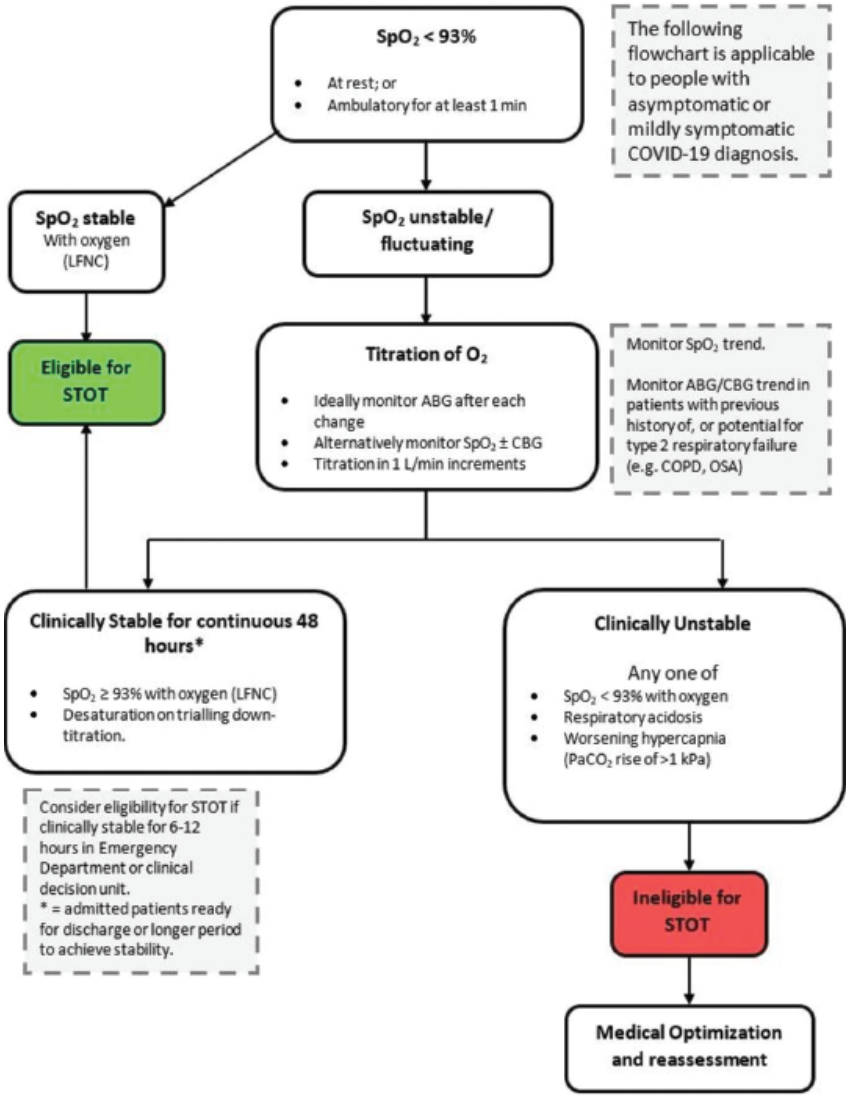
The NGH proposes some points of attention about O_2 use at home:

- Be aware of pressure ulcers behind the ears / on the nose
- Because air is not humidified, irritation of the nasal mucosa can occur. Recommend carbomer water gel (available without a prescription) or fat-free cetomacrogol (no vaseline because of the risk of facial burns)
- Consider patient and relatives counselling by a lung nurse (from home care)

Shah et al. found that home pulse oximetry monitoring identifies need for hospitalization in initially non-severe COVID-19 patients when a cutoff of SpO2 92% is used. Half of patients who ended up hospitalized had SpO2 <92% without worsening symptoms. Home SpO2 monitoring also reduces unnecessary ED revisits.[32]

Finally, an algorithm for short-term oxygen therapy at home (COVID-HOT algorithm) has been proposed by an **international team**[19]). They suggest a SpO_2 < 93% cut-off to begin oxygen therapy and keep the patient at home if the oximetry under supplemental oxygen is stable.[19] In this algorithm, patients are first evaluated in the emergency department with blood sample analysis and chest X ray (Figure 9).

Figure 9 – Determination of eligibility for short-term home oxygen therapy (STOT applicable for mild form of **SARS-Cov-2** infection). LFNC: low flow nasal cannula; ABG: arterial blood gas; OSA: obstructive sleep apnoea.[19]



10.6 Discussion

There are few sources of recommendations regarding oxygen therapy at home for patients with worrisome COVID-19 (see Chapter 1 for definition) and some thresholds can vary between sources.

10.6.1 Thresholds to start oxygen therapy:

Different decision thresholds are described in the literature. Moreover, there is sometimes confusion between the SpO2 threshold that has to be reached rather than the value below which it is needed to start oxygen therapy.

The BTS guidelines for oxygen use in adults proposes to start oxygen below SpO2 of 94%.[26] NIH indicates that optimal oxygen saturation in adults with COVID-19 is uncertain, but they consider that indirect evidence in critically ill patients suggest that SpO2 should range between 92% and 96%. The SpO2 threshold to start would be below 92%.[157] HAS considers the same threshold of 92%.[8]

Thus, we can summarise the information like this:

- There is evidence that SpO2 below 92% is potentially harmful in outpatient or inpatient settings.[32] Oxygen saturation below this threshold has been shown to be associated with bad outcomes.

- However, in the absence of clear threshold and evidence considering that SpO2<95% correspond to hypoxemia, we recommend to be cautious and to start oxygen therapy at the threshold of 94%.

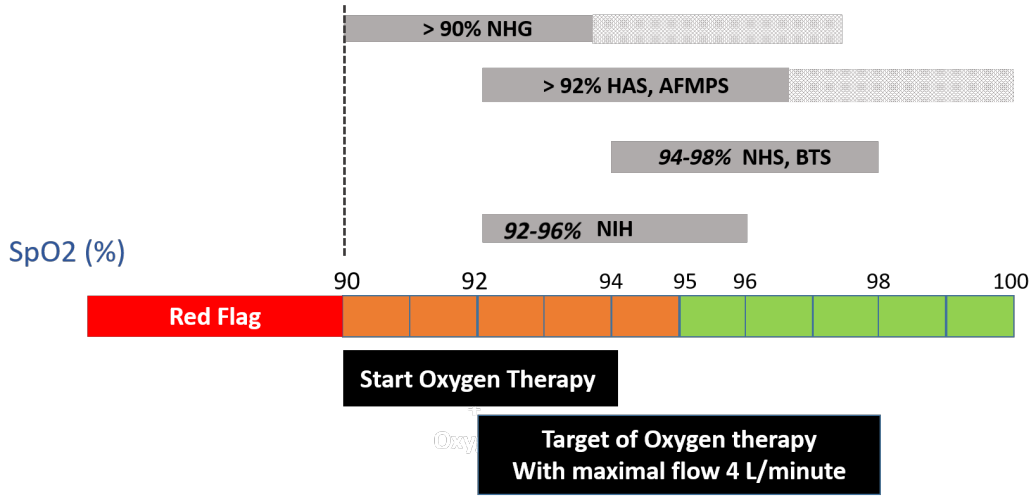
10.6.2 Targeted SpO2 under oxygen therapy:

Targeted SpO2 during oxygen therapy also vary according to the source. While BTS recommends targeting values ranging between 94 and 98%, the other institutions recommend to reach >92% (HAS) except NHG that suggests ≥90%.

The SpO2 should also be interpreted in the light of the amount of oxygen delivered to ensure the required value. The amount of delivered oxygen refers to which extent hypoxemia is severe. A need for increasing oxygen requirements is a sign of clinical worsening.

- Since there is evidence for worse evolution when SpO2 fall below 92%, we suggest to target SpO2 >92% with a maximal oxygen flow of 4 L/min which is almost the maximal flow that a nasal cannula can provide. This target of at least 92% SpO2 is also recommended by the AFMPS / FAGG in a patient with COVID-19 who presents hypoxemia treated with oxygen therapy regardless of the stage of the disease in their recommendations for patients after hospital discharge and for residents of nursing homes.

Figure 10 – Goals of oxygen therapy: Summary



10.6.3 Process of oxygen therapy

The NHG and the HAS provide advice for primary care providers in front of a COVID-19 patient receiving oxygen therapy at home. Even if both underline that this kind of patients would better be managed in hospital, they formulate practical recommendations that are useful at home.

- Preferably give oxygen **through nasal cannula**. A mouth mask can be used in case of a congested nose.
- Start at **2 L / min**,
- Check saturation at rest at a minimum 30 minutes after start.
- If necessary, increase the dosage with **1 L / min.**
- Maximum meaningful O_2 administration via nasal cannula is 5 L/min (NHG) but maximum O_2 flow administration 4L/min (HAS).

Some of these recommendations can complete the recommendations elaborated by the working group of the AFMPS / FAGG, for patients **after hospital discharge and for residents of nursing homes:**

In a patient with COVID-19 who presents hypoxemia treated with oxygen therapy, the target SpO_2 value should be at least 92%, regardless of the stage of the disease.

- For oxygen flow rates ≤ 3 L / min, an oxyconcentrator is the most suitable source of oxygen.
- For flow rates greater than 3 L / min, only oxygen cylinders or liquid oxygen can be used.
- When oxygen therapy is stopped, the supplier of the installation will be immediately informed.

However, since evidence and experiences in managing patients with moderate COVID-19 at home are scarce, further experimental and clinical studies are needed to define the optimal protocol for supplementing oxygen to reduce hypoxemia in these patients. As some authors highlight, we do not know which clinical criteria determines correctly the transition line between harm and therapy by supplementing oxygen.[160]

10.7 Proposed changes in the OST-Liège decision-aid tool

Based on several guidelines of other health institutions, we proposed some modifications to be incorporated in the decision-aid tool in the box “Oxygen therapy”:

- Nasal cannula: to be kept with addition of a footnote: “Preferably give oxygen through nasal cannula. A classical oxygen mask can be used in case of a congested nose.”
- Start at 2L/min, control after 30 min to be kept
- Start if SpO2 ≤94% to be added.
- Target SpO2 >92% instead of >90%
- If chronic hypoxaemic lung disease, target SpO2 88-92% instead of max 92%
- If necessary, increase the dosage stepwise by of 1L/min instead of steps of 0.5L-1L/min.
- Oxygen flow max 4L/min instead of 5L/min

11 TREATMENT WITH CORTICOSTEROIDS FOR PATIENTS WITH COVID-19 AT HOME

11.1 Summary

- **Systemic corticosteroids are not recommended in patients with COVID-19 without hypoxemia requiring supplemental oxygen.**
- **Systemic corticosteroids are recommended for patients with critical and severe COVID-19 (needing oxygen therapy). Dexamethasone 6 mg/day orally for 10 days is the recommended corticosteroid**
- **These recommendations are endorsed by the World Health Organization (WHO) and the Infectious Diseases Society of America (IDSA), among others. These recommendations which were elaborated in early September are still valid in November 2020 (no new evidence available). Although they have been elaborated for hospitalized patients, it is reasonable to infer that they also apply to outpatient settings**
- **Evidence for other corticosteroids in severe COVID-19 is very limited; Methylprednisolone 32 mg is on option of total daily dose equivalencies to dexamethasone 6 mg.**
- **Few changes are needed in the proposed OST-Liège decision-aid tool.**

11.2 Background

To date, a wide range of potential therapeutic agents have been suggested in the treatment of COVID-19. Since the virus-driven inflammatory host immune response is thought to play a key-role in the pathophysiology of lung damages, corticosteroids were considered as a potential therapeutic agent.[161](1)

In July 2020, the RECOVERY trial evidenced that the use of dexamethasone decreased 28-days-mortality among patients mechanically ventilated or receiving oxygen.[162](2) Dexamethasone 6 mg was given once daily up to 10 days. At the time of randomization, 60% of patients were receiving oxygen; 16% were mechanically ventilated and 24% were not receiving oxygen. The 28-days-mortality was decreased with the use of dexamethasone (22.9% in the dexamethasone-group *versus* 25.7% in the usual care-group; age adjusted risk ratio 0.83 [95% CI:0.75-0.93]). Subgroup analysis showed that the benefit in term of survival was present only in the group of patients with respiratory failure (mechanically ventilated or receiving oxygen). Besides, eight other smaller trials evaluated the effect of corticosteroid therapy *versus* conventional treatments on mortality and showed rather similar results in favor of corticosteroids therapy.[163]

Since July however, corticosteroids are also used at home in Belgian patients with mild COVID-19 and the question is raising on the place of this treatment for patients with worrisome COVID-19 (see chapter 1 for definition) who should be hospitalized but are not because of a saturation of hospitals.

11.3 Research questions

In this chapter, the research focuses on corticosteroids treatment in home-care. The global question is "*Are corticosteroids indicated, even in patients who do not need oxygen at home*?" Two questions are presented here:

- *Is dexamethasone useful for worrisome COVID-19 patients at home?*
- *Which other corticosteroids than dexamethasone can be used in worrisome COVID-19 patients?*

In the OST-Liège decision-aid tool, a box proposed dexamethazone 6 mg/day p.o. 10 days or methylprednisolone 32mg/day 10 days for confirmed COVID-19 patients with minimum 7 days of symptoms and a SpO_2<94% at ambient air. The tool proposed to add systematically proton pump Inhibitor (PPI) with corticosteroids in COVID-19 patients > 65 years old. The question on PPI is developed in the next chapter (See Chapter 12).

11.4 Methods

We based this chapter on the message and references gathered by the Agence fédérale des médicaments et produits de santé (FMPS) / Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten (FAGG). They compared different sources of guidelines on treatment by corticosteroids in COVID-19 patients such as the World health organization (WHO), Infectious Diseases Society of America (IDSA), Netherlands Huisartsen Genootschap (NHG), National Institute for health and care excellence (NICE), National Institutes of health (NIH), New England Journal of Medicine (NEJM), Sciensano and Stichting Werkgroep AntibioticaBeleid (SWAB). Several recommendations concern hospitalized patients and extrapolation is used to apply some of them in primary care setting in case of hospital saturation.

11.5 Results

Several sources of guidelines (WHO, IDSA, NICE, NEJM, NIH, SWAB) recommend the use of systematic corticosteroids rather than no corticosteroids in patients with severe and critical COVID-19.[163-168] As shown in Table 9, these recommendations are based on the effect on mortality at 28 days. More details are available in Appendix 18.18.

Conversely, several of these institutions (WHO, IDSA, NEJM, NIH) suggest not to use systemic corticosteroids in non-severe patients because an increase risk of mortality in those patients.[163, 164, 166, 167]

In Belgium, a document from Sciensano with the AFMPS / FAGG and the Société Belge d'infectiologie et de Microbiologie Clinique (SBIMC) / Belgische Vereniging voor Infectiologie en Klinische Microbiologie (BVIKM) titled “Interim clinical guidance for adults with suspected or confirmed COVID-19 in Belgium last updated on 2021, February 9th, confirms these recommendations.[169]

Table 10 – Impact on mortality of systemic use of corticosteroids in COVID-19 patients and recommendations from several guidelines

Source	Patients	Outcomes	Recommendation
WHO	Critical COVID-19 patients (n=1703)	28-day mortality RR 0.80 [95% CI:0.70–0.91]	*Strong recommendation Pro* *Moderate certainty evidence*
IDSA	Hospitalized critically ill patients	28-day mortality OR 0.66 [95% CI: 0.54-0.82]	*Strong recommendation Pro* *Moderate certainty of evidence*
WHO	Severe COVID-19 patients (n=3883)	28-day mortality RR 0.80 [95% CI: 0.70–0.92]	*Strong recommendation Pro* *Moderate certainty evidence*
IDSA	Hospitalized severely ill patients	28-day mortality RR 0.83 [95% CI: 0.74-0.92]	*Conditional recommendation Pro* *Moderate certainty of evidence*
WHO	Non-severe COVID-19 patients (n=1535)	28-day mortality RR 1.22 [95% CI: 0.93–1.61]	*Conditional recommendation Con* *Low certainty evidence*
IDSA	Hospitalized patients not on supplemental oxygen	28-day mortality RR 1.22 [95% CI: 0.86- 1.75]	*Conditional recommendation Con* *Low certainty of evidence*

Regarding the type of corticosteroids, evidence for other corticosteroids than dexamethasone in severe COVID is very limited. Some guidelines mention only dexamethasone (NHG, Sciensano and NEJM)[166, 169, 170] or refer to hydrocortison/prednison” without a lot of details (SWAB)[168] or hydrocortisone IV (NICE)[165]. IDSA and NIH highlight the possibility to use methylprednisolone 32 mg per day in case of dexamethasone shortcase.[164, 167] (more details in Appendix 18.18)

Finally, according to the NGH who focused on primary care, a concertation with a pneumologist is suggested before using corticosteroïds at home.[170]

11.6 Discussion

Although a strong recommendation is formulated for the systemic use of corticosteroids in critically or severe COVID-19 patients, the clinical benefits of systemic corticosteroids in patients with COVID-19 without hypoxemia requiring supplemental oxygen are not demonstrated and corticoids are not recommended in such patients. These recommendations are endorsed by the World Health Organization (WHO) and the Infectious Diseases Society of America (IDSA), among others. These recommendations which were elaborated in early September are still valid in November 2020 (no new evidence available). Studies on corticostreroids in non hospitalized COVID-19 patients are (still) lacking.

Although the above recommendations have been elaborated for hospitalized patients, it is reasonable to infer that they also apply to outpatient settings. Therefore, worrisome patients requiring oxygen therapy can be prescribed a corticosteroid treatment (dexamethasone 6mg/day orally for 10 days). Corticosteroids are not recommended in other patients.

For patients who are already treated by systemic corticotherapy for chronical diseases, it is recommended that they should not stop their treatment in case of non-severe SARS-Cov-2 infection. If the clinical condition of previously treated patients worsens, the optimal dose of corticoids remains unknown.

11.7 Proposed changes in the OST-Liège decision-aid tool

We proposed to highlight in the box “Corticosteroids” that the systemic corticosteroids are not recommended in patients with COVID-19 without hypoxemia requiring supplemental oxygen.

We suggest to replace the indication “for confirmed COVID-19 patients with minimum 7 days of symptoms and a SaO_2<94% at ambient air” by “In patients with hypoxemia requiring supplemental O_2”.

12 TREATMENT WITH PROTON PUMP INHIBITORS

12.1 Summary

- **The preliminary version of the OST-Liège decision-aid tool recommended the prescription of a proton pump inhibitor (PPI) in every patient >65 years receiving corticosteroids.**
- **PPI co-therapy is not routinely indicated in patients taking corticosteroids unless they present risks factors of gastrointestinal (GI) bleeding:**
  - **Concomitant use of non steroidal anti-inflammatory drugs (NSAIDs).**
  - **Concomitant use of anticoagulants or antiplatelets.**
  - **A history of gastroduodenal (GI) ulcer, bleeding, or perforation.**
  - **>65 ans**
  - **Serious comorbidity, such as advanced cancer.**
- **Strong evidence is lacking on most of the listed risk factors apart from NSAIDs. The clinical risk versus benefit of utilising a PPI should be assessed for each patient. The PPI should be prescribed only during the course of corticosteroids. That robust evidence on the harmlessness of PPIs in COVID-19 patients is lacking should also be kept in mind.**
- **We propose some adaptations of the OST-Liège decision-aid tool.**

12.2 Background

In the preliminary version of the OST-Liège decision-aid tool, the box focusing on corticosteroids mentioned the prescription of a proton pump inhibitor (PPI) for every patient >65 years.

The validity of this recommendation has been questioned by the AFMPS / FAGG and needed to be assessed, as robust evidence is lacking on the independent effect of corticosteroids on gastrointestinal bleeding.[171] This question is even more important since the emerging controversy on the possible adverse effects of PPI in COVID-19 patients. Indeed, several observational studies reported that PPI treatment may be a negative predictive factor for the development of secondary infections and consecutive acute respiratory distress syndrome (ARDS) in patients with COVID-19.[172-174]

12.3 Research question

In this chapter, we focus on the following specific question: "*Should PPIs be prescribed to COVID-19 patients receiving corticosteroids, and under which conditions*?"

12.4 Methods

Because of the very short time for the KCE to provide its response, we screened MEDLINE (PubMed) for systematic reviews (with the keywords: proton pump inhibitor AND corticosteroid* Filters: Systematic Review) and the Guidelines International Network (GIN) for guidelines. We also examined an ad-hoc sample of guidelines from Domus Medica - ACHG, the Netherlands Huisartsen Genootschap (NHG), NICE, and NHS UK, in collaboration with the AFMPS / FAGG.

12.5 Results

The search in MEDLINE and GIN yielded not hit on the use of PPIs in COVID-19 patients receiving corticosteroids. A systematic review from Dorlo et al. (2013; non-COVID-19 patients) reported that systemic corticosteroids only rarely causes a peptic ulcer, although the risk increases when used concomitantly with NSAIDs. The authors concluded that PPIs should be prescribed when corticosteroids and NSAIDs are combined.[175]

The references provided by the AFMPS / FAGG highlight the doubt on the prophylactic value of anti-ulcer therapy given with corticosteroids. (see Appendix 18.19)

No relevant guidelines were retrieved in **GIN**. The **Netherlands Huisartsen Genootschap (NHG) and Domus Medica - ACHG** do not provide guidance on the use of PPIs in COVID-19 patients. **NICE** (October 2020) simply recommends to follow local policies on gastroprotection during corticosteroid treatment in COVID-19 patients without providing more details on these local policies.[165] This recommendation is endorsed by the **NHS**. The NHS Greater Manchester recommends to consider giving a proton pump inhibitor (omeprazole 20mg daily) for gastrointestinal (GI) protection in COVID-19 patients at risk of gastro-intestinal bleeding or dyspepsia when prescribing dexamethasone. The risk versus benefit of utilising a PPI should be considered.[176]

Other guidelines on the preventive use of PPI when corticosteroids are prescribed in non COVID-19 patients can also provide relevant information.

The **west Essex NHS** (December 2019) recommends considering the prescription of a PPI in patients receiving corticosteroids if they present the following risk factors[177]:

- Older age (undefined)
- Serious comorbidity, such as advanced cancer.
- A history of gastroduodenal ulcer, GI bleeding, or gastroduodenal perforation.
- Concomitant use of medications that are known to increase the likelihood of upper GI adverse events (for example anticoagulants, antiplatelets, selective serotonin reuptake inhibitors (SSRIs) and NSAIDs).

The west Essex NHS also recommends that before commencing long-term treatment with a PPI, the risk-benefit balance should be evaluated by the physician. The PPI should be prescribed only during the course of corticosteroids, i.e. stopped when the corticosteroid treatment is over.

A publication from Scarpignato et al. also indicates that PPI should be used when corticosteroids and NSAID are combined.[171] The same article indicates that a history of peptic ulcer is also an indication for PPI in patients taking corticosteroids (p14).[171] Corticosteroids are listed among the risk factors for GI bleeding in patients taking anti-platelet or anti-coagulant (p14).[171] More details are available in Appendix 18.20.

Of note, in Belgium, the CBIP / BCFI also mentions corticosteroids in its recommendation on the use of PPIs in patients receiving NSAIDs and presenting an increased risk of GI bleeding (https://www.cbip.be/fr/chapters/4?frag=2493 / https://www.bcfi.be/nl/chapters/4?frag=2493):

- >65 years or presence of a serious comorbidity
- A history of gastroduodenal ulcer or ulcer with complications (bleeding, perforation)
- NSAID **or** corticosteroid treatment concomitant with an acetylsalicylic acid or another antiplatelet or anticoagulant treatment.

Therefore the CBIP/BCFI recommends the use of a PPI in patients receiving a corticosteroid when combined with an antiplatelet or an anticoagulant treatment.

12.6 Discussion

The NICE and NHS guidelines recommend using PPIs in patients receiving corticosteroids when they present with the usual risk factors of GI bleeding.[165,NHS, 2020, July 7 #308] Unfortunately, their background evidence is not accessible. That PPI should be used when corticosteroids and NSAID are combined is consistent across the literature.[171, 175, 178]

Although the association between corticosteroid use and GI adverse events in patients with risk factors other than NSAIDs use remains controversial, a history of peptic ulcer is also listed as a risk factor, as well as anti-platelet or anti-coagulant treatment, by other sources (Scarpignato et al.[171]; CBIP (https://www.cbip.be/fr/chapters/4?frag=2493) / BCFI (https://www.bcfi.be/nl/chapters/4?frag=2493).

As regards the potential bleeding risk associated with the use of low molecular-weight heparin (LMWH) for prophylaxis of venous thromboembolism, evidence remains inconclusive for low dose LMWH (<40 mg or < 4000 UI/day), as reported by a recent meta-analysis.[179] On the contrary,

intermediate-dose (≥4000 UI/day) of LMWH is associated with an increased risk of major bleeding.[180] Of note, the recommendation in the OST-Liège decision-aid tool is 4000 UI/day.

Whereas age >65 years should be considered as a stand-alone risk factor justifying the use of PPIs is unclear. The clinical risk versus benefit of utilizing a PPI should be assessed for each patient, particularly when more than one risk factor is present. This might turn out to be a difficult exercise in the absence of strong evidence on most of the listed risk factors apart from NSAIDs. On the other hand, the duration of the PPI prescription should not exceed the course of corticosteroids (10 days) whereas serious adverse events are rare and observed only during long-term use. However, that robust evidence on the harmlessness of PPIs in COVID-19 patients is lacking should also be kept in mind.[172-174]

12.7 Proposed changes in the OST-Liège decision-aid tool

Based on the elements mentioned above, we propose the following changes to the OST-Liège decision-aid tool:

- Remove from the box “Corticoïdes” the indication “IPP systématique si >65 ans »
- Add a box in the decision-aid tool : “ PPI to be considered if NSAID or corticosteroids when risks factors of GI bleeding »
- Add a footnote with “Risk factors for **GI bleeding**: combined use of NSAIDs and corticosteroids / NSAIDs or corticosteroids used jointly with anticoagulants or antiplatelet therapy / History of GI ulcer, bleeding, or perforation / >65 years and/or serious comorbidities”.

13 TREATMENT WITH HYDROXYCHLOROQUINE FOR PATIENTS WITH COVID-19 AT HOME

13.1 Summary

- **The current recommendation by the AFMPS / FAGG is to not use hydroxychloroquine in the home-based treatment of COVID-19 patients. This recommendation is congruent with many other international guidelines.**
- **The review by Ladapo et al. 2020[181] is very low quality and does not provide any relevant and valid information in favour of using HCQ in patients treated at home. Current recommendation should remain unchanged.**
- **No changes are needed in the proposed OST-Liège decision-aid tool.**

13.2 Background

There is so far no evidence of a benefit of hydoxychloroquine (HCQ) on SARS-Cov-2 infection in post-exposition prophylaxis[u], no evidence of reducing the infection risk when used in prevention among care providers and no benefit in COVID-19 patients with severe disease[v]. Consequently, the AFMPS / FAGG and the CBIP / BCFI recommend to not use HCQ in the prevention or treatment of COVID-19 infection. This recommendation is congruent with many other international guidelines (see references provided by the AFMPS/FAGG on 16/11/2020 in appendix 18.21).

Ladapo et al. 2020[181] recently published on medRxiv a systematic review and concluded that HCQ reduces the incidence of the composite outcome of SARS-Cov-2 infection, hospitalization, and death without serious adverse effects. This review has not yet been peer-reviewed. Following the pre-print of this review, the question whether current recommendations should be amended was submitted to KCE.

13.3 Research questions

In this chapter, the question focuses on a specific publication and can be formulated as : “Does the recent non peer-reviewed systematic review by Ladapo et al. 2020 (Randomized Controlled Trials of Early Ambulatory Hydroxychloroquine in the Prevention of COVID-19, Hospitalization, and Death: Meta-Analysis ; http://doi.org/10.1101/2020.09.30.20204693) provide new elements in favour of using hydroxychloroquine in patients with COVID-19 treated at home ? “

13.4 Methods

We have appraised this review to assess new insights on the use of HCQ in ambulatory patients with COVID-19 it could bring. The quality of the review was assessed following the AMSTAR 2 methodology[w] and the quality of evidence following the GRADE methodology.[x] We did not review the evidence-base of the current recommendation to not use HCQ in home-based treatment of COVID-19 patients.

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u https://www.cbip.be/fr/gows/3490

v https://www.cbip.be/fr/articles/3470?folia=3462

w https://amstar.ca/Amstar-2.php

x https://www.gradeworkinggroup.org/

13.5 Results

This systematic review included 5 randomized clinical trials in which participants were treated with HCQ or placebo/standard-of-care for pre-exposure prophylaxis, post-exposure prophylaxis, or outpatient therapy for COVID-19. The primary outcome was COVID-19 hospitalization or death. When unavailable, new SARS-Cov-2 infection was the outcome used.

This systematic review is very low quality according to the AMSTAR 2 criteria, and therefore the level of confidence in its results is minimal (see Table 11). Therefore, we did not assess the quality of evidence. Although included RCTs varied as regards dosages of HCQ, stages of the infection (pre-exposure, post-exposure, outpatient treatment) and outcomes (2 on new SARS-Cov-2 infection, 1 on hospitalization, 1 on death, 1 on hospitalization or death), the authors made an attempt to meta-analyse them. Despite this heterogeneity of methods and outcomes, no statistical heterogeneity across studies was found. The authors reported that HCQ was associated with a 24% reduction in SARS-Cov-2 infection, hospitalization or death (RR=0.76; 95% CI: 0.59 to 0.97; p=0.05). For the reasons explained above, these results should be considered with extreme caution. No valid recommendation could be elaborated on such basis.

Table 11 – Appraisal of the meta-analysis with AMSTAR 2 criteria

1. Did the research questions and inclusion criteria for the review include the components of PICO?	No. *Patient* characteristics are not defined. *Intervention* includes pre-exposure prophylaxis, post-exposure prophylaxis, or outpatient therapy for COVID-19, i.e. the intervention would be any use of HCQ in outpatient setting. *Outcomes* are described incoherently "*The most important clinical outcome is mortality, and for outpatients, hospitalization conveys high risk of mortality. Thus, where studies observed more than 1 unexposed deceased or hospitalized subject, we used mortality or hospitalization or the two together as the outcome of interest for our meta-analysis. In studies where this was not the case, we used the study principal outcome (newly occurring SARS-Cov-2 infection, which is in the causal pathway to COVID-19 hospitalization) as defined by the study investigators.*"
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No. The review was not registered.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes.
4. Did the review authors use a comprehensive literature search strategy?	Unclear. Medline, Embase, Cochrane Central Register of Controlled Trials were searched. Grey-literature was searched in medRxiv. Strangely enough, the authors also report having searched PROSPERO which is a repository of protocols for systematic reviews. The sensitivity of the search strategy might have been sub-optimal as "hydroxychloroquine" must appeared in the title only.
5. Did the review authors perform study selection in duplicate?	Unclear. Mentioned in the abstract, not in the text.
6. Did the review authors perform data extraction in duplicate?	Unclear. Mentioned in the abstract, not in the text.

7. Did the review authors provide a list of excluded studies and justify the exclusions?	No
8. Did the review authors describe the included studies in adequate detail?	Not enough details are provided, e.g. no patients' characteristics
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	None. It is remarkable that none of the 5 trials included was blinded.
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	No. The 5 studies reported on different interventions and outcomes (2 on new COVID-19 infection, 1 on hospitalization, 1 on death, 1 on hospitalization or death). The authors meta-analyzed the 5 studies regardless of these differences.
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	No
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Unclear Authors report to have done it, but results are not shown
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Dr. Risch acknowledged past advisory consulting work with two of the more than 50 manufacturers of hydroxychloroquine, azithromycin and doxycycline. No conflict of interest declared by other co-authors.

13.6 Conclusion

This review does not provide evidence in favour of the use of HCQ in patients with COVID-19 treated at home. Current recommendation should remain unchanged.

14 TREATMENT WITH ANTIBIOTICS FOR PATIENTS WITH COVID-19 AT HOME

14.1 Summary

- **Data on co-infection in patients presenting COVID-19 are sparse.**
- **Indiscriminate and inappropriate antibiotic use may reduce availability when needed.**
- **There is no evidence for the systematic use of antibiotics in patients with COVID-19 except when there is a bacterial co-infection,**
- **If bacterial co-infection is suspected in patients with COVID-19, CRP cannot be used to differentiate viral COVID-19 related pneumonia from bacterial co-infection.**
- **If bacterial pneumonia is suspected or confirmed in patients with COVID-19, the appropriateness of antibiotics depends on the local resistance profiles: in Belgium, the Belgian Antibiotic Policy Coordination Commission (BAPCOC) recommends high-dose amoxicillin or amoxicillin clavulanate.**
- **No change is needed in the OST-Liège decision-aid tool**.

14.2 Research questions

In the OST-Liège decision-aid tool, antibiotics are proposed in case of bacterial co-infection (based on clinical and biological signs). Because of the general context of antibiotic resistance and the needed precaution to use them, we propose to review this message and to answer to the question**:** **"***Are antibiotics useful in COVID-19 patients?* **"**

14.3 Methods

Because of the very short time for the KCE to provide its response, we report here results from a document prepared by the Agence Fédérale des Médicaments et Produits de Santé (AFMPS) / Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten (FAGG) on November 16th, 2020. This report gather guidelines from different key institutions website: National institute for Health and Care Excellence (NICE), Nederlands Huisartsen Genootschap (NHG), Sciensano, National Institute of health (NIH), New England Journal of Medicine (NEJM), Infectious Diseases Society of America (IDSA) and World Health Organisation (WHO).

Since the AFMPS-FAGG quotes the place of the C-reactive protein (CRP) in their recommendation, a search of systematic reviews was performed on the December 8th, 2020 in Medline with the search strategy "((COVID) AND (c-reactive protein)) AND (systematic review)" which provided 66 hits.

We also took into account the results of the Best Evidence Topic Report 18 (BestBET) on the role of antibiotics in COVID-19 performed by the Academisch Centrum Huisartsgeneeskunde - KU Leuven (ACHG) with search date March 20th, 2020 retrieved on December 3rd, 2020[y]

14.4 Results

In the guidelines gathered by the AFMPS / FAGG, authors highlight that evidence about frequency and microbiology of pulmonary co-infections and super-infections in patients with COVID-19 is limited (details in appendix 18.22). Moreover there is concern about the difficult differentiation between COVID-19 and bacterial co-infection. Clinical diagnosis and biological testing are not reliable and there is concern about the safety of pulmonary diagnostic procedures such as bronchoscopy or other airway sampling.
For example, the C-reactive protein test usually performed to distinguish viral from bacterial pneumonia (see BAPCOC guidelines chapter "Plaatsbepaling van antibiotica" (https://www.bcfi.be/nl/chapters/12?frag=8000010 or chapter "Positionnement des antibiotiques"

[y] https://cdn.nimbu.io/s/1kphvhi/assets/1586331998334/18_BestBET_Antibiotica_finale%20versie.pdf

(https://www.cbip.be/fr/chapters/12?frag=8000010)) cannot be used because CRP is often also (strongly) increased in patients with COVID-19.[182, 183]

Because of the adverse consequences of inappropriate antimicrobial therapy, they have to be used carefully. Both AFMPS-FAGG and Domus Medica - ACHG recommend not to use systematically antibiotics in COVID-19 except when bacterial co-infection occurs (details in appendix 18.22).

In case of co-infection, appropriateness of antibiotics depends on the local resistance profiles: in Belgium, the BAPCOC recommends high-dose amoxicillin or amoxicillin clavulanate (see https://www.bcfi.be/nl/gows/%203308 or https://www.cbip.be/fr/gows/%203308).

14.5 Proposed changes in the OST-Liège decision-aid tool

Based on the elements mentioned above, we propose the following changes to the OST-Liège decision-aid tool:

- To add “according to the BAPCOC recommendations” after “antibiotics only if bacterial co-infection;
- To add a footnote with “If bacterial pneumonia is suspected or confirmed in patients with COVID-19, the appropriateness of antibiotics depends on the local resistance profiles and patients allergy: in Belgium, the Belgian Antibiotic Policy Coordination Commission (BAPCOC) recommends high-dose amoxicillin or amoxicillin clavulanate.”

15 CONCLUSION

In the Sars-Cov2 pandemic context, it is not excluded that hospital capacity could be overstretched by a future wave of COVID-19 cases leading the primary care in front of more severe patients than usually.

A decision-aid tool for the home-based management of COVID-19 adult patients **in case of hospital saturation** was elaborated in October 2020 by the Outbreak Support Team in Liège (OST-Liège). Such tool aims to structure a global appraisal of the patient situation, including organizational and environmental aspects, and decide if a home-based management is appropriate. KCE was requested to review and validate this decision-aid tool. Because of the urgency of this request, KCE performed a rapid review on 12 research questions linked to the tool.

We started by defining the target population of this search: the **worrisome patients,** a subcategory of moderate COVID-19 cases as defined by WHO. This subcategory includes patients presenting at least one sign of pneumonia together with an oxygen saturation (SpO2) ≤94% or a respiratory rate (RR) ≥25/minute (see chapter 2) and no red flags (see chapter 3). We identified also the risk factors for severe COVID-19 (see chapter 4) because these factors can justify an intensified **monitoring** even in patients with no worrisome SpO_2 or RR.

Clinical aspects are not the only consideration to be taken into account when deciding to organize home-based intensified care for patients with worrisome COVID-19. Therefore environmental and organizational issues were analyzed: facilitator elements in chapter 5, oxygen provision in chapter 6, reliability of pulse oximeters in chapter 7 and the place of telemonitoring in chapter 8.

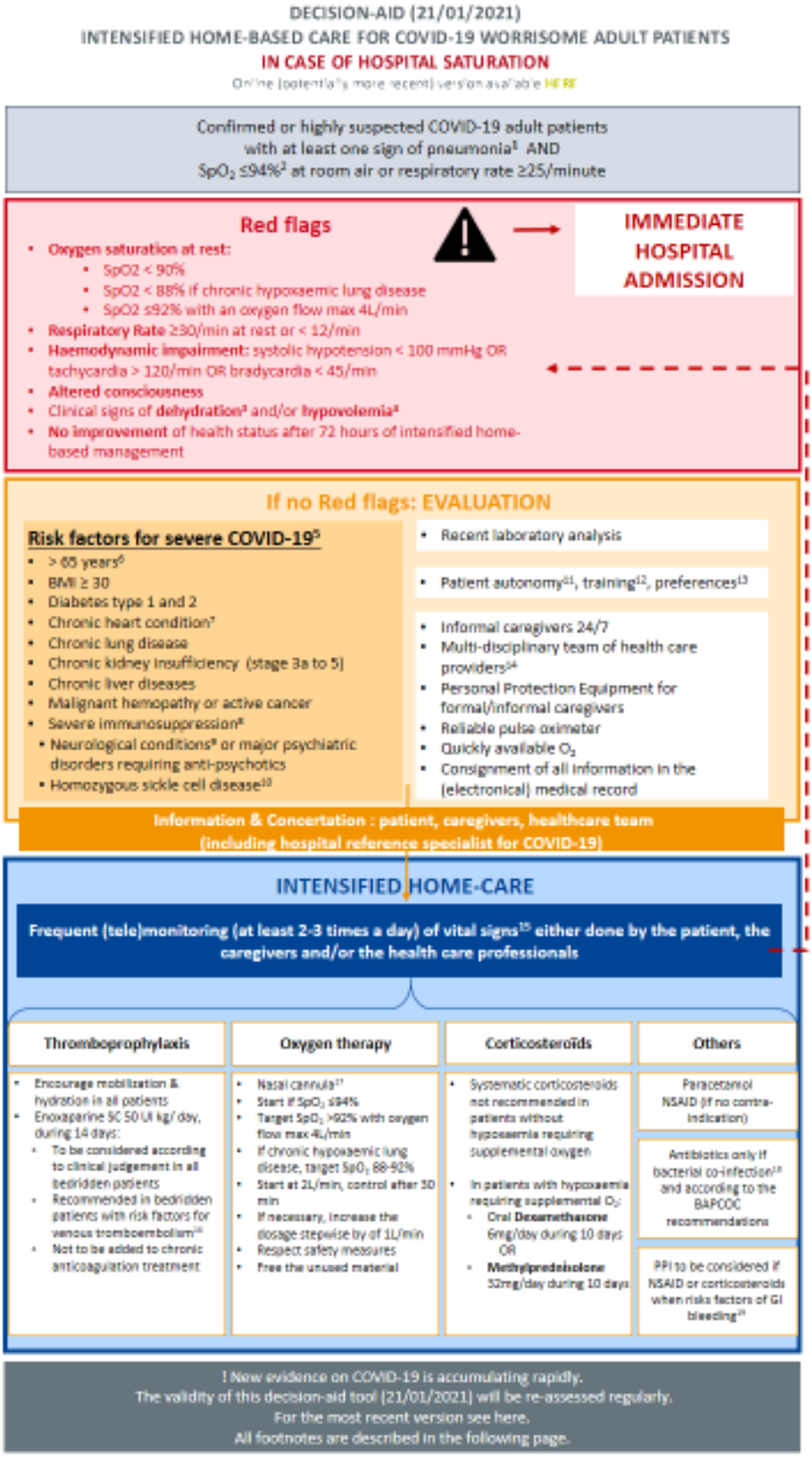
The '**intensified'** care required by the worrisome patients includes a close monitoring of health parameters (2 to 3 times a day) and the potential use of oxygen and corticosteroids. The therapeutic interventions are detailed in the chapters 9, 10, 11 and 12 respectively for the thromboprophylaxis, oxygen therapy, corticosteroids, and proton pump inhibitors. Potential use of hydroxychloroquine and antibiotics is discussed in chapters 13 and 14.

This work results in elaborating a new version of the decision-aid tool previously created by the OST-Liège. Each modifications to the original tool are presented in the table below (Chapter 17). The new decision-aid tool is available in Chapter 16.

As a reminder, all care decisions must include an **in-depth discussion with the patient and his/her caregivers,** notably on the agreement to be hospitalized in the presence of red flags.

Finally, given the continuous flow of new evidence on COVID-19, the validity of the revised decision-aid tool should be re-assessed regularly. New version if needed will be provided on the different websites of the institutions supporting this work.

16 NEW VERSION OF THE DECISION-AID TOOL



[1] **Pneumonia signs**: fever, cough, dyspnoea or fast breathing (RR > 20/min).

[2] **SpO_2** must be measured for at least 1-2 minutes. The level of SpO_2 prompting a hospital admission must be interpreted along with the clinical judgement of the patient's health.

[3] **Clinical signs of dehydration**: weight loss ≥ 5% (severe if > 10%), positive skin fold, thirst, dry mouth, possible confusion and decrease of urine flow.

[4] **Clinical signs of hypovolemia**: arterial hypotension, tachycardia, cold and marbled extremities and decrease of urine flow.

[5] The presence of one of the **risk factors** is a warning sign which should trigger, according to your clinical judgement, a twice more frequent home-based monitoring or, if not possible, an indication for a hospital admission (except when in contradiction with the advanced care planning).

Be aware that each additional age year after 65 years and each accumulation of risk factors induces a higher risk.

[6] For patients over **75 years old** that are residents in an institution, please refer to the therapeutic protocol for COVID-19: in French http://docs.foubipbip.be/docs/d574edb2e8fce1a0.pdf.

[7] **Chronic heart conditions**: heart failure, coronary disease, cardiomyopathy and pulmonary hypertension.

[8] **Severe immunosuppression**: ongoing chemotherapy, severe inherited immunodeficiency, transplant… See CBIP in French (https://www.cbip.be/fr/chapters/12?frag=8900094) or in Dutch (https://www.bcfi.be/nl/chapters/12?frag=8900094).

[9] **Neurological conditions**: dementia, Down syndrome, cerebral palsy…

[10] **For other rare diseases**, although there is no current evidence, be confident to your clinical judgement.

[11] **Patient autonomy** for food, hydration, monitoring, ability to call for help, therapy.

[12] **Patient and/or his/her caregiver training** to use appropriately oxygen therapy and pulse oximeter, or to identify red flags in order to react quickly and call the nearest hospital. A telephone number that can be reached 24/7 can be useful.

[13] **Importance of information and consultation** with the patient, in particular on the level of intensity of care that the patient wants to receive, including admission to hospital in the event of an urgent medical situation (red flags).

[14] This **team** can include a coordinating GP, nurses, physiotherapists and a reference hospital team, sharing information by the same communication channels, information; such a team allows integrated care with the consultation of all parties including the patient and his/her caregivers. Therapeutic options should be duly discussed with the patients.

[15] **Monitoring** can be carried out by the patient, relatives or a health professional (general practitioner, nurse, physiotherapist etc.) BUT the medical decision remains the responsibility of the general practitioner. Telemonitoring appears feasible in COVID-19 patients even though there is currently no evidence on the (cost)effectiveness of telemonitoring for COVID-19 patients cared for at home.

[16] **Risk of venous thromboembolism**: known thrombophilia; personal or familial history of VTE ; obesity (BMI>30); heart failure; respiratory failure; age >70; active cancer; major surgery in the last 3 months.

[17] Preferably give **oxygen** through nasal cannula. A classical oxygen mask can be used in case of a congested nose.

[18] If **bacterial pneumonia** is suspected or confirmed in patients with COVID-19, the appropriateness of **antibiotics** depends on the local resistance profiles and patients allergy: in Belgium, the Belgian Antibiotic Policy Coordination Commission (BAPCOC) recommends high-dose amoxicillin or amoxicillin clavulanate.

[19] Risk factors for **GI bleeding** : combined use of NSAIDs and corticosteroids / NSAIDs or corticosteroids used jointly with anticoagulants or antiplatelet therapy / History of GI ulcer, bleeding, or perforation />65 years and/or serious comorbidities.

More information on COVID-19: https://covid-19.sciensano.be/sites/default/files/Covid19/COVID-19_fact_sheet_ENG.pdf

With the support of:

KCE
Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

CMG
Collège de Médecine Générale de Belgique francophone

KU LEUVEN
ACADEMISCH CENTRUM HUISARTSGENEESKUNDE

SSMG
Société Royale

DOMUS MEDICA

17 TABLES OF CHANGES IN THE DECISION-AID TOOL

Box	Current criteria/recommendations	Proposed update
General	Confirmed cases of COVID-19 Severe cases	The decision-aid is for intensified home-based care of COVID-19 worrisome patients in case of hospital saturation
First assessment	Shortness of breath AND <94% O2 saturation in room air OR respiratory rate (RR) >24/minute	Confirmed or highly suspected COVID-19 adult patients with at least 1 sign of pneumonia[z] AND (SpO2 ≤ 94%[aa] at room air OR respiratory rate (RR) ≥25/min)

Red Flags	• Altered consciousness (lethargy, confusion, drowsiness)
	• State of dehydration: oligo-anuria
	• Systolic blood pressure<100mmHg
	• Respiratory rate >30/min or bradypnea
	• SpO2 <90% in room air (material and optimal conditions)
		• Oxygen saturation at rest:
		  ○ SpO2 <90%
		  ○ SpO2 <88% if chronic hypoxaemic lung disease
		  ○ SpO2 ≤92% with an oxygen flow max 4L/min
		• Respiratory Rate≥30/min at rest or < 12/min
		• Hemodynamic impairment: systolic hypotension < 100 mmHg OR tachycardia >120/min OR bradycardia <45/min
		• Altered consciousness
		• Clinical signs of dehydration[bb] and/or hypovolemia[cc]
		• No improvement of health status after 72 hours of intensified home-based management

Risk factors of severe COVID-19	• >65 years • Obesity (to be confirmed) • Type 2 diabetes (and cardiovascular comorbidities) • Arterial hypertension • Kidney, liver, cardiac or respiratory failure	Risk factors of severe COVID-19[dd] • >65 years[ee] • BMI ≥ 30 • Diabetes type 1 and 2 • Chronic heart condition[ff]

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z **Pneumonia signs**: fever, cough, dyspnoea or fast breathing (RR > 20/min).

aa **SpO_2** must be measured for at least 1-2 minutes. The level of SpO_2 prompting a hospital admission must be interpreted along with the clinical judgement of the patient's health.

bb **Clinical signs of dehydration**: weight loss ≥ 5% (severe if > 10%), positive skin fold, thirst, dry mouth, possible confusion and decrease of urine flow.

cc **Clinical signs of hypovolemia**: arterial hypotension, tachycardia, cold and marbled extremities and decrease of urine flow.

dd The presence of one of the **risk factors** is a warning sign which should trigger, according to your clinical judgement, a twice more frequent home-based monitoring or, if not possible, an indication for a hospital admission (except when in contradiction with the advanced care planning).

Be aware that each additional age year after 65 years and each accumulation of risk factors induces a higher risk.

ee For patients over 75 years old that are residents in an institution, please refer to the therapeutic protocol for COVID-19: in French http://docs.toubipbip.be/docs/d574edb2e8fce1a0.pdf.

ff **Chronic heart conditions**: heart failure, coronary disease, cardiomyopathy and pulmonary hypertension.

	• Immunosuppression (cancer ou chemotherapy)	• Chronic lung disease • Chronic kidney diseases (stage 3a to 5) • Chronic liver diseases • Malignant hemopathy or active cancer • Severe immunosuppression[gg] • Neurological conditions[hh] or major psychiatric disorders requiring anti-psychotics • Homozygous sickle cell disease[ii]
Capacity of health care team	• Recent basic biological assessment available • Presence of PPE for care team • Parameter taking 2x / day: BP, heartbeat, O2 saturation: nurse / doctor / physiotherapist • Supply of O2: pharmacy • Daily medical contact: media to be defined • RSW / Safelink® patient registration	• Recent laboratory analysis • Patient autonomy[jj], training[kk], preferences[ll] • Informal caregivers 24/7 • Multi-disciplinary team of health care providers[mm] • Personal Protection Equipment for formal/informal caregivers • Reliable pulse oximeter • Quickly available O2 • Consignment of all information in the (electronical) medical record • Frequent (tele)monitoring (at least 2-3 times a day) of vital signs[nn] either done by the patient, the caregivers and/or the health care professionals

Capacity of home-based follow-up	• Capacity for feed / hydration / call
	• Ability to follow the daily treatment
	• Ability to regularly monitor the situation
	  ○ Patient
	  ○ Entourage
	  ○ Care team	

gg **Severe immunosuppression**: ongoing chemotherapy, severe inherited immunodeficiency, transplant… See CBIP in French (https://www.cbip.be/fr/chapters/12?frag=8900094) or in Dutch (https://www.bcfi.be/nl/chapters/12?frag=8900094).

hh **Neurological conditions**: dementia, Down syndrome, cerebral palsy…

ii **For other rare diseases**, although there is no current evidence, be confident to your clinical judgement.

jj **Patient autonomy** for food, hydration, monitoring, ability to call for help, therapy

kk **Patient and/or his/her caregiver training** to use appropriately oxygen therapy and pulse oximeter, or to identify red flags in order to react quickly and call the nearest hospital. A telephone number that can be reached 24/7 can be useful.

ll **Importance of information and consultation** with the patient, in particular on the level of intensity of care that the patient wants to receive, including admission to hospital in the event of an urgent medical situation (red flags).

mm This **team** can include a coordinating GP, nurses, physiotherapists and a reference hospital team, sharing information by the same communication channels, information; such a team allows integrated care with the consultation of all parties including the patient and his/her caregivers. Therapeutic options should be duly discussed with the patients.

nn **Monitoring** can be carried out by the patient, relatives or a health professional (general practitioner, nurse, physiotherapist etc.) BUT the medical decision remains the responsibility of the general practitioner. Telemonitoring appears feasible in COVID-19 patients even though there is currently no evidence on the (cost-)effectiveness of telemonitoring for COVID-19 patients cared for at home.

	• Installation and use of the Safelink® application	

Thromboprophylaxis	• Indications
	  ○ >75 years OR BMI>30
	  ○ <75 years AND BMI<30 in bedridden patients
	  ○ <75 years AND D-dimers levels>2xnormal values
	• Enoxaparine (Clexane®) SC 4000 UI 1/ day, during 14 days
		• Encourage mobilization & hydration in all patients
		• Enoxaparine SC 50 UI kg/ day, during 14 days:
		  ○ To be considered according to clinical judgement in all bedridden patients
		  ○ Recommended in bedridden patients with risk factors for venous tromboembolism[oo]
		  ○ Not to be added to chronic anticoagulation treatment

Oxygen therapy	• Nasal cannula • Start 2l/min, control after 30 minutes to exceed the threshold of 90% saturation (max 92% if COPD) • Stages of 0.5l-1l / min • Maximum 5l /min • Think about de-escalation to free the material	• Nasal cannula[pp] • Start if SpO2 ≤94% • Target SpO2 >92% with oxygen flow max 4L/min • If chronic hypoxaemic lung disease, target SpO2 88-92% • Start at 2L/min, control after 30 min • If necessary, increase the dosage stepwise by of 1L/min • Respect safety measures • Free the unused material

Corticosteroïds	• Indicated for cases of confirmed COVID-19 + symptoms during min. 7 days + SpO2 <94% in room air
	• Oral Dexamethasone 6mg / day PO 10 days OR Methylprednisolone 32mg/d (Médrol®) 10 days max
		• Systematic corticosteroids not recommended in patients without hypoxemia requiring supplemental oxygen
		• In patients with hypoxemia requiring supplemental O_2, give either:
		  ○ Oral **Dexamethasone** 6mg/day during 10 days OR
		  ○ **Methylprednisolone** 32mg/day during 10 days

IPP+ Dexamethasone	• Systematic PPI in patients>65 years receiving dexamethasone	• PPI to be considered if NSAID or corticosteroids when risk factors of GI bleeding[qq]
Antibiotics	• Recommended if bacterial co-infection	• Antibiotics only if bacterial co-infection[rr] and according to the BAPCOC recommendations
Hydroxycloroquine	• Not indicated	• Remove

[oo] **Risk of venous thromboembolism**: known thrombophilia; personal or familial history of VTE; obesity (BMI>30); heart failure; respiratory failure; age >70; active cancer; major surgery in the last 3 months.

[pp] Preferably give **oxygen** through nasal cannula. A classical oxygen mask can be used in case of a congested nose.

[qq] Risk factors for **GI bleeding** : combined use of NSAIDs and corticosteroids / NSAIDs or corticosteroids used jointly with anticoagulants or antiplatelet therapy / History of GI ulcer, bleeding, or perforation />65 years and/or serious comorbidities.

[rr] If **bacterial pneumonia** is suspected or confirmed in patients with COVID-19, the appropriateness of **antibiotics** depends on the local resistance profiles and patients allergy: in Belgium, the Belgian Antibiotic Policy Coordination Commission (BAPCOC) recommends high-dose amoxicillin or amoxicillin clavulanate.

18 APPENDIX

18.1 WHO - Home care for patients with suspected or confirmed COVID-19 and management of their contacts: Interim guidance (last update 12/08/2020)

This document is an update of the guidance published on 17 March 2020 entitled “Home care for patients with COVID-19 presenting with mild symptoms and management of their contacts”.[3] This interim guidance has been updated with advice on safe and appropriate home care for patients with coronavirus disease 2019 (COVID-19) and on the public health measures related to the management of their contacts.

In this interim guidance, the WHO mentions that the decision as to whether to isolate and care for an infected person at home depends on three factors: clinical evaluation of the patient, home setting and ability to monitor the patient at home.

1) Clinical evaluation of the COVID-19 patient

“*The decision to isolate and monitor a COVID-19 patient at home should be made on a case-by-case basis. Their clinical evaluation should include:*
• clinical presentation
• any requirement for supportive care
• risk factors for severe disease (i.e. age (> 60 years), smoking, obesity and non-communicable diseases”

Patients who are asymptomatic or those with mild or ***moderate disease without risk factors for poor outcome may not require emergency interventions or hospitalization****, and could be suitable for home isolation and care, provided the following two requirements are fulfilled in the home setting:*
1. conditions for implementing appropriate ‘infection prevention and control’ (IPC) […] are met;
2. close monitoring for any signs or symptoms of deterioration in their health status by a trained health worker is feasible.

These two requirements also apply to pregnant and postpartum women, and to children.”

2) Evaluation of the home setting

“A trained health worker should assess whether the home in question is suitable for the isolation and the provision of cared of a COVID-19 patient, including whether the patient, caregiver and/or other household members have all they need to adhere to the recommendations for home care isolation. For example, they need hand and respiratory hygiene supplies, environmental cleaning materials, the ability to impose and adhere to restrictions on people’s movement around or from the house.[…]

3) Ability to monitor the clinical evolution of a person with COVID-19 at home.

“*Ensure that the patient can be adequately monitored at the home. Home-based care should be provided by health workers if possible. Lines of communication between the caregiver and trained health workers or public health personnel, or both, should be established for the duration of the home-care period, that is, until the patient’s symptoms have completely resolved. Monitoring patients and caregivers in the home can be done by trained community workers or outreach teams by telephone or email*.”

18.2 National Health Service: Pulse Oximetry to detect early deterioration of patients with COVID-19

The NHS from UK has published in June 2020 a document entitled 'Pulse oximetry to detect early deterioration of patients with COVID-19 in primary and community care settings'. In this document, an algorithm is designed for situations adapted to ambulatory care but outside hospital saturation situation (see Figure 12).

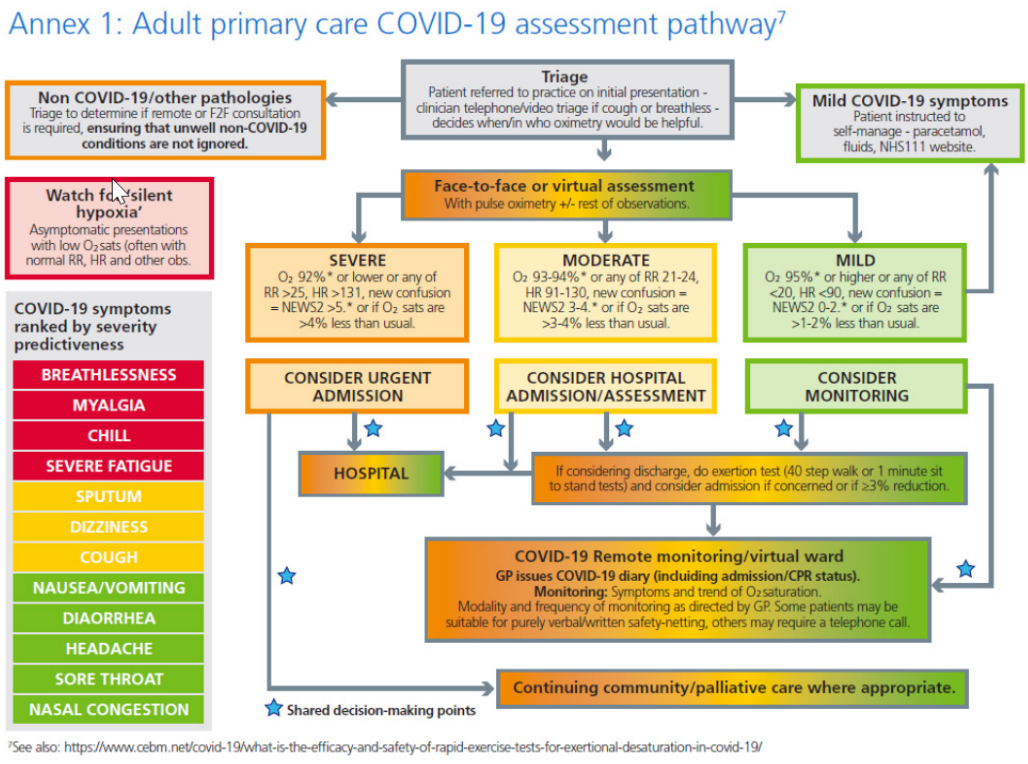
https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2020/06/C0445-remote-monitoring-in-primary-care-jan-2021-v1.1.pdf

This document sets out principles to support the remote monitoring, using pulse oximetry, of patients with confirmed or possible COVID-19. It should be read alongside the general practice and community health services standard operating procedures.

As shown in the figure below, first clinical assessment of patients in primary care setting determines three categories of patients:

One additional precaution is taken to confirm a decision of care at home in mild and moderate stages; the patient must do effort test: 40 steps walk or 1 minute sit to stand test. After this test, if the O_2 oximetry saturation drop for more than 2 %, the patient should be admitted into hospital.

Figure 11 – Adult primary care COVID-19 assessment pathway proposed by the NHS to detect early deterioration of COVID-19 patients in primary and community care settings



18.3 Haute Autorité de Santé: rapid response about home-based oxygen therapy

In France, the HAS edited a rapid response[8] regarding home care for two different profiles of patients with COVID-19 requiring oxygen therapy: profile A concerns hospitalized patient for Covid-19, discharged on oxygen therapy and patient profile B concerns patients not hospitalized for current infection. The aim of this document is to propose the modalities for the home care which guarantee the safety of a Covid-19 patient requiring oxygen therapy. The document highlights the importance of a coordinated care pathway between the primary care and the hospital and is exclusively reserved for the current epidemic context.

When a patient is discharged from hospital, the hospital doctor and the attending doctor check the patient's eligibility criteria (profile A). When the decision is made to undergo home oxygen therapy (profile B), the attending physician contacts the reference hospital service to check the patient's eligibility criteria. The eligibility criteria are linked to the environment (see also chapter 11) and to the patient.

Along the criteria related to the patient, they are:

- The patient must be autonomous (e.g. Katz > 3/6)
- The patient must have a SpO_2 < à 92 % and > 90 % at rest
- The patient do not present other sign of severe Covid-19
- There is no exclusion criteria.

The exclusion criteria are sorted in two categories: the major criteria and the minor criteria.

For major criteria, the presence of 1 criterion is sufficient to exclude oxygen therapy for moderate COVID level at home while for minor criteria, the presence of 2 criteria induces the exclusion to benefit from oxygen therapy at home. The major criteria concerning profile B are the followings:

- Refusal by the patient or his or her family and relatives
- No presence of a third person 24 hours a day, 7 days a week
- Incompatible place to live (no possibility of isolation in a room alone, unreliable telephone access, sanitary conditions, etc.).
- Dependence on oxygen therapy ≥ at 4 L/min.
- Chronic destabilized pathologies such as:
    - Acute cardiovascular pathology
    - Diabetes that is unbalanced or with complications
    - Chronic decompensated respiratory pathology
    - Chronic renal failure justifying dialysis or transplant patient
    - Cancer under chemotherapy
    - Congenital or acquired immunosuppression with active non-Covid-19 infection, uncontrolled HIV infection or with CD4 < 200/mm3, immunosuppressive therapy, bio-therapy and/or corticosteroid therapy in immunosuppressive doses. Splenectomy or homozygous sickle cell disease
    - Solid organ or haematopoietic stem cell transplant, related to a haematopoietic malignancy being treated
    - Decompensated Cirrhosis
    - Neurological or neuro-vascular disease that can impair respiratory function.
- Morbid obesity (Body Mass Index - BMI ≥ 40 kg/m^2)
- Suspicion of pulmonary embolism or pulmonary embolism not excluded (clinical arguments and D-dimers superior to the norm)
- Confirmed pregnancy regardless of term

The minor criteria are (at least 2 criteria are sufficient to exclude oxygen therapy for moderate COVID level at home)

- Age > 70 years old
- Severe cardiovascular pathologies: high blood pressure with polytherapy, stroke or coronary artery disease, heart surgery, heart failure.
- Balanced diabetes
- Chronic respiratory pathology
- Controlled cancer under treatment including radiotherapy < 6 months
- Non-decompensated cirrhosis
- Moderate to severe obesity (Body Mass Index-BMI ≥ 30 and <40 kg/m²)

18.4 Blazey-Martin, 2020: algorithm for remote management in Boston

This publication[11] concerns a study which took place in April 2020 in a large urban academic medical centre of primary care practice. They developed an innovative population management approach for managing COVID-19 patients remotely including an algorithm. The algorithm (Figure 12) is used to "guide triage decisions including how frequently to contact patients depending on symptom day and risk factors, and to identify clinical findings that indicate if the patient is safe to remain at home […]". In this algorithm, they use the cut-off of <95% and RR>25/min as criteria which induces an increased concern. The authors conclude that "our population management strategy helped us optimize at-home care for our COVID-19 patients and enabled us to identify those who require inpatient medical care in a timely fashion." At home oxygen therapy is not considered in the algorithm.

Figure 12 – Algorithm to guide triage decisions in primary care in Boston

COVID-19 OUTREACH/Population Management – As of 4/9/2020

	Day 1-5 COVID symptoms	Day 5-10 COVID Symptoms			COVID Post-Discharge Management
Risk Assessment **Using COVID outreach component**	**Risk assessment—** ✓ Low if no comorbidities, ✓ High if 1 or more Comorbidities: Age > 60, Immunocompromise, Chronic lung dz, Poorly controlled DM, CHF, Transplant, CKD 4/5 **Symptom assessment—** Fever, chills, myalgia, anosmia/ageusia, anorexia, pharyngitis **COVID-19 diagnosis—** Positive test? Clinical diagnosis? ✓ Add to problem list ✓ Document date symptoms started	Questions: 1) **Shortness of Breath—measure O2 sat vs subjective dyspnea** Mild dyspnea but improving? Trouble going up a flight of stairs without getting winded? Pleuritic chest pain? Elevated respiratory rate >22-25? O2 sat <95% 2) **Trouble remaining hydrated?** Decreased fluid intake, <50% normal Lightheaded on standing? Unable to keep fluids or meds down ?Vomiting and/or diarrhea? 3) **Fever >100.4, >102** Responding to antipyretics or not? Myalgias and headaches? 4) **Chronic conditions well-controlled?**			Add COVID outreach component to post discharge encounter Family support? Continue isolation for at least 7 d with mask for14 days from start of symptoms Follow recommendations for Symptom Day out reach (Day 1-5 vs 5-10) VNA involvement? Comorbidity management
Management	**Prevent spread-** 1) **Health care worker or group living?** Must be tested 2) **Home isolation** and social distancing (wash hands, own bathroom and bed, wipe surfaces) 3) Do they have VNA? Live alone? 4) Encourage hydration, take regular meds 5) Counsel about when to call 911, GMA	**Manage at home** • Breathing ok • Fevers controllable • Able to eat and drink • Comorbidities managed • Remain isolated	**UC Respiratory Clinic Assessment** • High risk comorbidities • CXR/O2 sat would help with triage • Other comorbidities need to be assessed • Testing might put patient on non-COVID service • Needs further assessment/support but not ED level of care	**Send to ED** • Immediate support needed—hydration, O2 • 911 vs family to drive patient • Comorbidity needs acute management (chest pain, etc)	**When to stop phone outreach** 1) Breathing ok 2) Afebrile w/o antipyretics 3) Back to baseline and >day 10 **Return to work advice** • 72 hours afebrile w/o antipyretics • AND >7 days total from start of symptoms • **Home isolation** and social distancing • COVID symptoms have resolved • Call your own Employee Health • Mask for 14 days total from date of symptom onset
OTHER	Low risk—call every 2 d High risk— call daily	Low risk call daily High risk 2x per day	Low risk call daily High risk 2x per day	Call 2x per day if not admitted	Call based on illness day (1-5 vs 5-10)

CDC Symptom Checker https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/index.html
CDC 10 things to care for self at home https://www.cdc.gov/coronavirus/2019-ncov/downloads/10Things.pdf
Produced By: Liz Barnhart, FNP, Deb Blazey-Martin, MD and Gabriela Andujar Vasquez, MD

18.5 Greenhalgh, 2020: RECAP score to assess covid-19 patients in primary care

The aim of this study[ss] was “to develop an early warning score called the RECAP (REmote COVID-19 Assessment in Primary Care) for patients with suspected COVID-19 who need escalation to next level of care”. (This next level of care could be the intensified care at home in case of saturation of the hospitals capacity.) “The study was based in UK primary healthcare and used a mixed-methods design including a rapid review, Delphi panel, interviews, focus groups and software development.” The authors conclude that “Items on RECAP-V0 align strongly with published evidence, clinical judgement and patient experience. The validation phase of this study is ongoing.”[12]

At the stage of the prevalidation, the tool (RECAP-V0) “comprises a red flag alert box and 10 assessment items: pulse, shortness of breath or respiratory rate, trajectory of breathlessness, pulse oximeter reading (with brief exercise test if appropriate) or symptoms suggestive of hypoxia, temperature or fever symptoms, duration of symptoms, muscle aches, new confusion, shielded list and known risk factors for poor outcome.” The algorithm here under gives the details of the tool content (see Figure 13).

As it is a tool in which severity of the disease and care requirement depends on a total calculation, we cannot extract cut-off. At the best, we can assume the proxy that the cut-offs used to attribute one or two points to the score are more or less related to a moderate level of COVID.

The tool is indeed composed of items to which 1, 2 or 3 points are attributed. So a saturation of 96% or above equal to 0 point, a saturation of 95%=1 point, a SpO_2 of 94% equal to 2 points and a saturation of 93% or less equal 3 points. And the range for the RR are; 12-20/min gives 0 point, 21 to 24 gives 1 points, 25-29 gives 2 points and 30 or more gives 3 points. Many other criteria are listed and received 0 to 3 points each. If the total is less than ‘, the risk is evaluated as low. If the score is between 4 and 6, the risk is moderate and if the score is bigger than 6, the risk is high. A high score leads to a referral to ER, a moderate score leads to a home visit, a low score leads to a remote follow-up.[12]

[ss] https://bmjopen.bmj.com/content/bmjopen/10/11/e042626.full.pdf?with-ds=yes

Figure 13 – Summary of the items including in the RECAP-V0 tool designed to identify COVID-patients who need escalation to the next level of care

RECAP-V0 ITEMS FOR PATIENTS WHO DO NOT HAVE RED ALERT SYMPTOMS OR SIGNS						
		0 points	1 point	2 points	3 points => refer urgently	Calculate
1	Heart rate (per minute) *(if heart rate not available, score 1)*	51-90	41-50 or 91-110 or missing data	111-130	≤ 40 OR > 130, if unexplained	
2a	Shortness of breath	Not breathless at all	Breathless on moderate exertion e.g. walking room to room	Breathless on mild exertion e.g. getting out of a chair	Severe breathing difficulty; can't complete sentences at rest	Highest of 2a or 2b
2b	or Respiratory rate (per minute)	12-20	21-24	9-11 or 25-29	8 or less, or 30 or more	
3	Trajectory of breathlessness	Same or better than yesterday	Breathless, worse than yesterday	-	Significant deterioration in last hour	
4a	Oxygen saturation at rest	96% or above	95% (don't do 40-step test unsupervised)	94% (don't do 40-step test unsupervised)	93% or below (don't do 40-step test)	Highest of 4a, 4b & 4c
4b	or Saturation after 40 steps	Fall of 0-1%	-	Fall of 2%	Fall of 3% or more	
4c	or Profound tiredness or fatigue	None or mild	Noticeably more tired doing usual activities	Struggling to get out of bed	Unable to speak because of tiredness	
5a	Temperature	≤ 38 °C	38.1-39 °C	> 39 °C or < 35 °C	-	Highest of 5a or 5b
5b	or Feeling feverish with shivers	None	Feverish or chills	Uncontrollable shivering	-	
6	Time from first symptom (days)	7 or fewer	8 or more	-		
7	Muscle aches	None or mild	Moderate	Severe		
8	Cognitive decline	No	Less mentally alert than usual	New and worsening confusion	Reduced level of consciousness	
9	On COVID-19 shielded list (or has been inadvertently left off it)?	No	Yes	-	-	
10	Other risk factors for poor outcome? e.g. age, ethnicity	0-2	3 or more	-	-	
TOTAL (simulated score)						

CLINICIANS' INTERPRETATION OF RECAP-V0 SIMULATED SCORE		
Number of points	Provisional interpretation	Provisional recommendation
7 or more total or 3 on any item or extremely high level of clinical concern	HIGH RISK	Consider urgent referral
4-6 or more total or high level of clinical concern	MODERATE RISK	See in hot hub or virtual ward, or arrange home visit
0-3 total	LOW RISK	Advice and monitor at home

Scores and calculation suggested by Delphi panel and used for simulation.
See A4 on bmj.com for full wording of items including cautions for specific groups.

18.6 Sciensano: Cohort of Belgian hospitalized COVID-19 patients – association study between previous comorbidities and death.[64]

Table 12 – Adjusted Odd Ratio (OR) and 95% Confidential Interval (CI) for death

Yes vs No (Except for Age)	Adjusted OR for death	95% CI
Age (for 10-year-increase)	1.97	1.90-2.04
Solid cancer	1.42	1.27-1.59
Hematological cancer	2.15	1.72-2.69
High Blood Pressure	0.97	0.90-1.05
Cardio-vascular disease	1.21	1.21-1.31
Diabetes	1.21	1.11-1.32
Obesity	1.28	1.13-1.44
Cognitive disorder	1.50	1.36-1.66
Immunodepression	1.64	1.25-2.16
Chronic lung disease	1.31	1.19-1.44
Chronic liver disease	1.64	1.33-2.02
Chronic renal disease	1.23	1.22-1.36
Chronic neurological disease	1.27	1.13-1.42

18.7 Haut Conseil de la Santé Publique (HCSP) – details on risk factors lists

HCSP 29/10/2020[tt] : Part concerning the risk factors[71]

Au total les données disponibles relatives aux facteurs de risque de forme grave de Covid-19 :

- appellent à une réserve concernant l'utilisation de modèles prédictifs, qui comportent des limites et ne peuvent être généralisés. Ils doivent être adaptés à l'évolution de l'épidémie et aux populations étudiées. Un seul des modèles rapportés prend en compte le cumul des comorbidités ;
- appellent au constat que des données manquent encore pour certaines situations (la grossesse par exemple) ou en raison de leur non inclusion dans l'analyse des dernières cohortes anglaises;
- relèvent un manque de données qualitatives et quantitatives pour la majorité des maladies rares;
- confirment que l'âge est un facteur de risque majeur tant pour le risque d'hospitalization que pour le risque de décès et ce particulièrement après 70 ans ;
- précisent que des comorbidités jouent un rôle important en termes de pronostic : l'obésité, le diabète sont notamment des facteurs de risque reconnus ;
- montrent que le cumul de comorbidités joue un rôle important pour le risque de forme grave de Covid-19 ;
- montrent que d'autres comorbidités ont été mises en évidence à partir d'études de cohorte évitant les biais de sélection et permettant d'estimer des risques ;
- apportent des précisions sur le risque en fonction du stade évolutif pour certaines affections et situations seulement (diabète, insuffisance rénale, asthme, cancer, chimiothérapie…) ;
- appellent au constat que le sur-risque individuel pour certaines maladies rares est difficilement évaluable et peut être inapparent dans les statistiques portant sur les patients hospitalisés ou en réanimation en raison de la trop faible prévalence de ces maladies ;
- permettent d'identifier des groupes à risque de forme grave ou de décès liés au Covid-19 allant de faible à très élevé, ces risques étant ajustés sur l'âge ;
- suggèrent que l'identification des personnes à très haut risque relève d'une approche individuelle en raison du poids de l'âge, du sexe, du niveau socio-économique, de l'ethnicité et des nombreuses comorbidités potentielles (à des stades évolutifs divers), parfois cumulées, connues pour être associées à un sur-risque de forme grave de Covid-19.

Le HCSP comprend l'urgence de la situation et adhère à la réalisation très rapide de cet avis. Malgré les efforts collectifs fournis, il précise que ce texte ne peut cependant prétendre à l'exhaustivité et à la prise de recul qu'il aurait souhaité atteindre dans des délais moins contraints. Cet avis est donc davantage d'un consensus d'experts, élaboré dans les délais aussi proches que possible de ceux demandés, qu'un avis basé sur des preuves solides et concordantes ; en outre la consultation des spécialistes des maladies rares n'a pas été possible dans le délai très contraint.

Les personnes présentant un très haut risque vital vis-à-vis du Covid-19

Il n'est pas possible de distinguer, au sein de la population française en âge de travailler, parmi les personnes à risque de forme grave de Covid-19, les groupes de population identifiés comme « à très haut risque vital » en déclinant une liste exhaustive univoque de pathologies. En effet, cette approche, doit tenir en compte les comorbidités, les facteurs démographiques (âge, sexe) ainsi que les facteurs socio-économiques, voire génétiques et ne peut donc être qu'individuelle.

Toutefois ce travail d'actualisation a permis d'identifier les situations ou les pathologies les plus à risque de forme grave de Covid-19 selon les données de la littérature récente (HR > 5) :

- âge ≥ 70 ans ;
- syndrome de Down (Trisomie 21) ;

[tt] https://www.hcsp.fr/Explore.cgi/avisrapportsdomaine?clefr=942

- greffe de cellules souches ;
- chimiothérapie grade B et C ;
- insuffisance rénale stade 5, patient greffé ;
- syndromes démentiels ;
- paralysie cérébrale.

[…]

Le HCSP recommande

1. De considérer comme à risque de forme grave de Covid-19
   a. Les situations qui ont été préalablement identifiées :
      - âge ≥ 65 ans ;
      - pathologies cardio-vasculaires : hypertension artérielle (HTA) compliquée (avec complications cardiaques, rénales et vasculo-cérébrales), antécédent d'accident vasculaire cérébral, antécédent de coronaropathie, antécédent de chirurgie cardiaque, insuffisance cardiaque stade NYHA III ou IV;
      - diabète non équilibré ou compliqué ;
      - pathologies respiratoires chroniques susceptibles de décompenser lors d'une infection virale : broncho pneumopathie obstructive, asthme sévère, fibrose pulmonaire, syndrome d'apnées du sommeil, mucoviscidose notamment ;
      - insuffisance rénale chronique dialysée ;
      - obésité avec indice de masse corporelle (IMC) ≥ 30 ;
      - cancer évolutif sous traitement (hors hormonothérapie) ;
      - cirrhose au stade B du score de Child Pugh au moins ;
      - immunodépression congénitale ou acquise ;
      - syndrome drépanocytaire majeur ou antécédent de splénectomie ;
      - maladies du motoneurone, myasthénie grave, sclérose en plaques, maladie de Parkinson, paralysie cérébrale, quadriplégie ou hémiplégie, tumeur maligne primitive cérébrale, maladie cérébelleuse progressive.
   b. Cette liste est complétée par les données récentes précisant une gradation du risque. La liste figurant ci-dessous inclut toutes les situations comportant un sur-risque significatif identifié (HR > 1)
      - Situations ou pathologies avec sur-risque significatif (HR > 1 et ≤ 3) :
        - âge de 60 à 69 ans ;
        - sexe masculin ;
        - obésité (IMC ≥ 35 kg/m2) ;
        - déprivation matérielle ;
        - plusieurs comorbidités ;
        - diabète avec HbA1c ≥ 58 mmol mol−1 ;
        - pathologies entrainant une immunodépression ;
        - cancer des voies respiratoires ou autres cancers solides de diagnostic datant de moins de 5 ans ;
        - hémopathies malignes y compris si le diagnostic date de plus de 5 ans ;
        - chimiothérapie grade A ;
        - radiothérapie dans les 6 mois précédents ;

- insuffisance rénale stade 3 à 5 (risque plus élevé si stade plus élevé) ;
- maladies neurologiques autres qu'AVC dont épilepsie ;
- BPCO, Hypertension artérielle pulmonaire, asthme nécessitant la prise de corticoïdes inhalés ;
- insuffisance cardiaque, artériopathies périphériques, fibrillation auriculaire ;
- maladie thrombo-embolique ;
- fracture ostéoporotique (hanche, rachis, poignet, humérus) ;
- troubles de l'apprentissage ;
- cirrhose du foie (sans définition de stade) ;
- polyarthrite rhumatoïde, lupus systémique, psoriasis.

o Situations ou pathologies avec sur-risque significatif élevé (HR >3 et ≤ 5) :

- diabète de type 1 ;
- drépanocytose ;
- déficit immunitaire combiné sévère ;
- insuffisance rénale stade 5 avec dialyse.

o Situations ou pathologies avec sur-risque significatif très élevé (HR > 5)

- âge ≥ 70 ans ;
- syndrome de Down (trisomie 21) ;
- greffe de cellules souches ;
- chimiothérapie grade B et C ;
- insuffisance rénale stade 5, ou greffée ;
- syndromes démentiels ;
- paralysie cérébrale.

o Cas particulier des maladies rares

- Par principe de précaution, les maladies rares, pouvant exposer les patients à une forme grave de Covid-19 doivent être également considérées comme des facteurs de risque, bien que n'ayant pas été évaluées, du fait d'un lien potentiel avec les pathologies citées ci-dessus.

Enfin, les multiples associations possibles de ces comorbidités, ou entre comorbidités et terrain génétique, peuvent entraîner un risque de forme grave élevé, voire supérieur, à celles des comorbidités isolées les plus à risque.

18.8 INAMI / RIZIV: Organisation of oxygen delivery at home

Two situations are described on the websites of INAMI / RIZIV: short term vs long term oxygen therapy.

18.8.1 Short term oxygen therapy (≤3 months/year)

Oxygen therapy by gas cylinder devices or oxyconcentrator are reimbursed. Three situations are considered for this reimbursement: acute hypoxemia; hypoxemia in palliative patients and cluster headache. More info in INAMI / RIZIV websites:

- **Oxygénothérapie de courte durée** (https://www.inami.fgov.be/fr/themes/cout-remboursement/par-mutualite/medicament-produits-sante/remboursement/oxygene/Pages/default.aspx)
- **Kortdurende zuurstoftherapie** (https://www.inami.fgov.be/nl/themas/kost-terugbetaling/door-ziekenfonds/geneesmiddel-gezondheidsproduct/terugbetalen/zuurstof/Paginas/default.aspx)

18.8.2 Long term oxygen therapy

This kind of chronic oxygen therapy can only be prescribed by a specialized centre which makes device available for the patient. Mutual fund of the patient is involved in the costs.

- **Oxygénothérapie de longue durée à domicile : intervention dans le coût du traitement** (https://www.inami.fgov.be/fr/themes/cout-remboursement/maladies/respiratoires/Pages/oxygenotherapie-longue-duree-domicile.aspx)
- **Langdurige zuurstoftherapie thuis: tegemoetkoming in de kosten van de behandeling**
- (https://www.inami.fgov.be/nl/themas/kost-terugbetaling/ziekten/ademhalingsziekten/Paginas/langdurige-zuurstoftherapie-thuis.aspx)

18.9 AFMPS / FAGG: Rational use of oxygen device

Coronavirus : l'AFMPS plaide à nouveau pour une utilisation rationnelle de l'oxygène

https://www.afmps.be/fr/news/coronavirus_l'afmps_plaide_a_nouveau_pour_une_utilisation_rationnelle_de_loxygene

Date: 09/11/2020

Pas de stockage inutile

Les appareils utilisés en oxygénothérapie doivent être remplis par le fournisseur, distribués au patient puis collectés, désinfectés et remplis à nouveau après utilisation. Il est donc important que les bouteilles d'oxygène vides et autre matériel usagé soient remis à la disposition des fournisseurs dès que possible. Ainsi, chaque utilisateur peut contribuer à assurer le bon déroulement de la distribution. Il est inutile et contre-productif de stocker des bouteilles d'oxygène, des récipients cryogéniques mobiles ou des concentrateurs d'oxygène. Un stock qui n'est pas utilisé peut entraîner une disponibilité réduite ailleurs. Si un utilisateur dispose de matériel ou d'un stock inutilisé, il doit le signaler immédiatement au fournisseur.

Utilisation rationnelle

Chaque acteur du secteur doit prendre ses responsabilités dans un esprit de solidarité, traiter de manière rationnelle le stock disponible et ne pas conserver des ressources qui sont nécessaires pour d'autres. Un traitement à l'oxygène ne peut être décidé que par le médecin. Les nouvelles installations ne peuvent être réalisées ou commandées que si le médecin a établi une prescription médicale au nom du patient. Les médecins ne peuvent prescrire de l'oxygène que s'il s'agit d'une nécessité médicale ou dans un cadre palliatif. Les pharmaciens ne peuvent commander de l'oxygène que s'ils sont en possession d'une prescription médicale.

Comment un pharmacien peut-il commander de l'oxygène ?

Les livraisons par les fournisseurs d'oxygène ne seront acceptées que si elles sont commandées par un pharmacien (hospitalier). Il s'agit avant tout du pharmacien habituel, également pour les maisons de repos et de soins. D'un autre côté, il existe également des pharmacies de garde que l'on peut joindre via www.pharmacie.be(link is external). Les demandes sans prescription médicale ne seront pas exécutées. Les maisons de repos et de soins et les patients ne peuvent pas commander

eux-mêmes auprès des fournisseurs. Les pharmaciens sont donc chargés de contacter et d'informer entre autres les patients et les maisons de repos et de soins.

Les fournisseurs d'oxygène en Belgique sont joignables pour les pharmaciens (hospitaliers) via des numéros d'urgence spéciaux. Grâce à une coopération mutuelle et à la rationalisation des demandes, ils travaillent dur pour aider tous les patients.

Les pharmaciens utiliseront de préférence le système de billetterie en ligne Covid-oxygen.be(link is external) pour introduire une demande d'oxygène en ligne. Grâce à ce système central en ligne, les pharmaciens n'ont plus besoin de contacter différents fournisseurs.

Coronavirus: het FAGG roept opnieuw op tot rationeel gebruik van zuurstof

(https://www.fagg.be/nl/news/coronavirus_het_fagg_roept_opnieuw_op_tot_rationeel_gebruik_van_zuurstof)

Datum: 09/11/2020

Door de tweede golf van de COVID-19 pandemie is er in België een verhoogde nood aan zuurstof voor patiënten met ademhalingsproblemen. Het FAGG vraagt aan alle actoren en gebruikers, om niet te hamsteren en niet gebruikt of leeg materiaal zo snel mogelijk terug te bezorgen aan de leverancier.

Geen onnodige voorraad aanleggen

Materiaal dat wordt gebruikt bij zuurstoftherapie moet worden gevuld door de leverancier, verdeeld tot bij de patiënt en na gebruik terug worden verzameld, gedesinfecteerd en opnieuw gevuld. Het is belangrijk dat lege flessen en ander gebruikt materiaal zo snel mogelijk opnieuw ter beschikking worden gesteld van de leveranciers. Iedere gebruiker kan zo helpen de verdeling vlot te laten verlopen. Een voorraad aanleggen van zuurstofflessen, mobiele cryogeenvaten of zuurstofconcentratoren is niet nodig en contraproductief. Een voorraad die niet wordt gebruikt kan elders voor een verminderde beschikbaarheid zorgen. Wanneer een gebruiker beschikt over ongebruikt materiaal of een stock moet dit onmiddellijk worden gemeld aan de leverancier.

Rationeel gebruik

Iedere actor in de sector moet solidair verantwoordelijkheid opnemen, rationeel omspringen met de beschikbare voorraad en niet de zorgmiddelen bijhouden die voor anderen noodzakelijk zijn. Een behandeling met zuurstof kan enkel worden beslist door de arts. Nieuwe installaties mogen enkel worden uitgevoerd of besteld wanneer de arts daar een medisch voorschrift op naam van de patiënt voor heeft opgemaakt. Artsen mogen enkel zuurstof voorschrijven als dit een medische noodzaak is of in palliatieve setting. Apothekers mogen enkel zuurstof bestellen wanneer ze over een medisch voorschrift op naam beschikken.

Hoe kan een apotheker zuurstof bestellen?

Leveringen door de zuurstofleveranciers worden enkel aanvaard als die worden besteld door een (ziekenhuis)apotheker. Dat kan via de gebruikelijk apotheker, ook voor de woonzorgcentra. Daarnaast zijn er ook de apotheken van wacht die kunnen worden bereikt via www.apotheek.be(link is external). Aanvragen zonder medisch voorschrift worden niet uitgevoerd. Woonzorgcentra en patiënten kunnen niet zelf bij de leveranciers bestellen. De apothekers staan vervolgens in voor het contact en het briefen van onder andere de patiënten en de woonzorgcentra.

De zuurstofleveranciers zijn voor de (ziekenhuis)apothekers in België bereikbaar via speciale noodnummers. Via onderlinge samenwerking en het stroomlijnen van de aanvragen werken ze hard om alle patiënten te helpen.

Apothekers maken bij voorkeur gebruik van het online ticketingsysteem Covid-oxygen.be(link is external) om een aanvraag voor zuurstof online in te dienen. Dankzij dit centrale online systeem hoeven apothekers niet langer verschillende leveranciers te contacteren.

18.10 HTSC: Creation of beds in Corona High Oxygen Care Unit

Covid-19 Communication : passage à la phase 2B, création de lits Corona High Oxygen Care.

https://organesdeconcertation.sante.belgique.be/sites/default/files/documents/2020_10_28_circ_htsc_passage_a_la_phase_2b_creation_de_places_hfno.pdf

28/10/2020

4. Création de lits Corona High Oxygen Care en dehors des soins intensifs, dans les lits non-ICU-COVID

La vague actuelle de COVID va mettre les hôpitaux à rude épreuve, plus que la première vague qui a débuté en mars. Le plan Surge Capacity prévoit que, dans la phase 2B, 1 200 lits seront fournis au départ de la capacité ICU agréée (60 %), et que 800 lits ICU supplémentaires seront créés en plus de cette capacité agréée (+ 40 %), ce qui se fera principalement dans les salles de réveil, ou encore les quartiers opératoires.

Les projections les plus pessimistes indiquent que cette capacité totale (théorique) de 2000 lits ICU pour le COVID pourrait ne pas être suffisante. Une proportion significative des patients COVID ont besoin d'Optiflow® ou d'une thérapie à haut débit d'oxygène nasal (HFNO) pendant leur séjour. Certains patients ne sont jamais ventilés et reçoivent de l'HFNO comme seule forme d'oxygénothérapie. Pour certains patients, l'HFNO est une forme de thérapie step-up ou step-down avant ou après la ventilation.

Dans le cas d'un step-down après une ventilation mécanique, ou chez les patients dont l' HFNO est la forme maximale d'assistance respiratoire, il existe un certain nombre de patients pour lesquels la thérapie HFNO ou Optiflow® est la seule raison de rester aux soins intensifs. Nous estimons que cela peut affecter jusqu'à 25 % des patients des unités de soins intensifs, selon le case-mix au sein de votre hôpital.

Comme solution provisoire, le HSTC propose de fournir la thérapie HFNO dans les services de soins conventionnels avec le suivi des paramètres nécessaires, et donc de ne pas garder ces patients dans les unités de soins intensifs, où ils n'utilisent pas et n'ont pas besoin de toute l'infrastructure des soins intensifs.

De cette manière, l'unité de soins intensifs peut être réservée aux patients ayant une ventilation mécanique ou une ventilation mécanique imminente, ou aux patients présentant une autre défaillance organique associée.

Nous demandons aux hôpitaux généraux et universitaire de s'organiser de manière à passer à la phase 2B et à crée, au sein de leur réseau, un nombre de lits HFNO égal à 15 % du nombre de lits à caractère intensif agréés dans le réseau. Si tous les lits COVID-ICU supplémentaires de la phase 2B ne peuvent pas être réalisés, nous demandons que cette capacité soit remplacée par des lits HFNO au sein du réseau.

Cela a un certain nombre d'implications de nature technique, mais cela peut aussi avoir un impact sur le staffing de ces services. Le gouvernement prendra les mesures nécessaires pour compenser correctement cette capacité.

Tant la technicité du HFNO que la sévérité des soins prodigués au patient nécessiteront une surveillance accrue. En ce qui concerne le staffing, nous tablons sur un rapport infirmier/patient de 1:6 à 1:4, selon l'organisation.

Afin de pouvoir administrer l HFNO, il y a un certain nombre d'exigences :

1. Les conduites d'oxygène du service doivent pouvoir fournir 40-50 litres d'oxygène par minute. En raison du débit élevé, il n'est pas possible de travailler avec des bouteilles d'oxygène. Nous demandons aux hôpitaux de contacter leur fournisseur et installateur de gaz médicaux afin de fournir l'installation technique nécessaire.

2. Un mélangeur de gaz et un humidificateur doivent être fournis par lit. Il est également possible de remplacer le mélangeur de gaz par 2 rotamètres, 1 pour l'oxygène et 1 pour l'air comprimé. Le gouvernement prend des initiatives pour l'achat centralisé de mélangeurs pour les hôpitaux qui n'en ont pas encore, ou pas suffisamment.

3. Il doit y avoir un stock suffisant de systèmes Optiflow® jetables. L'AFMPS surveille ce marché.

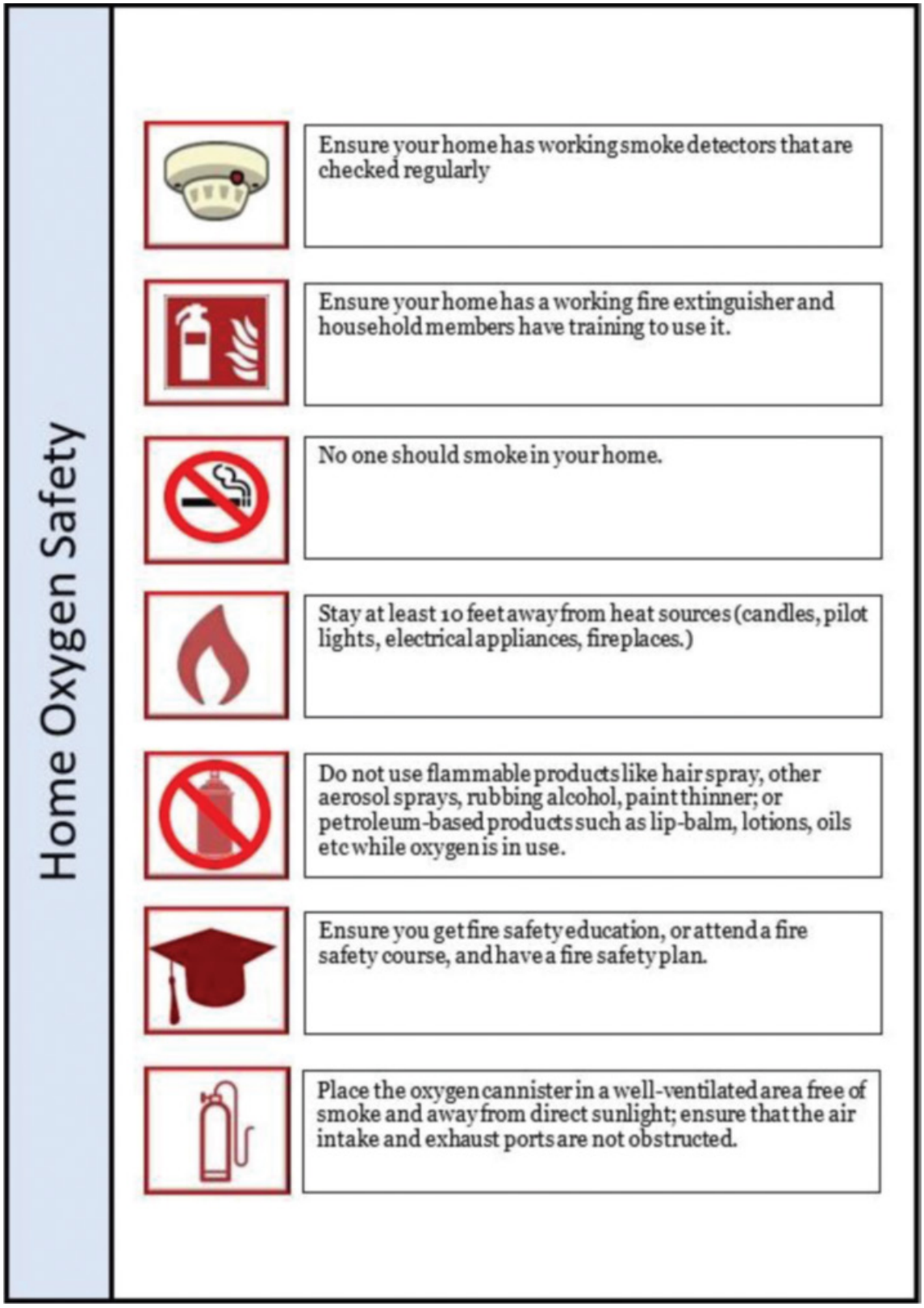
4. Creatie van Corona High Oxygen Care beddenbuiten intensieve zorgen, binnen de non-ICU-COVID

https://www.zorg-en-gezondheid.be/sites/default/files/atoms/files/Gezamelijke%20brief%20Surge%20Capacity%2029102020.pdf

De huidige COVID-golf zal een grotere belasting betekenen voor de ziekenhuizen dan de eerste golf die van start ging in maart. Het surge capacity plan voorziet dat, in fase 2B, 1200 bedden binnen de erkende ICU-capaciteit (60%) wordt voorzien, en dat er hier boven op nog 800 bedden bijkomende ICU capaciteit worden gecreëerd (+40%). Dit zal zich voornamelijk op ontwaakzalen en operatiekwartieren afspelen.
Worst-case projecties geven aan dat deze totale (theoretische) capaciteit van 2000 ICU bedden voor COVID ontoereikend zal zijn. Een significante proportie van de COVID-patiënten heeft tijdens het verblijf nood aan Optiflow® of High Flow Nasal Oxygen (HFNO) therapie. Sommige patiënten worden nooit beademd, en krijgen HFNO als enige vorm van zuurstoftherapie. Voor sommige patiënten is HFNO een vorm van step-up of step-down therapie voor of na beademing.
In step-down na mechanische beademing, of bij patiënten met HFNO als maximale vorm van ademhalingsondersteuning, zijn er een aantal patiënten voor wie HFNO of Optiflow® therapie de enige reden is waarom ze nog op intensive care verblijven. We schatten dat dit tot 25% van de ICU patiënten kan betreffen, afhankelijk van de case-mix in uw ziekenhuis.
Als noodoplossing stelt het HSTC voor om HFNO therapie te voorzien op conventionele verpleegafdelingen met de nodige parameter-opvolging, en deze patiënten dus niet op ICU te houden, waar ze niet de gehele ICU infrastructuur gebruiken en behoeven. Op die manier kan de ICU gereserveerd worden voor patiënten met mechanische beademing of dreigende mechanische beademing, of voor patiënten met ander geassocieerd orgaan falen.
Wij vragen aan de algemene en universitaire ziekenhuizen om zich zo te organiseren dat zij opschalen naar fase 2B en binnen hun netwerk een aantal HFNO-bedden creëren dat gelijk is aan 15% van het aantal erkende bedden met intensief karakter in het netwerk. Indien niet alle extra COVID-ICU-bedden van de fase 2Bgerealiseerd kunnen worden, vragen wij deze capaciteit te vervangen door HFNO-bedden binnen het netwerk.
Dit heeft een aantal implicaties van technische aard, maar ook mogelijk een impact op bestaffing van die afdelingen. De overheid zal de nodige maatregelen voorzien om deze capaciteit correct te vergoeden.
Zowel de techniciteit van de HFNO als de zorgzwaarte van de patiënt maakt dat er verhoogd toezicht zal nodig zijn. Qua bestaffing gaan we uit van een ratio van een nurse/patiënt-ratio van 1:6 tot 1:4, afhankelijk van de organisatie.
Om HFNO te kunnen toedienen zijn er een aantal vereisten:
1.De zuurstofleidingen op de afdeling moeten in staat zijn om 40-50 liter zuurstof per minuut te voorzien. Door het hoge debiet kan men niet werken met zuurstofflessen. Wij vragen aan de ziekenhuizen om contact op te nemen met hunleverancier en installateur van medische gassenteneinde de nodige technische installatie tevoorzien.
2.Er moeten per bed een gasblender en een bevochtiger voorzien worden. Eventueel kan ter vervanging van de gasblender ook gewerkt worden met 2 rotameters, 1 voor zuurstof en 1 voor perslucht. De overheid neemt initiatieven tot een centrale aankoop van blenders voor ziekenhuizen die daarover nog niet of onvoldoende beschikken.
3.Er moet voldoende voorraad zijn aan disposible Optiflow® systemen. Het FAGG volgt deze markt op.

18.11 Sardesai: Home safety measures

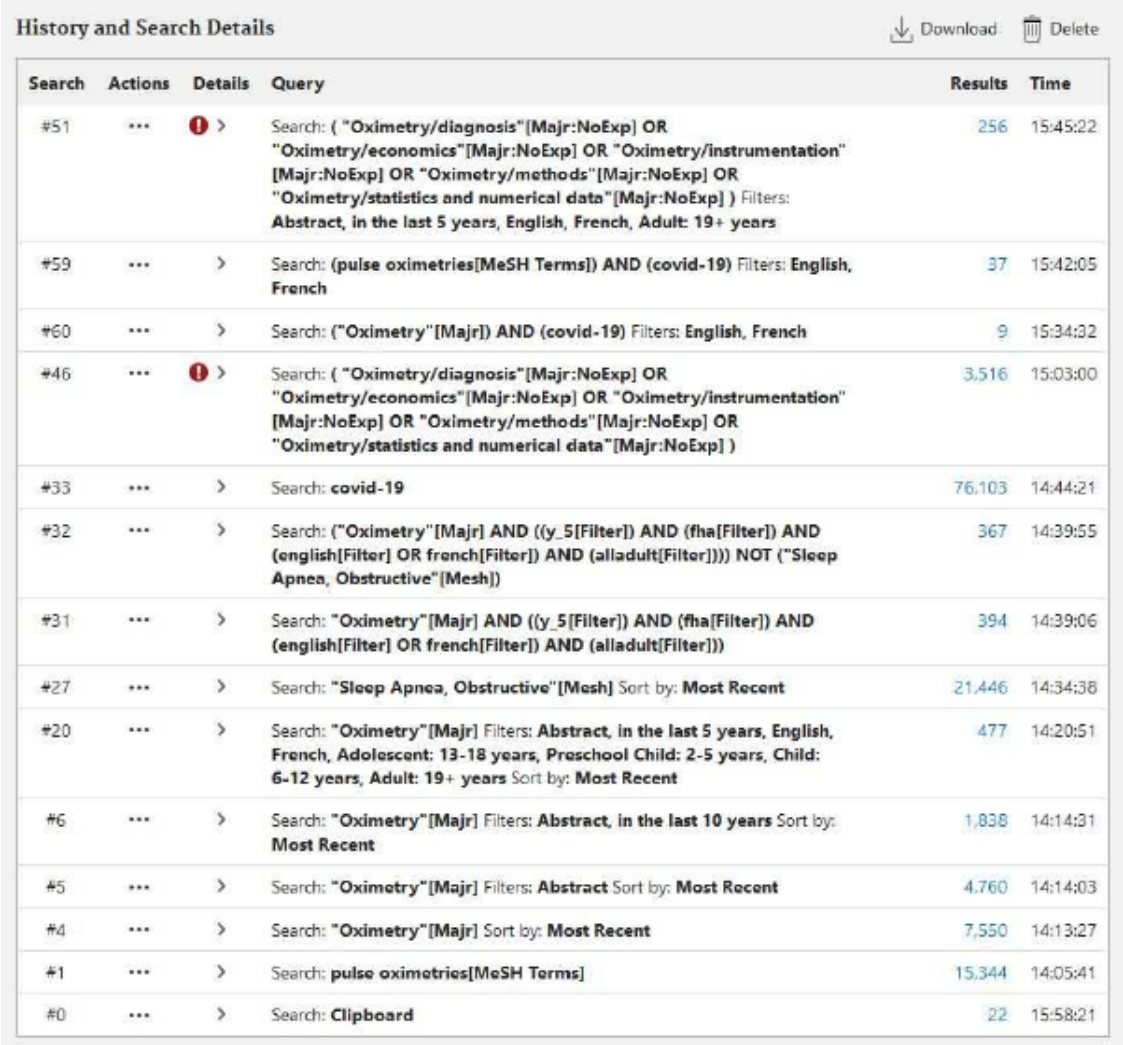
Figure 14 – Home oxygen safety poster (Sardesai, *et al.*: Short Term Home Oxygen Therapy for COVID-19) [19]



18.12 Search strategy on MEDLINE (Pubmed) on Pulse Oximeters

A researcher (GH) used the following research strategy (see Figure 15).

Figure 15 – Search strategy of the 21/11/2020



History and Search Details

Download Delete

Search	Actions	Details	Query	Results	Time
#51	···		Search: ("Oximetry/diagnosis"[Majr:NoExp] OR "Oximetry/economics"[Majr:NoExp] OR "Oximetry/instrumentation"[Majr:NoExp] OR "Oximetry/methods"[Majr:NoExp] OR "Oximetry/statistics and numerical data"[Majr:NoExp]) Filters: Abstract, in the last 5 years, English, French, Adult: 19+ years	256	15:45:22
#59	···		Search: (pulse oximetries[MeSH Terms]) AND (covid-19) Filters: English, French	37	15:42:05
#60	···		Search: ("Oximetry"[Majr]) AND (covid-19) Filters: English, French	9	15:34:32
#46	···		Search: ("Oximetry/diagnosis"[Majr:NoExp] OR "Oximetry/economics"[Majr:NoExp] OR "Oximetry/instrumentation"[Majr:NoExp] OR "Oximetry/methods"[Majr:NoExp] OR "Oximetry/statistics and numerical data"[Majr:NoExp])	3,516	15:03:00
#33	···		Search: covid-19	76,103	14:44:21
#32	···		Search: ("Oximetry"[Majr] AND ((y_5[Filter]) AND (fha[Filter]) AND (english[Filter] OR french[Filter]) AND (alladult[Filter]))) NOT ("Sleep Apnea, Obstructive"[Mesh])	367	14:39:55
#31	···		Search: "Oximetry"[Majr] AND ((y_5[Filter]) AND (fha[Filter]) AND (english[Filter] OR french[Filter]) AND (alladult[Filter]))	394	14:39:06
#27	···		Search: "Sleep Apnea, Obstructive"[Mesh] Sort by: Most Recent	21,446	14:34:38
#20	···		Search: "Oximetry"[Majr] Filters: Abstract, in the last 5 years, English, French, Adolescent: 13-18 years, Preschool Child: 2-5 years, Child: 6-12 years, Adult: 19+ years Sort by: Most Recent	477	14:20:51
#6	···		Search: "Oximetry"[Majr] Filters: Abstract, in the last 10 years Sort by: Most Recent	1,838	14:14:31
#5	···		Search: "Oximetry"[Majr] Filters: Abstract Sort by: Most Recent	4,760	14:14:03
#4	···		Search: "Oximetry"[Majr] Sort by: Most Recent	7,550	14:13:27
#1	···		Search: pulse oximetries[MeSH Terms]	15,344	14:05:41
#0	···		Search: Clipboard	22	15:58:21

The researcher (GH) identified 22 references based on the title. A second researcher (MM) subsequently selected seven references that were considered relevant. Twelve references were considered out of the scope because they did not discuss the reliability of oximeters, did not propose a minimum acceptable reliability, or discussed devices that could not be used in the primary care system. Three references did not provide any useful information during the reading, so they were not cited.

18.13 Identified studies on Pulse Oximeters

Table 13 – Simplified evidence table regarding pulse oximeters

	Publication type	Study weakness	Patient charac.	Intervention	Comparison	Outcomes	Key results
Luks *et al*,[66] 2020, USA	Review	No apparent review strategy					
Lipnick *et al*, [68] 2016, USA	Comparative study	Low sample size/selection bias (healthy subjects)	22 healthy subjects	Pulse oxymetry reading (SpO_2) by 6 devices not cleared by the FDA when stable SaO_2 between 70 and 100%	Arterial SaO_2 reading	Bias (SpO_2 – SaO_2) mean, precision (SD of the bias), and root mean square error (ARMS)	4/6 oximeters have large errors (up to −6.30% mean bias, precision 4.30%, 7.53 ARMS) when SaO_2 <80%, 3/6 oximeters have large errors when SaO2 is between 80 and 90%
Hudson *et al*. [69] 2018, USA	Controlled observational study	Multiple measurements for each study subject	60 patients (aged 18-85 years) who required continuous postoperative pulse oximetry and intermittent arterial blood gas monitoring	Pulse oxym. Reading (SpO_2) by 8 pulse oximeters not for medical use	1 pulse oximeter for medical use	Positive predictive value (PPV) and negative predictive value (NPV) of oximeters not for medical use for detecting hypoxemia (SpO_2<90%)	PPV=33% (12/36) NPV=99% (630/633)
Uchimura *et al*. [70] 2019, USA	Comparative study	Comparison devices considered with no bias (perfect accuracy) that underestimate the real bias of other devices, number of	38 healthy subjects	Monitoring activity sensing, step count, blood pressure, temperature, ECG, respiratory rate and pulse oximetry with 16 devices at rest and at effort	iWorx (Advanced Physiology, Inc.) for ECG, RR and SpO_2. Visual or video for step count. Braun Thermoscan for temperature. Manual measurement for BP	Mean, SD, Arms for pulse oximeters	Only 2/16 met the acceptable criteria for each biosignal measured. The Withings Pulse Ox and the Tinké, both dual-use devices, met the criterion accuracy for SpO_2 but not for Step

		subjects, selection bias					count and respiratory rate.
Teo J., [71] 2020, Malaysia	letter	3 referencesNo apparent review strategy					
Greenhalgh et al.[72] 2020, UK	Review	Only research strategy apparent					
Louie *et al.*[73] 2018, USA	Observational study	Low sample size / selection bias (healthy subjects)	10 healthy subjects	Pulse oxym. Reading (SpO_2) by 4 pulse oximeters during 3 types of motion when stable SaO_2 between 75 and 100%	Arterial reading SaO2	Bias, mean, SD, 95%, and root mean square error	3/4 oximeters had ARMS> 3% for SaO_2 70 to 100% during any motion Vs 1.8% without motion

18.14 Search strategies on telemonitoring

All searches were performed on 11/12/20; study selection on relevance was done by a single reviewer.

Four sources were checked.

18.14.1 PUBMED search in COVID collection

((Telemonitor OR "remote monitor" OR "hospital at home" OR "virtual visit" OR "virtual round" OR "virtual hospital" OR smartphone OR wearable OR "mobile health" OR mhealth) AND (corona OR covid) AND (respiratory OR breath OR hypoxia)) AND LitCTREATMENT[filter] Filters: Randomized Controlled Trial, Review, Systematic Review, in the last 1 year

N=231

18.14.2 Scholar google

(Telemonitor OR “remote monitor” OR “hospital at home” OR “virtual visit” OR “virtual round” OR “virtual hospital” OR smartphone OR wearable OR “mobile health” OR mhealth) AND (corona OR covid) AND (respiratory OR breath OR hypoxia)

18.14.3 MEDRXIV

https://www.medrxiv.org/

For title "remote telemonitor home" (match any words)

N=123

18.14.4 The Centre for Evidence-Based Medicine

https://www.cebm.net/ (COVID-19 Evidence)

‘symptom assessment’

18.15 Identified projects with telemonitoring for COVID-19 patients outside the hospital

Table 14 – Evidence table regarding telemonitoring for COVID-19 patients outside the hospital

Ref	Country	Type of study	Patient characteristics	Telemonitoring intervention	Conclusions
Agarwal et al. [128]	Canada	Observational	N=97 PRE HOSPITAL	GP-Led Remote monitoring, using telephone or video visits, 7-days a week by an interprofessional, family medicine led team. Patients also had access to a dedicated on-call service 24-hours a day. Care was charted using the EPIC Electronic Medical Record (EMR) which enables secure, EMR-integrated video visits via Zoom and bi-directional messaging using a patient portal. Patients could participate in video visits using a cell phone, tablet or computer. Care was also provided by telephone when the patient preferred or was unable to connect via video.	Analysis of the first 97 patients in the COVIDCare@Home program demonstrates that a team-based, family medicine-led remote monitoring program is a feasible and safe option to manage COVID-19 patients in the community. These results suggest that the COVIDCare@Home model may help limit the burden of COVID-19 on acute care settings and improve the system level response to the pandemic
Annis et al. [138]	USA	Observational	N=1496 PRE HOSPITAL	HOSPITAL-Led Within GetWell Loop, patients are enrolled in a specific “loop,” which contains a set of patient education messages, reminders, and questions specific to a disease state or surgical procedure. Loops vary by duration and frequency of check-ins with the patient. In our COVID-19 loop, patients were given information about COVID-19, reminders about social distancing and hygiene, and daily check-in questions each morning to assess their symptoms. Information was supplied to patients through a scrolling newsfeed, where they also had the option of sending comments and questions to their care team. Symptom monitoring questions answered with potentially concerning results (eg, reporting severe shortness of breath) were flagged with either a red or yellow alert and routed to a dashboard for action by a member of the first responder team.	Patients have been extremely grateful and positive about their experience using the tool and feel it has helped them stay safe at home

Ref	Country	Type of study	Patient characteristics	Telemonitoring intervention	Conclusions
Anonymous[122, 123, 125]	Belgium	Ongoing pilot	N= not yet available PRE HOSPITAL POST HOSPITAL	GP-led Patients receives warnings on smartphone to measure vital signs and submit them on special app (SAFELINK).	Not yet available
Bruni et al.[130]	Italy	Observational	N=1239 POST HOSPITAL	Hospital-led Remote monitoring of blood oxygen saturation, heart rate, body temperature, and respiratory rate are checked by respiratory physicians twice daily. Telephone help-desk support is available to patients, including direct contact with hotel nurses (or physicians, as appropriate) 24 hours a day. If deemed necessary, the physician visits the patient and, if needed, can alert the emergency room of the nearby hospital.	Use of telemedicine coordinated by respiratory physicians could represent a key tool for the long-term care of patients with COVID-19 and for other applications beyond COVID-19 treatment
Francis et al.[136]	UK	Observational	N=900 PRE HOSPITAL POST HOSPITAL.	Hospital-led Patients were followed up through periodic phone calls to check on their status. High risk patients were followed up by a respiratory consultant on days 2-5, 7, 10, 14 and beyond if needed, whereas lower risk patients were followed up by a consultant physician or GP on days 7 and 14.	This observational study of a real-world remote monitoring virtual hospital service, set up rapidly during the onset of the worst pandemic seen in decades, has demonstrated that it was possible to set up a service that resulted in a low incidence of deaths (2.0%) and readmissions (8.1%).
Gordon et al.[139]	USA	Observational	N=225 POST HOSPITAL	Hospital-led Enrolled patients had an app, and were provided with a pulse oximeter and thermometer. Patients self-reported symptoms, O_2 saturation, and temperature daily. Abnormal symptoms or vital signs were flagged and assessed by a pool of nurses. We deployed MyChart Care Companion, a module embedded in our patient portal software (Epic Systems Inc., Verona, Wisconsin, United States). Care Companion has both mobile and desktop version, and was available in English and Spanish. The app reminds	Our work suggests that remote patient monitoring reduces readmissions for patients with COVID-19 and provides scalable remote monitoring capabilities upon hospital discharge.

Ref	Country	Type of study	Patient characteristics	Telemonitoring intervention	Conclusions
				a patient each morning to complete a survey, at which point the patient is able to self-enter their device data (oxygen saturation and temperature), and answer five symptom questions related to shortness of breath, cough, appetite, weakness, and vomiting. Eligible patients were referred to the program at the time of discharge through an order in our electronic health record (EHR) and provided with a pulse oximeter (Masimo MightSat or the Sensogram Sensoscan), a thermometer (Care Line Inc., oral), and an instructional packet on the program.	
Grutters et al.[132]	The Netherlands	Observational	N=33 POST HOSPITAL	Hospital-led Home telemonitoring consisted of daily control of oxygen saturation measured by pulse oximeter, temperature, and COVID-19 respiratory symptoms scored on a 0–10 numerical rating scale via an application (Luscii, Amsterdam, the Netherlands) on smartphone or tablet. In the application, personalized thresholds with orange for moderate or red for severe deteriorations were set. Besides, patients could give comments. Warnings for deterioration or comments were sent directly to the dashboard available via a web browser. The dashboard updated several times a minute and was controlled by the home telemonitoring team consisting of medical residents supervised by pulmonologists. All data entries were saved and graphically displayed as trend to the team and patient. Patients received daily automatic reminders to fill in the app. Besides, the team could send personal messages to the patient. Furthermore, the team actively contacted patients by phone to assist in titration of oxygen therapy via nasal cannula and to control clinical follow-up.	We showed that early discharge is possible in this group if home telemonitoring with use of pulse oximetry is offered. The greatest reduction in hospitalization duration is seen in patients in need of home oxygen therapy. Home telemonitoring after early discharge in COVID-19 patients is a safe, cost-effective, and patient-friendly tool, which reduces mean duration of hospitalization, especially in patients in need of home oxygen therapy.
Hutchings et al.[119]	Australia	Observational	N=162 PRE HOSPITAL	Hospital-led Vital signs, including respiratory rate, oxygen saturation, pulse rate and temperature, are monitored	Using remote clinical appraisal, supported by home monitoring of clinical observations, there

Ref	Country	Type of study	Patient characteristics	Telemonitoring intervention	Conclusions
				at home. Patients are monitored three times per day, including a videoconference with the patient twice every 24 hours, allowing for further assessment of symptoms and signs of deterioration based on standard nursing assessment approaches. Vital signs are recorded electronically in the EMR and tracked against a standardised early warning system, known as 'Between The Flags', using the Standard Adult General Observation chart criteria. A wireless pulse oximeter (iHealth®Air pulse oximeter PO3M, iHealth Labs, Inc., Sunnyvale, CA, USA), provides peripheral oxygen saturation and pulse rate measurements. A single-use, wearable temperature monitor (Temp°Traq® Clinical, Blue Spark Technologies, Inc., Westlake, OH, USA) is self-applied in the axilla and provides continuous temperature monitoring. The device feeds continuously into a web-based dashboard, providing the Care Centre with a summary view of all patients. Each patch lasts for 72 hours and each patient is provided with three patches to cover the first 9-11 days of isolation. Both devices have Bluetooth® connectivity. Video consultations were implemented to sight the patient, confirm vital signs collected from wearables devices and to estimate the respiratory rate.	were low observed rates of deterioration requiring escalation and no patient deaths. Community-based virtual health care is feasible for managing most patients with COVID-19 and can be rapidly implemented.
Knight et al.[137]	UK	Observational	N=393 PRE HOSPITAL	Hospital-led Patients are reviewed remotely by phone within 24 hours of referral and triaged into high or low risk follow-up groups. Patients with risk factors for deterioration (age, comorbidities or concerning symptoms) receive oxygen saturation probes to facilitate home monitoring.	The covid-19 virtual hospital is a small but vital part of the armoury against COVID-19. It offers patient reassurance and safety, good clinical care and safety netting, appropriate escalation and readmission pathways and a means to reduce bed occupancy at a time of crisis.
Maillette de Buy Wenniger[133]	The Netherlands	Observational	N=150	Hospital-led	Patients considered this approach as pleasant and safe and for the hospital it meant that there were more beds available for other patients.

Ref	Country	Type of study	Patient characteristics	Telemonitoring intervention	Conclusions
			POST HOSPITAL	Patients measure oxygen saturation and temperature and submit these together with complaints by a special app. A medical team of lung specialist and residents assess and monitors the data.	
Martinez et al.[131]	Spain	Observational	N=313 PRE HOSPITAL POST HOSPITAL	Hospital-led Every patient completed a clinical questionnaire (fatigue, cough, expectoration) and temperature once per day and oxygen saturation levels three times per day. (a pulse oximeter, and a thermometer were delivered to their home) and send them electronically to the central hospital information system. Proactive monitoring was done by nurses by getting in touch via telephone with every patient at least once a day.	The data from this study suggest that at-home monitoring with telemedicine and telemonitoring in patients with COVID-19 is a well-accepted, useful, and safe system. Its use in higher-risk but not seriously ill patients allows for appropriate clinical monitoring, detects worsening of the disease early, helps order care at times of high demand, contributes to maintaining ‘‘social distancing’’ by preventing visits to emergency departments or clinics, and offers support to patients and their families. Our data suggest that telemedicine with at-home telemonitoring, when used proactively, allows for clinically useful and safe monitoring of high-risk patients with COVID-19.
Mayo Clinic[140]	USA	Ongoing pilot	N= not yet available PRE HOSPITAL	HOSPITAL LED Patients have remote monitoring armband and use the tablet to answer a brief daily questionnaire about symptoms and any anticipated or completed hospital visits.	Not yet available
Miller et al.[120]	Australia	Accuracy study	N=271 Not applicable	NOT APPLICABLE Respiratory rate, resting heart rate and heart rate variability were measured using the WHOOP wrist-worn strap. The WHOOP strap is a small, waterproof, and rechargeable device containing a photoplethysmogram, accelerometer, thermometer, capacitive touch sensor, and gyroscope, which can be worn comfortably 24-hours per day and lasts 5 days between charges. The wrist-worn strap wirelessly transfers data to mobile devices running the	This study presents a novel, non-invasive method for detecting SARS-CoV-2 infection prior to and during the first days of symptoms. The findings indicate that the early stages of the infection may have a detectable signature that could help identify individuals who should self-isolate and seek testing.

Ref	Country	Type of study	Patient characteristics	Telemonitoring intervention	Conclusions
				associated WHOOP app; from there, data is transferred to a secure cloud-based data storage and processing server, collectively known as the WHOOP system. In addition to automated tracking of physiological data, the WHOOP app supports tracking of manually reported contextual factors.	
Mishra et al.[141]	USA	Accuracy study	N=32 Not applicable	NOT APPLICABLE We investigated the use of wearable devices (fitness trackers) for the early detection of COVID-19 in a retrospective manner.	Our findings suggest that activity tracking and health monitoring via consumer wearable devices may be used for the large-scale, real-time detection of respiratory infections, often pre-symptomatically.
Moens [124]	Belgium	Ongoing pilot	N= not yet available PRE HOSPITAL POST HOSPITAL	GP LED HOSPITAL LED We developed an app (MoveUP) to support hospitals and general practitioners with triage and monitoring of (potential) COVID-19 patients from initial symptom onset. Patients receive information and counselling through the app, in which they also enter information about their health status. The central health care professional has a dashboard with an overview of all patients and their conditions. If necessary the patient can be contacted through a privacy compliant communication channel. Objective data from remote sensors (e.g. pulse oximetry) and patient symptom questionnaires can be integrated in the system.	Not yet available
Morris [142]	USA	Ongoing pilot	N= not yet available POST HOSPITAL	HOSPITAL LED Wireless sensor gently sits on throat to monitor coughs, fever and respiratory activity. The device monitors coughing intensity and patterns, chest wall movements (which indicate labored or irregular breathing), respiratory sounds, heart rate and body temperature, including fever. From there, it wirelessly transmits data to a HIPAA-protected cloud, where automated algorithms produce graphical	Not yet available

Ref	Country	Type of study	Patient characteristics	Telemonitoring intervention	Conclusions
				summaries tailored to facilitate rapid, remote monitoring.	
Philips[134]	The Netherlands	Ongoing pilot	N= not yet available POST HOSPITAL	HOSPITAL LED The Philips Biosensor BX100 is designed to address a new approach to vital signs measurements, supporting surveillance of higher acuity patients moving from intensive care units into lower acuity general care areas of a hospital. The lightweight, disposable biosensor is a 5-day, single-use wearable patch which can be integrated with a scalable hub to monitor multiple patients. It adheres discreetly to the chest to collect, store, measure and transmit respiratory rate and heart rate every minute – the top two predictors of deterioration – as well as contextual parameters such as posture, activity level and ambulation	Not yet available
Silven et al.[135]	The Netherlands	Observational	N=55 PRE HOSPITAL POST HOSPITAL	HOSPITAL LED The COVID Box is literally a box containing a thermometer (Withings Thermo), pulse oximeter (Masimo MightySatRx), blood pressure monitor (Microlife BP B2 Basic or Withings BPM Connect), and a safety bag (for return of the devices). All devices are approved for medical use in Europe. Patients receiving the COVID Box are instructed to measure their temperature, oxygen saturation, respiratory frequency, heart rate, and blood pressure three times a day. Patients are instructed on the use of the devices, the desired frequency of measurements, and their personalized reference values. A physician or physician assistant (supervised by a medical specialist) performs a daily video consultation to monitor the patient's symptoms and vital parameters, whereas physical consultations are only performed when the	Preliminary results of the evaluation of the telemonitoring program indicate that no adverse events (ie, deaths or emergency hospital admissions) occurred among patients in the telemonitoring care pathway, and that a worsening of symptoms and need for further medical attention could be effectively detected by means of this telemonitoring care program. Eventually, 5 patients (9%) had to be admitted to the hospital due to progression of symptoms. Both patients and health care providers viewed the use of the COVID Box positively. Innovative digital strategies such as telemonitoring have great potential to improve the management of COVID-19. Telemonitoring may optimize care for patients with COVID-19 by detecting clinical deterioration at an early stage. Additionally, telemonitoring reduces the number of hospital visits and admissions, thereby enabling the efficient use of scarce

Ref	Country	Type of study	Patient characteristics	Telemonitoring intervention	Conclusions
				physician or physician assistant suspects a deterioration of symptoms. In the first phase of implementation, measurements of vital parameters are collected during the video consultation and entered manually into the patient's EMR. In the second phase, patients install an app, developed by the Leiden University Medical Center (LUMC), which is linked to the devices via Bluetooth and transfers the measurements directly into the patient's EMR.	health care resources and lowering the risk of further transmission of the virus.
Sitammagari et al. [143]	USA	Observational	N=1477 PRE HOSPITAL POST HOSPITAL	HOSPITAL LED This virtual model, Atrium Health hospital at home (AH-HaH), enhanced existing primary care by providing daily telemonitoring by a nurse for all low-acuity patients to proactively identify disease progression and escalate care as needed. For higher-acuity patients who would otherwise be hospitalized, it provided the option for hospital-level care in the home by deploying a hybrid of virtual and in person services. A virtual hospital model providing proactive home monitoring and hospital-level care through a virtual observation unit (VOU) and a virtual acute care unit (VACU) in the home setting for eligible patients with COVID-19. After VACU admission, a team of mobile clinicians (paramedics and registered nurses) visits the patient's home by using Vidyo videoconferencing softwarE.	Virtual hospital programs have the potential to provide health systems with additional inpatient capacity during the COVID-19 pandemic and beyond.
University College Dublin[129]	Ireland	Ongoing pilot	N= not yet available PRE HOSPITAL	HOSPITAL LED Using the microphone of their smartphone, patients will record their breathing using a clearly defined protocol. Algorithms to extract respiration rate and related metrics from these audio recordings will be developed, providing additional vital signs monitoring to clinical data currently being monitored remotely.	Not yet available

Ref	Country	Type of study	Patient characteristics	Telemonitoring intervention	Conclusions
Vander-voort[121, 126]	Belgium	Ongoing pilot	N= not yet available POST HOSPITAL	HOSPITAL LED Patients receive a patch with sensors that measure vital signs. Patients register three times a day their vital signs and send these together with a medical questionnaire through their smartphone or computer. Health care professionals monitor these data. By this telemonitoring system (CovidCare@Home) patients are able to rehabilitate in their home setting.	Not yet available
Vlaanderen[127]	Belgium	Ongoing pilot	N= not yet available UNCLEAR	UNCLEAR ConeXuscare is application to support health care professionals with triage and monitoring and follow-up of (potential) COVID-19 patients and for sharing data across health care professionals.	Not yet available

18.16 Identified publications on thromboprophylaxis in COVID-19 patients

18.16.1 Folia Pharmacotherapeutica November 2020.

Update of the 30/04/2020 publication - 9 june 2020 – last update: 7 october 2020 but no change on management of COVID-19 patients outside the intensive care are required.

In French: COVID-19 et coagulopathie: qu'en est-il des patients en ambulatoire? (https://www.cbip.be/fr/articles/3469?folia=3462)

Les résultats de ces études portant sur des patients hospitalisés ne peuvent en aucun cas être extrapolés aux patients ambulatoires, qui ont un risque beaucoup plus faible de thrombose. Pour ces patients, on ne dispose donc toujours pas de suffisamment de données pour orienter la politique en matière de thromboprophylaxie. Les informations que nous avions publiées à ce sujet dans notre précédent communiqué Bon à savoir (mise à jour du 9 juin 2020) restent valables. Les directives consensuelles[3-5] qui y sont mentionnées restent inchangées à ce jour.

In Dutch: COVID-19 en coagulopathie: wat met ambulante patiënten? (https://www.bcfi.be/nl/articles/3469?folia=3462)

De resultaten van deze studies bij gehospitaliseerde patiënten kunnen in geen geval geëxtrapoleerd worden naar ambulante patiënten, die een veel kleinere kans op trombose hebben. Voor deze patiënten zijn er dus nog steeds onvoldoende gegevens beschikbaar om het beleid op vlak van tromboprofylaxe te sturen. De informatie hierover in ons vorig Goed om Weten bericht (update van 9 juni 2020) blijft geldig. De daarin aangehaalde op consensus gebaseerde richtlijnen3-5 blijven tot op heden ongewijzigd.

18.16.2 References gathered by the AFMPS / FAGG on thromboprophylaxis (16/11/2020)

18.16.2.1 Société Française de Médecine Vasculaire (SFMV)

https://www.portailvasculaire.fr/sites/default/files/docs/propositions_sfmv_covid_mtev.pdf

“On peut envisager une thrombo-prophylaxie chez les patients COVID-19 qui présentent en plus d’une réduction de mobilité importante au moins un facteur de risque parmi les suivants: IMC > 30; âge > 70, cancer en cours de traitement, antécédent personnel de MTEV, chirurgie majeure de moins de 3 mois.”

“HBPM à dose standard (daltéparine 5000UI, enoxaparine 4000UI) pendant 7 à 14 jours.”

“En l’état actuel des connaissances, il n’est pas licite de suivre l’évolution des dosages de D-dimères pour décider une thrombo-prophylaxie.”

18.16.2.2 Netherlands Huisartsen Genootschap (NHG)

https://www.nhg.org/sites/default/files/content/nhg_org/uploads/nhg-leidraad_stollingsafwijkingen_bij_covid-19_voor_de_huisarts__0.pdf (Augustus 2020)

“Adviseer patiënten die bedlegerig zijn door COVID-19 om toch regelmatig even te bewegen, bijvoorbeeld door twee tot drie keer per dag vijf tot tien minuten uit bed te komen.”

“Overweeg alleen profylactisch laagmoleculairgewichtheparine (LMWH) bij patiënten met (een hoge verdenking op) COVID-19 die hierdoor (arbitrair > 3 dagen**) bedlegerig zijn en een voorgeschiedenis van een DVT of longembolie of een actieve maligniteit hebben**, tenzij zij al een onderhoudsbehandeling met anticoagulantia (vitamine K-antagonisten, DOAC’s) krijgen.”

“Nadroparine 9500IU, enoxaparine 4000IU, in ieder geval zolang de patiënt bedlegerig is; verdubbel dosis bij lichaamsgewicht > 110 kg.”

“Verricht bij patiënten met COVID-19 alleen een D-dimeertest bij een klinische verdenking op diepveneuze trombose (DVT) of longembolie en niet om de ernst van de infectie te bepalen.”

18.16.2.3 World health organization (WHO)

(https://www.who.int/publications/i/item/home-care-for-patients-with-suspected-novel-coronavirus-(ncov)-infection-presenting-with-mild-symptoms-and-management-of-contacts)

WHO only recommends treating individuals with mild to moderate symptoms at home and do not consider anticoagulants (nor oxygen or corticosteroids), only symptomatic treatment as antipyretics and antibiotics (does not recommend prophylactic antibiotics).

18.16.2.4 National Institutes of health (NIH)

(https://www.covid19treatmentguidelines.nih.gov/adjunctive-therapy/antithrombotic-therapy/)

“For non-hospitalized patients with COVID-19, anticoagulants and antiplatelet therapy should not be initiated for prevention of venous thromboembolism (VTE) or arterial thrombosis unless there are other indications”

“Patients who are receiving anticoagulant or antiplatelet therapies for underlying conditions should continue these medications if they receive a diagnosis of COVID-19”

“In non-hospitalized patients with COVID-19, there are currently no data to support the measurement of coagulation markers (e.g., D-dimers, prothrombin time, platelet count, fibrinogen)”.

18.17 References provided by the AFMPS / FAGG on oxygen therapy (16/11/2020)

18.17.1 AFMPS / FAGG

Patients after hospital discharge and residents of nursery homes

In French: https://covid-19.sciensano.be/sites/default/files/Covid19/COVID-19_Bonne_utilisation_oxygene_sortieHopital_et_MRS_FR.pdf,

- Chez un patient atteint de COVID-19 qui présente une hypoxémie traitée par oxygénothérapie, la valeur cible de la SpO2 doit être au moins égale à 92 %, et ce quel que soit le stade de la maladie.
- Pour des débits en oxygène de 3 L/min ou inférieurs à 3 L/min, un oxyconcentrateur est la source d'oxygène la plus appropriée. Pour des débits supérieurs à 3 L / min, seules des bouteilles d'oxygène ou de l'oxygène liquide peuvent être utilisés.
- Lorsqu'une oxygénothérapie est arrêtée, le fournisseur de l'installation en sera immédiatement informé.

In Dutch : https://covid-19.sciensano.be/sites/default/files/Covid19/COVID-19_Goed_gebruik_van_O2_ziekenhuisontslag_en_zorgcentra_NL.pdf

- Als een hypoxemische patiënt met COVID-19 met zuurstof wordt behandeld, zal een zuurstofsaturatie van 92%, gemeten aan de hand van een pulsoxymeter, worden beoogd, onafhankelijk van de fase van de aandoening waarin de patiënt zich bevindt.
- Bij zuurstofdebieten van 3 L/min of minder is de oxyconcentrator de meest aangewezen zuurstofbron, voor debieten van meer dan 3 L/min kan enkel op zuurstofflessen of vloeibare zuurstof beroep worden gedaan.
- Bij stopzetting van een therapie met zuurstof zal de leverancier van de installatie hiervan onverwijld verwittigd worden

18.17.2 National Institutes of health (NIH)

In this chapter on COVID-19, “Oxygenation and Ventilation” (Last Updated: July 17, 2020), the NIH proposes some recommendations but it concerns hospitalized patients.

https://www.covid19treatmentguidelines.nih.gov/critical-care/oxygenation-and-ventilation/

“For hypoxemic patients, the recommendations below emphasize well-described and documented recommendations from the Surviving Sepsis Campaign Guidelines for adult sepsis, paediatric sepsis, and COVID-19, which provide more details about management and the data that support the recommendations.”

Recommendations

- For adults with COVID-19 who are receiving supplemental oxygen, the COVID-19 Treatment Guidelines Panel (the Panel) recommends close monitoring for worsening respiratory status and that intubation, if it becomes necessary, be performed by an experienced practitioner in a controlled setting (AII).
- For adults with COVID-19 and acute hypoxemic respiratory failure despite conventional oxygen therapy, the Panel recommends high-flow nasal cannula (HFNC) oxygen over noninvasive positive pressure ventilation (NIPPV) (BI).
- In the absence of an indication for endotracheal intubation, the Panel recommends a closely monitored trial of NIPPV for adults with COVID-19 and acute hypoxemic respiratory failure for whom HFNC is not available (BIII).
- For patients with persistent hypoxemia despite increasing supplemental oxygen requirements in whom endotracheal intubation is not otherwise indicated, the Panel recommends considering a trial of awake prone positioning to improve oxygenation (CIII).

- The Panel recommends against using awake prone positioning as a rescue therapy for refractory hypoxemia to avoid intubation in patients who otherwise require intubation and mechanical ventilation (AIII).

Rationale

Hypoxemia is common in hospitalized patients with COVID-19. The criteria for hospital admission, intensive care unit (ICU) admission, and mechanical ventilation differ between countries. In some hospitals in the United States, >25% of hospitalized patients require ICU care, mostly due to acute respiratory failure.[1-5]

In adults with COVID-19 and acute hypoxemic respiratory failure, conventional oxygen therapy may be insufficient to meet the oxygen needs of the patient. Options include HFNC, NIPPV, or intubation and invasive mechanical ventilation.

HFNC and NIPPV are preferable to conventional oxygen therapy based on data from non-COVID-19 clinical trials and meta-analyses that showed reductions in the need for therapeutic escalation and the need for intubation in patients who received HFNC or NIPPV.[6, 7]

HFNC is preferred over NIPPV in patients with acute hypoxemic respiratory failure based on data from an unblinded clinical trial that was performed prior to the COVID-19 pandemic. This trial found more ventilator-free days with HFNC than with conventional oxygen therapy or NIPPV (24 days vs. 22 days vs. 19 days, respectively; P = 0.02) and lower 90-day mortality with HFNC than with either conventional oxygen therapy (hazard ratio [HR] 2.01; 95% confidence interval [CI], 1.01–3.99) or NIPPV (HR 2.50; 95% CI, 1.31–4.78).[8]

In the subgroup of more severely hypoxemic patients with PaO2/FiO2 ≤200, HFNC reduced the rate of intubation compared to conventional oxygen therapy or NIPPV (HRs 2.07 and 2.57, respectively). These findings were corroborated in a meta-analysis that showed a lower likelihood of intubation (odds ratio [OR] 0.48; 95% CI, 0.31–0.73) and ICU mortality (OR 0.36; 95% CI, 0.20–0.63) with HFNC than with NIPPV.[9] In situations where the options for respiratory support are limited, reducing the need for intubation may be particularly important.

Prone positioning improves oxygenation and patient outcomes in patients with moderate-to-severe acute respiratory distress syndrome (ARDS) that requires mechanical ventilation.[10,11] Prone positioning is thought to improve oxygenation because it improves ventilation-perfusion matching and recruits collapsed alveoli in the dorsal lungs.[12] Two case series that were published prior to the COVID-19 pandemic reported improved oxygenation and low intubation rates after placing spontaneously breathing patients with hypoxemia in the prone position,[13,14] and several new case series reported similar results with awake prone positioning in patients with COVID-19 pneumonia who required supplemental oxygen.

In a case series of 50 patients with COVID-19 pneumonia who required supplemental oxygen upon presentation to a New York City emergency department (ED), awake prone positioning improved overall median oxygen saturation. However, 13 of these patients still required intubation due to respiratory failure within 24 hours of presentation to the ED.[15] Another case series from Jiangsu province used awake prone positioning as part of a treatment strategy in nonintubated patients with COVID-19 pneumonia and reported an intubation rate of less than 1%.[16] In a report of 24 patients who required either a nasal cannula or HFNC and who had a chest computed tomography scan that was consistent with COVID-19 pneumonia, 25% of patients tolerated prone positioning for at least 3 hours and showed >20% improvement in the partial pressure of oxygen in arterial blood. No complications were reported with prone positioning.[17] Another case series of 15 patients with ARDS due to COVID-19 pneumonia who received awake prone positioning while on noninvasive ventilation reported that all patients showed improvement in their oxygen saturation during prone positioning, with 80% of patients maintaining their improved oxygen saturation after resupination. Seven percent of patients required intubation.[18]

Appropriate candidates for awake prone positioning are those who are able to adjust their position independently and tolerate lying prone. Awake prone positioning is contraindicated in patients who are in respiratory distress and who require immediate intubation. Awake prone positioning is also contraindicated in hemodynamically unstable patients, patients who recently had abdominal surgery, and patients who have an unstable spine.[19] Awake prone positioning is acceptable and feasible for

pregnant patients and can be performed in the left lateral decubitus position or the fully prone position.[20]

It is essential that hypoxemic patients with COVID-19 be monitored closely for signs of respiratory decompensation. To ensure the safety of both the patient and health care workers, intubation should be performed in a controlled setting by an experienced practitioner.

Early intubation may be particularly appropriate when patients have additional acute organ dysfunction or chronic comorbidities, or when HFNC and NIPPV are not available. NIPPV has a high failure rate in both patients with non-COVID-19 viral pneumonia[21,22] and patients with ARDS.[23,24] NIPPV may generate aerosol spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and thus increase nosocomial transmission of the infection.[25,26] It remains unclear whether HFNC results in a lower risk of nosocomial SARS-CoV-2 transmission.

The use of supplemental oxygen in adults with COVID-19 has not been studied, but indirect evidence from other critical illnesses suggests the optimal oxygen target is an SpO2 between 92% and 96%:

A meta-analysis of 25 randomized controlled trials found that a liberal oxygen strategy (median SpO2 96%) was associated with an increased risk of hospital mortality (relative risk 1.21; 95% CI, 1.03–1.43).[27]

The LOCO2 randomized controlled trial compared a conservative oxygen strategy (target SpO2 88% to 92%) to a liberal oxygen strategy (target SpO2 ≥96%).[28] The trial was stopped early due to futility. Mortality increased among those who received the conservative oxygen therapy at Day 28 (risk difference +8%; 95% CI, -5% to +21%) and Day 90 (risk difference +14%; 95% CI, +0.7% to +27%). These differences would be important if they were real, but the study was too small to definitively confirm or exclude an effect.

18.17.3 World Health Organization (WHO)

In his interim guidance (27 May 2020), WHO recommends oxygen therapy in critical disease (Acute respiratory distress syndrome (ARDS)).

https://www.who.int/publications/i/item/clinical-management-of-covid-19

Oxygenation impairment in adults:

- Mild ARDS: 200 mmHg < PaO2/FiO2a≤ 300 mmHg (with PEEP or CPAP ≥ 5 cmH2O).[b]
- Moderate ARDS: 100 mmHg < PaO2/FiO2≤ 200 mmHg (with PEEP ≥ 5 cmH2O). [b]
- Severe ARDS: PaO2/FiO2≤ 100 mmHg (with PEEP ≥ 5 cmH2O). [b]

b. When PaO2 is not available, SpO2/FiO2≤ 315 suggests ARDS (including in non-ventilated patients).

In the chapter of Management of severe COVID-19: severe pneumonia treatment, it reads:

“All areas where severe patients may be cared for should be equipped with pulse oximeters, functioning oxygen systems and disposable, single-use, oxygen-delivering interfaces (nasal cannula, Venturi mask, and mask with reservoir bag).

Remark: This includes areas in any part of health facilities, including emergency units, critical care units, primary care/outpatient clinics, as well as pre-hospital settings and ad hoc community facilities that may receive patients with severe COVID-19. See WHO Oxygen sources and distribution for COVID-19 treatment centres (78).We recommend immediate administration of supplemental oxygen therapy to any patient with emergency signs and to any patient without emergency signs and SpO2 < 90%.”

Because of uncertainty around the potential for aerosolization, high-flow nasal oxygen (HFNO), NIV, including bubble CPAP, should be used with airborne precautions until further evaluation of safety can be completed. There is insufficient evidence to classify nebulizer therapy as an aerosol-generating procedure that is associated with transmission of COVID-19. More research is needed.

In the chapter of Management of critical COVID-19: acute respiratory distress syndrome (ARDS), it reads:

"We recommend prompt recognition of progressive acute hypoxaemic respiratory failure when a patient with respiratory distress is failing to respond to standard oxygen therapy and adequate preparation to provide advanced oxygen/ventilatory support.

Remark: Patients may continue to have increased work of breathing or hypoxemia even when oxygen is delivered via a face mask with reservoir bag (flow rates of 10–15 L/min, which is typically the minimum flow required to maintain bag inflation; FiO2 0.60–0.95). Hypoxaemic respiratory failure in ARDS commonly results from intrapulmonary ventilation-perfusion mismatch or shunt and usually requires mechanical ventilation."

18.17.4 National Institute for health and care excellence (NICE)

In his COVID-19 rapid guideline: managing symptoms (including at the end of life) in the community, (Published: 3 April 2020; Last updated October 2020), NICE mentions "when oxygen is available, consider a trial of oxygen therapy and assess whether breathlessness improves" without any protocol for delivery oxygen.

https://www.nice.org.uk/guidance/ng163/resources/covid19-rapid-guideline-managing-symptoms-including-at-the-end-of-life-in-the-community-pdf-66141899069893

18.17.5 British Thoracic Society

The guideline recommends aiming to achieve normal or near-normal oxygen saturation for all acutely ill patients apart from those at risk of hypercapnic respiratory failure or those receiving terminal palliative care.

1. Assessing patients

For critically ill patients, high concentration oxygen should be administered immediately (table 1 and figure 1) and this should be recorded afterwards in the patient's health record.

Clinicians must bear in mind that supplemental oxygen is given to improve oxygenation, but it does not treat the underlying causes of hypoxemia which must be diagnosed and treated as a matter of urgency.

The oxygen saturation should be checked by pulse oximetry in all breathless and acutely ill patients, 'the fifth vital sign' (supplemented by blood gases when necessary), and the inspired oxygen concentration should be recorded on the observation chart with the oximetry result. (The other vital signs are pulse rate, blood pressure, temperature and respiratory rate).

Pulse oximetry must be available in all locations where emergency oxygen is used. Clinical assessment is recommended if the saturation falls by ≥3% or below the target range for the patient.

All critically ill patients outside of a critical care area (e.g. intensive care unit (ICU), high dependency unit (HDU), respiratory HDU), should be assessed and monitored using a recognised physiological track and trigger system such as the National Early Warning Score (NEWS).

2.Target Oxygen prescription

Oxygen should be prescribed to achieve a target saturation of 94–98% for most acutely ill patients or 88–92 or patient-specific target range for those at risk of hypercapnic respiratory failure (tables 1–4).

Best practice is to prescribe a target range for all hospital patients at the time of admission so that appropriate oxygen therapy can be started in the event of unexpected clinical deterioration with hypoxemia and also to ensure that the oximetry section of the early warning score (EWS) can be scored appropriately.

The target saturation should be written (or ringed) on the drug chart or entered in an electronic prescribing system.

3. Oxygen administration

Oxygen should be administered by staff who are trained in oxygen administration.

These staff should use appropriate devices and flow rates in order to achieve the target saturation range.

Staff should be trained in the use of a range of different oxygen delivery devices to ensure oxygen is delivered safely.

4. Monitoring and maintenance of target saturation

Oxygen saturation and delivery system (including flow rate) should be recorded on the patient's monitoring chart.

Oxygen delivery devices and flow rates should be adjusted to keep the oxygen saturation in the target range. Prompt clinical assessment is required if oxygen therapy needs to be initiated or increased due to a falling saturation level.

Oxygen should be prescribed and a signature should be entered on the drug chart on each drug round.

5. Weaning and discontinuation of oxygen therapy

Oxygen should be reduced in stable patients with satisfactory oxygen saturation.

Oxygen should be discontinued once the patient can maintain saturation within or above the target range breathing air but the prescription for a target range should be left in place in case of future deterioration and to guide early warning scores (EWS/NEWS).

References

1. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32109013.
2. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72,314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32091533.
3. Arentz M, Yim E, Klaff L, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. JAMA. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32191259.
4. Alhazzani W, Moller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). Crit Care Med. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32224769.
5. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32031570.
6. Xu XP, Zhang XC, Hu SL, et al. Noninvasive ventilation in acute hypoxemic nonhypercapnic respiratory failure: a systematic review and meta-analysis. Crit Care Med. 2017;45(7):e727-e733. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28441237.
7. Zhao H, Wang H, Sun F, Lyu S, An Y. High-flow nasal cannula oxygen therapy is superior to conventional oxygen therapy but not to noninvasive mechanical ventilation on intubation rate: a systematic review and meta-analysis. Crit Care. 2017;21(1):184. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28701227.
8. Frat JP, Thille AW, Mercat A, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med. 2015;372(23):2185-2196. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25981908.
9. Ni YN, Luo J, Yu H, Liu D, Liang BM, Liang ZA. The effect of high-flow nasal cannula in reducing the mortality and the rate of endotracheal intubation when used before mechanical ventilation compared with conventional oxygen therapy and noninvasive positive pressure ventilation. A systematic review and meta-analysis. Am J Emerg Med. 2018;36(2):226-233. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28780231.
10. Guerin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med. 2013;368(23):2159-2168. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23688302.
11. Fan E, Del Sorbo L, Goligher EC, et al. An official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine clinical practice guideline: mechanical ventilation in adult patients with acute respiratory distress syndrome. Am J Respir

Crit Care Med. 2017;195(9):1253-1263. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28459336.
12. Nyren S, Mure M, Jacobsson H, Larsson SA, Lindahl SG. Pulmonary perfusion is more uniform in the prone than in the supine position: scintigraphy in healthy humans. J Appl Physiol (1985). 1999;86(4):1135-1141. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10194194.
13. Scaravilli V, Grasselli G, Castagna L, et al. Prone positioning improves oxygenation in spontaneously breathing nonintubated patients with hypoxemic acute respiratory failure: A retrospective study. J Crit Care. 2015;30(6):1390-1394. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26271685.
14. Ding L, Wang L, Ma W, He H. Efficacy and safety of early prone positioning combined with HFNC or NIV in moderate to severe ARDS: a multi-center prospective cohort study. Crit Care. 2020;24(1):28. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32000806.
15. Caputo ND, Strayer RJ, Levitan R. Early self-proning in awake, non-intubated patients in the emergency department: a single ED's experience during the COVID-19 pandemic. Acad Emerg Med. 2020;27(5):375-378. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32320506.
16. Sun Q, Qiu H, Huang M, Yang Y. Lower mortality of COVID-19 by early recognition and intervention: experience from Jiangsu Province. Ann Intensive Care. 2020;10(1):33. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32189136.
17. Elharrar X, Trigui Y, Dols AM, et al. Use of prone positioning in non intubated patients with COVID-19 and hypoxemic acute respiratory failure. JAMA. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32412581.
18. Sartini C, Tresoldi M, Scarpellini P, et al. Respiratory parameters in patients with COVID-19 after using noninvasive ventilation in the prone position outside the intensive care unit. JAMA. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32412606.
19. Bamford P, Bentley A, Dean J, Whitmore D, Wilson-Baig N. ICS guidance for prone positioning of the conscious COVID patient. Intensive Care Society. 2020. Available at: https://emcrit.org/wp-content/uploads/2020/04/2020-04-12-Guidance-for-conscious-proning.pdf. Accessed May 14, 2020.
20. Society for Maternal Fetal Medicine. Management Considerations for Pregnant Patients With COVID-19. 2020. Available at: https://s3.amazonaws.com/cdn.smfm.org/media/2336/SMFM_COVID_Management_of_COVID_pos_preg_patients_4-30-20_final.pdf. Accessed: May 20, 2020.
21. Alraddadi BM, Qushmaq I, Al-Hameed FM, et al. Noninvasive ventilation in critically ill patients with the Middle East respiratory syndrome. Influenza Other Respir Viruses. 2019;13(4):382-390. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30884185.
22. Esquinas AM, Egbert Pravinkumar S, Scala R, et al. Noninvasive mechanical ventilation in high-risk pulmonary infections: a clinical review. Eur Respir Rev. 2014;23(134):427-438. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25445941.
23. He H, Sun B, Liang L, et al. A multicenter RCT of noninvasive ventilation in pneumonia-induced early mild acute respiratory distress syndrome. Crit Care. 2019;23(1):300. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31484582.
24. Antonelli M, Conti G, Moro ML, et al. Predictors of failure of noninvasive positive pressure ventilation in patients with acute hypoxemic respiratory failure: a multi-center study. Intensive Care Med. 2001;27(11):1718-1728. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11810114.
25. Tran K, Cimon K, Severn M, Pessoa-Silva CL, Conly J. Aerosol generating procedures and risk of transmission of acute respiratory infections to healthcare workers: a systematic review. PLoS One. 2012;7(4):e35797. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22563403.
26. Yu IT, Xie ZH, Tsoi KK, et al. Why did outbreaks of severe acute respiratory syndrome occur in some hospital wards but not in others? Clin Infect Dis. 2007;44(8):1017-1025. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17366443.
27. Chu DK, Kim LH, Young PJ, et al. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. Lancet. 2018;391(10131):1693-1705. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29726345.
28. Barrot L, Asfar P, Mauny F, et al. Liberal or conservative oxygen therapy for acute respiratory distress syndrome. N Engl J Med. 2020;382(11):999-1008. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32160661.”

18.17.6 Haute Autorité de Santé (HAS)

HAS elaborated a rapid respons on oxygen therapy at home for COVID-19 patients “Réponses rapides dans le cadre de la Covid-19 –Prise en charge à domicile des patients atteints de la Covid-19 et requérant une oxygénothérapie. Validée par le Collège le 3 novembre 2020, Mise à jour le 9 novembre 2020

https://www.has-sante.fr/upload/docs/application/pdf/2020-11/20rr415_covid_19_oxygenotherapie_mel_vf.pdf

Their propose several answers :

- Réponse rapide n°1: la prise en charge à domicile des patients atteints de la Covid-19 et requérant une oxygénothérapie, dans le cadre d'un parcours de soins coordonné entre la ville et l'hôpital doit être exceptionnelle et réservée au contexte épidémique actuel.
- Réponse rapide n°2: cette prise en charge est réservée à 2 situations : les patients hospitalisés pour la Covid-19, sortant sous oxygénothérapie et les patients atteints de la COVID-19 non hospitalisés ayant des besoins en oxygène <4 L /min.
- Réponse rapide n°3:cette prise en charge est mise en place dans le cadre d’une équipe pluriprofessionnelle de premier recours en lien avec une équipe hospitalière de référence (pneumologie, maladies infectieuses, soins critiques, ...) et le SAMU.
- Réponse rapide n°4: les critères d’éligibilité des patients sont liés:
    - à l’environnement: domicile fixe et salubre, présence permanente d’un aidant, isolement possible, à moins de 30 minutes de l’établissement de santé de référence disposant d'une structure d'urgence ou d'un SMUR de proximité;
    - au patient: autonome, SpO2 < 92%, sans critère d’exclusion (1 critère majeur ou au moins 2 critères mineurs).
- Réponse rapide n°5: l’objectif de l’oxygénothérapie est de maintenir une SpO2 > 92%.
- Réponse rapide n°6: une anticoagulation prophylactique et des corticoïdes faible dose (dexaméthasone 6 mg/jour ou équivalent pendant 5 à10 jours) sont prescrits en complément de l’oxygénothérapie.
- Réponse rapide n°7: toute aggravation nécessite un contact:
    - avec une équipe hospitalière de référence si débit d'oxygène > 3 L/min avec désaturation rapide (quelques heures) ou apparition d'une complication quelle qu'elle soit, non amélioration après 72 heures, décision du médecin généraliste à tout moment;
    - avec le SAMU Centre 15 en vue d’une hospitalization soit en cas de: débits d’oxygène ≥4L/mn, désaturation à SpO2 <90% à deux prises consécutives.

18.17.7 Nederlands Huisartsen Genootschap (NHG)

In their chapter “Thuisbehandeling van COVID-19-patiënten met ernstig beloop”, the NHG mentions oxygen therapy.

https://corona.nhg.org/behandeling/#thuisbehandeling_van_covid19patienten_met_ernstig_beloop

Zuurstofbehandeling

Een kleine groep patiënten komt in aanmerking voor het opstarten van zuurstofbehandeling thuis. Het betreft: niet-terminale COVID-19-patiënten met ernstige hypoxie die kans maken op herstel met wie besloten is niet te verwijzen naar het ziekenhuis en thuis te behandelen. Het doel van zuurstoftoediening bij deze groep is het beperken van de kans op orgaanschade door hypoxie en daarmee de kans vergroten dat de patiënt COVID-19 doorstaat.

- Overweeg zuurstofbehandeling bij deze groep patiënten bij een saturatie < 90% en/of ademfrequentie > 24 / min (ook zonder klachten van dyspneu en/of vermoeidheid).
- Geef zuurstof bij voorkeur via een neusbril. Bij een verstopte neus kan een mondmasker gebruikt worden.

- Start met 2 l/min, controleer minimaal 30 minuten na start de saturatie in rust. Streefwaarde O2 saturatie > 90% (houd bij patiënten met COPD een streefwaarde aan van ≥ 90 èn < 92%). Hoog zo nodig de dosering op met 1 l/min tot max 5L O2/min).
- LET OP: Bespreek met patiënt, naasten en wijkverpleging dat snelle achteruitgang mogelijk is en tref voorbereidingen voor de dan benodigde zorg en medicatie (zie ook de toolkit Symptoombestrijding in de thuissituatie bij patiënten met een COVID-19 (Corona) in de laatste levensfase).
- Zie voor meer informatie de leidraad zuurstofgebruik thuis bij (verdenking op / bewezen) COVID-19 en de bijbehorende lijst.

In the guideline **Leidraad zuurstofgebruik THUIS bij (verdenking op / bewezen) COVID-19** (April 2020) mentioned above:

Algemene opmerkingen:

- Beschikbaarheid van O_2 is afhankelijk van regio en periode.
- O_2 wordt thuis met een concentrator toegediend; bij tekortschietende beschikbaarheid kunnen in overleg met O_2 leveranciers mogelijk O_2 cilinders thuis worden ingezet. Nadeel hiervan is dat deze vaak (dagelijks) vervangen moeten worden.
- Gezien het gebruikerscomfort gaat de voorkeur uit naar toediening m.b.v. een neusbril. Bij een verstopte neus kan een mondmasker gebruikt worden.
- Als een patiënt O_2 thuis krijgt, is adequate mantelzorg nodig. Indien die er niet is, overweeg dan patiënt naar een Corona-unit/ instelling te verwijzen.
- Toediening van O_2, via neusbril of mondmasker, vereist geen uitbreiding van de voorgeschreven persoonlijk beschermingsmiddelen(zie RIVM: PBM buiten het ziekenhuis)
- Roken/ meeroken/ risico op onvoorzichtigheid met open vuur zijn contra-indicaties voor O_2 thuis i.v.m. kans op aangezichtsverbrandingen ontploffingsgevaar.
- Over patiënten bij wie om andere redenen dan Covid-19 O_2 thuis wordt overwogen (bv exacerbatie COPD of hartfalen, eindstadium kanker) worden hier geen adviezen gegeven; het beleid is niet anders dan vóór de Corona pandemie.
- Patiënten met Covid-19 met behandelindicatie O_2 en zonder behandelbeperking voor opname in het ziekenhuis dienen niet thuis behandeld te worden. Zij kunnen dermate snel verslechteren, dat intensievere controle en hogere O_2 toediening mogelijk moet zijn. Verwijs deze patiënten naar het ziekenhuis.

Er zijn in de context van Covid-19 **verschillende patiënten categorieën** te onderscheiden, waarbij O_2 thuis overwogen kan worden:

1. Patiënt met (verdenking op) Covid-19 voor wie besloten is niet te verwijzen naar het ziekenhuis en thuis te behandelen:
    - op basis van co morbiditeit en/of kwetsbaarheid (zie leidraad triage thuisbehandeling versus verwijzen naar het ziekenhuis bij oudere patiënt met(verdenking op) Covid-19) en/of
    - omdat thuisbehandeling past bij de doelen en wensen van de patiënt;
2. Een stabiele patiënt die herstellend is van Covid-19 en het ziekenhuis verlaat met noodzaak tot continueren van O_2;
3. Een stervende patiënt met Covid-19.

Table 15 – NGH recommendations according to different categories of patients

Patiënten	
1	• Overweeg O_2 thuis als ondersteunende behandeling bij ernstig zieke patiënten, met saturatie1<90%en/of ademfrequentie > 24/min(ook zonderklachten van dyspneu en/of vermoeidheid)* • Doel: verkleinen van de kans op orgaanschade ten gevolge van hypoxie en daarmee vergroten van de kans dat de patiënt Covid-19 doorstaat. Mogelijk draagt O_2 bij aan het comfort van de patiënt. • Start met 2l/min. • Controleer minimaal 30 minuten na start de saturatie in rust. Streefwaarde O_2 saturatie ≥90%; bij patiënten met COPD streefwaarde O_2 saturatie ≥ 90 èn < 92%. Hoog zo nodig de dosering op met 1 l/min. • Maximale zinvolle O_2 toediening via neusbril bedraagt 5 l/min. • Als de patiënt dyspneu ervaart, combineer O2 toediening dan laagdrempelig met morfine; geef bij angst zo nodig een benzodiazepine(symptoombestrijding bij Covid-19 in de thuissituatie). De huisarts: • regelt O_2 thuis.-maakt met de wijkverpleging afspraken over monitoring**. • controleert minimaal dagelijks saturatie, ademfrequentie, temperatuur, dyspneu en uitputting (op schaal 0-10) (gemeten door patiënt/ mantelzorg/ wijkverpleging/ huisarts)en stelt zo nodig de O_2 dosering bij. • maakt in een persoonlijk behandelplan afspraken met patiënt en naasten over ondersteunende medicatie en over wie in welke situatie gebeld kan worden. • maakt een uitvoeringsverzoek voor de wijkverpleging waarin staat in welke situatie welke medicatie gegeven kan worden. • Bespreekt met patiënt, naasten en wijkverpleging dat snelle achteruitgang mogelijk is en treft voorbereidingen voor de dan benodigde zorg en medicatie (morfine, midazolam). • zorgt voor overdracht naar de HAP (*'huisartsenpost'*) over gemaakte afspraken. • bouwt bij verbetering van de conditie van de patiënt de O_2 af op geleide van de saturatie en comfort. Indien de patiënt verslechtert, zie advies bij 'stervende patiënt met Covid-19.
2	Continueer O_2 thuis om herstel te bevorderen • Doel: patiënten (sneller)naar de thuissituatie te laten terugkeren. De behandelend specialist: • beoordeelt wanneer de patiënt stabiel genoeg is om thuis verder te herstellen. • bepaalt streefwaarden voor O_2 saturatie voor de betreffende patiënt. • regelt O_2 thuis. • overlegt met de huisarts over de verdeling van verantwoordelijkheden bij de monitoring*** van de patiënt. De arts die verantwoordelijk is voor de monitoring: • controleert minimaal dagelijks saturatie, ademfrequentie, temperatuur, dyspneu en uitputting (op schaal 0-10) (gemetendoor patiënt/ mantelzorg/ wijkverpleging/ arts) en stelt zo nodig de O_2 dosering bij. • maakt in een persoonlijk behandelplan afspraken met patiënt en naasten over ondersteunende medicatie en over wie in welke situatie gebeld kan worden****. • regelt heropname bij achteruitgang in de conditie van de patiënt • bouwt bij verbetering van de conditie van de patiënt de O_2 af op geleide van de saturatie en comfort. De huisarts: • zorgt voor overdracht naar de HAP over gemaakte afspraken.
3	O_2 thuis is niet zinvol. De stervensfase van patiënten met ernstige Covid-19 verloopt vaak snel (uren-dagen). O_2 starten heeft geen toegevoegde waarde. • Behandel dyspneu met morfine en/of angst met een benzodiazepine (symptoombestrijding bij Covid-19 in de thuissituatie). • Start bij refractaire symptomen met palliatieve sedatie (Aandachtspunten voor de huisarts over palliatieve zorg bij Covid-19).

	Indien patiënt in een eerdere fase O_2 thuis heeft gekregen: • Bespreek met patiënt en naasten dat O_2 weinig tot geen verlichting geeft in de stervensfase en dat dyspneu sensatie beter verlicht wordt door (verhoging van de) morfine. • Bouw de toediening vanO_2 af op geleide van het comfort van de patiënt. • Als de patiënt i.v.m. refractaire symptomen gesedeerd wordt en de O_2 was eerder nog niet gestopt, stop de O_2 dan als patiënt adequaat gesedeerd is.

**Ervaring leert dat patiënten met Covid-19 minder dyspneu ervaren dan het klinisch beeld en de saturatie doen vermoeden*
***Stem af wie de benodigde saturatie-en thermometer verstrekt: patiënt zelf, huisarts, ook sommige ziekenhuizen verstrekken meters (bv LUMC leent zgn. Covid box uit). Als het niet mogelijk is bij patiënt thuis meter te regelen, dan kan de wijkverpleging met eigen meter controles doen. NB. goed reinigen voordat deze weer bij andere patiënten gebruikt wordt of saturatiemeterschoonhouden door gebruik van een plastic zakje er omheen. De saturatie wordt dan door het plastic heen gemeten*
****Stem af wie de benodigde saturatie-en thermometer verstrekt: patiënt zelf, huisarts, ook sommige ziekenhuizen verstrekken meters (bv LUMC leent zgn. Covid box uit). Als het niet mogelijk is bij patiënt thuis meter te regelen, dan kan de wijkverpleging met eigen meter controles doen. NB. goed reinigen voordat deze weer bij andere patiënten gebruikt wordt of saturatiemeterschoonhouden door gebruik van een plastic zakje er omheen. De saturatie wordt dan door het plastic heen gemeten.*
***** De manier waarop thuis begeleiding vanuit het ziekenhuis plaats vindt kan lokaal verschillen (app, telefoon, videobellen, huisbezoek). Deze afspraken kunnen worden opgenomen in een persoonlijk behandelplan.*

Aandachtspunten over O_2 gebruik thuis:

- Let op ontstaan van decubitus achter de oren/ op de neus
- Doordat lucht niet bevochtigd is, kan irritatie van het neusslijmvlies optreden. Adviseer carbomeerwatergel (zonder recept verkrijgbaar) of vetvrije cetomacrogol (geen vaseline in verband met risico op aangezichtsverbranding)
- Overweeg begeleiding patiënt en naasten doorlongverpleegkundige (van de thuiszorg)
- De patiënten folder Longfonds is niet specifiek voor Covid-19 patiënten, bevat wel algemene informatie voor patiënten.
- O_2 wordt vergoed door de ziektekostenverzekering van de patiënt.

18.17.8 Domus Medica - ACHG

The Domus Medica - ACHG synthesis “Thuisopvolging en behandeling van COVID-19 besmette personen/patiënten” [9] refers to the AFMPS / FAGG recommendations.

Covid-19 patiënten kunnen bij hun ontslag uit het ziekenhuis nog een milde respiratoire insufficiëntie vertonen waarbij in veel gevallen de nood tot zuurstof na verloop van tijd zal afnemen.

Over het goed gebruik van zuurstof bij COVID-19 patiënten na ontslag uit het ziekenhuis bestaat een consensusnota samengesteld door het Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten.

Another text focuses on the management in woonzorgcentra tijdens COVID (https://www.zorg-en-gezondheid.be/sites/default/files/atoms/files/Zuurstof%20in%20woonzorgcentra%20tijdens%20Covid%20versie%204.pdf). In de stap7, Zuurstoftoediening: “Als men in functie van de klinische toestand, na toepassing van voorgaande, toch beslist om zuurstof toe dienen, eventueel in combinatie met morfine, kan men dit doen. Wat volgt is vooral bestemd voor personen die zich in de palliatieve fase bevinden

- Zuurstofconcentrator (max5l/minuut)
- Zuurstofcylinders met ontspanner met maximum van 5 à 6liter/minuut
- Applicatie met

- Neusbril (kan tot 6 liter/minuut) gemakkelijk te plaatsen maar kan groter risico betekenen voor infectie-overdracht. Masker laat hoger debiet toe indien dit nodig is.
- Mondmasker indien meer dan 5 L/minuut. Denk dan ook aan bevochtiging van de zuurstofstroom om irritatie te voorkomen."

18.17.9 New England Journal of Medicine (NEJM)

In the article on mild and moderate COVID published on April 24, 2020, and updated on October 29, 2020, at NEJM.org, the authors do not mention an oxygen therapy protocol. https://www.nejm.org/doi/full/10.1056/NEJMcp2009249?query=featured_coronavirus

18.18 References provided by the AFMPS / FAGG on corticoïds (16/11/2020)

18.18.1 World health organization (WHO)

In order to provide ancillary evidence after de RECOVERY trial, WHO produced recommendations using the GRADE approach (*last update 02 September 2020*).[163] The guideline combined results from two meta-analysis pooling eight randomized trial.[184,Siemieniuk, 2020 #305] They classified patients according to the severity of illness in three subgroup: [1] critically ill patients with acute respiratory distress syndrome, [2] severely ill patients presenting signs of severe respiratory distress, oxygen saturation below 90% on room air and increased respiratory rate, [3] non-severe patients.

Based on data from 1703 critically ill patients in seven trials, the meta-analysis conducted by the WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group found that systemic corticosteroids compared with no corticosteroids probably reduce the risk of 28-day mortality (*moderate certainty evidence*; RR 0.80 [95% CI:0.70–0.91]; absolute effect estimate 87 fewer deaths for 1000 patients).

In patients with severe COVID-19 who are not critically ill, based on data from 3883 patients, systemic corticosteroids also probably reduce the risk of death (*moderate certainty evidence*; RR 0.80 [95% CI: 0.70–0.92]; absolute effect estimate 67 fewer deaths for 1000 patients).

Conversely, in patients with non-severe COVID-19, based on data from 1535 patients, systemic corticosteroids may increase the risk of 28-day mortality (*low certainty evidence*; RR 1.22 [95% CI: 0.93–1.61]; absolute effect estimate 39 more for 1000 patients).

WHO guidelines recommend the use of systemic corticosteroids rather than no corticosteroids in patients with severe and critical COVID-19 (*strong recommendation, moderate certainty evidence*) while they suggest not to use systemic corticosteroids in non-severe patients (*conditional recommendation, low certainty evidence*).

18.18.2 Infectious Diseases Society of America (IDSA)

The Infectious Diseases Society of America (IDSA) has also developed guidelines related to the corticosteroid therapy through a systematic review of the peer-reviewed and grey literature and using the GRADE approach for evidence assessment (*last update 25 September 2020*).[164]

https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/#toc-5

Severity is defined as:

**Critical illness is defined as patients on mechanical ventilation and ECMO. Critical illness includes end organ dysfunction as is seen in sepsis/septic shock. In COVID-19, the most commonly reported form of end organ dysfunction is ARDS*

***Severe illness is defined as patients with SpO_2 ≤94% on room air, including patients on supplemental oxygen.*

****Non-severe illness is defined as patient with a SpO_2 > 94% not requiring supplemental oxygen.*

Among **hospitalized critically ill patients***, the IDSA guideline panel recommends dexamethasone (6 mg daily for 10 days or equivalent glucocorticoid dose) rather than no dexamethasone. (*Strong recommendation, Moderate certainty of evidence*). The odds ratio for mortality at day 28 was 0.66 [95% CI: 0.54-0.82].

For **hospitalized severely ill patients** but non-critical**, COVID-19 the IDSA guideline panel suggests dexamethasone rather than no dexamethasone. (*Conditional recommendation, Moderate certainty of evidence*). The 28-day mortality was 17% lower in the group that received dexamethasone than in the group that did not receive dexamethasone (relative risk 0.83 [95% CI: 0.74-0.92]).

Among **hospitalized patients in the non-severe group***** without hypoxemia requiring supplemental oxygen, the IDSA guideline panel suggests against the use of glucocorticoids (*Conditional recommendation, Low certainty of evidence*) because of a trend toward harm with dexamethasone in participants who were not on supplemental oxygen (relative risk 1.22 [95% CI: 0.86- 1.75]).

In the same guidelines on the Treatment and Management of Patients with COVID-19 published by Infectious Diseases Society of America Guidelines (IDSA) on 4/11/2020 (Last updated, 9/25/2020), other corticosteroids are mentioned if dexamethasone is not available. However, they focus on hospitalized patients. https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/#toc-5.

Remark: Dexamethasone 6 mg IV or PO for 10 days (or until discharge) or equivalent glucocorticoid dose may be substituted if dexamethasone unavailable. Equivalent total daily doses of alternative glucocorticoids to dexamethasone 6 mg daily are methylprednisolone 32 mg and prednisone 40 mg.

Recommendations of IDSA (*last update 25 September 2020*) on corticosteroids:

Table 16 – GRADE evidence profile, IDSA Recommendation 4

Question: Glucocorticoids compared to no glucocorticoids for critically ill patients with COVID-19

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	corticosteroids	no corticosteroids	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: 28 days)												
7 [1]	randomized trials	not serious	not serious	not serious	not serious	none	280/749 (37.4%)	485/1095 (44.3%)	**OR 0.66** (0.54 to 0.82)	**99 fewer per 1,000** (from 143 fewer to 48 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
Hospital discharge (follow up: 28 days)												
1 [2]	randomized trials	not serious [a]	not serious	serious [b]	not serious	none	1360/2104 (64.6%)	2639/4321 (61.1%)	**RR 1.11** (1.04 to 1.19)	**67 more per 1,000** (from 24 more to 116 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Serious adverse events												
6 [1]	randomized trials	not serious	not serious	not serious	serious [c]	none	6 trials reported 64 events among 354 patients randomized to corticosteroids and 80 events among 342 patients randomized to standard care (Stern 2020).				⨁⨁⨁◯ MODERATE	CRITICAL

CI: Confidence interval; **OR:** Odds ratio; **RR:** Risk ratio

Explanations

a. Analysis adjusted for baseline age
b. Indirectness due to different health care system (allocation of intensive care resources in an unblinded study). Indirectness to other corticosteroids.
c. The 95% CI includes the potential for both harm as well as benefit. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

References

1. WHO Rapid Evidence Appraisal for COVID-19 Therapies Working Group, Sterne JAC, Murthy S, et al. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. JAMA **2020**.
2. Horby P, Lim WS, Emberson J, et al. Effect of Dexamethasone in Hospitalized Patients with COVID-19: Preliminary Report. medRxiv **2020**: 2020.06.22.20137273

Table 17 – GRADE evidence profile, IDSA Recommendation 5

Question: Glucocorticoids compared to no glucocorticoids for hospitalized patients with severe but not critical COVID-19

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	glucocorticoids	no glucocorticoids	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: 28 days)												
1 [1]	randomized trials	not serious [a]	not serious	serious [b]	not serious	none	454/2104 (21.6%)	1065/4321 (24.6%)	**RR 0.83** (0.74 to 0.92)	**42 fewer per 1,000** (from 64 fewer to 20 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Hospital discharge (follow up: 28 days)												
1 [1]	randomized trials	not serious [a]	not serious	serious [b]	not serious	none	1360/2104 (64.6%)	2639/4321 (61.1%)	**RR 1.11** (1.04 to 1.19)	**67 more per 1,000** (from 24 more to 116 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Adverse events												
							Patients receiving a short course of steroids may experience hyperglycemia, neurological side effects (e.g., agitation/confusion), adrenal suppression, and risk of infection (Salton 2020; Henzen 2000; Siemieniuk 2015).				-	CRITICAL

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
Indirectness: Applicability or generalizability to the research question
Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Analysis adjusted for baseline age.
b. Indirectness due to different health care system (allocation of intensive care resources in an unblinded study). Indirectness to other corticosteroids.

References

1. Horby P, Lim WS, Emberson J, et al. Effect of Dexamethasone in Hospitalized Patients with COVID-19: Preliminary Report. medRxiv 2020: 2020.06.22.20137273. **2020**.

Table 18 – GRADE evidence profile, IDSA Recommendation 6

Question: Glucocorticoids compared to no glucocorticoids for hospitalized patients with COVID-19 not receiving supplemental oxygen

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	glucocorticoids	no glucocorticoids	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: 28 days)												
1 [1]	randomized trials	serious [a]	not serious	not serious	serious [b]	none	85/501 (17.0%)	137/1034 (13.2%)	RR 1.22 (0.93 to 1.61)	29 more per 1,000 (from 9 fewer to 81 more)	⨁⨁◯◯ LOW	CRITICAL
Hospital discharge (follow up: 28 days)												
1 [1]	randomized trials	serious [a]	not serious	not serious	serious [b]	none	366/501 (73.1%)	791/1034 (76.5%)	RR 0.99 (0.87 to 1.12)	8 fewer per 1,000 (from 99 fewer to 92 more)	⨁⨁◯◯ LOW	IMPORTANT
Adverse events												
							Patients receiving a short course of steroids may experience: hyperglycemia, neurological side effects (e.g., agitation/confusion), adrenal suppression, and risk of infection (Salton 2020; Henzen 2000; Siemieniuk 2015).				-	CRITICAL

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
Indirectness: Applicability or generalizability to the research question
Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

CI: Confidence interval; **RR**: Risk ratio

Explanations

a. RoB due to post-hoc subgroup effect among persons not receiving supplemental oxygen.
b. The 95% CI includes the potential for appreciable harm and cannot exclude the potential for benefit. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

References

1. Horby P, Lim WS, Emberson J, et al. Effect of Dexamethasone in Hospitalized Patients with COVID-19: Preliminary Report. medRxiv **2020**. 2020.06.22.20137273.

18.18.3 Netherlands Huisartsen Genootschap (NHG)

NHG mentions only dexamethason in a litterature review (27/08/2020); search question: "*Wordt dexamethason aanbevolen bij de behandeling van patiënten met milde tot matige COVID-19-klachten in de huisartspraktijk*".[170]

Aanbevelingen

- Het toedienen van dexamethason aan COVID-19 patiënten in de eerste lijn wordt niet aanbevolen wegens het ontbreken van bewijs voor effectiviteit in de eerste lijn.
- Voor het toedienen van dexamethason bij zuurstofbehoeftige COVID-19 patiënten die zuurstofondersteuning krijgen in de thuissetting en die niet opgenomen willen worden, wordt consultatie van een longarts aanbevolen.
- Volg voor het gebruik van corticosteroïden voor andere indicaties dan een COVID-19 infectie de reguliere NHG-Standaarden COPD, Astma bij kinderen en Astma bij Volwassenen.

In another publication over corticosteroids in first line, NHG suggest a concertation with a pneumologist before using corticosteroïds in primary care (https://corona.nhg.org/2020/praktische-tips-voor-pbm-bij-non-covid-19-patienten/ Nieuw op 29 september at the end of the page).

- "Over het eventueel toedienen van dexamethason bij deze groep patiënten zijn geen eerstelijnsgegevens beschikbaar. Overweeg consultatie met een longarts als u een mogelijke indicatie ziet voor het toedienen van dexamethason bij deze patiënten."

18.18.4 Sciensano

Sciensano with the AFMPS / FAGG and SBIMC / BVIKM quotes only dexamethasone in his recommendation within the document "INTERIM CLINICAL GUIDANCE FOR ADULTS WITH SUSPECTED OR CONFIRMED COVID-19 IN BELGIUM" (16 October 2020; Version 14 Addition 30 October 2020).[169] https://covid-19.sciensano.be/sites/default/files/Covid19/COVID-19_InterimGuidelines_Treatment_ENG.pdf

18.18.5 National Institute for health and care excellence (NICE)

NICE mentions dexamethasone (per os or iv) or hydrocortisone iv in his recommendations based on a meta-analysis of 7 randomised controlled trials (October 2020).

https://www.nice.org.uk/guidance/ng159/resources/covid19-prescribing-briefing-corticosteroids-pdf-8839913581

The recommended dosage and duration of treatment for adults is:

- For dexamethasone: 6 mg once a day orally for 7 to 10 days (three 2 mg tablets or 15 ml of 2 mg/5 ml oral solution)or6 mg once a day intravenously for 7 to 10 days (1.8 ml of 3.3 mg/ml ampoules [5.94 mg]).
- For hydrocortisone: 50 mg every 8 hours intravenously (0.5 ml of 100 mg/ml solution, powder for solution for injection/infusion is also available). This may be continued for up to 28 days for patients with septic shock.

Treatment should stop if the person is discharged from hospital before the 10 day course is completed.

Note: The CAS alert states that there may be occasions when UK patients have COVID-19 that meets the WHO criteria of severe or critical but are not hospitalized, in which case the WHO guidance for treatment would apply.

For the dosage in children and young people, see the manufacturers' summaries of product characteristics and the BNF for Children.

18.18.6 New England Journal of Medicine (NEJM)

In an article on mild and moderate COVID published on April 24, 2020, and updated on October 29, 2020, at NEJM.org, the authors consider the place of dexamethasone only. https://www.nejm.org/doi/full/10.1056/NEJMcp2009249?query=featured_coronavirus

18.18.7 National Institutes of health (NIH)

The NIH (referred by CDC) mentions other corticosteroids in case of dexamethasone is not available in his guidelines chapter on "Therapeutic Management of Patients with COVID-19" (Last Updated: November 3, 2020). https://www.covid19treatmentguidelines.nih.gov/therapeutic-management/

- *If dexamethasone is not available, alternative glucocorticoids such as prednisone, methylprednisolone, or hydrocortisone can be used. See corticosteroids for more information.*
- *For these drugs, the total daily dose equivalencies to dexamethasone 6 mg (oral or intravenous [IV]) are:*
    - Prednisone 40 mg
    - Methylprednisolone 32 mg
    - Hydrocortisone 160 mg
- *Half-life, duration of action, and frequency of administration vary among corticosteroids.*
    - Long-acting corticosteroid: dexamethasone; half-life: 36 to 72 hours, administer once daily.
    - Intermediate-acting corticosteroids: prednisone and methylprednisolone; half-life: 12 to 36 hours, administer once daily or in two divided doses daily.

- Short-acting corticosteroid: hydrocortisone; half-life: 8 to 12 hours, administer in two to four divided doses daily.

- *Hydrocortisone is commonly used to manage septic shock in patients with COVID-19; see Care of Critically Ill Patients With COVID-19 for more information. Unlike other corticosteroids previously studied in patients with ARDS, dexamethasone lacks mineralocorticoid activity and thus has minimal effect on sodium balance and fluid volume.*

18.18.8 Stichting Werkgroep AntibioticaBeleid (SWAB)

The Stichting Werkgroep AntibioticaBeleid (SWAB) in the Netherlands recommends dexamethasone in "Medicamenteuze behandelopties bij patiënten met COVID-19" (November 2020) but quotes also methylprednisolone. https://swab.nl/nl/covid-19

"Conclusie: bij COVID-19 patiënten waarbij zuurstoftoediening geïndiceerd is vanwege saturatiedaling, en met name bij noodzaak tot mechanische ventilatie, is behandeling met dexamethason 6 mg per dag gedurende maximaal 10 dagen, een behandeloptie. Bij zeer ernstig zieke kinderen lijkt het logisch om dit advies naar deze leeftijdsgroep te extrapoleren. Helaas kan dit niet goed worden onderbouwd met gerandomiseerd onderzoek."

Additionele onderzoeken over het klinisch effect van corticosteroïden die recent verschenen zijn en deze bevindingen ondersteunen, zijn:

- *Pre-print van Corral et al (Glucocovid trial). Deze studie toonde in een partieel gerandomiseerde, open label, Spaans onderzoek bij 85 patiënten aan, dat 2 dd 40 mg methylprednisolon gedurende 6 dagen een significante afname gaf op het risico op een ongunstige uitkomst. Behandeling werd gestart bij nog niet geïntubeerde patiënten met een PaO_2:FiO_2 ratio < 300 mmHg. Ongunstige uitkomst was een gecombineerd eindpunt van overlijden, IC-opname of non-invasieve beademing.*

- *Pre-print van Salton et al. Dit is een observationeel onderzoek verricht in Italie, waarbij bij 83 patiënten gedurende gemiddeld 9.11 ± 2.4 (SD) dagen methylprednisolon 80 mg per dag werd toegediend. Deze werden vergeleken met 90 controles die dit niet hadden gekregen. Het gecombineerde eindpunt, IC-opname, mechanische ventilatie of overlijden, werd significant minder vaak bereikt in de behandelde groep.*

1. Corral-Gudino L, Bahamonde A, Arnaiz-Revillas F, et al. GLUCOCOVID: A controlled trial of methylprednisolone in adults hospitalized with COVID-19 pneumonia. *Preprint*. 2020. https://doi.org/10.1101/2020.06.17.20133579.

2. Salton F, Confalonieri P, Santos P, et al. Prolonged low-dose methylprednisolone in patients with severe COVID-19 pneumonia. *Preprint*. 2020. https://doi.org/10.1101/2020.06.17.20134031

18.19 References provided by the AFMPS/FAGG on PPI treatment

18.19.1 Martindale

In the Martindale references, doubts on the effects of corticosteroids on the gastrointestinal tract are evoked.

(https://about.medicinescomplete.com/publication/martindale-the-complete-drug-reference/)

Effects on the gastrointestinal tract.

- *It has long been considered that treatment with corticosteroids might lead to peptic ulcers. Some years ago a review of the data then available suggested that since an ulcer developed in 1% of control patients not receiving corticosteroids, the 2% incidence for patients receiving corticosteroids did not warrant the prophylactic use of anti-ulcer drugs in all patients.[1] Others have found little evidence of an increased risk of peptic ulcer produced by corticosteroids alone although there is some increased risk when using them with NSAIDs.[2] A later cohort study[3] found a modest increase in risk of gastrointestinal bleeding with current use of corticosteroids, which increased when NSAIDs were also used. It has been suggested that it might be prudent to avoid such combination therapy whenever possible.[4]*
- *Doubt has therefore been cast on the prophylactic value of anti-ulcer therapy given with corticosteroids.[1,5] If an ulcer does develop and there is good reason to continue treatment then corticosteroids may be continued along with some form of ulcer therapy.[1]*
- *There have been several reports of corticosteroids being associated with gastrointestinal perforation.[6-9] There is a risk that the anti-inflammatory properties of corticosteroids may mask the signs of perforation and delay diagnosis with potentially fatal results. (Last reviewed: 2010-07-28; last modified: 2004-03-21)*

1. Spiro HM. Is the steroid ulcer a myth? N Engl J Med 1983; 309: 45-7. (PubMed id:6134237)
2. Piper JM, et al. Corticosteroid use and peptic ulcer disease: role of nonsteroidal anti-inflammatory drugs. Ann Intern Med 1991; 114: 735-40. (PubMed id:2012355)
3. Nielsen GL, et al. Risk of hospitalization resulting from upper gastrointestinal bleeding among patients taking corticosteroids: a register-based cohort study. Am J Med 2001; 111: 541-5. (PubMed id:11705430)
4. Guslandi M, Tittobello A. Steroid ulcers: a myth revisited. BMJ 1992; 304: 655-6. (PubMed id:1571634)
5. Marcus P, McCauley DL. Steroid therapy and H2-receptor antagonists: pharmacoeconomic implications. Clin Pharmacol Ther 1997; 61: 503-8. (PubMed id:9164412)
6. Arsura EL. Corticosteroid-associated perforation of colonic diverticula. Arch Intern Med 1990; 150: 1337-8. (PubMed id:2353866)
7. Ng PC, et al. Gastroduodenal perforation in preterm babies treated with dexamethasone for bronchopulmonary dysplasia. Arch Dis Child 1991; 66: 1164-6. (PubMed id:1750771)
8. O'Neil EA, et al. Dexamethasone treatment during ventilator dependency: possible life threatening gastrointestinal complications. Arch Dis Child 1992; 67: 10-11. (PubMed id:1536578)
9. Epstein A, et al. Perforation of colon diverticula during corticosteroid therapy for pemphigus vulgaris. Ann Pharmacother 1993; 27: 979-80. (PubMed id:8364289)

18.19.2 Farmacotherapeutisch Kompas

According to the AFMPS / FAGG, Kompas mentions doubts “Of een ulcus pepticum door corticosteroïdtoediening kan worden veroorzaakt, wordt betwijfeld. Waarschijnlijk wordt wel de genezing van bestaande ulcera vertraagd en neemt de kans op recidieven toe. Het risico bestaat dat door hoge doses corticosteroïden de symptomen van een maagperforatie worden gemaskeerd.”

18.20 Other publications on PPI treatment and corticosteroids

An article "*When is proton pump inhibitor use appropriate?*" by **Yadlapati et al. published** in February 2017 in the BMC Medicine volume 15, shows the following table:

Table 19 – Summary of the conclusions by Scarpignato et al. regarding appropriatness of proton pump inhibitor (PPI) therapy in 13 clinical scenarios of uncertainty and common misuse

From: When is proton pump inhibitor use appropriate?

	Reason for use
Long-term PPI therapy appropriate	• Barrett's esophagus • Healing and maintenance of healed Los Angeles grade C or D erosive esophagitis[a] • PPI-responsive esophageal eosinophilia • Idiopathic (*H. pylori* and NSAID/aspirin negative) peptic ulcer disease • Zollinger–Ellison disease[a,b] • PPI-responsive GERD/non-erosive reflux disease[a,c] • Long-term non-selective NSAID users at high-risk for upper GI complications or long-term cox-2 inhibitor users with a prior episode of GI bleeding[a] • Anti-platelet therapy in patients at high-risk for upper GI complications (age > 65 years or concomitant use of corticosteroids or anticoagulants or history of peptic ulcer disease) • Steatorrhea refractory to enzyme replacement therapy in chronic pancreatitis
Short-term PPI therapy appropriate (4- to 12-week course)	• Healing of Los Angeles grade A or B erosive esophagitis[a] • Eosinophilic esophagitis • *H. pylori* eradication (in combination with antibiotics)[a,d] • Stress ulcer prophylaxis in high-risk patients (i.e., critically ill patients with respiratory failure or coagulopathy) • Functional dyspepsia • Treatment and maintenance of peptic ulcer disease[a] • Prior to endoscopy for acute upper GI bleeding • Following endoscopic treatment of a high-risk ulcer GI bleed
PPI use not appropriate	• Corticosteroid users without concomitant NSAID therapy • To prevent bleeding from hypertensive gastropathy in cirrhotic patients • Acute pancreatitis • Stress ulcer prophylaxis in non-critically ill hospitalized patients that are not at high-risk for ulcer formation and GI bleeding
PPI use of uncertain benefit	• PPI non-responsive GERD • Extra-digestive GERD

[a]FDA approved indications
[b]Requires 3–4 times the usual dose (PPI therapy is typically started as single dose)
[c]In these cases, a PPI taper should be attempted to the lowest effective dose, on demand dosing, or intermittent dosing
[d]In this case, a 1 to 2 week course of PPI therapy for *H. pylori* eradication in conjunction with antibiotics is appropriate
GERD gastroesophageal reflux disease, *GI* gastrointestinal, *NSAID* non-steroidal anti-inflammatory drugs

In Scarpignato C, Gatta L, Zullo A, et al. "*Effective and safe proton pump inhibitor therapy in acid-related diseases - A position paper addressing benefits and potential harms of acid suppression"n*. BMC Med. 2016;14:179, the summary of evidence in the PPIs for corticosteroids users showed:

"Corticosteroid therapy does not cause damage to the gastroduodenal mucosa, but can enhance the GI risk associated with NSAID use. Therefore, unless patients taking corticosteroid therapy have a PU or are under concomitant NSAID therapy, mucosal protection with a PPI is not routinely indicated.

Contrary to NSAIDs, corticosteroids do not cause any direct injury to the gastroduodenal mucosa [249], and indeed some experimental evidence actually suggests a mucosal protective effect [250, 251]. These drugs may, however, increase the GI risk of NSAID therapy and may hamper the healing of idiopathic or iatrogenic ulcers [252]. The association between corticosteroid use and GI adverse events in patients with risk factors other than NSAID use remains controversial. Indeed, some studies reported an increased risk of PU complications in corticosteroid users, while other investigators failed to demonstrate such an association after adjustment for confounding factors [253–257]. A meta-analysis also failed to show any significant risk for gastric or duodenal ulcers in patients receiving corticosteroid treatment compared to controls [258]. It is worthwhile emphasizing that the design of the studies included in the meta-analysis was quite heterogeneous as was the type of patients selected (outpatients or inpatients, presence of comorbidity and co-therapy) as well as PU definition. However, a systematic review of available meta-analyses as well as of published case–control studies reached the same conclusion [259].

A more recent systematic review and meta-analysis of 159 studies, appeared between 1983 and 2013, on GI bleeding and perforation in corticosteroid users [260], found that corticosteroid therapy may increase the risk of GI events (OR = 1.43) only in hospitalized patients. Here again, the diversity of GI bleeding definitions (widely varying from occult blood in stool to bleeding requiring transfusion or hospital stay) as well as the heterogeneity of the patients included do not allow drawing clinically relevant conclusions [260]. Taking these considerations into account, no evidence currently supports PPI therapy as prophylaxis for corticosteroid use in the absence of concomitant NSAID therapy.

In summary, PPI co-therapy is not routinely indicated in patients taking corticosteroids unless they have a history of PU or are taking NSAIDs. In hospitalized patients on corticosteroid therapy, prophylaxis against stress ulcers could be limited to those with a history of PU, clotting impairment or requiring mechanical ventilation for more than 48 hours [261]. Despite corticosteroids increase the risk of GI bleeding in patients with either diverticular disease of the colon or acute ischemic stroke [262, 263], PPI therapy is not expected to exert any preventive effect on eventual drug-induced GI bleeding in these patients.

249. Martinek J, Hlavova K, Zavada F, et al. "A surviving myth" – corticosteroids are still considered ulcerogenic by a majority of physicians. Scand J Gastroenterol. 2010;45:1156–61.
250. Filaretova L. Gastroprotective role of glucocorticoids during NSAID-induced gastropathy. Curr Pharm Des. 2013;19:29–33.
251. Filaretova L. The hypothalamic-pituitary-adrenocortical system: Hormonal brain-gut interaction and gastroprotection. Auton Neurosci. 2006;125:86–93.
252. Guslandi M. Steroid ulcers: any news? World J Gastrointest Pharmacol Ther.2013;4:39–40.
253. Luo JC, Chang FY, Lin HY, et al. The potential risk factors leading to peptic ulcer formation in autoimmune disease patients receiving corticosteroid treatment. Aliment Pharmacol Ther. 2002;16:1241–8.
254. Hernandez-Diaz S, Rodriguez LA. Steroids and risk of upper gastrointestinal complications. Am J Epidemiol. 2001;153:1089–93.
255. Weil J, Langman MJ, Wainwright P, et al. Peptic ulcer bleeding: accessory risk factors and interactions with non-steroidal anti-inflammatory drugs. Gut.2000;46:27–31.
256. Messer J, Reitman D, Sacks HS, Smith Jr H, Chalmers TC. Association of adrenocorticosteroid therapy and peptic-ulcer disease. N Engl J Med. 1983; 309:21–4.
257. Piper JM, Ray WA, Daugherty JR, Griffin MR. Corticosteroid use and peptic ulcer disease: role of nonsteroidal anti-inflammatory drugs. Ann Intern Med.1991;114:735–40.
258. Conn HO, Poynard T. Corticosteroids and peptic ulcer: meta-analysis of adverse events during steroid therapy. J Intern Med. 1994;236:619–32.
259. Dorlo TP, Jager NG, Beijnen JH, Schellens JH. Concomitant use of proton pump inhibitors and systemic corticosteroids. Ned Tijdschr Geneeskd. 2013;157:A5540.
260. Narum S, Westergren T, Klemp M. Corticosteroids and risk of gastrointestinal bleeding: a systematic review and meta-analysis. BMJ Open. 2014;4, e004587.
261. Cook DJ, Fuller HD, Guyatt GH, et al. Risk factors for gastrointestinal bleeding in critically ill patients. Canadian Critical Care Trials Group. N Engl J Med. 1994;330:377–81.
262. Jansen A, Harenberg S, Grenda U, Elsing C. Risk factors for colonic diverticular bleeding: a Westernized community based hospital study. World J Gastroenterol. 2009;15:457–61.
263. Ogata T, Kamouchi M, Matsuo R, et al. Gastrointestinal bleeding in acute ischemic stroke: recent trends from the Fukuoka stroke registry. Cerebrovasc Dis Extra. 2014;4:156–64.

In the JAMA, in 2016, **Jones et al**. also highlighted the misuse of PPI with a case study in "*Inappropriate Prescription of Proton Pump Inhibitors in the Setting of Steroid Use A Teachable Moment*" JAMA Intern Med. 2016;176(5):594-595. doi:10.1001/jamainternmed.2016.0603

A woman in her 60s with no significant medical history presented to her internist with ear fullness and asymmetric hearing loss. She was referred to an otolaryngologist, who diagnosed idiopathic asymmetric hearing loss. Before ordering brain imaging, he prescribed prednisone, 60 mg daily, and valacyclovir for possible herpes zoster infection. He also directed the patient to purchase over-the-counter omeprazole for peptic ulcer prophylaxis in the setting of steroid use, all medications to be taken for 14 days. On day 6 of this regimen, the patient developed subjective fevers and chills and had several episodes of nonbloody emesis and diarrhea. She felt better on day 7, with no vomiting or diarrhea. On day 8, she developed a red, blotchy, intensely pruritic cutaneous eruption that emerged simultaneously throughout the body. The patient visited her dermatologist that day for the cutaneous eruption, who performed a biopsy of the skin lesions and instructed her to stop all 3 medications, which she had already taken that day. The patient felt weak and went home, unable to go to an outside location for the blood tests that her dermatologist had ordered.

On the morning of day 9, the patient was taken by ambulance to the hospital, where she was found to have a temperature of 39°C, a pulse of 102 beats per minute, a respiratory rate of 18 breaths per minute, and dry mucous membranes. Her vital signs improved after a few hours on intravenous fluids. Physical examination revealed a blanching, macular cutaneous eruption with some papules involving the trunk and limbs and sparing the palms, soles, and mucous membranes. Given the patient's

clinical presentation and new medication regimen, drug reaction and viral exanthem were top on the list of differential diagnoses. Toxic shock syndrome was considered less likely owing to the rapid stabilization of the patient's vital signs.

Biopsy test results were consistent with interface and spongiotic dermatitis, suggestive of a dermatologic drug reaction. The distribution of the cutaneous eruption was consistent with the classic dermatologic drug reaction caused by a proton pump inhibitor (PPI). The dermatology department was consulted and confirmed PPI-related dermatologic drug reaction as the most likely etiology. Valacyclovir-related cutaneous eruption was considered to be unlikely given its classic involvement of symmetric intertriginous areas and absence of systemic signs or symptoms,[1] whereas our patient exhibited systemic manifestations. She was treated with hydroxyzine, a topical ointment, and betamethasone. Her cutaneous eruption and pruritus improved and she was discharged after a 2-day hospitalization.

Teachable Moment

The prevalence of PPI use is considerable, with estimated expenditures totaling over $11 billion annually in the United States. However, over one-third of PPI prescriptions in the ambulatory setting may not be associated with an appropriate, documented indication for PPI treatment. Among hospitalized, nonintensive care unit patients, none of the 22% of patients who received stress ulcer prophylaxis with PPIs met evidence-based criteria for such prophylaxis.[2] Another study[2] found that only 10% of such patients received PPIs for an appropriate, symptom-based indication for antisecretory therapy, while 38% were given antisecretory therapy for stress ulcer prophylaxis or corticosteroid-associated prophylaxis.

The case described herein reminds us to carefully consider indications for PPI treatment in the setting of steroid use. A recent literature search concluded that systemic corticosteroid therapy rarely causes peptic ulcers and thus there is no indication for PPI prophylaxis with short-term systemic corticosteroid use in the absence of concomitant treatment with nonsteroidal anti-inflammatory drugs (NSAIDs).[3] Nevertheless, corticosteroid users are commonly prescribed PPIs. This is particularly concerning given that higher doses of corticosteroids are thought to increase the risk of adverse events such as fractures and infection, which are also associated with PPI use.

PPI-related hypersensitivity reactions include type 1 hypersensitivity reactions such as urticaria, angioedema, and anaphylaxis, as well as toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms (DRESS). Cutaneous manifestations are most often mild, and include pruritus, urticaria, and maculopapular eruptions,[4] such as those present in our patient. However, patients with DRESS may progress from these initial dermatologic symptoms to more extensive presentations with mucosal involvement and desquamation, as well as multiorgan involvement that may eventually lead to multiorgan failure and death.

The literature suggests no benefit from PPI prophylaxis in patients taking systemic corticosteroids without concomitant NSAID use. Furthermore, PPIs have been linked to numerous adverse events. Studies[5] show a 2- to 3-fold increase in renal disease such as acute kidney injury in PPI users compared with nonusers and a 74% higher risk of developing Clostridium difficile infection. In addition to these adverse effects, the case described herein highlights the dermatologic drug reactions that may stem from PPI use. In both the inpatient and outpatient settings, it is important for clinicians to consider indications for PPI use and possible adverse reactions ranging from a mild dermatologic drug reaction to DRESS progressing to multiorgan failure. Avoiding the prescription of PPIs when it is not medically indicated has the potential to spare individuals from unnecessary distress, and reduce avoidable hospitalizations and health care spending.

1. Thyssen JP, Maibach HI. Drug-elicited systemic allergic (contact) dermatitis—update and possible pathomechanisms. *Contact Dermatitis*. 2008;59(4):195-202.
2. Heidelbaugh JJ, Kim AH, Chang R, Walker PC. Overutilization of proton-pump inhibitors: what the clinician needs to know. *Therap Adv Gastroenterol*. 2012;5(4):219-232.
3. Dorlo TP, Jager NG, Beijnen JH, Schellens JH. Concomitant use of proton pump inhibitors and systemic corticosteroids. *Ned Tijdschr Geneeskd*. 2013;157(19):A5540-A5540.
4. Chang Y-S. Hypersensitivity reactions to proton pump inhibitors. *Curr Opin Allergy Clin Immunol*. 2012;12(4):348-353.
5. Schoenfeld AJ, Grady D. Adverse effects associated with proton pump inhibitors. *JAMA Intern Med*. 2016;176(2):172-174.

18.21 References provided by the AFMPS / FAGG on hydroxychloroquine treatment in COVID-19 (16/11/2020)

18.21.1 National Institutes of health (NIH)

https://www.covid19treatmentguidelines.nih.gov/antiviral-therapy/chloroquine-or-hydroxychloroquine-with-or-without-azithromycin/ (Last Updated: October 9, 2020)

Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends against the use of chloroquine or hydroxychloroquine with or without azithromycin for the treatment of COVID-19 in hospitalized patients (AI).
- In non-hospitalized patients, the Panel recommends against the use of chloroquine or hydroxychloroquine with or without azithromycin for the treatment of COVID-19, except in a clinical trial (AI).
- The Panel recommends against the use of high-dose chloroquine (600 mg twice daily for 10 days) for the treatment of COVID-19 (AI).

Table 20 – Recommendation Rating Scheme according to NIH

Strength of Recommendation	Quality of Evidence for Recommendation
A: Strong recommendation for the statement **B:** Moderate recommendation for the statement **C:** Optional recommendation for the statement	**I:** One or more randomized trials with clinical outcomes and/or validated laboratory endpoints **II:** One or more well-designed, nonrandomized trials or observational cohort studies **III**: Expert opinion

18.21.2 Sciensano

https://covid-19.sciensano.be/sites/default/files/Covid19/COVID-19_InterimGuidelines_Treatment_ENG.pdf (16 October 2020; Version 14 Addition 30 October 2020)

Overall, based on these preclinical observations and the reported trial results it has been decided since beginning of June (version 10) not to recommend its off-label use for COVID-19 in Belgium anymore, except within ongoing registered clinical trials, and after timely interim analysis of the study-related risk/benefit.

"Chloroquine and hydroxychloroquine inhibits replication of SARS-CoV-2 in vitro. Chloroquine (CQ) inhibits the virus at concentrations (EC50 = 1.13 to 5.47 µM) that cannot be achieved in human plasma [21], but possibly in the intracellular compartment. This drug (not available in Belgium since 2015) has been used for decades (at a total of 25 mg/kg within 3 days) for malaria treatment without any monitoring and side effects, including in pregnant women. However, the therapeutic window is quite narrow (cardiotoxicity/arrhythmia), requiring caution for use at higher cumulative dosages in patients with co-morbidities and co-medication.

Hydroxychloroquine (HCQ, drug marketed in Belgium as Plaquenil®) has appeared to be more potent than chloroquine in vitro (EC50=0.72 µM), so that lower dosages (than initially recommended) could be used [22]. It has also a better safety profile than chloroquine (larger therapeutic window).

Several small retrospective studies could not demonstrate any independent benefit of hydroxychloroquine use compared to non-exposed hospitalized patients [23–27]. Some larger retrospective studies did find an independent association between HCQ use (low dosage, similar to the "Belgian" recommendations) and a reduction in COVID-19 associated in-hospital mortality [5,28–30]. No particular safety signals were observed with the use of HCQ (alone) in these large cohorts. However, the major limitation of all these studies was the retrospective observational design that precluded any definitive conclusion about treatment efficacy. The prospective randomized controlled trial (RCT) RECOVERY in UK has stopped enrolling patients on the 5th of June after finding no

beneficial effect of high dose hydroxychloroquine (9600 mg in total over 10 days) in patients hospitalized with COVID-19.. For the same reason (absence of efficacy in hospitalized patients), the SOLIDARITY trial has communicated the suspension of recruitment in the HCQ arm (9600 mg over 10 days) on 18th of June (link). Similarly, the DisCoVeRy trial stopped enrolling participants in the HCQ arm (5600 mg in total over 10 days) at the same period. The results of the large RECOVERY trial on HCQ efficacy in hospitalized COVID-19 patients have demonstrated that mortality at Day 28 was similar in HCQ recipients compared to standard of care (421/1561, 27% versus 790/3155, 25%; p=0.15). No benefit was observed for all secondary outcomes and subgroups of patients [31]. Another smaller RCT in Brazil conducted in mild-to-moderate hospitalized patients did not find any improvement of the clinical status (seven-level ordinal scale) in participants having received HCQ (total dosage: 5600 mg), alone or with azithromycin (500 mg/day for 7 days) [32].

Regarding other potential indications, an RCT using HCQ (low-dose) as post-exposure prophylaxis (PEP), showed no prevention of "illness compatible with COVID-19" [40]. This trial had however several limitations such as undocumented treatment adherence and no laboratory confirmation of SARS-CoV-2 infection in 85% of the participants. No serious adverse events were notified. Another RCT by the same group studied early administration of HCQ in mild/ambulatory patients with laboratory-confirmed or symptomatic contacts (n=423), and no substantial symptom reduction was observed in the HCQ arm compared to masked placebo [33]. Here again, many participants (about 40%) were not tested. In a well-designed Spanish RCT evaluating early treatment with HCQ in adults with mild disease (n=293), no clinical (shortening of symptoms) nor viral (reduction of shedding) benefits were observed [34]. The results of several other ongoing trials using HCQ are still awaited, including as chemoprophylaxis (PrEP).

Meanwhile, several preclinical studies have not demonstrated any antiviral effect of HCQ in animal models (hamsters, macaques, including one study from the KUL [35–38]. Overall, based on these preclinical observations and the reported trial results it has been decided since beginning of June (version 10) not to recommend its off-label use for COVID-19 in Belgium anymore, except within ongoing clinical registered trials, and after timely interim analysis of the study-related risk/benefit."

18.21.3 Netherlands Huisartsen Genootschap (NHG)

https://www.nhg.org/sites/default/files/content/nhg_org/uploads/nhg-advies_hydroxychloroquine_bij_covid-19_in_de_eerste_lijn_0.pdf (Augustus 2020)

Medicamenteuze behandeling COVID-19

Schrijf geen middelen voor waarvan de werkzaamheid nog niet is aangetoond, zoals antivirale middelen of (hydroxy)chloroquine (zie NHG-Advies Hydroxychloroquine bij COVID-19 in de eerste lijn, pdf). Vanwege onbewezen effect en risico op toxiciteit/bijwerkingen wordt deze medicatie alleen overwogen (in onderzoekssetting) bij de meest ernstig zieke COVID-19-patiënten die in het ziekenhuis zijn opgenomen (swab.nl | COVID-19).

***Aanbeveling 1**. We bevelen HCQ monotherapie niet aan als behandeling voor niet-gehospitaliseerde patiënten met (een vermoeden van) COVID-19, omdat er geen bewijs is dat dit een gunstig effect heeft op het aantal ziekenhuisopnamen of overlijden als gevolg van COVID-19. Bovendien kent de behandeling bijwerkingen, waarvan sommige potentieel ernstig.*

***Aanbeveling 2.** We bevelen HCQ/AZT-combinatiebehandeling niet aan wegens gebrek aan bewijs voor de effectiviteit. Bovendien neemt de kans op potentieel ernstige bijwerkingen toe bij gecombineerd gebruik van HCQ en AZT*

***Aanbeveling 3**. We bevelen HCQ-triple therapie met AZT en zink niet aan, wegens gebrek aan bewijs voor de effectiviteit. Bovendien neemt de kans op potentieel ernstige bijwerkingen toe bij gecombineerd gebruik van HCQ en AZT.*

Conclusies

- Er is beperkte informatie beschikbaar over de veiligheid van HCQ-(combinatie)behandeling bij niet-gehospitaliseerde COVID-19-patiënten door het ontbreken van afdoende gegevens.
- De meest gemelde bijwerkingen zijn gastro-intestinale klachten en huidreacties, zowel in de beschikbare COVID-19-eerstelijnsstudies als bij het gebruik bij andere indicaties.

- Cardiale bijwerkingen komen minder vaak voor. De kans hierop is echter groter bij het gelijktijdig gebruik van HCQ en AZT. Deze conclusies zijn in lijn met de resultaten zoals bekend uit de tweedelijnsonderzoeken en -richtlijnen.

18.21.4 New England Journal of Medicine (NEJM)

https://www.nejm.org/doi/full/10.1056/NEJMcp2009249?query=featured_coronavirus

In the article of Gandhi et al "Mild or Moderate COVID-19", published on April 24, 2020, and updated on October 29, 2020, at NEJM.org. N Engl J Med 2020; 383:1757-1766. DOI:10.1056/NEJMcp2009249

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Patients who have mild illness usually recover at home, with supportive care and isolation. It may be useful for people who are at high risk for complications to have a pulse oximeter to self-monitor the oxygen saturation.

Patients who have moderate disease should be monitored closely and sometimes hospitalized; those with severe disease should be hospitalized. If there is clinical evidence of bacterial pneumonia, empirical antibacterial therapy is reasonable but should be stopped as soon as possible. Empirical treatment for influenza may be considered when seasonal influenza transmission is occurring until results of specific testing are known.

*Treatment of Covid-19 depends on the stage and severity of disease (**Figure 1**).[41] Because SARS-CoV-2 replication is greatest just before or soon after symptom onset, antiviral medications (e.g., remdesivir and antibody-based treatments) are likely to be most effective when used early. Later in the disease, a hyperinflammatory state and coagulopathy are thought to lead to clinical complications; in this stage, antiinflammatory medications, immunomodulators, anticoagulants, or a combination of these treatments may be more effective than antiviral agents. There are no approved treatments for Covid-19 but some medications have been shown to be beneficial.*

Hydroxychloroquine and Chloroquine with or without Azithromycin

Chloroquine and hydroxychloroquine have in vitro activity against SARS-CoV-2, perhaps by blocking endosomal transport.[44] Results from single-group observational studies and small randomized trials led to initial interest in hydroxychloroquine for the treatment of Covid-19, but subsequent randomized trials did not show a benefit. The Randomized Evaluation of Covid-19 Therapy (RECOVERY) trial showed that, as compared with standard care, hydroxychloroquine did not decrease mortality among hospitalized patients.[45] In another randomized trial involving hospitalized patients with mild-to-moderate Covid-19, hydroxychloroquine with or without azithromycin did not improve clinical outcomes.[46] Moreover, no benefit was observed with hydroxychloroquine in randomized trials involving outpatients with Covid-19[47,48] or patients who had recent exposure to SARS-CoV-2 (with hydroxychloroquine used as postexposure prophylaxis).[49,50] Current guidelines recommend that hydroxychloroquine not be used outside clinical trials for the treatment of patients with Covid-19.

18.21.5 Agence nationale de sécurité du médicament et des produits de santé (ANSM)

L'Agence nationale de sécurité du médicament et des produits de santé (ANSM) publie sa décision sur la demande d'une recommandation temporaire d'utilisation (RTU) pour l'hydroxychloroquine dans la prise en charge de la maladie Covid-19 - Point d'Information

(23/10/2020)

Nous avons reçu une demande de recommandation temporaire d'utilisation (RTU) de l'hydroxychloroquine dans la prise en charge de la maladie Covid-19, de la part de l'IHU de Marseille. Afin d'évaluer cette demande, nous nous sommes appuyés sur les nombreuses études récentes publiées sur l'efficacité et la sécurité de l'hydroxychloroquine, ainsi que sur les dernières recommandations du Haut Conseil de Santé Publique (HCSP) du 23 juillet 2020 .

A ce jour, les données disponibles, très hétérogènes et inégales, ne permettent pas de présager d'un bénéfice de l'hydroxychloroquine, seule ou en association, pour le traitement ou la prévention de la maladie Covid-19. Dans ce contexte et au regard des données de sécurité disponibles faisant apparaître des risques majorés, notamment cardio-vasculaires,

il ne peut être présumé d'un rapport bénéfice/risque favorable de l'hydroxychloroquine quel que soit son contexte d'utilisation. Par conséquent nous ne pouvons pas répondre favorablement à la demande de RTU de l'hydroxychloroquine dans la prise en charge de la maladie Covid-19.

Cette décision est par ailleurs en phase avec la très grande majorité des recommandations thérapeutiques internationales. Elle pourra être révisée à tout moment, notamment si de nouveaux résultats d'études cliniques venaient modifier le constat fait à ce jour.

- Consulter la décision de l'ANSM (23/10/2020) (4889 ko)

Une Recommandation Temporaire d'Utilisation (RTU) peut-être mise en place par l'ANSM pour encadrer des prescriptions non conformes à l'autorisation de mise sur le marché (AMM), sous réserve que le rapport bénéfice/risque du médicament dans l'indication considérée soit présumé favorable, notamment à partir de données scientifiques publiées d'efficacité et de tolérance.

18.22 References provided by the AFMPS-FAGG on the place of antibiotics in COVID-19 patients (16/11/2020)

18.22.1 National institute for Health and Care Excellence (NICE)

Three NICE guidelines are mentioned by the AFMPS / FAGG

1. The "COVID-19 rapid guideline: managing symptoms (including at the end of life) in the community", NICE guideline [NG163] Published date: 03 April 2020 Last updated: 13 October 2020. (https://www.nice.org.uk/guidance/ng163)

This guidance highlights the risk of rapid deterioration of COVID patients and **refers to another guideline on pneumonia.**

2. The "COVID-19 rapid guideline: managing suspected or confirmed pneumonia in adults in the community", NICE guideline [NG165] Published date: 03 April 2020 Last updated: 23 April 2020 (https://www.nice.org.uk/guidance/ng165)

The purpose of this guideline is to ensure the best treatment for adults with suspected or confirmed pneumonia in the community during the COVID-19 pandemic and best use of NHS resources. The use of antibiotics is limited to bacterial pneumonia and the first choice in the UK is doxycycline 200 mg on the first day, then 100 mg once a day for 4 days, or alternatively amoxicillin 500 mg 3 times a day for 5 days.

Table 21 – NICE recommendations on antibiotic treatment for managing suspected or confirmed pneumonia

4.5 As COVID-19 pneumonia is caused by a virus, antibiotics are ineffective.
4.6 Do not offer an antibiotic for treatment or prevention of pneumonia if: • COVID-19 is likely to be the cause and • symptoms are mild. Inappropriate antibiotic use may reduce availability if used indiscriminately, and broad-spectrum antibiotics in particular may lead to *Clostridioides difficile* infection and antimicrobial resistance.
4.7 Offer an oral antibiotic for treatment of pneumonia in people who can or wish to be treated in the community if: • the likely cause is bacterial or • it is unclear whether the cause is bacterial or viral and symptoms are more concerning or • they are at high risk of complications because, for example, they are older or frail, or have a pre-existing comorbidity such as immunosuppression or significant heart or lung disease (for example bronchiectasis or COPD), or have a history of severe illness following previous lung infection.
4.8 When starting antibiotic treatment, the first-choice oral antibiotic is: • doxycycline 200 mg on the first day, then 100 mg once a day for 4 days (5-day course in total); doxycycline should not be used in pregnancy • alternative: amoxicillin 500 mg 3 times a day for 5 days. Doxycycline is preferred because it has a broader spectrum of cover than amoxicillin, particularly against *Mycoplasma pneumoniae* and *Staphylococcus aureus*, which are more likely to be secondary bacterial causes of pneumonia during the COVID-19 pandemic. [amended 23 April 2020]
4.9 Do not routinely use dual antibiotics.
4.10 For choice of antibiotics in penicillin allergy, pregnancy and more severe disease, or if atypical pathogens are likely, see the recommendations on choice of antibiotic in the NICE antimicrobial prescribing guideline on community-acquired pneumonia.
4.11 Start antibiotic treatment as soon as possible, taking into account any different methods needed to deliver medicines to patients during the COVID-19 pandemic (see recommendation 1.3).

3. The "COVID-19 rapid guideline: antibiotics for pneumonia in adults in hospital", NICE guideline [NG173] Published date: 01 May 2020 Last updated: 09 October 2020 https://www.nice.org.uk/guidance/ng173

The purpose of this guideline is to ensure the best antibiotic management of suspected or confirmed bacterial pneumonia in adults **in hospital** during the COVID-19 pandemic. This includes people presenting to hospital with moderate to severe community-acquired pneumonia and people who develop pneumonia while in hospital. It will enable services to make the best use of NHS resources.

The first choice is doxycycline 200 mg on first day, then 100 mg once day.

Table 22 – NICE key messages on COVID-19 rapid guideline: antibiotics for pneumonia in adults in hospital

To guide decision making about antibiotics use: • antibiotic prescribing table 1 for patients with suspected community-acquired pneumonia (that is, pneumonia that has developed before or within 48 hours of admission). • antibiotic prescribing table 2 for patients with suspected hospital acquired pneumonia (that is, pneumonia that develops 48 hours or more after admission and that was not incubating at admission).
When choosing antibiotics, also take account of local antimicrobial resistance data and other factors such as their availability.
Give oral antibiotics if the patient can take oral medicines and their condition is not severe enough to need intravenous antibiotics.
Review all antibiotics at 24 to 48 hours or as soon as test results are available.
Stop antibiotics if the pneumonia is due to COVID-19 and there is no evidence of bacterial infection (see section 4 in the COVID-19 rapid guideline on antibiotics for pneumonia in adults in hospital for more information, https://www.nice.org.uk/guidance/ng173/chapter/4-Assessing-the-ongoing-need-for-antibiotics).
Review antibiotic choice based on microbiological results and switch to a narrower spectrum antibiotic when appropriate.
If antibiotics are continued, give them for a total of 5 days, then stop them unless there is a clear indication to continue.
Review intravenous antibiotic use within 48 hours and think about switching to oral antibiotics.
See the British National Formulary (BNF) for appropriate use and dosing in specific populations, for example, for hepatic impairment, renal impairment, pregnancy and breastfeeding, and when administering intravenous antibiotics.

Source: https://www.nice.org.uk/guidance/ng173/resources/prescribing-tables-to-guide-decision-making-about-antibiotic-choice-pdf-8719038253

18.22.2 Nederlands Huisartsen Genootschap (NHG)

The NHG highlights that clinical differentiation between COVID-19 and bacterial pneumonia is very difficult and proposes amoxicilline 3 dd 500-750 mg for 5 days in case of suspected pneumonia (https://corona.nhg.org/behandeling/).

Medicamenteuze behandeling COVID-19

- Er is momenteel geen specifieke behandeling voor COVID-19 in de 1e lijn.
- Bij COVID-19 zijn antibiotica niet zinvol en niet geïndiceerd. Aangezien de differentiatie met een bacteriële verwekker op klinische grond lastig is, zijn antibiotica bij verdenking op een pneumonie wel geïndiceerd.

Overige medicamenteuze adviezen in de 1e lijn

Gecompliceerde luchtweginfectie

- **Patiënten met de waarschijnlijkheidsdiagnose pneumonie: start antibiotica conform de adviezen in de NHG-Standaard Acuut hoesten. Amoxicilline** is nog steeds het middel van eerste keus. De dosering van amoxicilline voor de behandeling van een pneumonie is aangepast naar 3 dd 500-750 mg voor 5 dagen. Amoxicilline 3dd 750 mg biedt met name op theoretische gronden mogelijk een voordeel boven 3dd 500 mg. Het is niet raadzaam om bij deze diagnose aan patiënten in de 1e lijn azitromycine als eerste keus voor te schrijven.
- Patiënten met een risicofactor op een gecompliceerd beloop (zie zowel 'Risicofactoren voor een ernstig beloop' als de NHG-Standaard Acuut hoesten): bij deze patiënten bepalen het klinisch beeld en de comorbiditeit of al dan niet met medicamenteuze behandeling wordt gestart.

Voor kinderen tot 18 jaar met onderliggend lijden zijn separaat adviezen opgesteld door de NVK. Op basis van gegevens over de leeftijdsspecifieke incidentie, is het risico op COVID-19 aanzienlijk lager bij kinderen. Er worden daarnaast in de gegevens uit China vrijwel geen ernstige uitkomsten gemeld voor personen onder de 19 jaar. Zie ook 'Kinderen en COVID-19'.

18.22.3 Sciensano

https://covid-19.sciensano.be/sites/default/files/Covid19/COVID-19_InterimGuidelines_Treatment_ENG.pdf (16 October 2020; Version 14 Addition 30 October 2020)

In confirmed severe COVID-19 (≥1 of the following: respiratory rate ≥30/min in adults or ≥40/min in children<5; blood oxygen saturation ≤93%; PaO_2/FiO_2ratio <300; lung infiltrates >50% of the lung field within 24-48 hours), Sciensano proposes to carefully consider antibiotics or antifungals according to local epidemiology.

18.22.4 National Institutes of health (NIH referred by CDC)

Therapeutic Management of Patients with COVID-19; Last Updated: October 9, 2020
https://files.covid19treatmentguidelines.nih.gov/guidelines/covid19treatmentguidelines.pdf

Bacterial Superinfection of COVID-19-Associated Pneumonia

Limited information exists about the frequency and microbiology of pulmonary coinfections and superinfections in patients with COVID-19, such as hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP). Some studies from China emphasize the lack of bacterial coinfections in patients with COVID-19, while other studies suggest that these patients experience frequent bacterial complications.[3-8] There is appropriate concern about performing pulmonary diagnostic procedures such as bronchoscopy or other airway sampling procedures that require disruption of a closed airway circuit. Thus, while some clinicians do not routinely start empiric broad-spectrum antimicrobial therapy for patients with severe COVID-19 disease, other experienced clinicians routinely use such therapy. For the treatment of shock, however, empiric broad-spectrum antimicrobial therapy is the standard of care. Antibiotic stewardship is critical to avoid reflexive or continued courses of antibiotics.

Regarding empiric broad-spectrum antimicrobial therapy, the NIH mentions:

- *In patients with COVID-19 and severe or critical illness, there are insufficient data to recommend empiric broad-spectrum antimicrobial therapy in the absence of another indication.*
- *If antimicrobials are initiated, the Panel recommends that their use should be reassessed daily in order to minimize the adverse consequences of unnecessary antimicrobial therapy (AIII).*

There are no reliable estimates of the incidence or prevalence of copathogens with severe acute respiratory syndrome coronavirus 2 at this time. Some experts routinely administer broad-spectrum antibiotics as empiric therapy for bacterial pneumonia to all patients with COVID-19 and moderate or severe hypoxemia. Other experts administer antibiotics only for specific situations, such as the presence of a lobar infiltrate on a chest X-ray, leukocytosis, an elevated serum lactate level, microbiologic data, or shock. Gram stain, culture, or other testing of respiratory specimens is often not available due to concerns about aerosolization of the virus during diagnostic procedures or when processing specimens. There are no clinical trials that have evaluated the use of empiric antimicrobial agents in patients with COVID-19 or other severe coronavirus infections.

The NIH recommends empiric antibiotic treatment in two situations:

- **In case of moderate COVID-19 illness** (evidence of lower respiratory disease during clinical assessment or imaging, with SpO_2 ≥94% on room air at sea level):

  "If bacterial pneumonia or sepsis is strongly suspected, administer empiric antibiotic treatment, re-evaluate the patient daily, and de-escalate or stop antibiotics if there is no evidence of bacterial infection. See Therapeutic Management of COVID-19 for recommendations regarding SARS-CoV-2-specific therapy."

- **In case of severe COVID-19 illness** (SpO_2 <94% on room air at sea level, respiratory rate of >30 breaths/min, PaO_2/FiO_2 <300 mmHg, or lung infiltrates >50%):

  "If secondary bacterial pneumonia or sepsis is suspected, administer empiric antibiotics, re-evaluate the patient daily, and de-escalate or stop antibiotics if there is no evidence of bacterial infection."

References

3. Suntronwong N, Thongpan I, Chuchaona W, et al. Impact of COVID-19 public health interventions on influenza incidence in Thailand. Pathog Glob Health. 2020;114(5):225-227. Available at: https://www.ncbi.Downloaded from https://www.ncbi.nlm.nih.gov/pubmed/32521210.
4. Lei H, Xu M, Wang X, et al. Non-pharmaceutical interventions used to control COVID-19 reduced seasonal influenza transmission in China. J Infect Dis. 2020; Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32898256.
5. Olsen SJ, Azziz-Baumgartner E, Budd AP, et al. Decreased influenza activity during the COVID-19 pandemic—United States, Australia, Chile, and South Africa, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(37):1305-1309. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32941415.
6. Centers for Disease Control and Prevention. Contraindications and precautions. General best practice guidelines for immunization: best practices guidance of the advisory committee on immunization practices (ACIP). 2020. Available at: https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html. Accessed October 16, 2020.
7. Hashemi SA, Safamanesh S, Ghasemzadeh-Moghaddam H, Ghafouri M, Azimian A. High prevalence of SARS-CoV-2 and influenza A virus (H1N1) coinfection in dead patients in Northeastern Iran. J Med Virol. 2020; Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32720703.
8. Huang BR, Lin YL, Wan CK, et al. Co-infection of influenza B virus and SARS-CoV-2: A case report from Taiwan. J Microbiol Immunol Infect. 2020; Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32646801

18.22.5 New England Journal of Medicine (NEJM)

In the article of Gandhi et al. "Mild or Moderate COVID-19", published on April 24, 2020, and updated on October 29, 2020, at NEJM.org, antibiotic treatment is mentioned only in case of clinical evidence of bacterial pneumonia.

https://www.nejm.org/doi/full/10.1056/NEJMcp2009249?query=featured_coronavirus

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Patients who have moderate disease should be monitored closely and sometimes hospitalized; those with severe disease should be hospitalized. ***If there is clinical evidence of bacterial pneumonia, empirical antibacterial therapy is reasonable but should be stopped as soon as possible****. Empirical treatment for influenza may be considered when seasonal influenza transmission is occurring until results of specific testing are known.*

Treatment of Covid-19 depends on the stage and severity of disease. Because SARS-CoV-2 replication is greatest just before or soon after symptom onset, antiviral medications (e.g., remdesivir and antibody-based treatments) are likely to be most effective when used early. Later in the disease, a hyperinflammatory state and coagulopathy are thought to lead to clinical complications; in this stage, antiinflammatory medications, immunomodulators, anticoagulants, or a combination of these treatments may be more effective than antiviral agents. There are no approved treatments for Covid-19 but some medications have been shown to be beneficial.

18.22.6 Infectious Diseases Society of America (IDSA)

Within the Infectious Diseases Society of America Guidelines on the treatment and management of Patients with COVID-19, published by IDSA on 11/4/2020. Last updated, 2/12/2020 https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/

Antibacterials and antifungals Last reviewed and updated 25/9/20 = 4 September https://www.idsociety.org/globalassets/idsa/practice-guidelines/covid-19/treatment/idsa-covid-19-gl-tx-and-mgmt-v3.3.0.pdf*Patients with COVID-19 often present to hospitals with viral pneumonia with accompanying febrile illness and respiratory symptoms.* ***Differential diagnoses may include bacterial pneumonia, for which antibiotics are prescribed. Concerns for bacterial superinfections also exist****. Studies performed early in the COVID-19 pandemic reported high percentages of antibiotic use in China (58-95%) [1, 142, 175], Spain (74%) [176], and New York (65%) [177]. These studies are not granular and do not report if they describe co-infection at presentation or the development of superinfection, limiting the ability to ascertain the reasons for antibiotic use.*

Data reporting co-infection in patients presenting with COVID-19 for care is sparse. *Rawson and colleagues reviewed 18 studies of human coronavirus infections reporting co-infections, of which nine were COVID-19 [178]. These cumulatively reported a bacterial and fungal co-infection rate of 8% (62/806). The studies evaluated were heterogeneous. One brief report of 393 patients in New York reported a bacteremia rate of 5.6%, which varied significantly between patients receiving invasive mechanical ventilation (15/126 [11.9%]) and those who were not (4/222 [1.8%]) [179]. Another study looked at 88,201 blood cultures performed during March 2020 in New York, comparing order volume, positivity, and etiologies between patients with COVID-19 and others during the time period [180]. The study found a significantly lower rate of bacteremia in COVID-19 patients (3.8%) than either COVID-19 negative (8%) or untested (7.1%) (p<0.001). When commensal skin organisms were excluded, the positivity rate in COVID-19 patients was 1.6% [180]. A study in Texas reviewed the use of antibiotics and incidence of co-infections in 147 PCR-positive COVID-19 patients [181]. Eighty-seven (59%) patients received empiric antibiotics, though none of the 47 (32%) patients with respiratory cultures had positive results. 112 patients (76%) had blood cultures collected also, and while nine were positive, eight of those were considered contaminants [181].*

The apparent discordance between bacterial and fungal co-infection in patients with COVID-19 at presentation and the use of antibacterial therapy has potential negative effects, namely in antimicrobial resistance. *Publications report on patients with severe and critical COVID-19 patients treated with immunomodulatory therapies, including corticosteroids, IL-6 antagonists, IL-1 antagonists, and others [182]. In one preprint examining outcomes in a cohort of 154 patients receiving invasive mechanically ventilation, mortality was reduced in patients treated with tocilizumab (IPTW-adjusted model, HR 0.55; 95% CI 0.33, 0.90); however, superinfections were more commonly reported (54% vs 26%, p<0.001), primarily due to ventilator-associated pneumonia [183].* ***Initiating and continuing empiric antibiotics at the time of admission may lead to superinfections that are antibiotic resistant*** *[184].*

References

1. Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020.
142. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020; 395(10223): 507-13.McCreary EK, Pogue JM. Coronavirus Disease 2019 Treatment: A Review of Early and Emerging Options. Open Forum Infect Dis 2020; 7(4): ofaa105.
175. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395(10229): 1054-62.
176. Rojo JMC, Santos JMA, Núñez-Cortés JM, et al. Clinical characteristics of patients hospitalized with COVID-19 in Spain: results from the SEMI-COVID-19 Network. medRxiv 2020.
177. Argenziano MG, Bruce SL, Slater CL, et al. Characterization and clinical course of 1000 Patients with COVID-19 in New York: retrospective case series. medRxiv 2020.
178. Rawson TM, Moore LSP, Zhu N, et al. Bacterial and fungal co-infection in individuals with coronavirus: A rapid review to support COVID-19 antimicrobial prescribing. Clin Infect Dis 2020.
179. Goyal P, Choi JJ, Pinheiro LC, et al. Clinical Characteristics of Covid-19 in New York City. N Engl J Med 2020; 382(24): 2372-4.
180. Sepulveda J, Westblade LF, Whittier S, et al. Bacteremia and Blood Culture Utilization during COVID-19 Surge in New York City. Journal of clinical microbiology 2020; 58(8).

181. Wei W, Ortwine JK, Mang NS, Joseph C, Hall BC, Prokesch BC. Limited Role for Antibiotics in COVID-19: Scarce Evidence of Bacterial Coinfection. Available at SSRN 3622388 2020.McCreary EK, Pogue JM. Coronavirus Disease 2019 Treatment: A Review of Early and Emerging Options. Open Forum Infect Dis 2020; 7(4): ofaa105.
182. McCreary EK, Pogue JM. Coronavirus Disease 2019 Treatment: A Review of Early and Emerging Options. Open Forum Infect Dis 2020; 7(4): ofaa105.
183. Somers EC, Eschenauer GA, Troost JP, et al. Tocilizumab for treatment of mechanically ventilated patients with COVID-19. Clin Infect Dis 2020.
184. 184. Clancy CJ, Nguyen MH. COVID-19, superinfections and antimicrobial development: What can we expect? Clin Infect Dis 2020.

18.22.7 World health organization (WHO)

(https://www.who.int/publications/i/item/home-care-for-patients-with-suspected-novel-coronavirus-(ncov)-infection-presenting-with-mild-symptoms-and-management-of-contacts)

WHO only recommends treating individuals with mild to moderate symptoms at home and do not consider anticoagulants (nor oxygen or corticosteroids), only symptomatic treatment as antipyretics and antibiotics (does not recommend prophylactic antibiotics).

18.23 Domus medica - ACHG. Best Evidence Topic Report18

“Wat is de meerwaarde van antibiotica voor het vermijden van hospitalisatie bij patiënten met een COVID-19 infectie? Wanneer opstarten?”

BestBET search date: March 20th 2020

https://cdn.nimbu.io/s/1kphvhi/assets/1586331998334/18_BestBET_Antibiotica_finale%20versie.pdf

- Bij gebrek aan voldoende studies werden ook studies die betrekking hadden op infecties met SARS-CoV geïncludeerd.
- De incidentie van bacteriële surinfectie was zeer uiteenlopend van 1%-23%, waarbij wel vooral atypische kiemen werden geobserveerd.
- De meeste patiënten die gehospitaliseerd werden kregen ook antibiotica voor de preventie en behandeling van bacteriële surinfectie.
- De enige Europese studie, betreffende behandeling met azithromycine en hydroxychloroquine, een kleine niet geblindeerde RCT, observeerde een gunstige evolutie die sneller verliep bij associatie van azithromycine in vergelijking met monotherapie in vorm van hydroxychloroquine.
- Het voorschrijven van (hydroxy)chloroquine in de ambulante setting wordt echter door de Belgische gezondheidsinstanties afgeraden om de beperkte voorraad beschikbaar te kunnen stellen voor gehospitaliseerde patiënten.
- De richtlijnen van de WHO, NHG en Domus medica zijn het er unaniem over eens dat het gebruik van antibiotica niet geïndiceerd is bij COVID-19 in de ambulante praktijk, ook al worden die in een ziekenhuissetting ter preventie/behandeling van surinfectie wel frequent gebruikt.
- A more recent synthesis document (unpublished on December 3rd, 2020) states that (Over de thuis opvolging en behandeling van COVID-19 patiëntenv2.docx):
    - Er zijn géén aanwijzingen dat het (profylactisch) gebruik van antibiotica bij COVID-19 patiënten met milde of matige symptomen het risico op hospitalisatie vermindert.
    - In principe is er geen plaats voor het toedienen van antibiotica in de behandeling van COVID-19 patiënten met milde symptomen thuis, behalve bij vermoeden van bacteriële surinfectie. Patiënten met een vermoeden van community acquired bacteriële pneumonie worden volgens gangbare richtlijnen behandeld

19 BIBLIOGRAPHY

[1] Armocida B, Formenti B, Ussai S, Palestra F, Missoni E. The Italian health system and the COVID-19 challenge. Lancet Public Health. 2020 May;5(5):e253.

[2] Legido-Quigley H, Mateos-Garcia JT, Campos VR, Gea-Sanchez M, Muntaner C, McKee M. The resilience of the Spanish health system against the COVID-19 pandemic. Lancet Public Health. 2020 May;5(5):e251-e2.

[3] World Health Organization. Home care for patients with suspected or confirmed COVID-19 and management of their contacts: interim guidance; 2020.

[4] Munn Z, Twaddle S, Service D, Harrow E, Okwen PM, Schünemann H, et al. Developing Guidelines Before, During, and After the COVID-19 Pandemic. Ann Intern Med. 2020 Dec 15;173(12):1012-4.

[5] World Health Organization. Clinical Management of COVID-19. Interim guidance. 27 May 2020. WHO reference number: WHO/2019-nCoV/clinical/2020.5 (https://www.who.int/publications/i/item/clinical-management-of-covid-19); 2020.

[6] NHS. Pulse oximetry to detect early deterioration of patients with COVID-19 in primary and community care settings. 2021 12/01/2021 [cited 25/01/2021]; Available from: https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2020/06/C0445-remote-monitoring-in-primary-care-jan-2021-v1.1.pdf

[7] NIH. Clinical Spectrum of SARS-CoV-2 Infection. 2020 17/12/2020 [cited 25/01/2021]; Available from: https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/

[8] Haute Autorité de Santé. Réponses rapides dans le cadre de la Covid-19 – Prise en charge à domicile des patients atteints de la Covid-19 et requérant une oxygénothérapie: HAS; 2020 Novembre 2020.

[9] Academisch Centrum Huisartsgeneeskunde. ACHG synthese nota: Thuisopvolging en behandeling van COVID-19-patiënten. 2021 [cited November 2020 (early version)]; Available from: https://www.domusmedica.be/actueel/achg-synthese-nota-thuisopvolging-en-behandeling-van-covid-19-patienten

[10] Academisch Centrum Huisartsgeneeskunde. Covid: klinische vragen die beantwoord kunnen worden met de BestBET methodologie. 2020 [cited November 2020]; Available from: https://www.achg.be/covid-19-01/vraag-en-antwoord

[11] Blazey-Martin D, Barnhart E, Gillis J, Jr., Vazquez GA. Primary Care Population Management for COVID-19 Patients. J Gen Intern Med. 2020 Oct;35(10):3077-80.

[12] Greenhalgh T, Thompson P, Weiringa S, Neves AL, Husain L, Dunlop M, et al. What items should be included in an early warning score for remote assessment of suspected COVID-19? qualitative and Delphi study. BMJ open. 2020 Nov 12;10(11):e042626.

[13] Oversteyns H, Oosterboos L, Nys B, Bekkering T, Verbakel J, Degryse J. Best Evidence Topic Report 20: Kan een sjabloon voor een teleconsult voor triage van patiënten met een mogelijke COVID-19 infectie ontworpen worden (flow-chart), wat wordt bevraagd en wanneer moet patiënt toch gezien worden? . Leuven: KULeuven; 2020 March 2020.

[14] Wouters A-S, Wierinck K, De Lepeleire J, Schoenmakers B. Best Evidence Topic Report: Which factors can help clinicians when to hospitalize patients infected with COVID-19?: Academisch Centrum Huisartsgeneeskunde; 2020.

[15] Michielsen L, Merckx C, Van Nuland M. Best Evidence Topic Report : Welke parameters worden best opgevolgd bij het monitoren van patiënten met een matig ernstige Covid-19 infectie? Leuven: KULeuven; 2020 18/03/2020.

[16] Collins JA, Rudenski A, Gibson J, Howard L, O'Driscoll R. Relating oxygen partial pressure, saturation and content: the haemoglobin-oxygen dissociation curve. Breathe (Sheff). 2015 Sep;11(3):194-201.

[17] Bossaert LL, Demey HE, De Jongh R, Heytens L. Haemodynamic monitoring. Problems, pitfalls and practical solutions. Drugs. 1991 Jun;41(6):857-74.

[18] Potter VA. Pulse oximetry in general practice: how would a pulse oximeter influence patient management? Eur J Gen Pract. 2007;13(4):216-20.

[19] Sardesai I, Grover J, Garg M, Nanayakkara PWB, Di Somma S, Paladino L, et al. Short Term Home Oxygen Therapy for COVID-19 patients: The COVID-HOT algorithm. J Family Med Prim Care. 2020 Jul;9(7):3209-19.

[20] Chorin E, Padegimas A, Havakuk O, Birati EY, Shacham Y, Milman A, et al. Assessment of Respiratory Distress by the Roth Score. Clin Cardiol. 2016 Nov;39(11):636-9.

[21] The Centre for Evidence-Based Medicine. Evidence Service to support the COVID-19 response. Are there any evidence-based ways of assessing dyspnoea (breathlessness) by telephone or video?. 2020 [cited; Available from: https://www.cebm.net/covid-19/are-there-any-evidence-based-ways-of-assessing-dyspnoea-breathlessness-by-telephone-or-video/

[22] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020 Mar 28;395(10229):1054-62.

[23] Tobin MJ, Laghi F, Jubran A. Why COVID-19 Silent Hypoxemia Is Baffling to Physicians. Am J Respir Crit Care Med. 2020 Aug 1;202(3):356-60.

[24] Gattinoni L, Chiumello D, Caironi P, Busana M, Romitti F, Brazzi L, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? Intensive care medicine. 2020 Jun;46(6):1099-102.

[25] Yao W, Wang T, Jiang B, Gao F, Wang L, Zheng H, et al. Emergency tracheal intubation in 202 patients with COVID-19 in Wuhan, China: lessons learnt and international expert recommendations. Br J Anaesth. 2020 Jul;125(1):e28-e37.

[26] O'Driscoll BR, Howard LS, Earis J, Mak V. British Thoracic Society Guideline for oxygen use in adults in healthcare and emergency settings. BMJ open respiratory research. 2017;4(1):e000170.

[27] Galwankar SC, Paladino L, Gaieski DF, Nanayakkara K, Somma SD, Grover J, et al. Management Algorithm for Subclinical Hypoxemia in Coronavirus Disease-2019 Patients: Intercepting the "Silent Killer". J Emerg Trauma Shock. 2020 Apr-Jun;13(2):110-3.

[28] Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, et al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med. 2019 Oct 1;200(7):e45-e67.

[29] Hardinge M, Annandale J, Bourne S, Cooper B, Evans A, Freeman D, et al. British Thoracic Society guidelines for home oxygen use in adults. Thorax. 2015 Jun;70 Suppl 1:i1-43.

[30] Majumdar SR, Eurich DT, Gamble JM, Senthilselvan A, Marrie TJ. Oxygen saturations less than 92% are associated with major adverse events in outpatients with pneumonia: a population-based cohort study. Clin Infect Dis. 2011 Feb 1;52(3):325-31.

[31] Bewick T, Greenwood S, Lim WS. What is the role of pulse oximetry in the assessment of patients with community-acquired pneumonia in primary care? Primary care respiratory journal : journal of the General Practice Airways Group. 2010 Dec;19(4):378-82.

[32] Shah S, Majmudar K, Stein A, Gupta N, Suppes S, Karamanis M, et al. Novel Use of Home Pulse Oximetry Monitoring in COVID-19 Patients Discharged From the Emergency Department Identifies Need for Hospitalization. Acad Emerg Med. 2020 Jun 17.

[33] Xie J, Covassin N, Fan Z, Singh P, Gao W, Li G, et al. Association Between Hypoxemia and Mortality in Patients With COVID-19. Mayo Clin Proc. 2020 Jun;95(6):1138-47.

[34] Akhavan AR, Habboushe JP, Gulati R, Iheagwara O, Watterson J, Thomas S, et al. Risk Stratification of COVID-19 Patients Using Ambulatory Oxygen Saturation in the Emergency Department. The western journal of emergency medicine. 2020 Sep 24;21(6):5-14.

[35] Blair PWB, Diane.; Jang, Minyoung.; Antar, Annukka A.R.; Keruly, Jeanne C.; Bachu, Vismaya S.; Townsend, Jennifer L.; Tornheim, Jeffrey.; Keller, Sara C.; Sauer, Lauren.;

Thomas, David L.; Manabe, Yukari C. . The clinical course of COVID-19 in the outpatient setting: a prospective cohort study. 2020.

[36] Douillet D, Mahieu R, Boiveau V, Vandamme YM, Armand A, Morin F, et al. Outpatient management or hospitalization of patients with proven or suspected SARS-CoV-2 infection: the HOME-CoV rule. Intern Emerg Med. 2020 Nov;15(8):1525-31.

[37] Brill SE, Wedzicha JA. Oxygen therapy in acute exacerbations of chronic obstructive pulmonary disease. International journal of chronic obstructive pulmonary disease. 2014;9:1241-52.

[38] Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med. 1997 Jan 23;336(4):243-50.

[39] Lim WS, van der Eerden MM, Laing R, Boersma WG, Karalus N, Town GI, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax. 2003 May;58(5):377-82.

[40] Metlay JP, Waterer GW. Update in adult community-acquired pneumonia: key points from the new American Thoracic Society/Infectious Diseases Society of America 2019 guideline. Curr Opin Pulm Med. 2020 May;26(3):203-7.

[41] Aujesky D, Auble TE, Yealy DM, Stone RA, Obrosky DS, Meehan TP, et al. Prospective comparison of three validated prediction rules for prognosis in community-acquired pneumonia. Am J Med. 2005 Apr;118(4):384-92.

[42] Charles PG, Wolfe R, Whitby M, Fine MJ, Fuller AJ, Stirling R, et al. SMART-COP: a tool for predicting the need for intensive respiratory or vasopressor support in community-acquired pneumonia. Clin Infect Dis. 2008 Aug 1;47(3):375-84.

[43] Bahl A, Van Baalen MN, Ortiz L, Chen NW, Todd C, Milad M, et al. Early predictors of in-hospital mortality in patients with COVID-19 in a large American cohort. Intern Emerg Med. 2020 Nov;15(8):1485-99.

[44] Smith GB, Prytherch DR, Meredith P, Schmidt PE, Featherstone PI. The ability of the National Early Warning Score (NEWS) to discriminate patients at risk of early cardiac arrest, unanticipated intensive care unit admission, and death. Resuscitation. 2013 Apr;84(4):465-70.

[45] Carr E, Bendayan R. Evaluation and Improvement of the National Early Warning Score (NEWS2) for COVID-19: a multi-hospital study. medRxiv preprint doi: https://doiorg/101101/2020042420078006; this version posted September 30, 2020.

[46] NIH. COVID-19 Treatment Guidelines: Hemodynamics. Last updated, October 9: 2020. [cited; Available from: https://www.covid19treatmentguidelines.nih.gov/critical-care/hemodynamics/

[47] Alhazzani W, Moller MH, Arabi YM, Loeb M, Gong MN, Fan E, et al. Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19). Crit Care Med. 2020 Jun;48(6):e440-e69.

[48] Kariyanna PT, Sutarjono B, Grewal E, Singh KP, Aurora L, Smith L, et al. A Systematic Review of COVID-19 and Myocarditis. American journal of medical case reports. 2020;8(9):299-305.

[49] Kochi AN, Tagliari AP, Forleo GB, Fassini GM, Tondo C. Cardiac and arrhythmic complications in patients with COVID-19. Journal of cardiovascular electrophysiology. 2020 May;31(5):1003-8.

[50] Royal College of Physicians. National Early Warning Score (NEWS) 2. 2017 19/12/2017 [cited 25/01/2021]; Working Party Report]. Available from: https://www.rcplondon.ac.uk/projects/outputs/national-early-warning-score-news-2

[51] Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA. 2020 May 26;323(20):2052-9.

[52] Ng JH, Hirsch JS, Wanchoo R, Sachdeva M, Sakhiya V, Hong S, et al. Outcomes of patients with end-stage kidney disease hospitalized with COVID-19. Kidney Int. 2020 Aug 15.

[53] Losy J. SARS-CoV-2 Infection: Symptoms of the Nervous System and Implications for Therapy in Neurological Disorders. Neurology and therapy. 2020 Nov 23.

[54] Evans TW, Smithies M. ABC of intensive care: organ dysfunction. BMJ (Clinical research ed). 1999 Jun 12;318(7198):1606-9.

[55] Eltzschig HK, Carmeliet P. Hypoxia and inflammation. N Engl J Med. 2011 Feb 17;364(7):656-65.

[56] Alqahtani JS, Oyelade T, Aldhahir AM, Alghamdi SM, Almehmadi M, Alqahtani AS, et al. Prevalence, Severity and Mortality associated with COPD and Smoking in patients with COVID-19: A Rapid Systematic Review and Meta-Analysis. PloS one. 2020;15(5):e0233147.

[57] Vultaggio A, Vivarelli E, Virgili G, Lucenteforte E, Bartoloni A, Nozzoli C, et al. Prompt Predicting of Early Clinical Deterioration of Moderate-to-Severe COVID-19 Patients: Usefulness of a Combined Score Using IL-6 in a Preliminary Study. J Allergy Clin Immunol Pract. 2020 Sep;8(8):2575-81 e2.

[58] Rice TW, Wheeler AP, Bernard GR, Hayden DL, Schoenfeld DA, Ware LB. Comparison of the SpO2/FIO2 ratio and the PaO2/FIO2 ratio in patients with acute lung injury or ARDS. Chest. 2007 Aug;132(2):410-7.

[59] Bazuaye EA, Stone TN, Corris PA, Gibson GJ. Variability of inspired oxygen concentration with nasal cannulas. Thorax. 1992 Aug;47(8):609-11.

[60] McNally M, Curtain J, O'Brien KK, Dimitrov BD, Fahey T. Validity of British Thoracic Society guidance (the CRB-65 rule) for predicting the severity of pneumonia in general practice: systematic review and meta-analysis. The British journal of general practice : the journal of the Royal College of General Practitioners. 2010 Oct;60(579):e423-33.

[61] Lacey J, Corbett J, Forni L, Hooper L, Hughes F, Minto G, et al. A multidisciplinary consensus on dehydration: definitions, diagnostic methods and clinical implications. Annals of medicine. 2019 May-Jun;51(3-4):232-51.

[62] El-Sharkawy AM, Sahota O, Lobo DN. Acute and chronic effects of hydration status on health. Nutrition reviews. 2015 Sep;73 Suppl 2:97-109.

[63] Van Goethem N, Vilain A, Wyndham-Thomas C, Deblonde J, Bossuyt N, Lernout T, et al. Rapid establishment of a national surveillance of COVID-19 hospitalizations in Belgium. Archives of public health = Archives belges de sante publique. 2020 Nov 18;78(1):121.

[64] Van Beckhoven D, Duysburgh E, Montourcy M, De Rouck M, Vilain A, Catteau L, et al. Points clés de la surveillance des patients hospitalisés atteints d'une infection COVID-19 confirmée: Résultats jusqu'au 14 juin 2020. Bruxelles, Belgique, : Sciensano; 2020.

[65] De Mol W, Galouchka M, Vermandere M. Best Evidence Topic Report: Which groups are at higher risk for complications caused by COVID-19?: Academisch Centrum HuisartsGeneeskunde; 2020.

[66] Superior Health Council. Vaccination strategy against COVID-19 in Belgium. Brussels: Federal Public Service Health, Food Chain Safety and Environment; 2020 July 2020.

[67] Medscape Drugs and Disease. Symptoms and Management of Coronavirus Disease 2019 FAQ: Who is at risk for severe coronavirus disease 2019? 2020 [cited 2020 10-12-2020]; Available from: https://emedicine.medscape.com/article/2500122-overview#a4

[68] Mayo Clinic Staff. COVID-19: Who's at higher risk of serious symptoms? 2020 [cited; Available from: https://www.mayoclinic.org/diseases-conditions/coronavirus/in-depth/coronavirus-who-is-at-risk/art-20483301

[69] COVID-19 Scientific Advisory Group. Rapid Evidence Report: What risk factors (such as age, medical conditions, or lifestyle factors) are associated with the development of severe outcomes in COVID-19?: Alberta Health Service; 2020.

[70] Rijksinstituut voor Volksgezondheid en Milieu. COVID-19 Richtlijn. Richtlijnen en draaiboeken 2020 [cited 2020 01-12-2020]; Available from: https://lci.rivm.nl/richtlijnen/covid-19

[71] Haut Conseil de la Santé Publique. Avis du 29-10-2020 relatif à l'actualisation de la liste des facteurs de risque de forme grave de Covid-19. Paris: HCSP; 2020.

[72] Centers for Disease Control and Prevention. COVID-19: People with Certain Medical Conditions. 2020 [cited 2020 10-12-2020]; Available from: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fneed-extra-precautions%2Fgroups-at-higher-risk.html

[73] BMJ Best Practice. Coronavirus disease 2019: Risk factors. 2020 [cited 2020 10-12-2020]; Available from: https://bestpractice.bmj.com/topics/en-gb/3000201/epidemiology

[74] European Center for Disease Prevention and Cntrol. COVID-19: latest evidence: Risk factors and risk groups. 2020 [cited 2020 01-12-2020]; Available from: https://www.ecdc.europa.eu/en/covid-19/latest-evidence/epidemiology

[75] Norwegian Institute of Public Health. COVID-19 and risk factors for hospital admission, severe disease and death - a rapid review, 3rd update. 2020 [cited 2020 01-12-2020]; Available from: https://www.fhi.no/en/publ/2020/COVID19-and-risk-factors-for-hospital-admission-severe-disease-and-death-3rd_update/

[76] Domus Medica. Welke patiëntengroepen lopen een hoger risico op complicaties veroorzaakt door COVID-19? Coronavirus 2020 [cited 25/01/2021]; Available from: https://www.domusmedica.be/richtlijnen/coronavirus/wetenschappelijk/welke-patientengroepen-lopen-een-hoger-risico-op

[77] Academisch Centrum Huisartsgeneeskunde. Welke patiëntengroepen lopen een hoger risico op complicaties veroorzaakt door COVID-19? 2020 [cited 25/01/2021]; Available from: https://www.achg.be/covid-19-01/vraag-en-antwoord#complicaties

[78] Lisker G, Narasimhan M, Greenberg H, Ramdeo R, McGinn T. Ambulatory Management of Moderate to High Risk COVID-19 Patients: The Coronavirus Related Outpatient Work Navigators (CROWN) Protocol. Home Health Care Management & Practice. 2020;0(0):5.

[79] Borgen I, Romney MC, Redwood N, Delgado B, Alea P, George BH, et al. From Hospital to Home: An Intensive Transitional Care Management Intervention for Patients with COVID-19. Popul Health Manag. 2020 Oct 14.

[80] Sagar A, Gottridge J, LaVine N. Practical Tips for Ambulatory Care in COVID-19: Lessons Learned in a New York Health System. Am J Med Qual. 2020 Sep 8:1062860620954273.

[81] Sartor Z, Hess B. Increasing the Signal-to-Noise Ratio: COVID-19 Clinical Synopsis for Outpatient Providers. J Prim Care Community Health. 2020 Jan-Dec;11:2150132720922957.

[82] FAGG. Goed gebruik van zuurstof bij COVID-19 patiënten na ontslag uit het ziekenhuis of verblijvende inwoonzorgcentra. 2020, May 15 [cited; Available from: https://covid-19.sciensano.be/sites/default/files/Covid19/COVID-19_Goed_gebruik_van_O2_ziekenhuisontslag_en_zorgcentra_NL.pdf

[83] AFMPS. Bonne utilisation de l'oxygène chez les patients COVID-19 après leur sortie de l'hôpital ou résidant dans une maison de repos et de soins. 2020, May 15 [cited; Available from: https://covid-19.sciensano.be/sites/default/files/Covid19/COVID-19_Bonne_utilisation_oxygene_sortieHopital_et_MRS_FR.pdf

[84] FAGG. Coronavirus: maatregelen van het FAGG en de betrokken stakeholders om de bevoorrading van zuurstof te blijven garanderen. 2020, April 10. [cited; Available from: https://www.fagg.be/nl/news/coronavirus_maatregelen_van_het_fagg_en_de_betrokken_stakeholders_om_de_bevoorrading_van

[85] AFMPS. Coronavirus : mesures prises par l'AFMPS et les partenaires concernés pour continuer à garantir l'approvisionnement en oxygène. . 2020, April 10. [cited; Available from:

https://www.afmps.be/fr/news/coronavirus_mesures_prises_par_lafmps_et_les_partenaires_concernes_pour_continuer_a_garantir

[86] APB. Wetenschappelijke vragen en aanbevelingen - Coronavirus (COVID-19): Zuurstof: maatregelen, richtlijnen en communicatie. 2020 [cited; Available from: https://www.apb.be/nl/corp/volksgezondheid/Info-Corona/Wetenschappelijke-vragen-en-aanbevelingen/Pages/Zuurstof-maatregelen,-richtlijnen-en-communicatie.aspx

[87] APB. Recommandations & questions scientifiques - Coronavirus (COVID-19): Oxygène: mesures, recommandations et communication. 2020 [cited; Available from: https://www.apb.be/fr/corp/sante-publique/Info-Corona/Recommandations-questions-scientifiques/Pages/oxygene.aspx

[88] FAGG. Aanpak voor respiratoire behandeling van gehospitaliseerde patiënten met COVID-19. 2020, May 15 [cited; Available from: https://covid-19.sciensano.be/sites/default/files/Covid19/COVID-19_Respiratoire_behandeling_ziekenhuizen_NL.pdf

[89] AFMPS. Prise en charge et traitement respiratoires pour les patients COVID-19 hospitalisés. 2020, May 15 [cited; Available from: https://covid-19.sciensano.be/sites/default/files/Covid19/COVID-19_Traitements_respiratoires_hopitaux_FR.pdf

[90] Faggion CM, Jr., Bakas NP, Wasiak J. A survey of prevalence of narrative and systematic reviews in five major medical journals. BMC Med Res Methodol. 2017 Dec 28;17(1):176.

[91] Pulse oximetry - UpToDate. [cited; Available from:

[92] Acute Respiratory Failure - Approach to the Patient. [cited; Available from:

[93] Luks AM, Swenson ER. Pulse Oximetry for Monitoring Patients with COVID-19 at Home. Potential Pitfalls and Practical Guidance. Ann Am Thorac Soc. 2020 Sep;17(9):1040-6.

[94] Health Center for Devices and Radiological. Pulse Oximeters - Premarket Notification Submissions [510(k)s]: Guidance for Industry and Food and Drug Administration Staff. US Food and Drug Administration 2020 Fri, 02/28/2020 - 14:07 [cited; Available from:

[95] Lipnick MS, Feiner JR, Au P, Bernstein M, Bickler PE. The Accuracy of 6 Inexpensive Pulse Oximeters Not Cleared by the Food and Drug Administration: The Possible Global Public Health Implications. Anesthesia & Analgesia. 2016 August 2016;123(2):338–45.

[96] Hudson AJ, Benjamin J, Jardeleza T, Bergstrom C, Cronin W, Mendoza M, et al. Clinical Interpretation of Peripheral Pulse Oximeters Labeled “Not for Medical Use”. Annals of Family Medicine. 2018 2018-11;16(6):552-4.

[97] Uchimura KD, Adamson TL, Karaniuk KM, Spano ML, La Belle JT. Feasibility of Commercially Marketed Health Devices for Potential Clinical Application. Critical Reviews in Biomedical Engineering. 2019 2019;47(2):159-67.

[98] Teo J. Early Detection of Silent Hypoxia in Covid-19 Pneumonia Using Smartphone Pulse Oximetry. J Med Syst. 2020 Jun 19;44(8):134.

[99] Greenhalgh T, Knight M, A’Court C, Buxton M, Husain L. Management of post-acute covid-19 in primary care. BMJ (Clinical research ed). 2020 2020/08/11;370:m3026.

[100] Louie A, Feiner JR, Bickler PE, Rhodes L, Bernstein M, Lucero J. Four Types of Pulse Oximeters Accurately Detect Hypoxia during Low Perfusion and Motion. Anesthesiology. 2018 03 2018;128(3):520-30.

[101] Angelucci A, Aliverti A. Telemonitoring systems for respiratory patients: technological aspects. Pulmonology. 2020 2020/07/01/;26(4):221-32.

[102] Barbosa MT, Sousa CS, Morais-Almeida M, Simões MJ, Mendes P. Telemedicine in COPD: An Overview by Topics. Copd. 2020 Oct;17(5):601-17.

[103] Baroi S, McNamara RJ, McKenzie DK, Gandevia S, Brodie MA. Advances in Remote Respiratory Assessments for People with Chronic Obstructive Pulmonary Disease: A

Systematic Review. Telemedicine journal and e-health : the official journal of the American Telemedicine Association. 2018 Jun;24(6):415-24.

[104] Blakey JD, Bender BG, Dima AL, Weinman J, Safioti G, Costello RW. Digital technologies and adherence in respiratory diseases: the road ahead. Eur Respir J. 2018 Nov;52(5).

[105] Buekers J, De Boever P, Vaes AW, Aerts JM, Wouters EFM, Spruit MA, et al. Oxygen saturation measurements in telemonitoring of patients with COPD: a systematic review. Expert review of respiratory medicine. 2018 Feb;12(2):113-23.

[106] Gaveikaite V, Grundstrom C, Winter S, Chouvarda I, Maglaveras N, Priori R. A systematic map and in-depth review of European telehealth interventions efficacy for chronic obstructive pulmonary disease. Respiratory medicine. 2019 Oct-Nov;158:78-88.

[107] McDowell G, Sumowski M, Toellner H, Karok S, O'Dwyer C, Hornsby J, et al. Two-way remote monitoring allows effective and realistic provision of home-NIV to COPD patients with persistent hypercapnia. medRxiv. 2020:2020.11.08.20227892.

[108] Rodriguez Hermosa JL, Fuster Gomila A, Puente Maestu L, Amado Diago CA, Callejas González FJ, Malo De Molina Ruiz R, et al. Compliance and Utility of a Smartphone App for the Detection of Exacerbations in Patients With Chronic Obstructive Pulmonary Disease: Cohort Study. JMIR Mhealth Uhealth. 2020 2020/3/19;8(3):e15699.

[109] Golinelli D, Boetto E, Carullo G, Nuzzolese AG, Landini MP, Fantini MP. Adoption of Digital Technologies in Health Care During the COVID-19 Pandemic: Systematic Review of Early Scientific Literature. Journal of medical Internet research. 2020 Nov 6;22(11):e22280.

[110] Hare N, Bansal P, Bajowala SS, Abramson SL, Chervinskiy S, Corriel R, et al. Work Group Report: COVID-19: Unmasking Telemedicine. J Allergy Clin Immunol Pract. 2020 Sep;8(8):2461-73.e3.

[111] Islam MM, Mahmud S, Muhammad LJ, Islam MR, Nooruddin S, Ayon SI. Wearable Technology to Assist the Patients Infected with Novel Coronavirus (COVID-19). SN Computer Science. 2020 2020/10/01;1(6):320.

[112] Iyengar K, Mabrouk A, Jain VK, Venkatesan A, Vaishya R. Learning opportunities from COVID-19 and future effects on health care system. Diabetes & metabolic syndrome. 2020 Sep-Oct;14(5):943-6.

[113] Watson AR, Wah R, Thamman R. The Value of Remote Monitoring for the COVID-19 Pandemic. Telemedicine and e-Health. 2020 2020/09/01;26(9):1110-2.

[114] Massaroni C, Nicolò A, Schena E, Sacchetti M. Remote Respiratory Monitoring in the Time of COVID-19. Frontiers in Physiology. 2020 2020-May-29;11(635).

[115] Michard F, Shelley K, L'Her E. COVID-19: Pulse oximeters in the spotlight. Journal of Clinical Monitoring and Computing. 2020 2020/06/23.

[116] Greenhalgh T, Kotze K, Van Der Westhuizen HM. Are there any evidence-based ways of assessing dyspnoea (breathlessness) by telephone or video? 2020 [cited; Available from: https://www.cebm.net/covid-19/are-there-any-evidence-based-ways-of-assessing-dyspnoea-breathlessness-by-telephone-or-video/

[117] Tarassenko L, Greenhalgh T. Can we use smartphones to measure oxygen saturation? Oxford COVID-19 Evidence Service Rapid Review. 2020.

[118] Whiting P, Elwenspoek M. Accuracy of self-monitoring heart rate, respiratory rate and oxygen saturation in patients with symptoms suggestive of COVID infection. Bristol: National Institute for Health Research 2020.

[119] Hutchings O, Dearing C, Jagers D, Shaw M, Raffan F, Jones A, et al. Virtual health care for community management of patients with COVID-19. medRxiv. 2020:2020.05.11.20082396.

[120] Miller DJ, Capodilupo JV, Lastella M, Sargent C, Roach GD, Lee VH, et al. Analyzing changes in respiratory rate to predict the risk of COVID-19 infection. medRxiv. 2020:2020.06.18.20131417.

[121] Anonymous. Elf ziekenhuizen volgen coronapatiënten vanop afstand via telemonitoring. Numericare. 2020.

[122] Anonymous. SafeLink – Covid19 – eMonitoring First Line. Een app voor thuismonitoring van covid-19-patiënten door de huisarts werd dit weekend met succes gelanceerd. 2020 [cited; Available from: https://brusselshealthnetwork.be/nl/safelink-covid19-emonitoring-first-line/

[123] Anonymous. Covid-19 : un nouvel outil web qui épaule les MG dans le suivi de leurs patients. 2020 [cited; Available from: https://brusselshealthnetwork.be/covid-19-un-nouvel-outil-web-qui-epaule-les-mg-dans-le-suivi-de-leurs-patients/

[124] Moens B. COVID-19 App voor triage & monitoring ondersteund door federale overheid! Digitale opvolging COVID symtomen. 2020 [cited; Available from: https://www.moveup.care/post/covid-19-applicatie-in-gebruik?lang=nl

[125] The Faktory. Covid19 eMonitoring First Line. Guide d'utilisation à destination des patients. Liège: FRATEM asbl 2020.

[126] Vandervoort P. ZOL volgt bijna herstelde COVID-19-patiënten op via telemonitoring. Zolarium. 2020;76:43.

[127] Vlaanderen Helemaal Digitaal. Optimalisatie triage COVID-19 & Remote monitoring Patiënten. 2020 [cited; Available from: https://www.vlaanderen.be/vlaanderen-helemaal-digitaal/aanbod/optimalisatie-triage-covid-19-remote-monitoring-patienten

[128] Agarwal P, Mukerji G, Laur C, Chandra S, Pimlott N, Heisey R, et al. COVIDCare@Home: Lessons from a Family Medicine Led Remote Monitoring Program. medRxiv. 2020:2020.07.20.20158386.

[129] University College Dublin. Home monitoring of respiration in Covid-19 patients using smartphone technology. 2020 [cited; Available from: https://www.ucd.ie/research/covid19response/news/homemonitoringofrespiration/

[130] Bruni T, Lalvani A, Richeldi L. Telemedicine-enabled Accelerated Discharge of Patients Hospitalized with COVID-19 to Isolation in Repurposed Hotel Rooms. Am J Respir Crit Care Med. 2020 Aug 15;202(4):508-10.

[131] Martínez-García M, Bal-Alvarado M, Santos Guerra F, Ares-Rico R, Suárez-Gil R, Rodríguez-Álvarez A, et al. Monitoring of COVID-19 patients via telemedicine with telemonitoring. Revista Clínica Española (English Edition). 2020 2020/11/01/;220(8):472-9.

[132] Grutters LA, Majoor KI, Mattern ESK, Hardeman JA, van Swol CFP, Vorselaars ADM. Home telemonitoring makes early hospital discharge of COVID-19 patients possible. Journal of the American Medical Informatics Association. 2020;27(11):1825-7.

[133] Maillette de Buy Wenniger L. Virtuele covid-19-afdeling ontlast zorg. Nederlands Tijdschrift voor Geneeskunde. 2020;164(C4722).

[134] Philips. Philips launches next generation wearable biosensor for early patient deterioration detection, including clinical surveillance for COVID-19. 2020 [cited; Available from: https://www.philips.com/a-w/about/news/archive/standard/news/press/2020/20200526-philips-launches-next-generation-wearable-biosensor-for-early-patient-deterioration-detection-including-clinical-surveillance-for-covid-19.html

[135] Silven AV, Petrus AHJ, Villalobos-Quesada M, Dirikgil E, Oerlemans CR, Landstra CP, et al. Telemonitoring for Patients With COVID-19: Recommendations for Design and Implementation. J Med Internet Res. 2020;22(9):e20953-e.

[136] Francis NA, Stuart B, Knight M, Vancheeswaran R, Oliver C, Willcox M, et al. Predictors of adverse outcome in patients with suspected COVID-19 managed in a 'virtual hospital' setting: a cohort study. medRxiv. 2020:2020.11.09.20228189.

[137] Knight M, Evans D, Vancheeswaran R, Van der Watt M, Newland Smith A, Oliver C, et al. A virtual hospital model can help tackle the covid-19 pandemic. Health Service Journal. 2020;april.

[138] Annis T, Pleasants S, Hultman G, Lindemann E, Thompson JA, Billecke S, et al. Rapid implementation of a COVID-19 remote patient monitoring program. Journal of the American Medical Informatics Association : JAMIA. 2020 Aug 1;27(8):1326-30.

[139] Gordon WJ, Henderson D, DeSharone A, Fisher HN, Judge J, Levine DM, et al. Remote Patient Monitoring Program for Hospital Discharged COVID-19 Patients. Appl Clin Inform. 2020 25.11.2020;11(05):792-801.

[140] Mayo Clinic. Remote monitoring of COVID-19 symptoms. Early prediction of aggressive COVID-19 progression and hospitalization. 2020 [cited; Available from: https://www.mayo.edu/research/remote-monitoring-covid19-symptoms/people-with-covid19

[141] Mishra T, Wang M, Metwally AA, Bogu GK, Brooks AW, Bahmani A, et al. Pre-symptomatic detection of COVID-19 from smartwatch data. Nature Biomedical Engineering. 2020 2020/12/01;4(12):1208-20.

[142] Morris A. Monitoring COVID-19 from hospital to home: First wearable device continuously tracks key symptoms. 2020 [cited; Available from: https://news.northwestern.edu/stories/2020/04/monitoring-covid-19-from-hospital-to-home-first-wearable-device-continuously-tracks-key-symptoms/

[143] Sitammagari K, Murphy S, Kowalkowski M, Chou S-H, Sullivan M, Taylor S, et al. Insights From Rapid Deployment of a "Virtual Hospital" as Standard Care During the COVID-19 Pandemic. Annals of Internal Medicine. 2020.

[144] Vindrola-Padros C, Singh KE, Sidhu MS, Georghiou T, Sherlaw-Johnson C, Tomini S, et al. Remote home monitoring (virtual wards) during the COVID-19 pandemic: a systematic review. medRxiv. 2020:2020.10.07.20208587.

[145] Fulop N, Vindrola-Padros C, Sidhu M, Sherlaw-Johnson C, Georghiou T, Tomini SM, et al. Rapid evaluation of remote home monitoring models during COVID-19 pandemic in England. Birmingham: National Institute for Health Research 2020.

[146] Vindrola-Padros C, Sidhu MS, Georghiou T, Sherlaw-Johnson C, Singh KE, Tomini SM, et al. The implementation of remote home monitoring models during the COVID-19 pandemic in England. medRxiv. 2020:2020.11.12.20230318.

[147] Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, et al. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020 Jun 16;75(23):2950-73.

[148] Haemostasis BSoTa. Anticoagulation management in COVID-19 positive patients-BSTH consensus guideline: BSTH; 2020.

[149] Flumignan R, Tinôco J, Pascoal P, Areias L, Cossi M, Fernandes M, et al. Prophylactic anticoagulants for people hospitalised with COVID-19 (Review). Cochrane Library. 2020(Issue 10. Art. No.: CD013739.).

[150] Malas MB, Naazie IN, Elsayed N, Mathlouthi A, Marmor R, Clary B. Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: A systematic review and meta-analysis. EClinicalMedicine. 2020 Dec;29:100639.

[151] Maldonado E, Tao D, Mackey K. Antithrombotic Therapies in COVID-19 Disease: a Systematic Review. J Gen Intern Med. 2020 Sep;35(9):2698-706.

[152] SFMV. Propositions de la Société Française de Médecine Vasculaire pour la prévention, le diagnostic et le traitement de la maladie thromboembolique veineuse des patients avec COVID 19 non hospitalisés. 2020 [cited; Available from: https://www.portailvasculaire.fr/sites/default/files/docs/propositions_sfmv_covid_mtev.pdf

[153] NHG. NHG-leidraad Stollingsafwijkingenbij COVID-19 voor de huisarts 2020 [cited; Available from: https://www.nhg.org/sites/default/files/content/nhg_org/uploads/nhg-leidraad_stollingsafwijkingen_bij_covid-19_voor_de_huisarts__0.pdf

[154] NIH. Antithrombotic Therapy in Patients with COVID-19. 2020 [cited 17/12/2020]; Available from: https://www.covid19treatmentguidelines.nih.gov/adjunctive-therapy/antithrombotic-therapy/

[155] Carmona LEO, Nielfa M, Alvarado ALD. The Covid-19 pandemic seen from the frontline. Int Braz J Urol. 2020 Jul;46(suppl.1):181-94.

[156] Cheng A, Caruso D, McDougall C. Outpatient Management of COVID-19: Rapid Evidence Review. Am Fam Physician. 2020 Oct 15;102(8):478-86.

[157] NIH. Oxygenation and Ventilation. 2020 [cited 17/12/2020]; Available from: https://www.covid19treatmentguidelines.nih.gov/critical-care/oxygenation-and-ventilation/

[158] NICE. COVID-19 rapid guideline: managing symptoms (including at the end of life) in the community. NICE Guideline 2020 13 October 2020 [cited; Available from: https://www.nice.org.uk/guidance/ng163

[159] NHG. Leidraad zuurstofgebruik THUIS bij (verdenking op / bewezen) COVID-19 2020 [cited; Available from: https://www.nhg.org/sites/default/files/content/nhg_org/uploads/050620_zuurstof_thuis_ten_tijde_van_corona_definitieve_versie_1.1_nvalt-nhg-pznl.pdf

[160] Yilmaz O, Yilmaz E. Supplemental oxygen in COVID-19: a friend or foe? Clin Med (Lond). 2020 Sep;20(5):e137.

[161] Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. N Engl J Med. 2020 Jul 9;383(2):120-8.

[162] Group RC, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. N Engl J Med. 2020 Jul 17.

[163] World Health Organization. Corticosteroids for COVID-19. 2020 [cited 02/09/2020]; Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1

[164] ISDA. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. 2020, November 4 2021, February 10 [cited; Available from: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/#toc-5

[165] NICE. COVID-19 prescribing briefing: corticosteroids. 2020 February 2021 [cited; Available from: https://www.nice.org.uk/guidance/ng159/resources/covid19-prescribing-briefing-corticosteroids-pdf-8839913581

[166] Gandhi RT, Lynch JB, Del Rio C. Mild or Moderate Covid-19. N Engl J Med. 2020 Oct 29;383(18):1757-66.

[167] NIH. COVID-19 Treatment Guidelines: Therapeutic Management of Adults With COVID-19. 2020 2021 February 11 [cited; Available from: https://www.covid19treatmentguidelines.nih.gov/therapeutic-management/

[168] SWAB. Medicamenteuze behandeling voor patiënten met COVID-19 (infectie met SARS–CoV-2). 2020 [cited; Available from: https://swab.nl/nl/covid-19

[169] AFMPS / FAGG SB, . Sciensano,. Interim Clinical Guidance for adults with suspected or confirmed COVID-10 in Belgium. 2020 2021 February 9 [cited; Available from: https://covid-19.sciensano.be/sites/default/files/Covid19/COVID-19_InterimGuidelines_Treatment_ENG.pdf

[170] NHG. Gebruik dexamethason bij COVID-19 in de eerste lijn 2020 [cited; Available from: https://www.nhg.org/sites/default/files/content/nhg_org/uploads/gebruik_dexamethason_bij_covid-19_in_de_eerste_lijn_.pdf

[171] Scarpignato C, Gatta L, Zullo A, Blandizzi C, Group S-A-F, Italian Society of Pharmacology tIAoHG, et al. Effective and safe proton pump inhibitor therapy in acid-related diseases - A position paper addressing benefits and potential harms of acid suppression. BMC Med. 2016 Nov 9;14(1):179.

[172] Kow CS, Hasan SS. Use of proton pump inhibitors and risk of adverse clinical outcomes from COVID-19: a meta-analysis. J Intern Med. 2020 Oct 20.

[173] Luxenburger H, Sturm L, Biever P, Rieg S, Duerschmied D, Schultheiss M, et al. Treatment with proton pump inhibitors increases the risk of secondary infections and ARDS in

hospitalized patients with COVID-19: coincidence or underestimated risk factor? J Intern Med. 2020 Jul 1.

[174] Lee SW, Ha EK, Yeniova AO, Moon SY, Kim SY, Koh HY, et al. Severe clinical outcomes of COVID-19 associated with proton pump inhibitors: a nationwide cohort study with propensity score matching. Gut. 2020 Jul 30.

[175] Dorlo TP, Jager NG, Beijnen JH, Schellens JH. [Concomitant use of proton pump inhibitors and systemic corticosteroids]. Ned Tijdschr Geneeskd. 2013;157(19):A5540.

[176] NHS GM, Mental Health,. Use of Dexamethasone in the treatment of COVID-19. 2020, July 7 [cited; Available from: https://www.gmmh.nhs.uk/download.cfm?doc=docm93jijm4n7645.pdf&ver=10221

[177] NHS WECCG. Proton Pump Inhibitors (PPIs)and corticosteroidsAdvisory guidance on when to initiate a PPIfor gastro-protection. 2019, Décember [cited; Available from: https://westessexccg.nhs.uk/your-health/medicines-optimisation-and-pharmacy/clinical-guidelines-and-prescribing-formularies/01-gastro-intestinal-system/3341-ppi-advisory-guidance-on-when-to-iniaite-with-corticosteroid-for-gastro-protection/file

[178] Yadlapati R, Kahrilas PJ. When is proton pump inhibitor use appropriate? BMC Med. 2017 Feb 21;15(1):36.

[179] Eck RJ, Bult W, Wetterslev J, Gans ROB, Meijer K, van der Horst ICC, et al. Low Dose Low-Molecular-Weight Heparin for Thrombosis Prophylaxis: Systematic Review with Meta-Analysis and Trial Sequential Analysis. J Clin Med. 2019 Nov 21;8(12).

[180] Eck RJ, Bult W, Wetterslev J, Gans ROB, Meijer K, Keus F, et al. Intermediate Dose Low-Molecular-Weight Heparin for Thrombosis Prophylaxis: Systematic Review with Meta-Analysis and Trial Sequential Analysis. Semin Thromb Hemost. 2019 Nov;45(8):810-24.

[181] Ladapo J.A.; McKinnon J.E. MPA, Risch H.A. . Randomized Controlled Trials of Early Ambulatory Hydroxychloroquine in the Prevention of COVID-19 Infection, Hospitalization, and Death: Meta-Analysis ; http://doi.org/10.1101/2020.09.30.20204693). 2020.

[182] Malik P, Patel U, Mehta D, Patel N, Kelkar R, Akrmah M, et al. Biomarkers and outcomes of COVID-19 hospitalisations: systematic review and meta-analysis. BMJ Evid Based Med. 2020 Sep 15.

[183] Wang L. C-reactive protein levels in the early stage of COVID-19. Med Mal Infect. 2020 Jun;50(4):332-4.

[184] WHO Rapid Evidence Appraisal for COVID-19 Therapies Working Group, Sterne JAC, Murthy S, Diaz JV, Slutsky AS, Villar J, et al. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. JAMA. 2020 Oct 6;324(13):1330-41.

Colophon

Title: Intensified home-management for worrisome COVID-19 adult patients

Authors: Pascale Jonckheer, Jean-Luc Belche, Diego Castanares-Zapatero, Gilles Henrard, Vicky Jespers, Chris De Laet, Patriek Mistiaen, Maxime Mouillet, Thomas Orban, Céline Ricour, Dominique Roberfroid

Facilitator Christophe Janssens, Els Van Bruystegem

Reviewers: Christophe Barbut, Paul De Munck, Stefan Heytens, Reinier Hueting, Greet Van Kersschaeve, Jan Verbakel, Johan Wens, Stefan Teughels

Conflict of Interest: Membership of a stakeholder group on which the results of this report could have an impact: Jean-Luc Belche (Team member Outreach Support Team - Liège-Ouest)

Participation in scientific or experimental research as an initiator, principal investigator or researcher: Gilles Henrard (KCE Trials report 17016 Blended Care)

Grants, fees or funds for a member of staff or another form of compensation for the execution of research described above: Gilles Henrard (Fondation Leon Fredericq, fund for research in GP)

Presidency or accountable function within an institution, association, department or other entity on which the results of this report could have an impact: Gilles Henrard (CEBAM administrator); Johan Wens (president PHA – Palliatieve Hulpverlening Antwerpen vzw)

At the request of: Collège de Médecine générale (CMG)

Acknowledgement: Koen Blot (Sciensano), Isabelle Dagneaux (CASU), Jan De Maeseneer (UGent), Jan Degryse (ACHG), Dirk Devroey (VUB), Germaine Hanquet (KCE), Greet Musch (AFMPS/FAGG), Fabrice Peters (CSS/HGR), Joachim Vandenhoven (CBIP/BCFI), Marcel Van der Auwera, Yves Van Laethem (CHU Saint-Pierre), Roel Van Loock (AFMPS/FAGG), Chloé Wyndham Thomas (Sciensano).

Disclaimer: This document is a rapid review of scientific literature retrieved from several publicly funded COVID-19 resource collections. The literature included in these repositories is not always peer-reviewed or externally validated. KCE synthesised the evidence in short time frames to respond to urgent questions and could therefore not follow its regular methodological procedures. This work is used to inform guidance of other governmental agencies (like Sciensano, CSS/HGR, AFMPS/FAGG and SPF/FOD).

Publication date: 10 March 2021

Legal depot: D/2021/10.2733/01

ISSN: 2684-5830