Clinical Synopsis of COVID-19

Evolving and Challenging

Hemanshu Prabhakar
Indu Kapoor
Charu Mahajan
Editors

Springer

Clinical Synopsis of COVID-19

Hemanshu Prabhakar • Indu Kapoor
Charu Mahajan
Editors

Clinical Synopsis of COVID-19

Evolving and Challenging

Springer

Editors
Hemanshu Prabhakar
Neuroanaesthesiology and Critical Care
All India Institute of Medical Sciences
New Delhi
India

Indu Kapoor
Neuroanaesthesiology and Critical Care
All India Institute of Medical Sciences
New Delhi
India

Charu Mahajan
Neuroanesthesiology and Critical Care
All India Institute of Medical Sciences
New Delhi
India

ISBN 978-981-15-8680-4 ISBN 978-981-15-8681-1 (eBook)
https://doi.org/10.1007/978-981-15-8681-1

This Springer imprint is published by the registered company Springer Nature Singapore Pte Ltd.
The registered company address is: 152 Beach Road, #21-01/04 Gateway East, Singapore 189721, Singapore

To the humankind who are navigating through this pandemic with all their strength and hope.

Preface

Coronavirus disease is the latest pandemic that has affected humans. The disease has manifested itself in several forms and is now the focus of research worldwide.

In this book, we have tried covering all clinical aspects of the coronavirus disease. The volume includes topics related to basic sciences, such as the virology and pathophysiology of the disease. Chapters related to the symptomatology of the disease and making diagnosis have been included. Chapters related to the preparation of the healthcare workers to deal with coronavirus disease have also been included. Anesthetic and intensive care management of coronavirus disease victims is of vast importance, and so chapters covering these issues have also been included. As this pandemic has taken many lives across the world, issues have been raised regarding disposal of bodies of the victims. Therefore, a chapter dealing with this issue has been included, which will throw light on ethical aspects. Special considerations have been given in a chapter to patient population such as geriatrics, pediatrics, and pregnant women.

The book will be useful for trainees and clinicians in any field of medicine. It would be very useful for residents and fellows pursuing their courses in emergency medicine, anesthesia, and critical care. Fellows, resident doctors, postgraduates, and even undergraduates would be benefited by this book. With contributions from renowned authors from across the globe, this book would be a ready reckoner in clinical practice of physicians from varied specialities.

New Delhi, India — Hemanshu Prabhakar
New Delhi, India — Indu Kapoor
New Delhi, India — Charu Mahajan

Acknowledgments

We wish to acknowledge the support and the administration of All India Institute of Medical Sciences (AIIMS), New Delhi (India), for allowing us to carry out this academic task.

We thank Professor Arvind Chaturvedi, Head of Department of Neuroanaesthesiology and Critical Care at AIIMS, New Delhi, for his support and encouragement. We also thank the staff in the department for their support.

Special thanks are due to the team at Springer Dr. Naren Aggarwal, Gaurav Singh, Saanthi Shankhararaman and all those involved in this project.

Hemanshu Prabhakar
Charu Mahajan
Indu Kapoor

Contents

About the Editors

Indu Kapoor is Associate Professor in the Department of Neuroanaesthesiology and Critical Care at All India Institute of Medical Sciences (AIIMS), New Delhi, India. She received her training in neuroanesthesia at the same institute. Dr. Kapoor has a special interest in evidence-based practice in neuroanesthesia. She has several publications in national and international journals to her credit and has written numerous chapters for various national and international books. She is also a reviewer of national and international journals and a review author for the Cochrane Collaboration. She is a recipient of many awards. Additionally, she is a member of various national societies and has been an invited faculty member at various national conferences. She is an editor of several books on the subject of neuroanesthesia and neurocritical care.

Charu Mahajan is Associate Professor in the Department of Neuroanaesthesiology and Critical Care at All India Institute of Medical Sciences (AIIMS), New Delhi, India. After completing MD in Anesthesia, she completed DM in neuroanesthesia at AIIMS and later joined AIIMS as a faculty member. She has over a decade of research experience and has received various awards for scientific presentations. She has several publications in various national and international journals, edited several books, and authored chapters in many books. She is a reviewer for the Cochrane Collaboration. Dr. Mahajan is also a member of various scientific societies and is a reviewer for several reputable scientific journals.

Hemanshu Prabhakar is a Professor in the Department of Neuroanaesthesiology and Critical Care at All India Institute of Medical Sciences (AIIMS), New Delhi, India. He received his training in neuroanesthesia and completed his PhD in the same institute. He is the first Indian to be awarded the degree of PhD in Neuroanesthesia in the country. He is a recipient of the AIIMS Excellence Award 2012 for his notable contribution to academia and has published over 250 papers in peer-reviewed national and international journals. Dr. Prabhakar is a reviewer for various national and international journals and is also a review author for the Cochrane Collaboration. He has special interest in evidence-based practice of neuroanesthesia. Dr. Prabhakar is a member of various national and international neuroanesthesia societies and is past secretary of the Indian Society of Neuroanesthesia

and Critical Care. He is an invited speaker for various national and international conferences. He is on the editorial board of the *Indian Journal of Palliative Care* and is the past executive editor of the *Journal of Neuroanaesthesiology and Critical Care*. He is the first Indian to publish international books in the speciality of neuroanesthesia. He is an active member of the SNACC (*Society of Neurosciences in Anesthesiology and Critical Care*), NCS (Neurocritical Care Society), and NACCS (Neuroanaesthesia and Critical Care Society of Great Britain and Ireland). He was featured in the Limca Book of Records 2019 for publishing several books on a niche subject.

Introduction: History of Coronavirus Disease Pandemic

1

Indu Kapoor, Hemanshu Prabhakar, and Charu Mahajan

Coronaviruses are group of ribonucleic acid [RNA] viruses that broadly infect vertebrates including humans, birds, bats, snakes, mice, and other wild animals [1]. To our interest, human coronaviruses are divided into four subgroups: alpha, beta, gamma, and delta. There are seven strains of coronavirus that may infect humans. The common human strains that produce mild symptoms include 229E [alpha], NL63 [alpha], OC43 [beta], and HKU1 [beta]. In humans, the common sign and symptoms include cough, sore throat, fever, muscle ache, and difficulty in breathing. Some patients even may present with uncommon symptoms like anosmia, chest pain, and stroke. The severity of these symptoms can vary from very mild to very lethal ones like, Middle East respiratory syndrome [MERS], severe acute respiratory syndrome [SARS], and coronavirus disease [COVID-19].

Virus: Coronaviruses are enveloped viruses who have a positive-sense single-stranded RNA genome and a nucleocapsid of helical symmetry [2]. The virus size ranges from 26 to 32 kilobases and is one of the largest virus among RNA viruses [3]. On their surface, they have club-shaped spikes, which in electron micrographs form an image reminiscent of the solar corona, from which their name derives [4]. The name of this virus is derived from Latin word "corona," which means "crown or wreath" [5]. This name "coronavirus" was first coined by June Almeida and David Tyrrell who first observed and studied human coronaviruses [6]. In an infected person, the viral spike protein in the virus attaches to host cell receptor, the virus particle is uncoated, and its genome enters the cell cytoplasm. A number of nonstructural proteins coalesce to form a multiprotein replicase-transcriptase complex (RTC). The main replicase-transcriptase protein is the RNA-dependent RNA polymerase (RdRp). The other nonstructural proteins assist in the replication and transcription process. The exoribonuclease nonstructural protein, for instance, provides

I. Kapoor (✉) · H. Prabhakar · C. Mahajan
Department of Neuroanaesthesiology and Critical Care, All India Institute of Medical Sciences, New Delhi, Delhi, India

H. Prabhakar et al. (eds.), *Clinical Synopsis of COVID-19*,
https://doi.org/10.1007/978-981-15-8681-1_1

extra fidelity to replication by providing a proofreading function which the RNA-dependent RNA polymerase lacks [7]. In humans, epithelial cells of the respiratory tract are mainly targeted by the coronavirus, while animal coronaviruses generally infect the epithelial cells of the digestive tract [8]. The main route of transmission from one host to another host, depending on the coronavirus species, is by either an aerosol, fomite, or fecal-oral route [9]. SARS coronavirusis transmitted via an aerosol route, [10] binds to the angiotensin-converting enzyme 2 receptor, and infect human epithelial cells of the lungs [11].

History: The family of coronavirus has been around us for a long time. Coronavirus was first identified in 1930, which was responsible for bronchitis in birds caused by infectious bronchitis virus [IBV] [12]. A decade later, in 1940s, two animal coronaviruses, mouse hepatitis virus (MHV) and transmissible gastroenteritis virus (TGEV), were isolated [13]. Researchers discovered evidence of human coronaviruses in the 1960. The virus B814s was isolated from the nose of a boy having common cold [14]. This isolated virus when inoculated into the nose of volunteers caused a cold and was inactivated by ether since it had a lipid envelope [14]. Meanwhile, another novel virus 229E was isolated, and like the virus B814, when inoculated in volunteers, it induced common cold and inactivated by ether [15]. Not only these two viruses were related to each other but were related to IBV also. The National Institutes of Health during the same time isolated another member of this new group of viruses, named OC43 [16]. All these viruses on electron microscope had distinctive club-like spikes [17]. This new group of viruses because of their distinctive morphological appearance is known as coronaviruses [13]. Since then other human coronaviruses were discovered which include SARS-CoV (2003), HCoV NL63 (2004), HCoV HKU1 (2005), MERS-CoV (2012), and SARS-CoV-2 (2019) [18, 19].

MERS-CoV was isolated from a patient in Saudi Arabia in 2012 [20]. It was responsible for 2494 cases and 858 deaths from 27 different countries (case-fatality rate: 34.4%) [21]. SARS-CoV was first recognized in China in 2003. It caused a total of 8422 probable SARS cases, 919 SARS-related deaths (case-fatality rate: 11%), and spread to 32 different countries or regions between November 2002 and August 2003 [22]. SARS-CoV-2 was also first recognized in China. Since December 2019 to date, the SARS-CoV-2 has infected many people around the world and caused significant number of deaths. The number of COVID-19 infected patients is increasing very fast around the world, although there is increase in number of recovered patients as well. The 2019 novel coronavirus lead to global pandemic, after the outbreak of disease from Wuhan, China. This disease is known as coronavirus disease-19 [COVID-19] caused by a virus now known as severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] [19]. At present there is no vaccine or treatment dedicated to treat COVID-19 patients. Although various drugs have been tested and with some trials are still going on, till date none of the medication has been proved to be beneficial in killing the virus or decreasing the mortality rate in coronavirus infected patients. The list of drugs which have been tried on patients with coronavirus disease includes antimalarial drugs, antiviral drugs like remdesivir, antibiotics like azithromycin, teicoplanin, corticosteroids, antiaging drugs like

doxycycline, antiparasitic drugs like ivermectin, immunoglobulins, and convalescent plasma. However, results with these drugs are not satisfactory. Worldwide scientists are doing research to invent the wonder drug as an antidote to defeat this crisis. At present we are lacking with a good-quality research on this disease. On literature search, most of the articles are either editorials, case reports, correspondences, review article, or case control or observational studies. One can also come across some randomized controlled trials including different interventions or drugs. Till date, none of the studies have shown a satisfactory result with significant clinical benefits to the COVID-19 patients. A well-designed, high-quality randomized clinical trial with good sample size is the need of hour in this pandemic to provide the world a clear direction toward a specific drug or intervention which can be used to treat COVID-19 patients.

References

1. Weiss SR, Leibowitz JL. Coronavirus pathogenesis. Adv Virus Res. 2011;81:85–164.
2. James C, Harrison GJD, Kaplan SL, Steinbach WJ, Hotez P. Feigin and Cherry's textbook of pediatric infectious diseases. 7th ed. San Diego: Elsevier; 2017. p. PT6615.
3. Woo PC, Huang Y, Lau SK, Yuen KY. Coronavirus genomics and bioinformatics analysis. Viruses. 2010;2:1804–20.
4. Almeida JD, Berry DM, Cunningham CH, Hamre D, Hofstad MS, Mallucci L, et al. Virology: coronaviruses. Nature. 1968;220:650.
5. Definition of coronavirus by Merriam-Webster. Merriam-Webster. Archived from the original on 2020-03-23. Accessed 24 March 2020.
6. Tyrrell DA, Fielder M. Cold wars: the fight against the common cold. 1st ed. Oxford: Oxford University Press; 2002. p. 96.
7. Sexton NR, Smith EC, Blanc H, Vignuzzi M, Peersen OB, Denison MR. Homology-Based identification of a mutation in the coronavirus RNA-dependent RNA Polymerase that confers resistance to multiple mutagens. J Virol. 2016;90:7415–28.
8. De Groot RJ, Baker SC, Baric R, Enjuanes L, Gorbalenya AE, Holmes KV, et al. Family Coronaviridae. In: King AM, Lefkowitz E, Adams MJ, Carstens EB, International Committee on Taxonomy of Viruses, International Union of Microbiological Societies, Virology Division, editors. Ninth report of the International Committee on Taxonomy of Viruses. Oxford: Elsevier; 2011. p. 806–28.
9. Decaro N, Tidona C, Darai G. Alphacoronavirus. The Springer index of viruses. New York: Springer; 2011. p. 371–83.
10. Decaro N, Tidona C, Darai G. Betacoronavirus. The Springer index of viruses. New York: Springer; 2011. p. 385–401.
11. Li F, Li W, Farzan M, Harrison SC. Structure of SARS coronavirus spike receptor-binding domain complexed with receptor. Science. 2005;309:186468.
12. Estola T. Coronaviruses, a new group of animal RNA viruses. Avian Dis. 1970;14:330–6.
13. McIntosh K. Coronaviruses: a comparative review. In: Arber W, Haas R, Henle W, Hofschneider PH, Jerne NK, Koldovský P, Koprowski H, Maaløe O, Rott R, editors. Current topics in microbiology and immunology/Ergebnisse der Mikrobiologie und Immunitätsforschung. Berlin: Springer; 1974. p. 87.
14. Kendall EJ, Bynoe ML, Tyrrell DA. Virus isolations from common colds occurring in a residential school. Br Med J. 1962;2:82–6.
15. Hamre D, Procknow JJ. A new virus isolated from the human respiratory tract. Proceedings of the Society for Experimental Biology and Medicine. Soc Exp Biol Med. 1966;121:190–3.

16. McIntosh K, Becker WB, Chanock RM. Growth in suckling-mouse brain of "IBV-like" viruses from patients with upper respiratory tract disease. Proc Natl Acad Sci U S A. 1967;58:2268–73.
17. McIntosh K, Dees JH, Becker WB, Kapikian AZ, Chanock RM. Recovery in tracheal organ cultures of novel viruses from patients with respiratory disease. Proc Natl Acad Sci U S A. 1967;57:933–40.
18. Su S, Wong G, Shi W, Liu J, Lai AC, Zhou J, et al. Epidemiology, s. Trends Microbiol. 2016;24:490–502.
19. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382:727–33.
20. Zaki AM. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N Engl J Med. 2012;367:1814–20.
21. World Health Organization. Middle East respiratory syndrome coronavirus (MERS-CoV). 30 Jan 2019. http://www.who.int/emergencies/mers-cov/en/ [cited Jan 30, 2020].
22. World Health Organization. Summary table of SARS cases by country, November 1, 2002-August 7, 2003. 2020. http://www.who.int/csr/sars/country/2003_08_15/en/.

Basic Virology and Pathophysiology of COVID-19

2

Vishwendra Singh, Ankur Luthra, Rajeev Chauhan, and Shyam C. Meena

Abbreviations

ACE	Angiotensin-converting enzyme
CoV	Coronavirus(es)
COVID	Coronavirus disease
E	Envelope protein
HCoV	Human coronavirus
IFN	Interferon
Ig	Immunoglobulin
IL	Interleukin
IRF	Interferon response factor
JAK-STAT	Janus kinase-signal transducer and activator of transcription
kDa	Kilodaltons
M	Membrane protein
M^{pro}	Main protease
MCP	Monocyte chemoattractant protein
MERS	Middle East respiratory syndrome
MHC	Major histocompatibility complex
N	Nucleocapsid protein
ORF	Open reading frame
PL^{pro}	Papain-like protease
PRR	Pattern recognition receptors
RdRp	RNA-dependent RNA polymerase
RNA	Ribonucleic acid

V. Singh
Department of Oral Health Sciences, GMCH Sector 32, Chandigarh, India

A. Luthra (✉) · R. Chauhan · S. C. Meena
Department of Anesthesia and Intensive Care, PGIMER, Chandigarh, India

H. Prabhakar et al. (eds.), *Clinical Synopsis of COVID-19*,
https://doi.org/10.1007/978-981-15-8681-1_2

S	Spike protein
SARS	Severe acute respiratory syndrome
STAT 1	Signal transducer and activator of transcription 1
TGF	Transforming growth factor
TLR	Toll-like receptors
TNF	Tumor necrosis factor
VLPs	Virus-like particles

2.1 Introduction

A hitherto unknown virus emerged in Wuhan, China, during late December, 2019. Since then it has spread globally and has taken numerous lives. It is a highly transmissible virus which can afflict apparently healthy individuals even with momentary contact. The virus responsible for the current pandemic is the severe acute respiratory syndrome virus (SARS-CoV-2), and the disease it causes is known as COVID-19. The disease can have serious manifestations like respiratory distress, severe dry cough, high-grade fever, and in some cases even death [1]. Coronaviruses measure approximately 125 nm in diameter and contain single-stranded positive sense RNA. "Spikes" (club-like projections) on their surface give them the name Corona (crown) [2]. They are mainly zoonotic (only four coronaviruses are known in humans) and can be found in bats, birds, cats, dogs, mice, pigs, horses, and whales. Since the start of the twenty-first century, fatal pneumonia has been caused by three coronaviruses—severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), and SARS-CoV-2. All these are understood to have crossed over from animals to humans [3]. The following sections deal with the basic virology and pathophysiology of SARS-CoV-2 in detail.

2.2 Classification

The International Committee on Taxonomy of Viruses is responsible for giving out classification of all known viruses. Coronaviruses have been identified to be in the *Coronaviridae* family of the order *Nidovirales*. In order for a virus to be classified under *Coronaviridae* family, it should have the following characteristics [4]:

1. Enveloped virions having large (15–20 nm) surface projections.
2. A helical nucleocapsid, made up of genome and several copies of a single basic phosphoprotein species.
3. An envelope having varying number of viral membrane proteins, at least two of which are the same (conserved) family-wide and are essential for virion morphogenesis and/or infectivity.
4. A 200–250-aa triple spanning N^{exo} C^{endo} integral membrane protein M.

5. A 1100–1600-aa class I fusion protein S which forms peplomers and is highly N-glycosylated.
6. A positive sense RNA, linear, unimolecular, infectious, 26–32 kb long, capped, polyadenylated, and structurally polycistronic genome.
7. Follows a 5′-UTR-replicase-S-M-N-UTR-3′ general genome organization with the genome acting as mRNA for replicase gene.
8. The replicase gene is made of overlapping open reading frames (ORFs) 1a and 1b which code for two huge polyproteins—pp1a and pp1ab. The synthesis of pp1ab should require a programmed 21 ribosomal frameshift, and both pp1a and pp1ab should be processed autoproteolytically.
9. Expression of the downstream ORF should be mediated by (−1) ribosomal frameshifting.
10. Virion assembly (morphogenesis) should take place through budding of preformed nucleocapsids of smooth intracellular membranes of endoplasmic reticulum/early Golgi compartments.

Coronaviridae has two subfamilies—*Coronavirinae* and *Torovirinae. Coronavirinae* has four genera: alpha (α), beta (β), gamma (Y), and delta (δ). α and β coronaviruses are known to infect only warm-blooded animals, while Y and δ coronaviruses mainly affect birds. Some Y and δ coronaviruses, however, are known to affect mammals [5]. The novel coronavirus (SARS-CoV-2) belongs to the subgenus *Sarbecovirus* of genus *Betacoronavirus* (Fig. 2.1).

2.3 Jump from Animals to Humans

Coronaviruses are mainly zoonotic and produce diseases in animals mostly. Coronaviruses were thought to be minor pathogens for humans that generally caused mild respiratory infections in otherwise healthy immunocompetent individuals. These infections usually passed off as common cold with the rare exceptions of severe illnesses in infants, young children, and the older population [6]. However, this understanding took a paradigm shift with the advent of the highly pathogenic severe acute respiratory syndrome (SARS) in 2002, which was caused by the severe acute respiratory syndrome coronavirus (SARS-CoV) [7]. Up until the novel coronavirus pandemic, only six known coronaviruses caused diseases in humans. These included HCoV-229E, HCoV-NL63, HCoV-OC43, HCoV-HKU1, SARSCoV, and Middle East respiratory syndrome coronavirus (MERS-CoV). These viruses along with their hosts and associated diseases are shown in Table 2.1. The novel coronavirus is the seventh coronavirus known to produce disease in humans.

Since coronaviruses are mainly localized to animals, the novel coronavirus is thought to have been transmitted from an animal host to humans. This “jump” is thought to have occurred via an intermediate host. Knowledge of this intermediate host is important in preventing further spread of the disease [8]. Based on codon usage, snakes were thought to be the possible source of the novel coronavirus [9]. However, it is now hypothesized that mammals or birds may be the source or

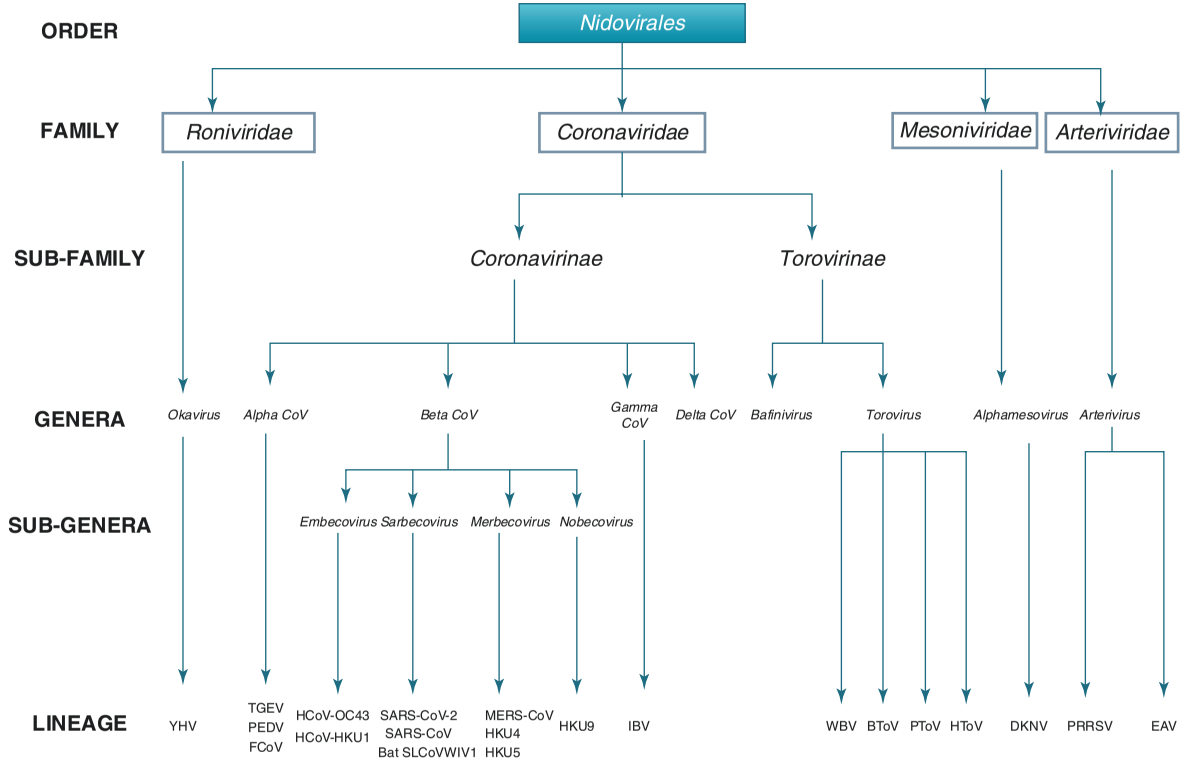


Fig. 2.1 Classification of coronaviruses. *Bat SL-CoV-WIV1* Bat SARS-like coronavirus WIV1, *BToV* bovine torovirus, *DKNV* Dak Nong virus, *EAV* equine arteritis virus, *FCoV* feline coronavirus, *HCoV-HKU1* human coronavirus HKU1, *HCoV-OC43* human coronavirus OC43, *HKU4* (human coronavirus), *HKU5* (human coronavirus), *HKU9* (human coronavirus), *HToV* human torovirus, *IBV* infectious bronchitis virus, *MERS-CoV* Middle East respiratory syndrome coronavirus, *MHV* mouse hepatitis virus, *PRRSV* porcine reproductive and respiratory syndrome virus, *PEDV* porcine epidemic diarrhea virus, *PToV* porcine torovirus, *TGEV* transmissible gastroenteritis coronavirus, *YHV* yellow head virus, *WBV* white bream virus. (Adapted from Cong Y, Verlhac P, Reggiori F. The interaction between nidovirales and autophagy components. Viruses. 2017;9 (7):182–196)

Table 2.1 Coronaviruses known to afflict humans

Genus	Virus	Natural host	Disease severity	Target receptor in human body
Alphacoronavirus	HCoV-NL63	Bats	Mild respiratory infections	Angiotensin-converting enzyme 2
	HCoV-229E	Bats	Mild respiratory infections	Human aminopeptidase N
Betacoronavirus	HCoV-OC43	Rodents	Mild respiratory infections	9-O-acetylsialic acids
	HCoV-HKU1	Rodents	Mild respiratory infections and pneumonia	9-O-acetylsialic acids
	SARS-CoV	Bats	Severe acute respiratory syndrome	Angiotensin-converting enzyme 2
	MERS-CoV	Bats	Severe acute respiratory syndrome	Dipeptidyl peptidase-4
	SARS-CoV-2	Bats	Severe acute respiratory syndrome	Angiotensin-converting enzyme 2

intermediate hosts. Genetic analysis of the genome of SARS-CoV-2 showed that it is related to the bat CoV RaTG13. It is, thus, a separate lineage than SARS and bat SARS-like CoVs. It is now suggested that the 2019 novel coronavirus is a new human-infecting coronavirus which most probably originated from bats and, thereafter, jumped to human via intermediate hosts [7]. Liu et al. [8] predicted the interaction between receptor binding domain of coronavirus spike protein and the host receptor after analyzing coronavirus genome sequences and spike protein residues. They suggest that bats are the natural host, while pangolins, snakes, and even turtles can serve as intermediate hosts for the novel coronavirus. A definite conclusion about the natural and intermediate hosts is, however, still missing.

2.4 Morphology of SARS-CoV-2

As mentioned above, a virus has to fulfill certain criteria to be called a coronavirus. Members of *Coronaviridae* family are relatively large, enveloped, single-stranded RNA viruses. In fact, they are the largest known RNA viruses with the virion sizes ranging from 118 to 136 nm in diameter and genomes ranging from 25 to 32 kilobase pair (kbp) in length. The virions are spherical in shape and are characterized by relatively large spikes that emerge from the virus envelope [10]. Park et al. [11] isolated and reported the morphology of the novel coronavirus in a 35-year-old female patient. For identification, monolayers of vero cells were inoculated with the oropharyngeal samples of the patient. Five days after this first inoculation, blind passage of the culture supernatant was done. Thereafter, vero cell monolayers showing cytopathic effects were fixed using 2% formaldehyde and 2.5% glutaraldehyde. These fixed cells were sectioned and observed under an electron microscope.

Observation revealed spherical particles with crown-like spikes. These spherical particles were 66–81 nm in diameter and were observed within the cytoplasmic vesicles and in the extracellular space next to the cell membrane.

Four main proteins, called the structural proteins, and other accessory proteins make up and define the visible structure of the novel coronavirus. The structural proteins starting from the inside out include nucleocapsid (N) protein, membrane (M) glycoprotein, envelope (E) glycoprotein, and the spike (S) glycoprotein [12].

The nucleocapsid also known as the N proteins functions primarily to bind to the CoV RNA genome, making up the nucleocapsid [13]. It is located in the endoplasmic reticulum-Golgi region which is bound to the nucleic acid of the virus. It is involved in functions of the viral genome, replication of the virus, and the host response to viral infections [12]. It is heavily phosphorylated and is thought to lead to structural modifications that enhance affinity for viral RNA. Transient expression of the nucleocapsid proteins has, however, been shown to increase the production of virus-like particles (VLPs) markedly in some coronaviruses, thus suggesting that this protein might be required for complete virion formation and not envelope formation [14].

The next is the membrane or M protein. It is the most well-structured and the most abundant of all structural proteins in SARS-CoV-2. It determines the shape of the viral envelope. It is considered to be the central organizer of coronavirus assembly. It can bind and interact with all other major structural proteins [14]. Homotypic interactions among M proteins are responsible for the formation of virion envelope, but the M protein is not sufficient for virion formation by itself [15]. Interactions between M and N proteins stabilize the nucleocapsid proteins (N) and help in completion of viral assembly [12]. The interaction of spike (S) and membrane (M) proteins is essential for retention of S in the endoplasmic reticulum-Golgi intermediate compartment and also for the incorporation of S into new virions. However, it is not required for the assembly process [14, 16]. The M and E proteins together make up the viral envelope, and their interaction leads to the production and release of VLPs [14].

The envelope (E) protein is the smallest among the major structural proteins. It is a short, integral membrane protein of 76–109 amino acid sequences and ranges from 8.4 to 12 kDa in weight [14, 17, 18]. E has a short, hydrophilic amino terminus containing 7–12 amino acids and a large hydrophobic transmembrane domain of 25 amino acids. It ends with a long, hydrophilic carboxyl terminus which makes up a majority of the protein [14, 19, 20]. The envelope protein is needed for production and maturation of the virus. It is copiously expressed inside an infected cell, but only a small portion of this is incorporated into the virion envelope [14]. It is mainly localized at sites of intracellular trafficking—the endoplasmic reticulum, Golgi apparatus, and the endoplasmic reticulum-Golgi complex. Here it partakes in the assembly and budding of the virus [21]. Its importance in virus production and maturation can be gauged from the fact that recombinant coronaviruses which lack the envelope protein display markedly reduced viral titers, affected viral maturation, or produce incompetent progeny [14, 22].

The outermost protein responsible for giving a characteristic appearance and name to the coronavirus family is the spike (S) protein. It is a transmembrane protein and has a molecular weight of around 150 kDa. It mediates the entry of the virus into the host cell and hence also receives particular attention from scientists. The S glycoprotein forms homotrimers that project up from the viral structure and promote binding to the host cells by attraction and attachment to the angiotensin-converting-enzyme 2 (ACE2) receptors [12]. This protein is made up of two functional subunits—S_1 and S_2. These can be recognized upon cleavage of the S protein by host cell furin-like protease [3, 16]. Subunit S_1 binds to the host cell receptor and thus determines the host range and the types of cells that a virus can affect. Subunit S_2 mediates fusion of virus with the host cell membrane. Both these subunits remain non-covalently bound in the prefusion state [3]. The distal S_1 subunit makes up the receptor-binding domains (RBDs) and stabilizes the S_2 subunit that has the machinery needed for fusion in the prefusion state [23]. The S homotrimers contain numerous N-linked glycans which are needed for achieving the correct structure and access to host proteases and neutralizing antibodies [3]. Compared to the S protein of SARS-CoV (and other beta coronaviruses), the spike protein of SARS-CoV-2 has 12 extra nucleotides at its cleavage site which is similar to a canonical furin-like cleavage site. The presence of this furin-like cleavage site might increase the efficiency of spread of SARS-CoV-2 as compared to other beta coronaviruses [24].

Some beta coronaviruses exhibit an additional structural protein called the hemagglutinin-esterase (HE) protein. This protein binds to sialic acid present on the virion surface, and this binding and the esterase activity together help the virus enter into the host cell. This entry is further facilitated by the spike protein. The HE protein also helps in mucosal spread of the virus [24]. A difference between SARS-CoV and SARS-CoV-2 is that HE proteins are present in SARS-CoV although they lack membrane fusion activity and are accessory to the spike protein. It is also debatable whether they help in virion attachment or not [25]. However, the genome of SARS-CoV-2 lacks the hemagglutinin esterase gene [26]. A graphical representation of the structural proteins and genomic material of the novel coronavirus is given in Fig. 2.2.

All these proteins along with other nonstructural proteins are coded for by the genome of the virus which is discussed in the next section.

2.5 Genome of the Novel Coronavirus

Coronaviruses possess a single-stranded positive sense RNA (+ssRNA). There is a 5′-cap and 3′-poly-A-tail. The novel coronavirus genome is about 30 kb long and has at least six open reading frames (ORFs). At the 5′ end, ORF1a and ORF1b, the first open reading frame genes, constitute around two thirds of the complete genome length and codes for pp1a and pp1b proteins, respectively. These together make up 16 nonstructural proteins (nsp1–nsp16) [27]. These nonstructural proteins are required for the maintenance, replication, and optimum function of the virion.

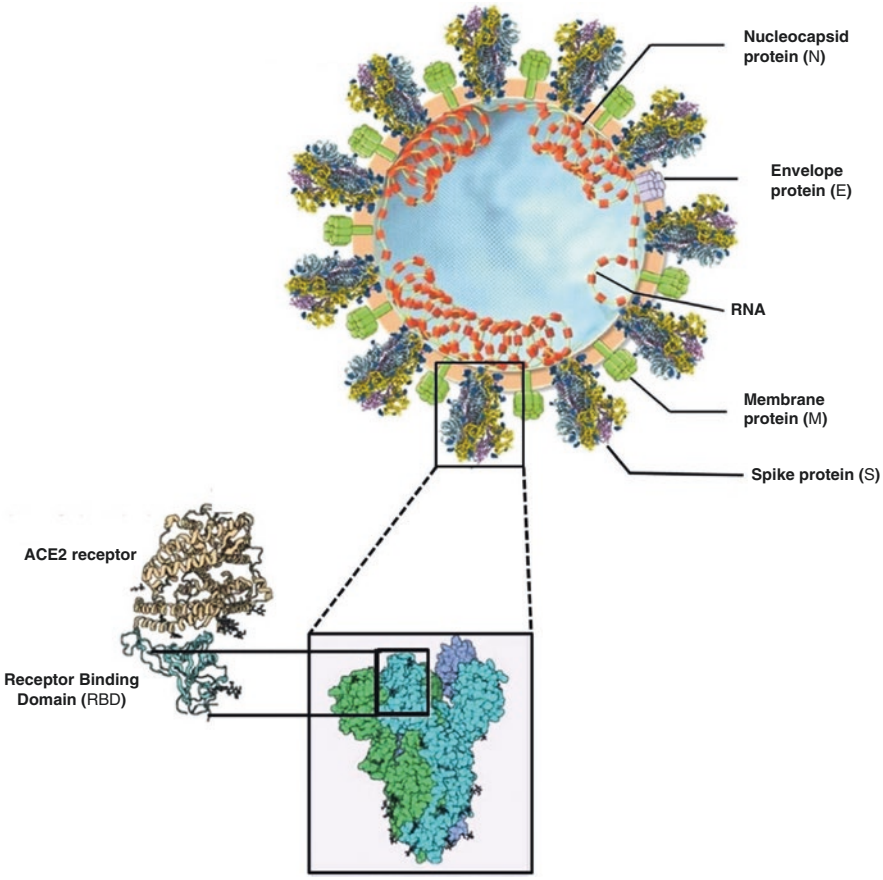


Fig. 2.2 Structure of the novel coronavirus-SARS-CoV-2. SARS-CoV-2 has four structural proteins—N, M, S, and E. S protein mediates binding of the virus with the host cell surface receptor—ACE2. The M and E proteins are embedded in the host membrane-derived lipid bilayer which encapsulates the single-stranded helical (positive sense) viral RNA around the N protein

A summary of their purpose in the virion is presented in Table 2.2. The four structural proteins mentioned in the previous section are coded for by the ORFs near the 3′-end of the genome [28].

The 30 bp long nucleotides of the virus can be broken down as follows [1]:

1. 8.903 (29.86%) Adenosines
2. 5.482 (18.39%) Cytosines
3. 5.852 (19.63%) Guanines
4. 9.54 (32.12%) Thymines.

Table 2.2 Functions of the 16 nonstructural proteins of SARS-CoV-2

Protein	Process mediated
nsp1	Inhibition of interferon signaling, degradation of cellular mRNA
nsp2	Not known
nsp3	Cleaving of papain-like protease domains, blocking host innate immune response, promoting cytokine expression, tether RNA genome to the replicase/transcriptase complex
nsp4	Formation of double membrane vesicle (membrane remodeling), transmembrane scaffold
nsp5	Inhibition of interferon signaling, splitting chymotrypsin like proteins and main protease
nsp6	Formation of double membrane vesicle, restrict expansion of autophagosome
nsp7	Acts as a co-factor of nsp8 and nsp12
nsp8	Acts as a co-factor of nsp7 and nsp12, primase, can function as a processivity clamp for RNA-dependent-RNA-polymerase (RdRp)
nsp9	Dimerization and binding of single-stranded RNA
nsp10	Acts as building protein for nsp14 and nsp16
nsp11	Not known
nsp12	RNA-dependent-RNA-polymerase primer
nsp13	RNA 5′ triphosphatase (cap synthesis), RNA helicase
nsp14	N7-methyltransferase, exo N 3′-5′ exonuclease (provides proofreading function for coronavirus RdRp)
nsp15	N endo U endonuclease (cleaves single- and double-stranded RNA downstream of uridylate residues, producing 2–3 cyclic phosphates), evasion of double-stranded DNA sensors
nsp16	Methyltransferase, helps avoid MDA5 (melanoma-differentiation-associated protein 5) recognition, downregulates innate immunity

Also, five mutations exist in this genome, namely [1]:

1. T8782C (ORF1, codons AGT to AGC-silent mutation).
2. T9561C (ORF1a, codons TTA to TCA-nonsilent mutation).
3. C15607T (ORF1b, codons CTA to TTA-silent mutation).
4. C28144T (ORF8b, codons TCA to TTA-nonsilent mutation).
5. T29095C (nucleocapsid, codons TTT to TTC-silent mutation).

It is also known that these mutations in the novel coronavirus exist at the nucleotide level in S gene, nsp1, nsp3, and nsp15, and not at the amino acid level [1].

Lu et al. [29] have described the genomic characteristics of the novel coronavirus in detail. Their analysis revealed that the novel coronavirus is most closely related to bat-SL-CoVZC45 and SARS-like betacoronavirus of bat origin, bat-SL-CoVZXC21. The sequence resemblances were more than 90% in five gene regions—E, M, 7, N, and 14. Out of these, the E gene displayed a sequence similarity of 98.7% (the highest). The lowest similarity, between the novel coronavirus

and the other bat-SLCoVs, was seen in the S gene region being only around 75%. An interesting finding was the low genetic resemblance between SARS-CoV and SARS-CoV-2 (about 79%) and between SARS-CoV-2 and MERS-CoV (about 50%). Compared to previous coronaviruses—the SARS-CoV, MERS-CoV, and the bat SARS-like coronaviruses—SARS-CoV-2 codes for a longer spike protein. As mentioned earlier, the spike (S) protein facilitates binding to host receptor and fusion with cell membrane and is functionally composed of the S1 domain and S2 domain—the functions of them both have been discussed in the previous section. The S2 protein of the novel coronavirus exhibits a 93% similarity to bat-SL-CoVZC45 and bat-SL-CoVZXC21, while the S1 protein displays a similarity of only 68% with these viruses. It is seen that the receptor binding domain of the mentioned bat coronaviruses is located in the C-terminal domain of S1; however, despite similarities in the S1 and S2 domains, the receptor binding domain of SARS-CoV-2 falls within lineage B and is hence closer to that of SARS-CoV. Thus, in terms of the whole genome sequence, the novel coronavirus is closer to bat SARS-like coronaviruses than SARS-CoV. Based on the observations above, certain differences in the genome sequences of the novel coronavirus (SARS-CoV-2) and SARS-CoV are given in Table 2.3. However, it remains to be seen how these differences affect the pathogenesis and functionality of the novel coronavirus. A basic representation of the genomes of the novel coronavirus and that of SARS-CoV is given in Fig. 2.3.

Upon analysis and comparison of the genome of SARS-CoV-2, it is evident that it resembles the genome of bat coronaviruses. Hence, the host and intermediate hosts of this virus can also be identified. As seen earlier, bats are purported to be the natural host of this virus. However, there are several factors suggesting that the conjecture of a direct transmission from bats to humans is fraught with inadequacies as mentioned below:

1. An outbreak was reported in late December 2019. This is a period of winter when bats are hibernating.

Table 2.3 Differences in genome of SARS-CoV and SARS-CoV-2

Trait	SARS-CoV	SARS-CoV-2
Vulnerability to mutations in spike protein-cell receptor interface-associated amino acids	Low	High
Length of S protein	Shorter (1255 amino acids)	Longer (1273 amino acids)
Receptor-binding domain	Lineage B	Lineage B (similar)
Free-binding energy of S protein-human ACE2-binding complex	Low	28 times more than that of SARS-CoV
Protein 8a	Present	Absent
Protein 8b	Shorter (84 amino acids)	Longer (121 amino acids)
Protein 3b	Longer (154 amino acids)	Shorter (22 amino acids)

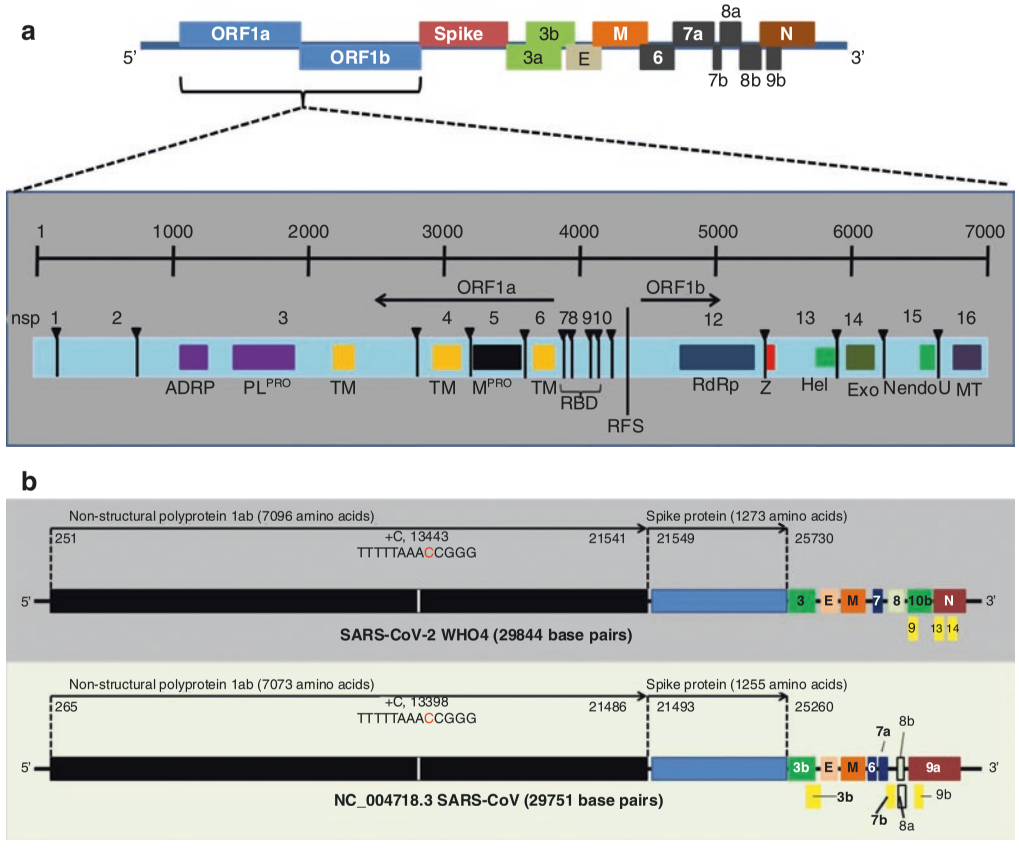


Fig. 2.3 (**a**) Organization of the genome of SARS-CoV-2. The size of the genome can range from 26 to 32 kilobase pair (kbp) and contains 6–11 open reading frames (ORFs) which encode 9680 amino acids. The first ORF constitutes about 67% (nearly two-thirds) of the genome and codes for 16 nonstructural proteins (nsp), while accessory and structural proteins are coded by the remaining ORFs. The functions of nsps are given in Table 2.2. (**b**) Coding regions of SARS-CoV-2 and SARS-CoV. Only ORFs of more than 100 nucleotides have been shown

2. No bats were sold or found in the wet seafood market which is supposed to be the starting point of the pandemic, although there were several nonaquatic animals being sold.
3. The overall sequence similarity between SARS-CoV-2 and other bat coronaviruses is less than 90%; hence, bat coronaviruses cannot be said to be the direct ancestors of the novel coronavirus.
4. Coronaviruses are mainly zoonotic. Even in previous SARS and MERS outbreaks, there were intermediate hosts (masked palm civet for SARS and dromedary camels for MERS), and bats were the natural hosts of the virus.

Hence, based on the above points, the hypothesis that bats are the natural hosts while some other animal acted as an intermediate host of the virus is further strengthened [29]. However, making conclusive remarks about definitive and intermediate hosts is not possible at the moment.

2.6 Life Cycle of SARS-CoV-2

Viruses are like parasites which need another living body to survive. Outside this body, they either lie dormant or cannot survive for long. Similarly, the novel coronavirus too needs the human body to survive. The virus can enter the body either through direct contact, indirect transmission through aerosols, or through droplets [30]. There are different steps involved in entry and propagation of the virus inside the human body which are given below:

1. *Attachment*: Angiotensin-converting enzyme 2 (ACE2) receptor is a zinc-binding carboxypeptidase receptor expressed on the cell surfaces of different organ systems, viz., lungs, heart, ileum, small intestine, kidney, bladder, and others [10, 31]. This receptor has been identified as the target receptor for SARS-CoV-2. Receptor recognition is the first step in viral infection. It is also a key determinant of host cell and tissue tropism. As discussed earlier, the spike (S) protein of SARS-CoV-2 is responsible for recognition and attachment to human ACE2 (hACE2) receptors. It contains a receptor binding domain (RBD) that specifically recognizes ACE2 as its receptor. The RBD contains a core and a receptor-binding motif (RBM) that mediates contact with the receptor. The surface of ACE2 contains two virus-binding hotspots that are essential for binding with the virus. While binding to the receptor, the S protein RBM forms a concave surface with a ridge on one side which binds to the exposed outer surface of the "claw-like" ACE2 receptor. As compared to SARS-CoV, the RBM of SARS-CoV-2 forms a larger binding interface and more contacts with its receptor. SARS-CoV-2 RBM contains a four-amino-acid residue motif: glycine-valine/glutamine-glutamate/threonine-glycine. Due to these bulky residues and flexible glycine, the binding loop takes a different conformation as compared to SARS-CoV. This structural difference leads to the formation of an additional main chain hydrogen bond between Asn487 and Ala475 in the RBM of the novel coronavirus. Due to

this the ridge takes an even more compact arrangement, and the loop containing Ala475 gets even closer to ACE2. As a result the ridge forms more contacts with the N-terminal helix of ACE2 [32]. Two virus-binding hotspots have been identified in ACE2-SARS-CoV-2 interface: hotspot Lys31 (also known as hotspot 31) and hotspot Lys353 (also known as hotspot 353). These hotspots are relatively weak in SARS-CoV; however, in SARS-CoV-2, they are stronger and well-stabilized due to different conformations. These hotspots are important for coronavirus binding [32].

2. *Penetration:* As mentioned earlier, the S protein is made of two subunits—S_1 and S_2—which are non-covalently bound. The presence of the four amino acid residue at the boundary between S_1 and S_2 subunits results in the introduction of a furin cleavage site. The cleavage of the subunits occurs by furin present in the Golgi compartment. One reason, why the novel coronavirus affects different organs and is highly transmissible, could be the presence of this polybasic cleavage site in the fusion glycoprotein (S) which is cleaved by furin—a protease which is found ubiquitously in the body [3]. Once attachment occurs, type II transmembrane serine protease (TMPRSS2), which is present on the host cell surface, clears the ACE2 and activates the receptor-attached S protein. S protein is also activated by furin via cleavage. Activation of the S protein causes conformational changes and allows the virus to enter host cell either by fusion of the envelope (E) protein with the host cell surface or by the endosomal pathway [12, 33]. If virions are taken up into endosomes, cathepsin L activates the spike protein. However, this cysteine protease can be blocked by lysosomotropic agents (like bafilomycin A1 or ammonium chloride inhibitors). Thus, it is not an efficient mode of viral replication. Alternatively, if the S protein is activated by TMPRSS2, the viral membrane fuses with the plasma membrane [34]. This fusion is less likely to activate host cell immunity and is thus a more efficient method of viral replication.
3. *Biosynthesis:* Once the virus enters a host cell, it releases its genetic material in the cytoplasm. The first synthetic event in the life cycle of coronavirus is the translation of viral genome by host cell ribosomes. As the released viral genome is positive stranded, 5′ capped, and 3′ polyadenylated, it can be directly translated to proteins by the host ribosomes. The virus has 14 open reading frames (ORFs) which code for a variety of proteins—structural as well as nonstructural. The gene segments which code the nonstructural proteins (nsp) are translated first into ORF1a and ORF1b. This translation produces two large overlapping polyproteins—pp1a and pp1ab through a ribosomal frame-shifting mechanism. These polyproteins are supplemented by protease enzymes—papain-like proteases (PL^{pro}) and a serine-type M^{pro} [chymotrypsin-like protease ($3CL^{pro}$)] protease which are coded in nsp3 and nsp5. Thereafter, cleavage occurs between pp1a and pp1ab into nsp1–nsp11 and nsp1–nsp16, respectively [12]. These nsps play important roles in various processes in the virus and host cells which are mentioned in Table 2.2. Several of these nsps form replicase-transcriptase complex (RTC) with RNA-dependent RNA polymerase (RdRp) in double membrane vesicles (DMVs). This complex leads to transcription of positive sense mRNAs, and this process is mediated by RdRp [12].

4. *Maturation:* During biosynthesis, the subgenomic proteins get translated to structural (and nonstructural and accessory) proteins—N, M, S, and E. These proteins are bound/ formed on smooth-walled vesicles in the endoplasmic reticulum and then moved to the endoplasmic reticulum-Golgi intermediate compartment (ERGIC) [12]. Genomic RNA is bound by N protein. This associates with M protein and buds into endoplasmic reticulum/Golgi membranes. M packs into membranes and is thought to produce membrane curvatures which leads to budding. S and E are acquired during budding [10].
5. *Release of virions:* The synthesized virions are released from the host cell via exocytosis. The ion channel activity of E protein is that of a viroporin. It alters the cell secretory pathways to expedite the release of virions from the cell. It increases the pH of transport vesicles [10]. Once these vesicles fuse with the plasma membrane, virions are released to continue infecting other cells.

Figure 2.4 shows the different steps involved in the life cycle of the novel coronavirus.

2.7 Host Immune Response

(a) *Innate immunity:* Host immune response is triggered as the virus enters the host cell. The viral antigens are presented to the antigen-presenting cells (APCs) which include dendritic cells and macrophages. These constitute a central part of the body's antiviral immunity. APCs possess pattern recognition receptors (PRRs) including Toll-like receptors (TLRs), NOD-like receptors (NLRs), RIG-I like receptors (RLRs), and other free molecules located in various places in host cells like the plasma membranes, endosomal membrane, lysosomes, endocytolysosomes, and cytosol. These recognize different molecules present in viruses such as the nucleic acids, carbohydrate moieties, glycoproteins, lipoproteins, and other molecules or intermediate products like dsRNA and bring about cascade signaling to produce immune system cell effectors. Each PRR is capable of inducing a different biological response to different proteins [35, 36].

TLR-4 recognizes the spike protein. Through mediation of MyD88, it triggers activation of NF-κB transcription factors and the pathogen-activated protein kinase pathway to produce pro-inflammatory proteins. Activation of endosomal receptors like the TLR-3 and TLR which can recognize the RNA or dsRNA genome of coronavirus leads to recruitment of TRIF adapter protein directly. TRIF in turn directs interferon response factor 3 (IRF 3) and nuclear factor NF-κB transcription factors to induce pro-inflammatory cytokines like interferon-α (IFN-α) and tumor necrosis factor-beta (TNF-β). Type I IFN complexes with its receptors and activates the JAK-STAT pathways. JAK1 and TYK2 kinases phosphorylate STAT1 and STAT2 followed by its complexing with IFN-9. Both these migrate to the nucleus to start transcription of IFN-stimulated genes and lead to suppression of viral replication and prevent the severity of the disease [12]. This process can cause exhaustion, weakness, and

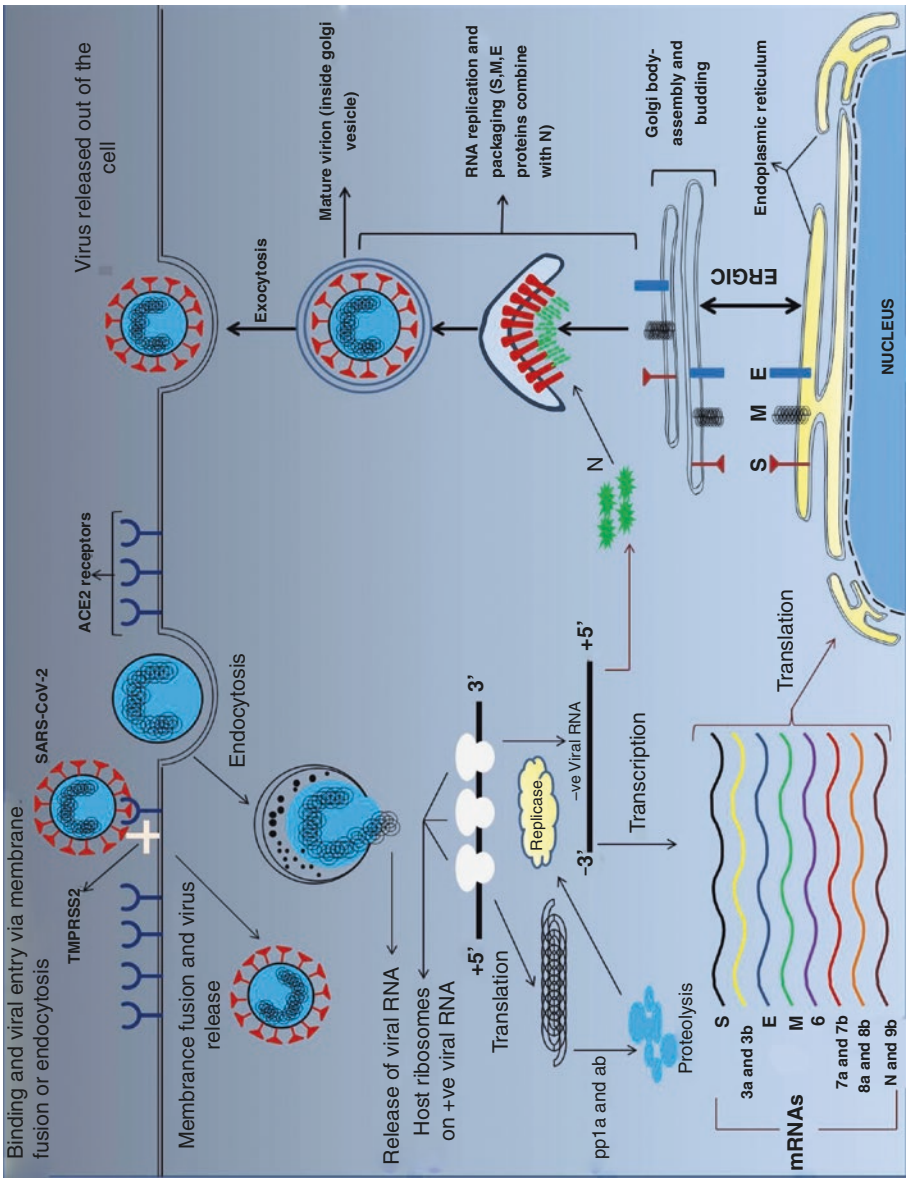


Fig. 2.4 SARS-CoV-2 life cycle inside a host cell

cough in patients. An important observation in case of SARS-CoV-2 infection is that immune response by type 1 IFN is suppressed [37]. It is seen that SARS-CoV-2 infection produces an aberrant immune response wherein the release of pro-inflammatory cytokines like IFN-α, IFN-γ, IL-1β, IL-6, IL-12, IL-18, IL-33, TNF-α, and TGFβ, and chemokines CCL2, CCL3, CCL5, CXCL8, CXCL9, and CXCL10 in excessive quantities from immune effector cells leads to hyperinflammation leading to acute respiratory distress syndrome (ARDS) [12].

(b) *Cell-mediated immunity:* The APCs present the CoV antigens to CD4+ T-helper (Th) cells via major histocompatibility complex (MHC) class 1. This causes release of IL-12—a stimulatory molecule which stimulates Th1 cell activation. In addition to the stimulation of Th1, other processes like the release of IL-12 and IFN-α, increase in MHC class I expression, and activation of natural killer (NK) cells are also required for thwarting viral replication and eradication of virus-infected cells. Antigen presentation also causes production of pro-inflammatory cytokines via the NF-κB signaling pathway. These cytokines recruit neutrophils and monocytes to the infection site and activate other pro-inflammatory cytokines and chemokines including IL-1, IL-6, IL-8, IL-21, TNF-β, and MCP-1 [12]. Activation of Th1 cells stimulates CD8+ T cells which target and kill cells infected with the coronavirus. Simultaneously, CD4 T cells stimulate humoral immune response by activating T-dependent B cells [12, 38].

It is seen that in COVID-infected patients, the number and function of CD8+ T cells is greater than CD4+ T cells. Also, virus-specific T cells from severely infected patients tend to possess a central memory phenotype with a significantly higher polyfunctional CD4+ and CD8+ T cells. Strong T cell responses have been shown to have higher neutralizing antibody, while more serum Th2 cytokine secretion (e.g., IL-4, IL-5, IL-10—which increase production of antibodies) have been observed in deceased patients [37].

(c) *Humoral immunity:* The production of neutralizing antibodies plays a protective role in limiting infection. It also prevents re-infections in the future. The antibodies produced against SARS-CoV-2 infection are IgM and IgG which display a unique presence pattern. Usually IgM produced against SARS-CoV-2 lasts for only 12 weeks, but IgG will last longer [12]. SARS-CoV-2 infection induces production of IgG against the N protein, and this can be detected as early as day 4 after the onset of disease with most patients seroconverting by day 14 [37]. In addition to antibody formation, exposure to the novel coronavirus also leads to formation of CD4 T cells and CD8 memory cells as seen above, and these can last for up to 4 years [12].

2.8 Immune Evasion by Coronaviruses

Over the course of evolution, viruses have developed mechanisms to protect them from immune system cells. This ability enables them to survive and infect host cells efficiently. Such an avoidance strategy can be applied to different processes

both before and after entering a host cell. As seen earlier, host immune cells recognize a virus by various PRRs. The virus can avoid recognition by forming double membrane vesicles which lack these PRRs. This way they can replicate inside such vesicles without their dsRNA being detected [39].

Additionally, the virus has proteins that block IFN and thus avoid the immune system onslaught. nsp1 can suppress IFN 1 by inactivating the host translation mechanism, degrading host RNA and inhibition of STAT1 phosphorylation. This mechanism can cause IFN 1 failure and can lead to dissemination of viruses at an early stage and hence an increased severity of the disease [12, 40]. nsp14 and nsp16 can help the virus mimic the host capping mechanism. nsp14 initiates cap formation (5′ end similar to host cell RNA), and nsp16 later modifies it to viral RNA. This way the virus seems similar to host cell RNA and thus can escape being recognized by immune cells [12, 41, 42].

nsp3 is another nonstructural protein which encodes two functional proteins, macro-domains and PL^{pro} (which cleaves nsps). This nsp also helps the virus evade host cell immune response. Besides nonstructural proteins, the virus may also use accessory proteins to escape immune response. As an example, a protein coded for by ORF3b can antagonize the IFN signaling pathway and thus lead to inhibition of effector cell activation cascade responsible for eradication and inhibition of viral replication. Similarly, proteins coded in ORF6 can inactivate JAK-STAT signaling pathway by complexing with karyopherin-α2 and tethering karyopherin-β1 on internal membranes thus blocking nuclear translocation of transcription factor STAT-1 [12].

The novel coronavirus is a new virus, and limited literature is available on its different attributes. Hence, conclusive remarks about its life cycle or immune responses cannot be made at the present moment. Much understanding of how it behaves inside the human body comes from research on SARS-CoV which has been studied in detail in the past years. The immune evasion methods described above are also based on SARS-CoV research. As such, readers are encouraged to update themselves about immune mechanisms and responses of SARS-CoV-2 as and when additional information is added in the literature about it.

2.9 Pathogenesis

Knowledge about the life cycle and immune response to the novel coronavirus can help us better understand the progression of the disease that it causes. Various hypotheses have been proposed to explain the course of COVID-19 in the human body. From a cellular biology perspective, COVID-19 can be divided into three stages [43]:

1. First stage: asymptomatic period (the first 1–2 days of infection).
   The virus which has gained entry inside the body most likely binds to epithelial cells in the nasal cavity and begins multiplying. Through research conducted on SARS-CoV, it is surmised that ciliated cells are the first cells to be infected in

conducting airways. However, this understanding remains to be validated as conducting airways show low levels of ACE2 expression. At this stage, the virus progresses locally, and there is a limited innate immune response. The virus can be detected via nasal swabs during this period.

The clinical significance of this period is that in spite of having low viral load, the infected individuals can transmit the virus to others.

2. Second stage: upper airway and conducting airway period (the next few days).

The virus multiplies and migrates downward along the conducting airways. A stronger immune response is elicited at this stage. For testing purposes, both nasal swabs and sputum samples should theoretically yield the virus. The disease COVID-19 manifests itself clinically at this stage. The host immune responses given in the previous section are activated and amplified during this stage. Thus biochemical markers (cytokines, interferons, antibodies, etc.) can be tested for during this period. A majority of the infected patients (about 80%) experience the disease till this stage only, and they can be monitored at home via symptomatic therapy.

3. Third stage: hypoxia, pulmonary infiltrates, and progression to respiratory distress.

Around 20% infected patients progress to this stage of COVID-19. In this stage, the virus reaches the alveoli (gas exchange units) and infects type II pneumocytes. The virus proliferates in these cells releasing large number of viral particles which can affect other organs. The infected cells, however, undergo apoptosis and die. This way, large areas of the lungs may lose their type II cells, and thus epithelial regeneration is triggered. COVID-19 causes diffuse alveolar damage with fibrin-rich hyaline membranes and a few multinucleated giant cells. An aberrant wound healing leads to even more scarring and fibrosis.

Cytokine storm in COVID-19: The viral infection, if not controlled at stage 2 or 3, can lead to the death of the infected individual. A major cause of death from COVID-19 is the acute respiratory distress syndrome (ARDS). A severely lethal, uncontrolled systemic inflammatory response due to the release of large amounts of pro-inflammatory cytokines and chemokines (refer to Innate immunity under host immune response section) is called a "cytokine storm." This cytokine storm triggers a violent attack to the body by its own immune system which can lead to ARDS, multi-organ failure, and eventually death [44].

Some other investigation parameters which have been reported from COVID-19 patients are given in Table 2.4.

The clinical presentation of COVID-19 varies with age—most severely affecting the elderly [43] while the pediatric age group remains relatively unaffected [31]. It is interesting because infants and young children are a high-risk group for other respiratory infections like the respiratory syncytial and influenza virus infection. The reason for this finding remains unknown; however, some possible explanations have been proposed [30, 31]:

Table 2.4 Blood investigation parameters from COVID patients [37]

Parameter	Percentage of patients
Lymphopenia	89.2
Neutrophilia	74.3
Thrombocytopenia	24.3
High (>5) neutrophil to lymphocyte ratio	94.5
High (>500) systemic immune inflammation index	89.2
Increased C-reactive protein level	100
Increased lactate dehydrogenase	93.2
Increased D-dimer	97.1
High level (>10 pg/ml) of IL-6	100
High levels of pro-inflammatory cytokines (IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1A, TNF-α) during cytokine storm	100

1. Immature and quantitatively less ACE2 receptors in children.
2. Growing immune system in children reacts differently to SARS-CoV-2 as compared to adults.
3. Presence of other viruses in airways and lungs of children which can limit growth of SARS-CoV-2.

The target receptor for the novel coronavirus (ACE2) is found abundantly in the lungs and small intestine and is highly expressed in endothelial cells and smooth muscle cells of virtually all organs. Thus, SARS-CoV-2 is a threat not only to the respiratory system but also to the gastrointestinal, central nervous, and circulatory systems [45]. These systems along with their specific pathophysiology and symptoms are discussed below:

1. *Respiratory system:* The mechanism of infection of type II pneumocytes in lungs has been discussed previously. Three classical symptoms of COVID-19 related to the respiratory system are fever, cough, and shortness of breath. Other symptoms may include sore throat, nasal congestions, and dyspnea.

   Radiographically, bilateral lung involvement in the form of sub-pleural and peripheral areas of ground glass opacity and consolidation is seen [46].

   Histopathological examination reveals pulmonary edema, cellular fibromyxoid exudates with diffuse alveolar damage, pneumocyte desquamation, and formation of hyaline membrane. Lungs also exhibit interstitial mononuclear patchy inflammatory infiltrates dominated by lymphocytes. Intra-alveolar spaces show multinucleate syncytial cells with atypical enlarged pneumocytes showing virus-induced cytopathic effect [33].
2. *Gastrointestinal system:* The clinical features representing involvement of the digestive system are not very specific. Diarrhea, vomiting, and abdominal pain have been reported by affected patients [47]. Though these symptoms are not

very severe and are also not reported by all patients, they do point to the fact that the gastrointestinal system might get affected and also contribute in transmission of the virus. The intestinal epithelium comes in direct contact with exogenous pathogens, and, hence, it possibly gets affected first after consumption of a SARS-CoV-2-infected animal. The nucleic acids of SARS-CoV-2 have also been detected in stool samples of the affected patients strengthening the assumption that gastrointestinal system is a potential route of transmission [45].

Other than this, patients can also suffer from liver injury with raised enzymes found in blood tests. It is assumed that liver injury can occur in three ways—direct viral infection of hepatocytes, immune-related injury, or due to drug hepatotoxicity. The possible mechanism of liver involvement could be the binding of the virus to ACE2 receptors on cholangiocytes. Histopathology of liver samples from deceased COVID-19 patient has revealed microvesicular steatosis and mild lobular activity. However, no viral inclusions were seen [47].

3. *Urogenital system:* COVID-19 patients exhibit increased serum creatinine, urea nitrogen, and urine protein indicating renal damage. Different studies have shown that 3–10% of COVID patients have renal insufficiency and 7% have acute kidney injury. Viral nucleic acids have also been isolated from urine samples of these patients. The CT scan of kidneys in COVID patients suggests inflammation and edema in parenchymal region [45]. Apart from renal tubular and mesenchymal cells, ACE2 is expressed in testicular and vas deferens cells as well. It is thought that SARS-CoV-2 binds to these receptors and leads to dysfunction of kidneys and testis [48]. It is, therefore, important for clinicians to assess the risk of testicular lesions in young patients to lessen the impact of COVID-related reproductive injury.
4. *Central nervous system (CNS):* It is known that viruses can travel along infected nerve endings. As the nasal mucosa is usually the first affected part of the body, it is possible that the olfactory tract can act as a channel for viral transmission to brain. The potential invasion of the brainstem by the novel coronavirus can lead to acute respiratory failure. Headache, epilepsy, and confusion have been reported by some COVID patients all of which point to intracranial infection. Pulmonary injury can lead to hypoxia in the CNS leading to interstitial edema, obstruction of cerebral blood flow, congestion, and even coma. CNS can also get damaged from the cytokines released by glial cells as a result of SARS-CoV-2 infection [45].
5. *Cardiovascular system:* COVID patients have been known to present with circulatory system symptoms like palpitations, chest tightness, and shortness of breath. Elevated creatinine kinase, creatinine kinase-MB, and hs-cTnl have been also reported in COVID patients. It is presently believed that SARS-CoV-2 causes myocardial injury through three possible mechanisms:
   (a) The virus infects the heart and causes direct myocardial injury.
   (b) The virus binds to ACE2 receptors in the cardiovascular system and causes myocardial injury via signaling pathways.
   (c) The cytokine storm that occurs in COVID patients causes myocardial injury.

Additionally, hypoxemia and respiratory dysfunction caused by the virus can also damage myocardial cells [45]. Biopsies performed on COVID patients have revealed infiltration of myocardium by interstitial mononuclear inflammatory cells [46].

6. *Oral cavity:* ACE2 receptors are ubiquitously present in the respiratory tract as well as salivary gland duct epithelium in the mouth [30]. As such, the oral cavity and its functions can also be affected in COVID-19. Symptoms like irregular ulcers on dorsal surface of the tongue [49], hyposmia/anosmia and dysjeusia [50], glossodynia, unilateral ulcers (resembling recurrent herpetic stomatitis) on keratinized as well as non-keratinized mucosa, pain in the palate, and sore throat [51] have been reported. Some authors have also speculated that these might be the first manifestations of COVID in the human body [50]. However, this claim remains to be validated.
7. *Ocular manifestations:* It has been previously suggested that respiratory disease could be transmitted through the nasolacrimal system. It is known that the ocular mucosal system clears and drains fluid from the eye to the inferior meatus of the nose. Hence, it is possible that if a respiratory droplet is deposited in the eye, the infected ocular fluid can enter the respiratory system. Moreover, ACE2 receptors have been demonstrated on corneal and conjunctival cells. Conjunctival hyperemia, chemosis, epiphora, unilateral or bilateral conjunctivitis, foreign body sensation, tearing without blurred vision, inferior palpebral conjunctival follicles, and tender palpable preauricular lymph nodes have all been reported as the ocular manifestations of COVID-19. These findings are consistent with acute viral conjunctivitis. However, they have not been reported in all patients, and patients who presented with these complaints have not consistently tested positive for COVID. This paradox has been attributed to low viral load in ocular secretions and improper collection techniques [52, 53].
8. *Dermatological manifestations:* The commonly reported skin anomalies include chilblain-like lesions, maculopapular lesions, vesicular lesions, urticarial lesions, livedoid/necrotic lesions, pain, and burning. Skin lesions have been reported especially on acral sites like the digits of feet. These lesions begin as erythematous violaceous patches which turn to purpuric lesions, blisters, and necrotic lesions and finally return to normal [54]. Improvement in skin lesions has also been reported to be concomitant with improvement in laboratory markers (bilirubin transaminases and coagulation parameters) [55]. Once again the exact mechanisms of dermatological manifestations are not fully understood; however, a few plausible explanations have been suggested [56]:
   (a) Viral particles in cutaneous blood vessels lead to a lymphocytic vasculitis induced by immune complexes which activate cytokines. Immune reaction to COVID infection activates Langerhans cells leading to vasodilation and spongiosis.
   (b) Accumulation of microthrombosis from other organs can reduce blood flow to cutaneous microvascular system.

(c) Accumulation of deoxygenated blood in veins due to hypoxia and low-grade generalized intravascular coagulation can also cause such lesions.
(d) Pauci-inflammatory thrombogenic vasculopathy with deposition of C5b-9 and C4d can also cause such manifestations.

None of the above given theories can explain the cutaneous manifestations on its own, and such features are most likely a result of these mechanisms acting together. Cutaneous manifestations could also be late manifestations of the inflammatory phase of a primary respiratory infection [55].

Thus, it can be appreciated that once the novel coronavirus reaches the blood stream, it can affect any organ in the body; however, its target remains the same—the ACE2 receptor. This is of concern because patients might present with symptoms other than the recognized classical features of COVID, and misclassification or incorrect diagnosis of patients can negatively impact community transmission control efforts. Therefore, a sound knowledge and understanding of the pathophysiological mechanisms and manifestations of SARS-CoV-2 can help in its early diagnosis and management.

2.10 Conclusion

The novel coronavirus has ravaged the world since it first came to light in December 2019. It is a beta-coronavirus approximately 66–81 nm in diameter. Having originated in bats, it has jumped from its natural host into humans via an intermediate host which is still not known. Four main structural proteins—N, M, E, and S—provide the necessary framework for establishing its characteristic morphology and also define its pathologic ability. These as well as other nonstructural and accessory proteins are coded for by the genome of the virus which displays significant differences from its predecessor—the SARS-CoV. The virus can enter the body by direct contact, aerosols, and droplet transmission and attaches to its target receptor ACE2 via the spike protein. This spike protein exhibits considerable differences from other coronaviruses which might explain its increased transmissibility. Post attachment, it multiplies and also escapes detection by host immune cells via specific strategies. SARS-CoV-2 can affect pulmonary as well as extrapulmonary sites due to the ubiquitous distribution of ACE2 receptors. An understanding of its structure, immune response, and pathophysiology can help in better management of affected patients and possibly arrest the spread of this pandemic.

References

1. Dagur HS, Dhakar SS. Genome Organization of Covid-19 and emerging severe acute respiratory syndrome Covid-19 outbreak: a pandemic. EJMO. 2020;4(2):107–15.
2. Malik YA. Properties of coronavirus and SARS-CoV-2. Malays J Pathol. 2020;42(1):3–11.
3. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell. 2020;180(2):281–92.

4. International Committee on Taxonomy of Viruses. ICTV 9th Report 2011. Available from: https://talk.ictvonline.org/ictv-reports/ictv_9th_report/positive-sense-rna-viruses-2011/w/posrna_viruses/222/coronaviridae. Accessed 31 May 2020.
5. Jaiswal NK, Saxena SK. Classical coronaviruses. In: Saxena SK, editor. Coronavirus disease 2019 (COVID-19). 1st ed. Singapore: Springer; 2020. p. 141–50.
6. Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Semin Immunopathol. 2017;39(5):529–39.
7. Salata C, Calistri A, Parolin C, Palu G. Coronaviruses: a paradigm of new emerging zoonotic diseases. Pathog Dis. 2019;77(9):1–5.
8. Liu Z, Xiao X, Wei X, Li J, Yang J, Tan H, et al. Composition and divergence of coronavirus spike proteins and host ACE2 receptors predict potential intermediate hosts of SARS-CoV-2. J Med Virol. 2020;92(6):595–601.
9. Ji W, Wang W, Zhao X, Zai J, Li X. Homologous recombination within the spike glycoprotein of the newly identified coronavirus may boost cross-species transmission from snake to human. J Med Virol. 2020. (Accepted manuscript).https://doi.org/10.1002/jmv.25682.
10. Payne S. Chapter 17- Family Coronaviridae. In: Viruses. Academic Press. 2017. pp. 149–158.
11. Park WB, Kwon NJ, Choi SJ, Kang CK, Choe PG, Kim JY, et al. Virus isolation from the first patient with SARS-CoV-2 in Korea. J Korean Med Sci. 2020;35(7):e84.
12. Astuti I, Ysrafil. Severe acute respiratory syndrome coronavirus 2 (SARSCoV-2): an overview of viral structure and host response. Diabetes Metab Syndr Clin Res Rev. 2020;14(4):407–12. https://doi.org/10.1016/j.dsx.2020.04.020.
13. de Haan CA, Rottier PJ. Molecular interactions in the assembly of coronaviruses. Adv Virus Res. 2005;64:165–230.
14. Schoeman D, Fielding BC. Coronavirus envelope protein: current knowledge. Virol J. 2019;16(1):69.
15. Neuman BW, Kiss G, Kunding AH, Bhella D, Baksh MF, Connelly S, et al. A structural analysis of M protein in coronavirus assembly and morphology. J Struct Biol. 2011;174(1):11–22.
16. Fehr AR, Perlman S. Coronaviruses: an overview of their replication and pathogenesis. Coronaviruses. 2015;1282:1–23.
17. Kuo L, Hurst KR, Masters PS. Exceptional flexibility in the sequence requirements for coronavirus small envelope protein function. J Virol. 2007;81(5):2249–62.
18. Arbely E, Khattari Z, Brotons G, Akkawi M, Salditt T, Arkin IT. A highly unusual palindromic transmembrane helical hairpin formed by SARS coronavirus E protein. J Mol Biol. 2004;341(3):769–79.
19. Li Y, Surya W, Claudine S, Torres J. Structure of a conserved Golgi complex targeting signal in coronavirus envelope proteins. J Biol Chem. 2014;289(18):12535–49.
20. Liao Y, Yuan Q, Torres J, Tam J, Liu D. Biochemical and functional characterization of the membrane association and membrane permeabilizing activity of the severe acute respiratory syndrome coronavirus envelope protein. Virology. 2006;349(2):264–75.
21. Nieto-Torres JL, DeDiego ML, Álvarez E, Jiménez-Guardeño JM, Regla-Nava JA, Llorente M, et al. Subcellular location and topology of severe acute respiratory syndrome coronavirus envelope protein. Virology. 2011;415(2):69–82.
22. Kuo L, Masters PS. The small envelope protein E is not essential for murine coronavirus replication. J Virol. 2003;77(8):4597–608.
23. Gui M, Song W, Zhou H, Xu J, Chen S, Xiang Y, et al. Cryo-electron microscopy structures of the SARS-CoV spike glycoprotein reveal a prerequisite conformational state for receptor binding. Cell Res. 2017;27(1):119–29.
24. Rabaan AA, Al-Ahmed SH, Haque S, Sah R, Tiwari R, Malik YS, et al. SARS-CoV-2, SARS-CoV, and MERS-CoV: a comparative overview. Infez Med. 2020;28(2):174–84.
25. Zeng Q, Langereis MA, van Vliet AL, Huizinga EG, de Groot RJ. Structure of coronavirus hemagglutinin-esterase offers insight into corona and influenza virus evolution. Proc Natl Acad Sci. 2008;105(26):9065–9.

26. Chan JF, Kok KH, Zhu Z, Chu H, To KK, Yuan S, et al. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. Emerg Microb Infect. 2020;9(1):221–36.
27. Chen Y, Liu Q, Guo D. Emerging coronaviruses: genome structure, replication, and pathogenesis. J Med Virol. 2020;92(4):418–23.
28. Mirza MU, Froeyen M. Structural elucidation of SARS-CoV-2 vital proteins: computational methods reveal potential drug candidates against main protease, Nsp12 polymerase and Nsp13 helicase. J Pharm Anal. 2020 (Accepted manuscript). https://doi.org/10.1016/j.jpha.2020.04.008.
29. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020;395(10224):565–74.
30. Singh V, Lehl GK, Talwar M, Luthra A. The novel coronavirus and challenges for general and paediatric dentists. Occup Med (Oxford, England). 2020 (Ahead of print). https://doi.org/10.1093/occmed/kqaa055.
31. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: a review. Clin Immunol. 2020;215(108427):1–7.
32. Shang J, Ye G, Shi K, Wan Y, Luo C, Aihara H, et al. Structural basis of receptor recognition by SARS-CoV-2. Nature. 2020;581(7807):221–4.
33. Kumar S, Nyodu R, Maurya VK, Saxena SK. Morphology, genome organization, replication, and pathogenesis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In: Saxena SK, editor. Coronavirus disease 2019 (COVID-19). 1st ed. Singapore: Springer; 2020. p. 23–31.
34. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181(2):271–80.
35. Li G, Fan Y, Lai Y, Han T, Li Z, Zhou P, et al. Coronavirus infections and immune responses. J Med Virol. 2020;92(4):424–32.
36. Yi Y, Lagniton PN, Ye S, Li E, Xu R. COVID-19: what has been learned and to be learned about the novel coronavirus disease. Int J Biol Sci. 2020;16(10):1753–66.
37. Rokni M, Ghasemi V, Tavakoli Z. Immune responses and pathogenesis of SARS-CoV-2 during an outbreak in Iran: comparison with SARS and MERS. Rev Med Virol. 2020;30(3):e2107. https://doi.org/10.1002/rmv.2107.
38. Rabi FA, Al Zoubi MS, Kasasbeh GA, Salameh DM, Al-Nasser AD. SARS-CoV-2 and coronavirus disease 2019: what we know so far. Pathogens. 2020;9(3):231–44.
39. Snijder EJ, Meer Y, Dobbe J, Onderwater JM, Meulen J, Koerten H, et al. Ultrastructure and origin of membrane vesicles associated with the severe acute respiratory syndrome coronavirus replication complex. J Virol. 2006;80(12):5927–40.
40. Prompetchara E, Ketloy C, Palaga T. Immune responses in COVID-19 and potential vaccines: lessons learned from SARS and MERS epidemic. Asian Pac J Allergy Immunol. 2020;38(1):1–9.
41. Chen Y, Cai H, Xiang N, Tien P, Ahola T, Guo D. Functional screen reveals SARS coronavirus nonstructural protein nsp14 as a novel cap N7 methyltransferase. Proc Natl Acad Sci. 2009;106(9):3484–9.
42. Daffis S, Szretter KJ, Schriewer J, Li J, Youn S, Errett J, et al. 2′-O methylation of the viral mRNA cap evades host restriction by IFIT family members. Nature. 2010;468(7322):452–6.
43. Mason RJ. Pathogenesis of COVID-19 from a cell biology perspective. Eur Respir J. 2020;55:2000607. https://doi.org/10.1183/13993003.00607-2020.
44. Li X, Geng M, Peng Y, Meng L, Lu S. Molecular immune pathogenesis and diagnosis of COVID-19. J Pharm Anal. 2020;10(2):102–8.
45. Zhang Y, Geng X, Tan Y, Li Q, Xu C, Xu J, et al. New understanding of the damage of SARS-CoV-2 infection outside the respiratory system. Biomed Pharmacother. 2020;127:110195.

46. Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential effects of coronaviruses on the cardiovascular system: a review. JAMA Cardiol. 2020:E1–E10 (Ahead of print). https://doi.org/10.1001/jamacardio.2020.1286.
47. Wong SH, Lui RN, Sung JJ. Covid-19 and the digestive system. J Gastroenterol Hepatol. 2020;35(5):744–8.
48. Fan C, Li K, Ding Y, Lu WL, Wang J. ACE2 expression in kidney and testis may cause kidney and testis damage after 2019-nCoV infection. BMJ. 2020 (Pre-print). https://doi.org/10.1101/2020.02.12.20022418.
49. Chaux-Bodard AG, Deneuve S, Desoutter A. Oral manifestation of Covid-19 as an inaugural symptom? J Oral Med Oral Sur. 2020;26(2):18.
50. Vinayachandran D, Balasubramanian S. Is gustatory impairment the first report of an oral manifestation in COVID-19? Oral Dis. 2020;00:1–2.
51. Presas M, Sánchez A, López AF, Jané E, Pérez ML. Oral vesiculobullous lesions associated with SARS-CoV-2 infection. Oral Dis. 2020: 1–3 (Ahead of print). https://doi.org/10.1111/odi13382.
52. Aiello F, Afflitto GG, Mancino R, Li JP, Cesareo M, Giannini C, et al. Coronavirus disease 2019 (SARS-CoV-2) and colonization of ocular tissues and secretions: a systematic review. Eye. 2020:1–6 (Ahead of print). https://doi.org/10.1038/s41433-020-0926-9.
53. Dockery DM, Rowe SG, Murphy MA, Krzystolik MG. The ocular manifestations and transmission of COVID-19; recommendations for prevention. J Emerg Med. 2020 (Article in press). https://doi.org/10.1016/j.jemermed.2020.04.060.
54. Guarneri C, Rullo EV, Pavone P, Berretta M, Ceccarelli M, Natale A et al. Silent COVID-19: what your skin can reveal. Lancet Infect Dis. 2020 (Ahead of print). https://doi.org/10.1016/S1473-3099(20)30402-3.
55. Morey-Olivé M, Espiau M, Mercadal-Hally M, Lera-Carballo E, García-Patos V. Cutaneous manifestations in the current pandemic of coronavirus infection disease (COVID 2019). Anales De Pediatria. 2020 (Ahead of print). https://doi.org/10.1016/j.anpede.2020.04.002.
56. Sachdeva M, Gianotti R, Shah M, Lucia B, Tosi D, Veraldi S, et al. Cutaneous manifestations of COVID-19: report of three cases and a review of literature. J Dermatol Sci. 2020;98(2):75–81.

Clinical Manifestations of Corona Virus Disease

3

Piyush Srivastava and Nidhi Gupta

3.1 Introduction

COVID-19, formerly called "2019 novel coronavirus" or "2019-nCoV," is the name given to the disease caused by a new strain of coronavirus, called severe acute respiratory syndrome coronavirus-2 or SARS-CoV-2. SARS-CoV-2 belongs to the family of highly contagious β-coronaviruses, including the fatal severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). However, compared to its predecessors, SARS-CoV-2 is less fatal, with a greater number of asymptomatic cases, thereby resulting in extensive spread of COVID-19 in significantly larger number of individuals worldwide.

As per the latest World Health Organization (WHO) situation report, SARS-CoV-2 has an overall case fatality rate of 1.4%, with the documented rates varying widely from <1% to >7%, depending on the study population demographics [1]. However, the results of recently conducted seroprevalence studies from across the world have demonstrated that that the actual number of infected cases is much higher than the cumulative number of confirmed infections, probably due to lack of screening of asymptomatic or mildly symptomatic (paucisymptomatic) individuals [2, 3]. Hence, the reported fatality rates based on confirmed cases may be higher than rates based on number of infections, falsely elevating the rates of hospitalization, critical condition, and disease fatality. Nevertheless, SARS-CoV-2 appears to have a complex and unpredictable disease course and needs further elucidation. The enormous wealth of data generated on SARS-CoV-2 to date suggests that it can

P. Srivastava
Department of Liver Transplant Anaesthesia and Critical Care, Fortis Hospital, Noida, Uttar Pradesh, India

N. Gupta (✉)
Department of Neuroanaesthesia, Indraprastha Apollo Hospital, New Delhi, India

H. Prabhakar et al. (eds.), *Clinical Synopsis of COVID-19*,
https://doi.org/10.1007/978-981-15-8681-1_3

affect anyone—from infants to the elderly, male and female, newborn and pregnant women—resulting in a wide variety of clinical signs and symptoms, with varying disease severity.

3.2 Clinical Manifestations of COVID-19

COVID-19 has indeed baffled the healthcare professionals worldwide with its widespread symptomatology, multiorgan involvement, and a wide spectrum of disease severity ranging from asymptomatic to symptomatic but mild or moderate, to severe requiring intensive care management, and to the disease being fatal (Table 3.1). As per WHO, approximately 80% of infections in COVID-19 are mild-to-moderate or asymptomatic; 15% develop severe disease that requires supplemental oxygen; and 5% have critical disease with complications such as respiratory failure, acute respiratory distress syndrome (ARDS), sepsis and septic shock, acute kidney injury, thromboembolism, and/or multiorgan failure [4]. Other acute and life-threatening conditions that have been described in COVID-19 patients include acute pulmonary embolism, acute coronary syndrome, delirium, and acute stroke.

Symptomatic cases often develop a wide spectrum of clinical manifestations on an average of 5–6 days (can be up to 14 days) after exposure to the virus (Table 3.2).

Table 3.1 Clinical criteria for assessing the severity of COVID-19 disease in adults

Disease severity	Clinical criteria
Asymptomatic	No clinical symptoms No findings on chest imaging
Mild disease	Symptomatic patients with minimal symptoms No hypoxia No evidence of viral pneumonia in chest imaging studies
Moderate disease	Pneumonia Presence of fever, cough, dyspnea, and fast breathing but no signs of severe pneumonia $SpO_2 \geq 90\%$ on room air Multiple limited patchy shadows and interstitial changes in chest imaging
Severe disease	Severe pneumonia Presence of fever, cough, dyspnea, and fast breathing with either respiratory rate of >30 breaths per minute or severe respiratory distress or $SpO_2 < 90\%$ on room air or $PaO_2/FiO_2 \leq 300$ mmHg Multilobular disease or lesion progression of >50% within 48 h Sequential organ failure assessment of ≥2 points and/or other clinical conditions requiring hospitalization
Critical disease	Acute respiratory distress syndrome with chest imaging showing bilateral opacities, not fully explained by volume overload, lobar or lung collapse, or nodules Sepsis Septic shock Multiorgan dysfunction

SpO_2 blood oxygen saturation level, *PaO_2* arterial blood partial pressure of oxygen, *FiO_2* fraction of inspired oxygen

Table 3.2 Organ-specific clinical manifestations of COVID-19

General	Fever, anorexia, soreness in throat, rhinorrhea, nasal stuffiness or congestion, dizziness, fatigue or myalgia and arthralgia
Respiratory	Cough, dyspnea or shortness of breath, chest tightness or tachypnea, silent hypoxemia, excessive mucus production with expectoration, hemoptysis Chest computed tomography findings: Bilateral, peripheral/subpleural, posterior ground-glass opacities, with or without consolidations; pulmonary vascular Enlargement, intralobular septal thickening, adjacent pleural thickening, air bronchograms, subpleural lines, and crazy paving
Neurological	Headache, myalgia, dizziness, anosmia or hyposmia, hypogeusia, impaired consciousness, acute cerebrovascular disease (acute ischemic stroke and acute cerebral hemorrhage), ataxia, seizure, meningitis/encephalitis, acute disseminated encephalomyelitis, acute encephalopathy, acute transverse myelitis, Guillain–Barré syndrome and its variants, nerve injury Delirium, anxiety, depression, mood swings, insomnia, psychosis, and suicidal ideation
Cardiovascular	Acute myopericarditis, myocarditis, pericardial effusion and /or cardiac tamponade, arrhythmias, acute myocardial injury, new or worsening heart failure, stress cardiomyopathy, arrhythmias, cardiogenic shock, arterial and venous thromboembolic events, and cardiac arrest
Gastrointestinal and hepatic	Anorexia, nausea and vomiting, abdominal pain, diarrhea, abnormal liver function tests (increased levels of alanine aminotransferase, aspartate aminotransferase and bilirubin; hypoalbuminemia)
Hematological and biochemical	Leukopenia or normal WBC count, leukocytosis, lymphopenia, thrombocytosis, thrombocytopenia, consumptive coagulopathy, increased levels of cytokines (IL-6, IL-10, and TNF-α) and inflammatory markers (ferritin, LDH, CRP, ESR, and procalcitonin)
Ophthalmic	Conjunctivitis, epiphora, anterior uveitis, retinitis, or optic neuritis
Dermatological	Exanthematous rash, vascular lesions, urticarial rash, and acro-papular eruption. Adverse drug skin reactions including Steven-Johnson syndrome and toxic epidermal necrolysis

IL interleukin, *TNF* tumor necrosis factor, *LDH* lactate dehydrogenase, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate

In addition, COVID-19 is characterized by a high proportion of asymptomatic cases, who despite being infected [i.e., detected positive for nucleic acid of SARS-CoV-2 by reverse transcriptase-polymerase chain reaction (RT-PCR)] does not develop any typical clinical symptoms or signs and no apparent abnormalities in images, including lung computed tomography (CT). Al-Sadeq et al. performed a systematic review of 63 studies from around the world to estimate the incidence of asymptomatic COVID-19 cases [5]. Authors found a great heterogeneity in the reported data, with studies having a large sample size (n > 1000 cases), showing a lower incidence, ranging from 1.2 to 12.9%, while studies with a smaller sample size (n < 1000) reported a much higher incidence of up to 87.9%. Apparently, the term "asymptomatic cases" in literature has been broadly applied to include all those cases who are either completely asymptomatic, have mild symptoms or CT chest

findings, and do not seek medical advice (paucisymptomatic), or develop symptoms beyond the incubation period (presymptomatic). A follow-up study of 24 asymptomatic RT-PCR-positive patients done in China showed that 60% of them were presymptomatic and showed COVID-19 symptoms after a period of 1–3 weeks [6] Similarly, in a meta-analysis of 38 studies with 506 asymptomatic cases, abnormal chest CT imaging was found in approximately 62% of cases, with ground-glass opacity being the most frequently observed abnormality (43.09%) [7]. Of note, patients with normal CT scan findings were younger than patients with abnormal CT. However, irrespective of the terminology applied for these asymptomatic cases in general, recent virologic, epidemiologic, and modeling reports have supported the possibility of SARS-CoV-2 transmission from either of them, therefore reinforcing the adoption of isolation measures by everyone infected with this virus [8].

SARS-CoV-2 apparently infects mostly adults, with the average age of hospitalized patients being 49–56 years [9–12]. Children account for approximately 1–5% of diagnosed COVID-19 cases and appear to have a mild course of disease with an overall good prognosis [13]. Very old people and immunosuppressed patients in particular may present with atypical symptoms such as fatigue, absence of fever or low-grade fever, reduced alertness, reduced mobility, diarrhea, loss of appetite, and delirium [14, 15]. Available literature also reveals a slight male predominance (54–73%) in the incidence of COVID-19, suggesting that males are more susceptible to SARSCoV-2 infection than females [12]. However, this observed gender difference could be the result of differences in susceptibility and exposure to the virus, along with bias in reporting or diagnosis of infection. Elderly male patients (over 60 years), smokers, and those with underlying conditions such as hypertension, diabetes, cardiovascular disease, chronic respiratory disease, cerebrovascular disease, chronic kidney disease, immunosuppression, and cancer are at the highest risk of getting severe disease and death, probably due to the attenuated early immune response [16, 17].

3.2.1 General Systemic Manifestations

To date, fever, cough, and/or shortness of breath have been described as the three most prevalent and typical clinical manifestations in COVID-19 patients, which are similar to any other respiratory viral illness [9–11]. In a systematic literature review with meta-analysis on clinical findings of COVID-19, fever (88.7%), cough (57.6%), and dyspnea (45.6%) were identified as the most common presenting symptom in 632 hospitalized patients with confirmed COVID-19 [10]. In another recent meta-analysis of 80 studies, fever (87%) and cough (68%) were the most commonly reported symptoms by a bigger cohort of 61,742 patients infected with SARS-CoV-2 [11].

Apparently, most initial studies on COVID-19 clinical manifestations highlighted only fever and cough as the common symptom, since in the initial stages of the pandemic the diagnostic testing was limited to only severe symptomatic cases [18]. However, the clinical data collected after the expansion of the number and

types of patients eligible for diagnostic testing reflects a more complete COVID-19 symptom profile, including symptoms such as new changes in taste and smell (anosmia/hyposmia and ageusia/ hypogeusia), anorexia, soreness in throat, rhinorrhea, nasal stuffiness or congestion, dyspnea, chest tightness or heaviness, cough with excessive mucus production and expectoration, hemoptysis, headache, dizziness, fever with chills, fatigue or myalgia, arthralgia, nausea, vomiting, abdominal pain, and diarrhea [19]. In addition, some patients may report even nonspecific or vague symptom such as chills and a "tickle in throat," without cough and normal chest radiograph.

3.2.2 Respiratory Manifestations

Lung involvement is the most common manifestation of COVID-19, ranging from mild pneumonia to severe disease associated with hypoxia and finally critical disease associated with ARDS and death. [9, 12, 14, 16–18, 20] The most common clinical manifestations of pneumonia cases associated with COVID-19 include fever, non-productive cough, and dyspnea, which are consistent with the manifestation of lower respiratory tract infections. Compared with moderate cases, severe cases more frequently report chest tightness along with tachypnea and dyspnea [with oxygen saturation level (SpO_2) of 90% or lower and showing no improvement even with high-flow nasal cannula [12]. Out of 82 patients admitted at a single institution in India with confirmed COVID-19, up to 75% patients were admitted with severe pneumonia, with a mortality rate as high as 28% [20].

Hypoxia is frequently a presenting feature of COVID-19 pneumonia [21]. However, one atypical presentation is the occurrence of extremely low SpO_2 levels along with normal breathing, commonly being referred to as "silent hypoxemia" or "apathetic hypoxia" or "happy hypoxia." [22] Though it is insidious in onset and initially well tolerated by patients, it can be a harbinger of sudden clinical deterioration with rapid progression to severe hypoxia and respiratory failure [21, 23]. Elucidating the different clinical findings of severe hypoxemia, Gattinoni et al. have identified two distinct phenotypes of COVID-19 pneumonia [24]. At the beginning, COVID-19 pneumonia presents with Type L phenotype characterized by low elastance (i.e., high compliance), low ventilation-to-perfusion ratio, low lung weight with only ground-glass densities present on CT scan (primarily located subpleurally and along the lung fissures), and very little amount of non-aerated recruitable tissue. The near-normal lung compliance and increased respiratory drive explains absence of dyspnea with hypoxemia. As the disease progresses, Type L may evolve into Type H COVID-19 pneumonia in nearly 20–30% of patients. It is characterized by severe hypoxemia, decreased respiratory system compliance, increased lung weight with bilateral infiltrates on chest CT scan, and potential for lung recruitment. Serial CT chest imaging of patients thus could help to continuously monitor the disease changes and establish the basis for appropriate treatment.

In chest radiological findings, chest X-ray are usually normal in mild to moderate cases. However, in patients with severe pneumonia, bilateral patchy nodular or

interstitial infiltration is seen in more than 90% of cases. (Fig. 3.1) Ground-glass haziness or opacification, with or without subsegmental areas of consolidation, are the most common chest CT scan findings, seen in approximately 50% and 44% cases, respectively [25]. Most of these lesions are bilateral (seen in >80% patients), located peripherally or subpleural, and posterior with a lower lobe predominance [9–11, 25] (Figs. 3.2 and 3.3). Other common findings include pulmonary vascular

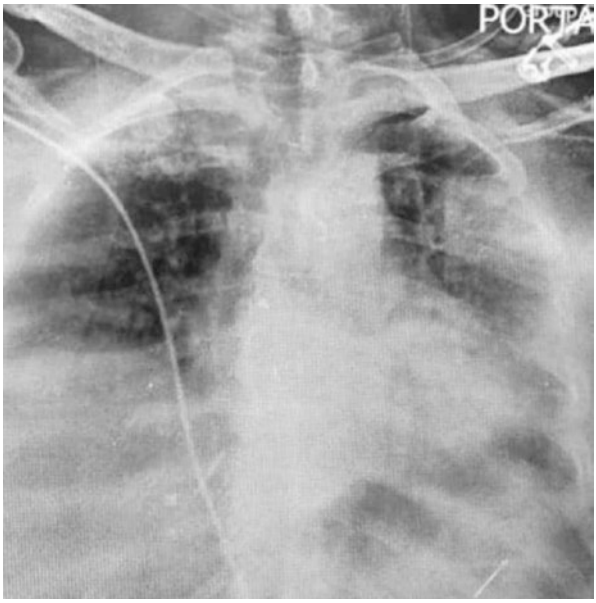


Fig. 3.1 A 62-year-old male, known case of hypothyroidism, presented with fever, cough, dyspnea, anorexia, and diarrhea. Chest X ray shows bilateral heterogenous chest infiltrates consistent with severe pneumonia

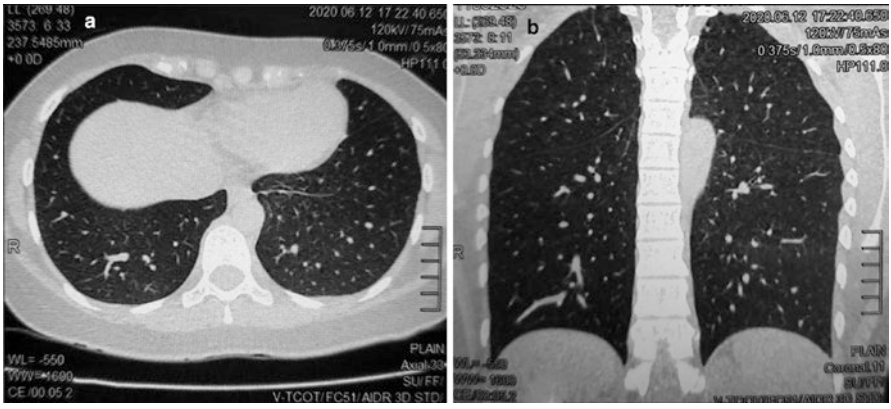


Fig. 3.2 A 30-year-old female presented with mild COVID-19 symptoms including fever, cough, sore throat, fatigue and anosmia. CT scan chest (**a**, axial view and **b**, coronal view) shows near-normal findings with a documented small patchy area of ground glass opacity in postero-basal segment of right lower lobe

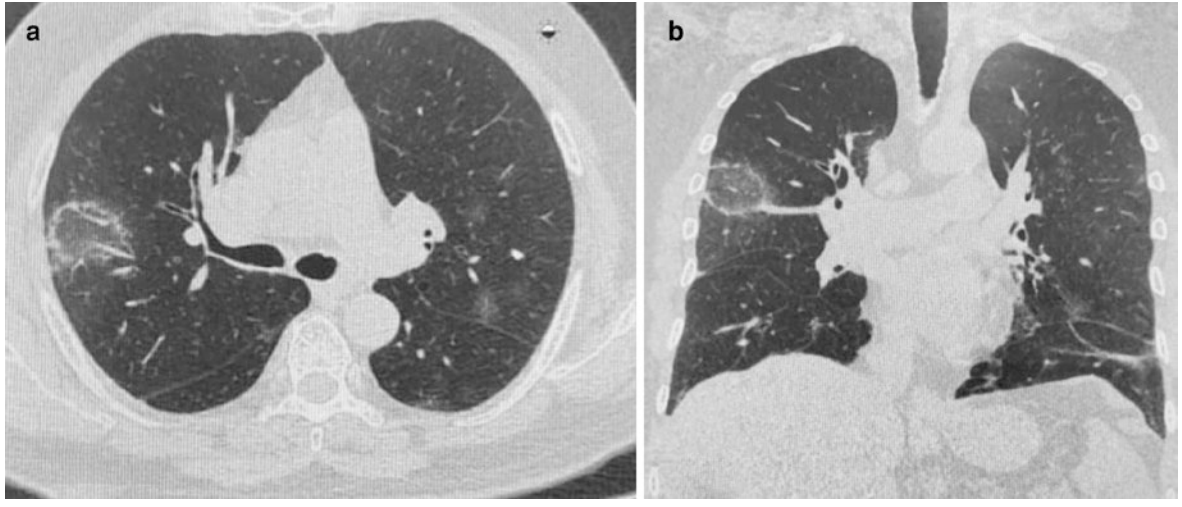


Fig. 3.3 A 72-year-old male, known case of multiple myeloma on chemotherapy, presented with mild fever, cough, and myalgia. CT scan chest (**a**, axial view and **b**, coronal view) shows a peripheral ground glass opacity with consolidation in right lower lobe and few pure ground-glass opacities in left lower lobe, with fibrous stripes

enlargement (64%), intralobular septal thickening (60%), adjacent pleural thickening (41.7%), air bronchograms (41.2%), subpleural lines, crazy paving, bronchus distortion, bronchiectasis, and interlobular septal thickening (Figs. 3.4 and 3.5). In severe and critically ill patients, chest CT scan may demonstrate extensive multilobular and diffuse infiltrates which can rapidly evolve into full lung consolidation (Fig. 3.5).

3.2.3 Neurological Manifestations

There has been a consistently growing literature regarding the neurological manifestations of SARS-CoV-2 virus, which share structural homology to other known neurotropic coronaviruses, such as the SARS-CoV and MERS [26–28]. However, the neurotropism and neuropathogenicity of SARS-CoV-2 is complex and not yet fully elucidated [29]. Direct entry of virus to the nervous system could plausibly be achieved via the transcribial route infecting the olfactory nerve, axonal transport, and trans-synaptic transfer across infected neurons, hematogenous and/or lymphatic spread leading to infection of vascular endothelium, or leukocyte migration across the inflamed blood-brain barrier. In addition, various indirect mechanisms such as hypoxia, coagulation dysfunction, cytokine storm, immune-mediated neuroinflammation, altered lung-brain and gut-brain crosstalk, and presence of cardiovascular comorbidities, like hypertension or diabetes (especially in elderly population), may contribute to the neuropathogenesis of severe neurological manifestations.

The most common neurological manifestations of SARS-CoV-2 include headache, myalgia, dizziness, new onset smell and taste dysfunction, and impaired consciousness. In an initial investigational study of neurologic manifestations of 214 COVID-19 patients from Wuhan, China; a total of 78 patients (36.4%) manifested

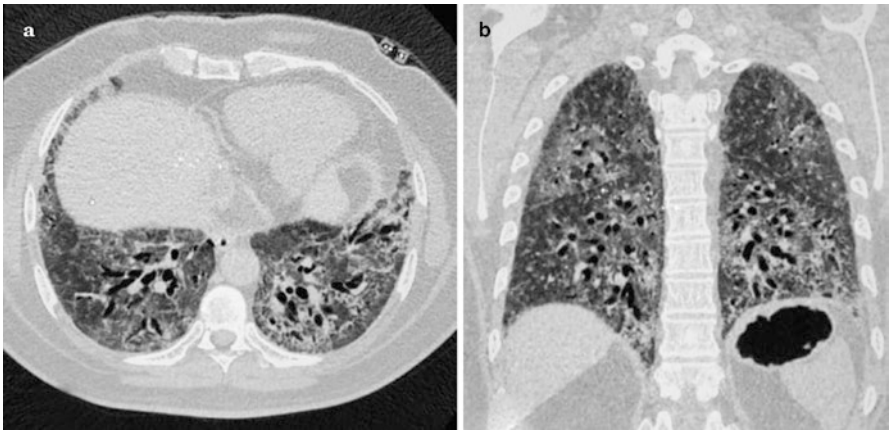


Fig. 3.4 A 57-year-old male, known hypertensive, diabetic and asthmatic, presented with fever, productive cough, and chest pain. CT scan chest (**a**, axial view and **b**, coronal view) shows bilateral interlobular septal thickening with ground glass opacities and traction bronchiectasis

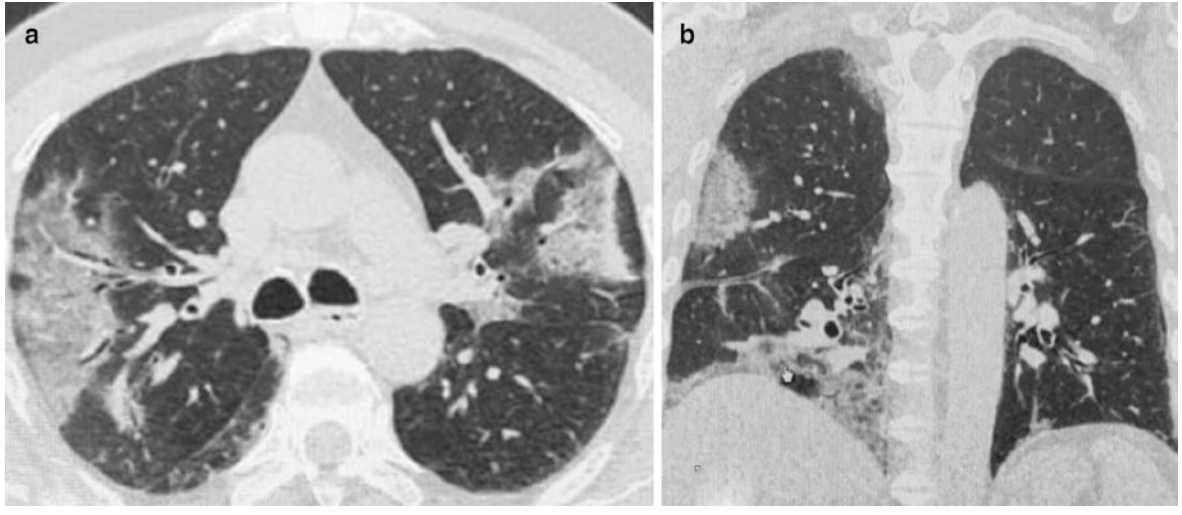


Fig. 3.5 A 59-year-old male, known case of hypertension and diabetes, presented with complaints of fever, dry cough, and headache. CT scan chest (**a**, axial view and **b**, coronal view) shows peripheral patchy areas of ground-glass opacities with consolidation and fibrosis in both lungs

neurological symptoms including central nervous system (CNS) manifestations (dizziness, headache, impaired consciousness, acute cerebrovascular disease, ataxia, and seizure), peripheral nervous system manifestations (new changes in smell or taste, vision impairment, and nerve pain), and skeletal muscular injury manifestations [27]. Compared to patients with mild to moderate disease, patients with severe COVID-19 were found to have a higher incidence of neurologic symptoms, including acute cerebrovascular diseases (5.7% vs. 0.8%), impaired consciousness (14.8% vs. 2.4%), and skeletal muscle injury (19.3% vs. 4.8%).

A recent systematic review of 92 studies on neurological symptoms of COVID-19 revealed headache [(observed in 3308 patients out of total 16,446 of patients (3308/16,446; 20.1%)], dizziness (151/2236; 6.8%), headache or dizziness as a combined manifestation (79/654; 12.1%), taste and smell dysfunctions (536/906; 59.2% and 430/846; 50.8%, respectively), and impaired consciousness (146/2890; 5.1%, ranging from 1.4 to as high as 69.0% in different studies) as the most frequently described neurological symptoms of SARS-CoV-2 infection [28]. New onset of smell and taste dysfunction and headache were more commonly reported by patients with mild or moderate COVID-19 (65.0% and 66.0%; and 10.8% respectively), as compared to patients who were serious or critically ill (3.4% and 8.3%, respectively). On the other hand, impaired consciousness (also described as confusion or agitation in certain studies) was more frequently observed among seriously ill patients (11.9%) in comparison with patients who presented with either mild or moderate COVID-19 (3.2%). Dizziness has been described as a vague symptom in majority of studies with no clear difference between vertigo and dizziness. Furthermore, the exact etiology of dizziness, such as generalized weakness, myalgia, stroke, or eight cranial nerve involvement, remains undisclosed. COVID-19 infection has been shown to have a significant independent association with acute ischemic stroke secondary to pathophysiologic mechanisms such as the proinflammatory prothrombotic state and cytokine storm [30]. Hence, COVID-19 patients without any other comorbidities may present in neurological emergency with an acute stroke.

Recent literature has revealed that new-onset smell and taste dysfunction (anosmia/hyposmia and ageusia/ hypogeusia) are well-established symptoms of COVID-19, with a reported prevalence of 52.73% (29.64–75.23%) and 43.93% (20.46–68.95%) [31]. These symptoms are more prevalent early in the clinical course of infection, with a large study of 417 patients with mild to moderate SARS-CoV-2 infection showing smell dysfunction in 85.6% and taste dysfunction in 88.8% of patients [32]. This high prevalence of olfactory and gustatory dysfunction indicates neurotropism of SARS-CoV-2, resulting in direct damage to the olfactory receptor neurons. For many patients with COVID-19, especially in paucisymptomatic patients, olfactory dysfunction may be the first or the only presenting symptom [33, 34]. Though most patients gradually regain their sense of taste and smell as they recover, some may have persistent symptoms even after complete recovery from SARS-COV-2 infection.

The complete spectrum of neuropsychiatric manifestations of COVID-19 is still unclear. Delirium is now recognized as one of the potential neurological

manifestations of COVID-19 and may be the sole presenting feature in absence of any respiratory symptom [35]. Other common neuropsychiatric manifestations reported in COVID-19 patients include anxiety, depression, mood swings, insomnia, psychosis, and suicidal ideation [36, 37].

Several other severe neurological manifestations observed in serious or critically ill COVID-19 patients reported in literature include acute cerebrovascular complications including stroke, acute cerebral hemorrhage, and cerebral venous sinus thrombosis; generalized seizures; meningitis/encephalitis; acute disseminated encephalomyelitis; acute hemorrhagic necrotizing encephalopathy; acute flaccid myelitis; Guillain–Barré syndrome and its variants (Miller Fisher syndrome, polyneuritis cranialis); and CNS demyelination [38–45].

3.2.4 Cardiovascular Manifestations

Cardiac involvement in COVID-19 patients is the commonest associated comorbidity in the form of hypertension and the commonest complication associated with mortality in the form of acute myocardial injury as a result of acute coronary syndrome, new or worsening heart failure, myocarditis, stress cardiomyopathy, arrhythmias, cardiogenic shock, and cardiac arrest [46]. Furthermore, cardiac involvement has been shown to occur both in the presence as well as absence of respiratory involvement [47].

The most plausible causative mechanisms of cardiac manifestations include direct viral invasion of myocardium, hypoxemia, unstable hemodynamic status with hypoperfusion, instability of coronary plaque, enhanced systematic inflammation, ACE2 receptor downregulation, cytokine storm, increased catecholamine production, and concurrent medication toxicity [48]. COVID-19 patients may present with acute myopericarditis with typical chest pain and pericardial effusion and/or cardiac tamponade, myocarditis, acute myocardial injury, and de novo arrhythmias [47, 49–51]. Arterial and venous thromboembolic events, presenting either as aortic thrombosis, deep vein thrombosis, acute pulmonary embolism, ischemic stroke, or myocardial infarction, secondary to COVID-19-associated coagulopathy, are common cardiovascular manifestation among severe COVID-19 patients [52, 53].

Laboratory testing, including serial cardiac troponin and D-dimer levels, electrocardiography (ECG), echocardiography, and CT coronary angiography, in suspected individuals with recent symptoms of an acute cardiac illness helps in early identification and prompt treatment of COVID-19-related cardiovascular manifestations. An analysis of ECGs from 50 patients with proven COVID-19 pneumonia showed ST-T abnormalities in 30% of patients and left ventricular hypertrophy in 33% of patients at baseline [54]. During hospitalization, 26% of patients developed new ECG abnormalities which included atrial fibrillation, ST-T changes, tachybrady syndrome, and changes consistent with acute pericarditis. Pavri et al. have demonstrated that abnormal PR interval behavior (paradoxical prolongation or lack of shortening) with an increasing heart rate is associated with increased severity of disease and mortality [55].

Cardiac injuries have more frequently been observed in patients with severe disease and leads to the higher mortality rate (10.5%) than those without cardiac injuries [48]. In a cohort of 54 patients with COVID-19, troponin I (TnI) elevation was found in 42.6% of all the 39 severe and 15 critical patients [56]. Sinus tachycardia was the most common type of arrhythmia, present in all critical patients and 23 severely ill patients. Atrioventricular block and ventricular tachycardia were observed in critically ill patients at end stage, while bradycardia and atrial fibrillation were less common. Of note, persistent hypotension during treatment, presence of pericardial effusion, and severe myocardial injury have been found as independent risk predictors for severity of COVID-19 [46–48, 56].

3.2.5 Gastrointestinal and Hepatic Manifestations

Though initially overlooked in the course of pandemic, the frequent involvement of the gastrointestinal (GI) tract and the hepatic system by SARS-CoV-2 is now being increasingly recognized in the literature. SARS-CoV-2 infects the GI tract via its viral angiotensin-converting enzyme II receptor, which is found to be highly expressed both in GI epithelial cells and in liver [57, 58].

GI symptoms can manifest with a frequency as high as 39.6–50% in COVID-19 patients [58]. The most common GI presentation in patients with COVID-19 includes anorexia (1.0–78.64% %), diarrhea (3.8–34%), nausea and/or vomiting (3.9–10.1%), and abdominal pain (1.1–5%) [11, 58–60]. These GI symptoms may either coexist, occur prior to the onset of, or may even manifest in the complete lack of respiratory manifestations of COVID-19. It is important for gastroenterologist to recognize that diarrhea may be the only presenting feature of COVID-19. Most cases of diarrhea are mild and present as nondehydrating loose stools. In a cross-sectional multicentric study focusing on the prevalence of digestive symptoms of COVID-19, Pan et al. found that nearly 50% patients presented with one or more digestive symptom, including lack of appetite (78.6% of cases), diarrhea (35% of cases), vomiting (3.9% of cases), and abdominal pain (1.9% of cases). Of the total 103 patients, 97 had developed respiratory symptoms along with digestive symptoms, while 6 presented with only digestive symptoms in the absence of respiratory symptoms [59]. Authors also found that patients with digestive symptoms were more likely to exhibit elevated liver enzymes and prolonged coagulation on laboratory testing.

Mao et al. performed a systematic review and meta-analysis of 35 studies, comprising 6686 patients, to determine the prevalence and prognosis of digestive system involvement, including gastrointestinal symptoms and liver injury, in patients with COVID-19 [60]. Authors found that the pooled prevalence of all GI symptoms was 15%, with nausea and/or vomiting, diarrhea, and loss of appetite being the three most common symptoms, while the pooled prevalence of abnormal liver functions was 19%. Of concern, patients with GI symptoms were found to have a delayed diagnosis, severe course of disease, and a higher prevalence of complications. Recent literature also confirms fecal–oral transmission of COVID-19, indicating

that the virus can replicate in both respiratory and digestive tract [61]. Mao et al. demonstrated a pooled estimate of 54% for SARS-CoV-2 viral RNA positivity in fecal samples, with positivity persisting for up to 47 days after symptom onset [60]. However, isolating virus from stool samples does not necessarily equate to virus infectivity, and more research is needed to establish the direct role of feco-oral route in disease transmission.

In addition to the GI manifestations, the SARS-CoV-2 infection may also lead to a broad spectrum of liver impairment, secondary to hepatocyte invasion, hepatotoxic potential of drugs used for COVID-19 treatment, or immune-mediated liver injury. The reported incidence of liver function abnormalities in patients with COVID-19 ranges from 1% to 53% [59, 60, 62]. These abnormalities commonly include increased levels of hepatocyte-related enzymes, including alanine aminotransferase (ALT) and aspartate aminotransferase (AST) along with total bilirubin concentrations, with greater elevations seen in severe cases compared with moderate cases [12]. Cholangiocyte-related enzymes, such as alkaline phosphatase and γ-glutamyl transpeptidase, have also been reported to be slightly increased in a few patients [62]. Hypoalbuminemia (<35 g/L) is seen in severe cases and may predict the outcome of COVID-19 independent of age and comorbidity [12, 63]. Most patients only have mild elevation of liver enzymes levels, which resolves as the patient improves clinically. However, the risk of hepatic injury increases with the increasing severity of COVID-19, with a noted pooled prevalence of 22.8% (11.7–39.8%) among 288 death cases [64].

3.2.6 Hematological and Biochemical Manifestations

COVID-19 cases commonly present with wide variation in white blood cell (WBC) counts, ranging from leukopenia or normal WBC count, leukocytosis, and lymphopenia. Lymphopenia is the most common WBC derangement (noted in approximately 35–75% of patients) and is believed to represent a defective immune response to the virus [9, 10, 65]. SARS-CoV-2 primarily affects T lymphocytes, in particular CD4+ and CD8+ T cells, causing lymphopenia and a decrease in interferon γ (IFN-γ) production by CD4+ T cells. Since the production of IFN-γ is essential for the resistance against infection of various pathogens including viruses, the suppression of IFN-γ production in severe cases seems to correlate with disease severity of COVID-19 [12].

Compared to leukopenia, leukocytosis (either neutrophilia, lymphocytosis, or both) is noted in a minority of COVID-19-infected patients and may represent a superimposed bacterial infection or the hyperinflammatory state associated with cytokine storm (particularly neutrophilia). Thrombocytopenia is more frequently found in severe cases and is associated with nearly fivefold increased risk of mortality [66]. Recent laboratory findings analysis of 61,742 patients with SARS-CoV-2 infection revealed thrombocytosis in 61%, lymphopenia in 57.5%, leukopenia in 28%, leukocytosis in 18.3%, and thrombocytopenia in only 13% of patients [11].

The evaluation of serum cytokines on admission reveal significantly increased levels of macrophage-related proinflammatory cytokines [interleukin (IL) 2R, IL-6, IL-10, and tumor necrosis factor α (TNF-α)], particularly in severe COVID-19 cases [12]. Neutrophil/lymphocyte ratio and peak platelet/lymphocyte ratio can be used as independent prognostic markers in determining disease severity [67]. Coagulation parameters, particularly the values of prothrombin time and activated partial thromboplastin time, D-dimer, fibrin, and fibrin/fibrinogen degradation products, are more frequently deranged in patients with severe or critical COVID-19 and are suggestive of onset of consumptive coagulopathy [68].

In association with hematological markers, multiple biochemical markers of systemic inflammation, and organ injury, including serum levels of ferritin, lactate dehydrogenase, C-reactive protein (CRP), erythrocyte sedimentation rate, procalcitonin, and cortisol, liver enzymes (ALT and AST), serum creatinine, and cardiac-specific troponin levels tend to be higher in severe cases compared to mild and moderate cases and denotes poor prognosis [9–12, 69].

3.2.7 Ophthalmic Manifestations

The ophthalmic manifestations of COVID-19 may develop in the form of conjunctivitis, epiphora, anterior uveitis, retinitis, or optic neuritis [70–72]. Conjunctivitis may even manifest as the sole symptom, with either redness, irritation, foreign body sensation, or tearing in eyes, thus predisposing the ophthalmologists to the risk of contracting the virus in undiagnosed or unsuspected cases [73]. Examination findings are consistent with clinical diagnosis of mild follicular conjunctivitis and may include unilateral or bilateral bulbar conjunctival hyperemia, follicular reaction of the palpebral conjunctiva, watery discharge, and mild eyelid edema. Bilateral chemosis alone may represent third-spacing in a critically ill patient rather than a true ocular manifestation of the virus.

In a retrospective analysis of 38 patients with clinically confirmed COVID-19, 12 patients (31.6%) had ocular manifestations suggestive of conjunctivitis [71]. Patients with ocular symptoms were found to have higher values of WBC and neutrophil counts procalcitonin, CRP, and LDH. While 11 of 12 patients (91.7%) had positive RT-PCR test results from nasopharyngeal swabs, only two (16.7%) tested positive for SARS-CoV-2 from both nasopharyngeal and conjunctival swabs. Conjunctival specimens usually demonstrate the presence of viral RNA during the middle phase of illness and may not be useful in early diagnosis [72, 74]. Nonetheless, despite the low prevalence and rapid regression of viral presence in the conjunctiva, SARS-CoV-2 transmission through tears may be possible, even in patients without apparent ocular involvement [75].

3.2.8 Dermatological Manifestations

SARS-CoV-2 infection can affect skin like any other organ system. The patterns of dermatological manifestations associated with SARS-CoV-2 could be classified into four main categories: exanthema (varicella-like, papulovesicular, and morbilliform rash), vesicular (chilblain-like, purpuric/petechial, and livedoid lesions), urticarial, and acro-papular eruption [76]. In addition, one should also consider the cutaneous adverse drug reactions to the prescribed drugs for the treatment of COVID-19 in the differential diagnosis of skin lesions [77]. Rare occurrence of oral ulceration and blistering has also been described as one of the dermatological manifestations of COVID-19 [78].

Highlighting the wide spectrum of cutaneous manifestations associated with COVID-19, Freeman et al. demonstrated morphologies such as morbilliform (22%), pernio-like (18%), urticarial (16%), macular erythema (13%), vesicular (11%), papulosquamous (9.9%), and retiform purpura (6.4%) in 171 patients from an international registry from the American Academy of Dermatology [79]. In a nationwide study from Spain, Casas C et al. have described five cutaneous clinical patterns and several subpatterns associated with COVID-19 in the form of pseudo-chilblain (19%), vesicular eruptions (9%), urticarial lesions (19%), maculo-papules (47%), and livedo or necrosis (6%) [80]. They also showed that the large groups appear at different times in the disease and are associated with different duration, severity, and probably prognosis. Hence, accurate diagnosis of the varied skin lesions seen in COVID-19 may help in early diagnosis and categorization of the disease.

3.3 Summary

SARS-CoV-2 viral infection has been shown to infect people across all the ages and range in severity from completely asymptomatic, to symptomatic with multisystemic manifestations, to being lethal with dramatic complications. As our knowledge about COVID-19 is rapidly evolving, new and atypical symptoms are being added to the existing broad list of clinical manifestations. It is important that public healthcare professionals and clinicians are aware of the entire clinical spectrum of SARS-CoV-2 infection so as to aid prompt recognition of infected cases. Timely diagnosis can lead to appropriate isolation and treatment measures, thus helping to curb the growing menace of this global pandemic.

Acknowledgments Authors wish to acknowledge Dr. Pooja Chapegadikar and Dr. Shraya Banerjee (DNB Neuroanaesthesiology and Critical Care students at Indraprastha Apollo Hospitals, New Delhi, India) for providing the Chest Imaging findings of COVID-19 patients.

References

1. World Health Organization. Coronavirus disease (COVID-19) situation report – 196. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200801-covid-19-sitrep-194.pdf?sfvrsn=401287f3_2. Accessed 3 Aug 2020.
2. Sood N, Simon P, Ebner P, et al. Seroprevalence of SARS-CoV-2-specific antibodies among adults in Los Angeles County, California, on April 10-11, 2020 [published online ahead of print, 2020 May 18]. JAMA. 2020;323(23):2425–7.
3. Pollán M, Pérez-Gómez B, Pastor-Barriuso R, et al. Prevalence of SARS-CoV-2 in Spain (ENE-COVID): a nationwide, population-based seroepidemiological study [published online ahead of print, 2020 Jul 3]. Lancet. 2020;396:535–44. pii: S0140-6736(20)31483-5.
4. World Health Organization (WHO). Clinical management of COVID-19. Interim guidances; 27 May 2020.
5. Al-Sadeq DW, Nasrallah GK. The incidence of the novel coronavirus SARS-CoV-2 among asymptomatic patients: a systematic review [published online ahead of print, 2020 Jul 2]. Int J Infect Dis. 2020;98:372–80. pii: S1201-9712(20)30533-6.
6. Hu Z, Song C, Xu C, et al. Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. Sci China Life Sci. 2020;63(5):706–11.
7. Kronbichler A, Kresse D, Yoon S, Lee KH, Effenberger M, Shin JI. Asymptomatic patients as a source of COVID-19 infections: a systematic review and meta-analysis [published online ahead of print, 2020 Jun 17]. Int J Infect Dis. 2020;98:180–6.
8. Furukawa NW, Brooks JT, Sobel J. Evidence supporting transmission of severe acute respiratory syndrome coronavirus 2 while presymptomatic or asymptomatic. Emerg Infect Dis. 2020;26(7):e201595.
9. Zhu J, Ji P, Pang J, Zhong Z, Li H, He C, Zhang J, Zhao C. Clinical characteristics of 3062 COVID-19 patients: a meta-analysis. J Med Virol. 2020. https://doi.org/10.1002/jmv.25884. Online ahead of print.
10. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, et al; Latin American Network of Coronavirus Disease 2019-COVID-19 Research (LANCOVID-19). Clinical, laboratory and imaging features of COVID-19: a systematic review and meta-analysis. Travel Med Infect Dis. 2020;34:101623. https://www.lancovid.org.
11. Pormohammad A, Ghorbani S, Baradaran B, et al. Clinical characteristics, laboratory findings, radiographic signs and outcomes of 61,742 patients with confirmed COVID-19 infection: a systematic review and meta-analysis [published online ahead of print, 2020 Jul 15]. Microb Pathog. 2020;147:104390.
12. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest. 2020;130(5):2620–9.
13. Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. Acta Paediatr. 2020;109(6):1088–95.
14. Rui L, Sirui L, Xuebei D, Xujun Y, Yanggan W. Clinical observations in very elderly patients with COVID-19 in Wuhan. Geriatr Gerontol Int. 2020;20(7):709–14.
15. Guillen E, Pineiro GJ, Revuelta I, et al. Case report of COVID-19 in a kidney transplant recipient: does immunosuppression alter the clinical presentation? Am J Transplant. 2020;20(7):1875–8.
16. 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;395(10229):1054–62. Epub 2020/03/15.
17. Li X, Xu S, Yu M, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol. 2020;146(1):110–8.
18. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708–20.

19. Burke RM, Killerby ME, Newton S, et al. Symptom profiles of a convenience sample of patients with COVID-19 - United States, January-April 2020. MMWR Morb Mortal Wkly Rep. 2020;69(28):904–8.
20. Aggarwal A, Shrivastava A, Kumar A, Ali A. Clinical and epidemiological features of SARS-CoV-2 patients in SARI Ward of a Tertiary Care Centre in New Delhi. J Assoc Physicians India. 2020;68(7):19–26.
21. Ottestad W, Seim M, Mæhlen JO. COVID-19 with silent hypoxemia. Covid-19 med stille hypoksemi. Tidsskr Nor Laegeforen. 2020;140(7). https://doi.org/10.4045/tidsskr.20.0299.
22. Tobin MJ, Laghi F, Jubran A. Why COVID-19 silent hypoxemia is baffling to physicians. Am J Respir Crit Care Med. 2020;202(3):356–60.
23. Wilkerson RG, Adler JD, Shah NG, Brown R. Silent hypoxia: A harbinger of clinical deterioration in patients with COVID-19 [published online ahead of print, 2020 May 22]. Am J Emerg Med. 2020;S0735-6757(20)30390-9.
24. Gattinoni L, Chiumello D, Caironi P, Busana M, Romitti F, Brazzi L, Camporota L. COVID-19 pneumonia: different respiratory treatments for different phenotypes? Intensive Care Med. 2020;46(6):1099–102.
25. Ojha V, Mani A, Pandey NN, Sharma S, Kumar S. CT in coronavirus disease 2019 (COVID-19): a systematic review of chest CT findings in 4410 adult patients [published online ahead of print, 2020 May 30]. Eur Radiol. 2020;1–10.
26. Montalvan V, Lee J, Bueso T, De Toledo J, Rivas K. Neurological manifestations of COVID-19 and other coronavirus infections: a systematic review. Clin Neurol Neurosurg. 2020;194:105921.
27. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, Chang J, Hong C, Zhou Y, Wang D, Miao X, Li Y, Hu B. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol. 2020;77(6):1–9.
28. Chen X, Laurent S, Onur OA, Kleineberg NN, Fink GR, Schweitzer F, Warnke C. A systematic review of neurological symptoms and complications of COVID-19. J Neurol. 2020;20:1–11.
29. Yachou Y, El Idrissi A, Belapasov V, Ait Benali S. Neuroinvasion, neurotropic, and neuroinflammatory events of SARS-CoV-2: understanding the neurological manifestations in COVID-19 patients. Neurol Sci. 2020;28:1–13.
30. Belani P, Schefflein J, Kihira S, et al. COVID-19 Is an Independent Risk Factor for Acute Ischemic Stroke [published online ahead of print, 2020 Jun 25]. AJNR Am J Neuroradiol. 2020. https://doi.org/10.3174/ajnr.A6650.
31. Tong JY, Wong A, Zhu D, Fastenberg JH, Tham T. The prevalence of olfactory and gustatory dysfunction in COVID-19 patients: a systematic review and meta-analysis. Otolaryngol Head Neck Surg. 2020;163(1):3–11.
32. Lechien JR, Chiesa-Estomba CM, De Siati DR, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multi-center European study. Eur Arch Otorhinolaryngol. 2020;277:2251–61.
33. Spinato G, Fabbris C, Polesel J, et al. Alterations in smell or taste in mildly symptomatic outpatients with SARS-CoV-2 infection. JAMA. 2020;323:2089–90.
34. Vaira LA, Salzano G, Deiana G, De Riu G. Anosmia and Ageusia: common findings in COVID-19 patients. Laryngoscope. 2020 Jul;130(7):1787.
35. Beach SR, Praschan NC, Hogan C, et al. Delirium in COVID-19: a case series and exploration of potential mechanisms for central nervous system involvement. Gen Hosp Psychiatry. 2020;65:47–53.
36. Nalleballe K, Reddy Onteddu S, Sharma R, et al. Spectrum of neuropsychiatric manifestations in COVID-19 [published online ahead of print, 2020 Jun 17]. Brain Behav Immun. 2020;88:71–4.
37. Dinakaran D, Manjunatha N, Naveen Kumar C, Suresh BM. Neuropsychiatric aspects of COVID-19 pandemic: a selective review [published online ahead of print, 2020 may 30]. Asian J Psychiatr. 2020;53:102188.

38. Li Y, Li M, Wang M, et al. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study [published online ahead of print, 2020 Jul 2]. Stroke Vasc Neurol. 2020;svn-2020-000431.
39. Moriguchi T, Harii N, Goto J, et al. A frst case of meningitis/encephalitis associated with SARS-Coronavirus-2. Int J Infect Dis. 2020;94(55–58):40.
40. Duong L, Xu P, Liu A. Meningoencephalitis without respiratory failure in a young female patient with COVID-19 infection in downtown Los Angeles, early April 2020. Brain Behav Immun. 2020;87:33.
41. Parsons T, Banks S, Bae C, Gelber J, Alahmadi H, Tichauer M. COVID-19-associated acute disseminated encephalomyelitis (ADEM). J Neurol. 2020;30:1–4.
42. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19-associated acute hemorrhagic necrotizing encephalopathy: imaging features. Radiology. 2020;296(2):E119–20.
43. Munz M, Wessendorf S, Koretsis G, et al. Acute transverse myelitis after COVID-19 pneumonia. J Neurol. 2020;267(8):2196–7.
44. Paybast S, Gorji R, Mavandadi S. Guillain-Barré syndrome as a neurological complication of novel COVID-19 infection: a case report and review of the literature. Neurologist. 2020;25(4):101–3.
45. Zanin L, Saraceno G, Panciani PP, Renisi G, Signorini L, Migliorati K, et al. SARS-CoV-2 can induce brain and spine demyelinating lesions. Acta Neurochir. 2020;162:1491–4.
46. Kang Y, Chen T, Mui D, Ferrari V, Jagasia D, Scherrer-Crosbie M, Chen Y, Han Y. Cardiovascular manifestations and treatment considerations in COVID-19. Heart. 2020;106(15):1132–41.
47. Inciardi RM, Lupi L, Zaccone G, Italia L, Raffo M, Tomasoni D, Cani DS, Cerini M, Farina D, Gavazzi E, Maroldi R, Adamo M, Ammirati E, Sinagra G, Lombardi CM, Metra M. Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19). JAMA Cardiol. 2020;5(7):1–6.
48. Ma L, Song K, Huang Y. Coronavirus disease-2019 (COVID-19) and cardiovascular complications. J Cardiothorac Vasc Anesth. 2020;S1053-0770(20)30400-6.
49. Tung-Chen Y. Acute pericarditis due to COVID-19 infection: an underdiagnosed disease? Med Clin (Barc). 2020;155(1):44–5.
50. Purohit R, Kanwal A, Pandit A, Patel BM, Meininger GR, Brown JJ, Kaliyadan AG, Saini A. Acute myopericarditis with pericardial effusion and cardiac tamponade in a patient with COVID-19. Am J Case Rep. 2020;21:e925554.
51. Dabbagh MF, Aurora L, D'Souza P, Weinmann AJ, Bhargava P, Basir MB. Cardiac tamponade secondary to COVID-19. JACC Case Rep. 2020;2(9):1326–30.
52. de Carranza M, Salazar D-E, Troya J, Alcázar R, Peña C, Aragón E, Domínguez M, Torres J, Muñoz-Rivas N. Aortic thrombus in patients with severe COVID-19: review of three cases. J Thromb Thrombolysis. 2020;9:1–6.
53. Lushina N, Kuo JS, Shaikh HA. Pulmonary, cerebral, and renal thromboembolic disease associated with COVID-19 infection. Radiology. 2020;23:201623.
54. Angeli F, Spanevello A, De Ponti R, Visca D, Marazzato J, Palmiotto G, Feci D, Reboldi G, Fabbri LM, Verdecchia P. Electrocardiographic features of patients with COVID-19 pneumonia. Eur J Intern Med. 2020 20;78:101–6.
55. Pavri BB, Kloo J, Farzad D, Riley JM. Behavior of the PR interval with increasing heart rate in patients with COVID-19. Heart Rhythm. 2020;S1547-5271(20)30551-8.
56. Chen Q, Xu L, Dai Y, Ling Y, Mao J, Qian J, Zhu W, Di W, Ge J. Cardiovascular manifestations in severe and critical patients with COVID-19. Clin Cardiol. 2020;43(7):796–802.
57. Cha MH, Regueiro M, Sandhu DS. Gastrointestinal and hepatic manifestations of COVID-19: a comprehensive review. World J Gastroenterol. 2020;26(19):2323–32.
58. Kopel J, Perisetti A, Gajendran M, Boregowda U, Goyal H. Clinical insights into the gastrointestinal manifestations of COVID-19. Dig Dis Sci. 2020;65(7):1932–9.
59. Pan L, Mu M, Yang P, Sun Y, Wang R, Yan J, et al. Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: a descriptive, cross-sectional, multicenter study. Am J Gastroenterol. 2020;115(5):766–73.
60. Mao R, Qiu Y, He JS, Tan JY, Li XH, Liang J, Shen J, Zhu LR, Chen Y, Iacucci M, Ng SC, Ghosh S, Chen MH. Manifestations and prognosis of gastrointestinal and liver involvement

in patients with COVID-19: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2020;5(7):667–78.
61. Gandhi PA, Singh T. Feco-Oral transmission of SARS-CoV-2: a review. Asia Pac J Public Health. 2020;9:1010539520940931.
62. Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. Lancet Gastroenterol Hepatol. 2020;5:428–30.
63. Huang J, Cheng A, Kumar R, Fang Y, Chen G, Zhu Y, Lin S. Hypoalbuminemia predicts the outcome of COVID-19 independent of age and co-morbidity. J Med Virol. 2020. https://doi.org/10.1002/jmv.26003.
64. Samidoust P, Samidoust A, Samadani AA, Khoshdoz S. Risk of hepatic failure in COVID-19 patients. A systematic review and meta-analysis. Infez Med. 2020;28(Suppl 1):96–103.
65. Lippi G, Plebani M. Laboratory abnormalities in patients with COVID-2019 infection. Clin Chem Lab Med. 2020;58(7):1131–4.
66. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a meta-analysis. Clin Chim Acta. 2020;506:145–8.
67. Chan AS, Rout A. Use of neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios in COVID-19. J Clin Med Res. 2020;12(7):448–53.
68. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18(4):844–7.
69. Tan T, Khoo B, Mills EG, et al. Association between high serum total cortisol concentrations and mortality from COVID-19. Lancet Diabetes Endocrinol. 2020;8(8):659–60.
70. Singh G, Sharma PK, Malviya R, Awasthi R. Novel corona virus disease (COVID-19) and ophthalmic manifestations: Clinical evidences [published online ahead of print, 2020 Jun 11]. Dermatol Ther 2020;e13814.
71. Wu P, Duan F, Luo C, Liu Q, Qu X, Liang L, Wu K. Characteristics of ocular findings of patients with coronavirus disease 2019 (COVID-19) in Hubei Province, China. JAMA Ophthalmol. 2020;138(5):575–8.
72. Chen L, Liu M, Zhang Z, Qiao K, Huang T, Chen M, Xin N, Huang Z, Liu L, Zhang G, Wang J. Ocular manifestations of a hospitalised patient with confirmed 2019 novel coronavirus disease. Br J Ophthalmol. 2020;104(6):748–51.
73. Ozturker ZK. Conjunctivitis as sole symptom of COVID-19: a case report and review of literature. Eur J Ophthalmol. 2020;24:1120672120946287.
74. Kumar K, Prakash AA, Gangasagara SB, Rathod SBL, Ravi K, Rangaiah A, et al. Presence of viral RNA of SARS-CoV-2 in conjunctival swab specimens of COVID-19 patients. Indian J Ophthalmol. 2020;68(6):1015–7.
75. Valente P, Iarossi G, Federici M, Petroni S, Palma P, Cotugno N, De Ioris MA, Campana A, Buzzonetti L. Ocular manifestations and viral shedding in tears of pediatric patients with coronavirus disease 2019: a preliminary report. J AAPOS. 2020;S1091-8531(20)30115.
76. Gisondi P, PIaserico S, Bordin C, Alaibac M, Girolomoni G, Naldi L. Cutaneous manifestations of SARS-CoV-2 infection: a clinical update. J Eur Acad Dermatol Venereol. 2020. https://doi.org/10.1111/jdv.16774.
77. Davoodi L, Jafarpour H, Kazeminejad A, Soleymani E, Akbari Z, Razavi A. Hydroxychloroquine-induced Stevens-Johnson syndrome in COVID-19: a rare case report. Oxf Med Case Rep. 2020(6):omaa042. Published 2020 Jun 25.
78. Sinadinos A, Shelswell J. Oral ulceration and blistering in patients with COVID-19. Evid Based Dent. 2020;21(2):49.
79. Freeman EE, McMahon DE, Lipoff JB, Rosenbach M, Kovarik C, Desai SR, et al. The spectrum of COVID-19-associated dermatologic manifestations: an international registry of 716 patients from 31 countries. J Am Acad Dermatol. 2020;S0190-9622(20)32126-5.
80. Galván Casas C, Català A, Carretero Hernández G, Rodríguez-Jiménez P, Fernández-Nieto D, Rodríguez-Villa Lario A, et al. Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. Br J Dermatol. 2020;183(1):71–7.

Diagnostic Approach to a Patient with Coronavirus Disease

4

Vasudha Singhal

4.1 Introduction

The highly contagious and infectious Severe Acute Respiratory Syndrome Coronavirus-2 (SARS CoV-2) has taken the world by a storm and has impacted the globe socially, mentally and economically in a big way. Social distancing, quarantine and contact tracing are the primary tools adopted for limiting the disease spread. Owing to a high rate of human-to-human transmission of the Coronavirus disease (Covid-19), the primary challenge in the containment of this pandemic is to identify asymptomatic carriers of the disease, which cause a rapid spread. Moreover, the pathogenic potential or reproduction number (R_0) of the SARS CoV-2 is >2.5 (up to 4 in some studies), reflecting the high number of secondary cases that can be infected by an individual, if not isolated at an early stage [1, 2]. The widespread use of accurate, rapid and convenient diagnostic methods can effectively aid in the early identification and elimination of the silent spread of the pandemic by asymptomatic carriers.

Structure of SARS CoV-2: SARS CoV-2 virus is an enveloped, positive-sense RNA (+ssRNA) virus of zoonotic origin, belonging to the beta-coronavirus family, and is found to be infectious to humans with a high fatality rate. It is typically spherical or pleomorphic in form, with a diameter of approximately 60–140 nm, and a single-stranded RNA genome of around 30 kb, which typically has an RNA-dependent RNA polymerase (RdRp) sequence. The viral genome and subgenomes may present six or more open reading frames (ORF). The first ORF (ORF1a/b) encodes 16 non-structural proteins (nsp1–16) involved in viral replication and encompasses around 66% of the entire genome. The remaining one third of the genome encodes the structural proteins of the virus.

SARS CoV-2 contains four structural proteins—envelope (E), spike (S), membrane (M) and nucleocapsid (N). The S, M and E proteins form the envelope of the

V. Singhal (✉)
Medanta—The Medicity, Gurgaon, Haryana, India

H. Prabhakar et al. (eds.), *Clinical Synopsis of COVID-19*,
https://doi.org/10.1007/978-981-15-8681-1_4

virus, while the N protein remains associated with the RNA forming the nucleocapsid inside the envelope. Polymers of S protein remain embedded in the envelope, giving it a crown-like appearance (hence the name *coronavirus*) (Fig. 4.1). Spike glycoproteins comprising of S1 and S2 subunits bind to receptors on the human cell surface called angiotensin-converting enzyme 2 (ACE-2), causing the infection [3]. Since the ACE-2 receptors are abundantly present in the epithelia of the lung and the small intestine, the commonest symptoms seen with the coronavirus disease relate to those of the respiratory and gastrointestinal tract. Two strains of the Covid-19 virus, namely, the L-type and the S-type, have been known, out of which the L-type (a mutated strain of the S-type) is more aggressive and contagious. The error prone nature of the viral replication process accounts for the easy mutation and recombination of this group of viruses, causing an adaptive evolution and sequence diversity. This would necessitate a long-term genomic surveillance of the SARS CoV-2, as it may cause a constant and long-term health threat, even if a vaccine is developed anytime soon.

4.2 Diagnostic approach to Covid-19

The primary transmission of the Covid-19 disease occurs via direct, indirect, or close contact with the respiratory droplets of the infected person. The incubation period of COVID-19, or the time between viral exposure to symptom onset in an individual, is 5–6 days on an average, but can be as long as 14 days [4]. Therefore, rapid and accurate identification of cases through appropriate testing and isolation of infectious cases is mandatory to prevent disease transmission. The diagnostic approach to the SARS CoV-2 may either involve detecting the viral RNA in the acute phase of infection via molecular assays, or by detecting the antibodies that may have developed as a result of viral exposure in the patient's blood, which may be possible only after a few weeks of infection. All symptomatic patients, or individuals with any recent international travel history, or those in contact with confirmed or suspected patients, need to be tested for the virus. The World Health Organization

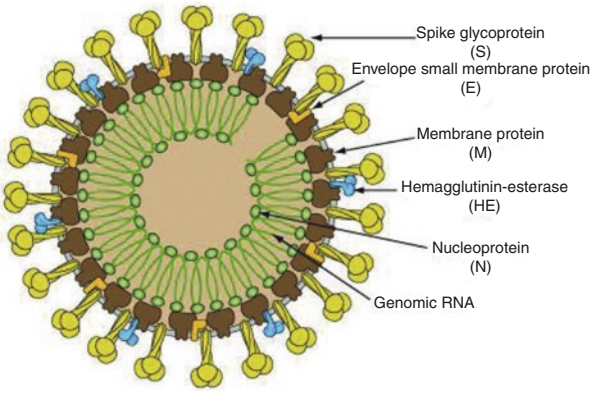


Fig. 4.1 Schematic of a coronavirus—this new virus probably looks a lot like this. (From Biowiki http://ruleof6ix.fieldofscience.com/2012/09/a-new-coronavirus-should-you-care.html)

(WHO) recommends the collection of upper respiratory specimens using nasopharyngeal or oropharyngeal swabs for the diagnosis of the Covid-19 in ambulatory patients. For severely ill patients, sputum, bronchoalveolar lavage (BAL) or tracheal aspirate from the lower respiratory tract yield better results. Collection and processing of respiratory specimens require compliance with the guidelines for aerosol-generating procedures and use of a biosafety level 2 (BSL-2) facility with stringent BSL-3 work practices. The efficacy of blood and stool samples in viral detection techniques, in addition to the respiratory specimens, is still unclear in the absence of sufficient data on viral shedding in these samples [5]. Correct handling of specimens during transportation is essential. The specimens should be stored and shipped at 2–8 °C until testing. In the event of a delay in testing, the use of viral transport media is strongly recommended. The specimens may be shipped on dry ice at −70 °C if further delays are expected [6].

Chest CT in diagnosis of Covid-19: In addition to the molecular assays for viral detection, imaging methods like the CT (computed tomography) chest were initially recommended as an auxiliary diagnostic method for Covid-19. It was claimed that the chest CT had a higher sensitivity for diagnosis of the corona virus disease and may be considered as a primary diagnostic tool for Covid detection, especially during the early course of the disease [7]. Typical CT findings included bilateral pulmonary parenchymal ground-glass and consolidative pulmonary opacities, progressing to 'crazy paving' patterns, and peripheral lung distribution [8]. Bai et al. reported the most discriminating features of Covid-19 pneumonia on chest CT to be a peripheral distribution (80%), ground glass opacity (91%), fine reticular opacity (56%), and vascular thickening (59%) [9] (Fig. 4.2). But these recommendations were not supported by major medical organizations and societies in view of the low specificity of the CT chest findings to the Covid-19 disease. The American College of Radiology recommends that CT scan should not be used as a first line test to diagnose the disease and should be reserved for hospitalized, symptomatic patients with specific clinical indications for CT [10]. The Society of Thoracic Radiology and American Society of Emergency Radiology, in their joint statement, said that chest CT scans should be restricted to patients who are tested Covid positive and are suspected to have pulmonary complications, and not as a routine screening tool for the disease.

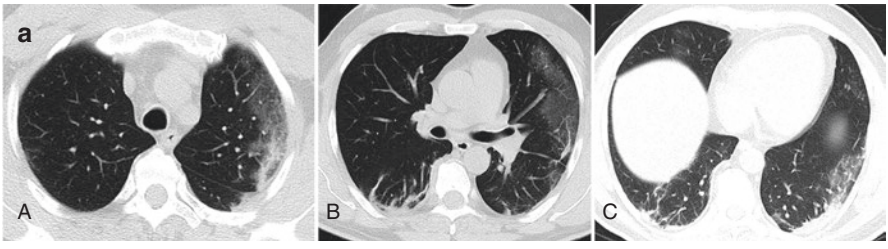
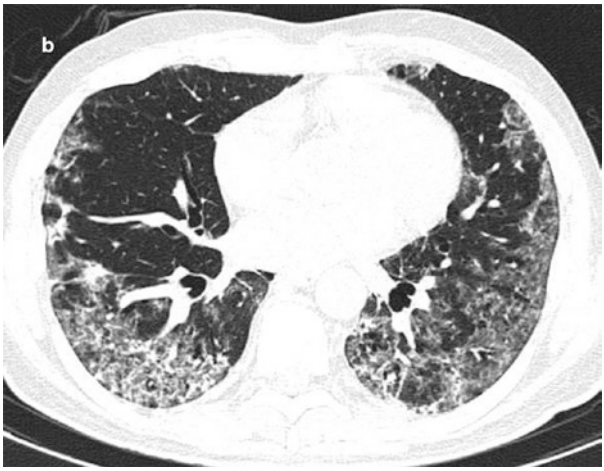


Fig. 4.2 (**a**) Peripheral patches of consolidations and ground glass haziness in left upper (*A*) and lower lobes (*B* and *C*). (**b**) Ground glass haze with interstitial thickening and subpleural reticulations bilateral lower lobes. (Image courtesy: Dr Anshu Mahajan)

Fig. 4.2 (continued)



The commonly available testing methods for Covid-19 are, therefore, classified into two major categories:

1. Molecular nucleic acid detection assays.
2. Serological or immunological assays.

4.3 Molecular Assays for Viral Nucleic Acid Detection

The evolution of SARS CoV-2 specific testing has been greatly facilitated by the availability of detailed genetic sequence of the virus, resulting in the development of various primers and probes needed for nucleic acid amplification. The various molecular assays available at present include:

1. Reverse Transcription-Polymerase Chain Reaction (RT-PCR).
2. Isothermal Nucleic Acid Amplification:
   (a) Reverse Transcription Loop-Mediated Isothermal Amplification (RT-LAMP).
   (b) Transcription-Mediated Amplification (TMA).
   (c) CRISPR-Based Assays.
   (d) Rolling Circle Amplification.
3. Microarray Hybridization Assay.
4. Amplicon-Based Metagenomic Sequencing.

4.3.1 Reverse Transcription-Polymerase Chain Reaction (RT-PCR)

RT-PCR assay is the gold standard for identification of SARS CoV-2 virus. It is a technique that combines reverse transcription of viral RNA template into

complementary DNA (cDNA) and the amplification of specific targets on cDNA inside a thermal cycler, using polymerase chain reaction (PCR). In real-time PCR techniques, the amplification in each PCR cycle is monitored real time using a fluorescent dye, enabling quantification, and hence is known as quantitative PCR, or qRT-PCR. The amplification curve is analysed to obtain a cycle threshold (Ct) value, with lower Cts indicative of abundant target nucleic acid in the sample.

RT-PCR is conventionally performed as a one-step or a two-step approach. Single step quantitative RT-PCR is the preferred diagnostic approach for the detection of SARS CoV-2, as it is quicker, with minimal handling of the viral sample and decreased bench time, and also has reduced chances of error and cross-contamination. Various molecular targets within the +ssRNA genome of the virus are used for RT-PCR, including the ORF1ab or ORF8 genes; envelope (E), spike (S) or nucleocapsid (N) proteins; or genes encoding RNA-dependent RNA polymerase (RdRp). The WHO has provided primers for the genes that encode the E, N and RdRp [11], although different targets may be preferred by different authorities. As per the standard protocol, a patient is confirmed of infection when both the selected target genes come to be positive. Further improvement in detection methods and better automation of the RT-PCR tests play an instrumental role in facilitating greater safety, lower costs and higher sensitivity.

The variable sensitivity and specificity of qRT-PCR remains one of the major challenges in the diagnosis of Covid-19. Multiple factors may contribute to the low sensitivity of the RT-PCR test, including:

1. Viral load kinetics:
   (a) *Sampling site*: Different anatomic sites have different diagnostic efficacy for SARS CoV-2 detection rates. The sensitivity of lower respiratory tract specimens like BAL and sputum is more as compared to other sites, including the upper respiratory tract [12]. Testing of specimens from multiple sites may improve the sensitivity and reduce false-negative test results.
   (b) *Sampling timing*: Viral load is shown to be greatest at the time of viral onset, the rate of positivity declining thereafter [13]. Prolonged viral shedding may however be seen in older patients and those with comorbidities [14].
   (c) *Sampling quality*: Poor quality of the specimen containing little patient material due to inappropriate collection techniques, improper transportation or handling of the specimen may yield false-negative results.
2. Technical reasons inherent in the test, e.g. *virus mutation* or *PCR inhibition*, may result in a false-negative test.
3. Mismatches between primers and probes and the target sequences can lead to decrease in assay performance and potential false-negative results, as different kit manufacturers use different viral genome sequence data [15]. Multiple target gene amplification, in the form of multiplex RT-PCR kits, is being used increasingly to avert this issue. An example of the multiplex PCR technique is the *TaqPath COVID-19 Combo kit*, developed by the ThermoFisher-Applied Biosystems, which contains three primer/probe sets specific to N, S and ORF1ab regions of SARS-CoV-2, making it highly sensitive in the detection of the Covid-19 virus.

If a negative RT-PCR result is obtained from a patient with a high index of suspicion for COVID-19 virus infection, particularly when only upper respiratory tract specimens were collected, additional specimens, including from the lower respiratory tract if possible, should be collected and tested [16].

Similarly, patients showing positive RT-PCR results after repeated negative tests and clinical recovery, should be interpreted with caution. A positive RT-PCR result may not necessarily mean the person is still infectious or that they still have any meaningful disease. The RNA could be from non-viable virus, and the amount of live virus may be too low for transmission [17].

Despite being widely used for the diagnosis of Covid-19 disease, the RT-PCR technique has its set of drawbacks, which include requirement of sophisticated lab equipment and technical expertise and the possible biological safety hazards during transport and sample processing [18]. Though most of these techniques yield results in less than 2–3 h, the need for sample transportation to the specific lab may make the overall process time-consuming.

4.3.2 Isothermal Nucleic Acid Amplification

It is a molecular amplification technique based on the synthesis of target DNA at a constant temperature of 60–65 °C, instead of thermal cycling used in RT-PCR techniques, making it faster and highly efficient. The cost effectiveness of isothermal platforms clears the way for their use in resource limited settings. They have a higher sensitivity and specificity in comparison to PCR, primarily due to the utilization of strand displacement amplification methods. These technologies have proved revolutionary, as they propose to improve the turnaround time to results and need minimal training to conduct at the community level, thereby helping to recognize both symptomatic as well as asymptomatic patients and preventing the disease spread. Swift collection of the upper respiratory swabs directly into a lysis buffer (containing an inactivating agent like guanidinium thiocyanate to inactivate any viable virus and a non-denaturing detergent to prevent RNA degradation), combined with personal protective equipment (latex hand gloves, laboratory coat, appropriate face mask and eye goggle), makes isothermal nucleic acid amplification testing safe for non-laboratory personnel at community outreach clinics [19]. Several methods have been developed on the basis of the isothermal nucleic acid amplification technique, and these include:

- *Reverse Transcription Loop-Mediated Isothermal Amplification (RT-LAMP):* It is a rapid and simple test that combines reverse transcription and isothermal amplification, eliminating the need for RNA extraction, to achieve the detection of SARS CoV-2 virus in less than 30 min at a constant temperature of 65 °C. The LAMP method employs four sets of primers to target RNA encoding ORF1ab, S protein and two regions in N protein of the virus. The results of RNA amplification can be visualized by the naked eye and has a good sensitivity and specificity. The technology is therefore promising to be used for screening individuals for

SARS CoV-2 virus at the point of care testing [20]. A few currently available molecular assays that have come up using this user-friendly technology are *ID NOW COVID-19 test* from Abbott Diagnostics and *iAMP COVID-19 detection kit* from Atila Biosystems, Inc.

- *Transcription-Mediated Amplification (TMA):* It is an isothermal, autocatalytic target amplification method, which involves RNA transcription (via RNA polymerase) and DNA synthesis (via reverse transcriptase), to produce an RNA amplicon from a target nucleic acid. This method is easy to use and has a high throughput capability on a sensitive molecular detection platform. The *Hologic Aptima SARS-CoV-2 Assay*, utilizing TMA as a target amplification mechanism, has been shown to have a markedly higher analytical sensitivity than RT-PCR in the detection of SARS CoV-2 [21].
- *CRISPR-Based Assays:* CRISPR technology, popularly used as a genome editing tool, is adapted from the natural antiviral defence mechanisms of prokaryotes, like bacteria. Clustered regularly interspaced short palindromic repeats (CRISPR) are specialized stretches of DNA with two distinct characteristics – nucleotide repeats, and spacers or DNA bits interspersed among these repeats. In case of bacteria, the spacers are taken from viruses that attacked the organism previously and are used to detect and destroy DNA from similar viruses during subsequent infections. Once a spacer is incorporated and the virus attacks again, a portion of the CRISPR is transcribed and processed into CRISPR RNA, which helps Cas (or 'CRISPR-associated') proteins to act like a pair of molecular scissors, cutting strands of foreign pathogenic DNA. These Cas proteins or nucleases can be used as a tool for molecular testing due to their ability to specifically target viral RNA sequences, e.g. the Cas12 and the Cas13 families of nucleases are used for the detection of SARS CoV-2 viruses. Sherlock Biosciences have used the Cas13 enzyme that is effective in cutting out reporter RNA sequences in response to activation by the SARS CoV-2 virus. Similarly, Mammoth Biosciences have come up with a dipstick test (*DETECTR assay*) that depends upon the excising of fluorescent reporter RNA by Cas12a [22]. Both these tests are quick (require less than an hour), low cost, simple and reliable and provide a novel alternative for the portable, sensitive and specific detection of the Covid-19 virus [23, 24].
- While both SHERLOCK and DETECTR employ target amplification as the primary step, two amplification-free biosensing systems using CRISPR technology have recently been introduced: *Cardean Transistors, 2020* using CRISPR Cas9, and *Diagnostics with molecular, 2020* employing Cas13a. Both techniques promise a handheld corona virus detection device, which also have the potential to address potential mutations of SARS CoV-2 in a timely manner, owing to their multiplexed microfluidic chip technology.
- *Rolling Circle Amplification (RCA):* It is an isothermal nucleic acid amplification technique that can amplify target nucleic acid sequences with high fidelity and specificity by using strand displacing polymerases [25]. This enzymatic process is capable of amplifying the nucleic acid 10^9-fold in each circle within 90 min. It requires only a few reagents and generates minimal false positive results and may prove to be a useful assay in the detection of SARS CoV-2 virus.

4.3.3 Microarray-Based Hybridization Techniques

A microarray is a laboratory tool used to detect gene expression. It has thousands of DNA fragments or oligonucleotides of known sequence (called probes or oligos) arrayed in a known sequence of rows and columns on a chip. Nucleic acid hybridization using microarray involves reverse transcription of viral RNA to cDNA, labelling of cDNAs with specific probes on the chip, their hybridization by the formation of hydrogen bonds between complementary nucleotide base pairs, and finally, washing away of non-specific bonding DNA sequences, generating a signal depending upon the amount of target sample bound to the probes. The advantage of microarray-based detection is that it can combine powerful nucleic acid amplification strategies with the massive screening capability of microarray technology, resulting in a high level of sensitivity, specificity and throughput capacity [26].

PathogenDx's novel *DetectX-RV* technology combines RT-PCR with powerful DNA microarray technology for multiplex testing in Covid-19. Following RNA extraction and PCR amplification, the resulting cDNA is labelled with a fluorophore and added to the DNA microarray containing 144 synthetic ssDNA probes. DetectX-RV supports rapid analysis, with results in 6–8 h, and the microarray design enables 12 individual specimens per slide, and up to 16 slides are tested simultaneously for improved throughput. The test is still in research phase and has not yet been approved by the Food and Drug Administration (FDA) for use in laboratory for diagnostic purposes.

4.3.4 Amplicon-Based Metagenomic Sequencing

These are two complementary techniques used to identify and sequence SARS CoV-2. First, an amplicon-based next generation sequencing enables complete genome sequencing via a highly multiplexed target enrichment panel, from RNA to sequence-ready libraries in a short time (<6 h). Secondly, a metagenomics approach helps in assessing the background microbiome, besides the SARS CoV-2 genome, helping in the identification of co-infections with other viruses or bacteria, thereby aiding in future treatment decisions and predicting patient outcomes. Based on these principles, *Illumina* has devised two workflows for sequencing SARS CoV-2 from clinical samples—one based on shotgun metagenomics and the other on target enrichment [27]. This dual technique of next generation sequencing provides many advantages. Specific amplicon-based sequencing of SARS CoV-2 helps in effective epidemiological studies and contact tracing. The use of metagenomics approach, e.g. sequence-independent single primer amplification (SISPA), provides a check on genomic divergence for amplicon-based approaches. This may help in identifying viral mutations and recombination, thereby influencing vaccine and antiviral efficacy [28].

4.4 Serological or Immunological Assays

Serological testing, or analysis of the patient's blood or plasma for monitoring the immune response to the disease, plays an important role in the diagnostic, surveillance and epidemiological progress of the SARS CoV-2 disease. These immunoassays work on the principle of specific antigen-antibody reaction and mainly target the immunogenic proteins of the SARS CoV-2 virus—the S (spike) and the N (nucleocapsid) proteins. The S1 subunit-based immunoassay may be more specific than the entire S antigen for diagnosing SARS-CoV-2 infections. Also, the receptor-binding domain (RBD) located along the S protein that binds ACE-2 in humans is a target of interest to detect the presence of SARS CoV-2 specific antibodies. Exposure to the Covid-19 virus is determined by the detection of either IgM or IgG antibodies specific for these viral antigens. Rapid antigen tests, wherein the presence of viral antigens in swab samples is detected by the SARS CoV-2 antibodies, may be used in conjunction with the antibody detection tests in Covid-19.

SARS-CoV-2 infection follows a seroconversion timeline similar to other viral infections. The seroconversion rate and antibody levels rise quickly during the fortnight after symptom onset, and the cumulative seropositive rate is 50% on day 11 and 100% on day 39 [29]. The SARS CoV-2 specific IgM antibodies peak between 2 and 3 weeks after symptom onset, while the IgG antibodies peak after 17 days of infection. A high titre of total antibodies is independently associated with a more severe clinical disease. The characterization of antibody profiles suggests that any suspected individual with undetectable antibody levels against SARS CoV-2 after 20 days of symptom onset may be a true negative case. There is no specific chronological order in terms of IgM or IgG seroconversion, suggesting the importance to test for both IgM and IgG antibodies to confirm a positive infection [30]. Also, seroconversion does not imply a rapid decline in the viral load, and people may continue to remain infectious despite being truly positive in the antibody testing [31] (Fig. 4.3).

The primary application of antibody testing in Covid-19 is to detect previous infections in individuals who had few or no symptoms, to guide serosurveillance and epidemiological studies, as well as to facilitate effective contact tracing in the community. These tests may also be used in the screening of eligible convalescent plasma donors from individuals who have recuperated from the infection, and in evaluating the immune response and effectiveness of candidate vaccines in their research phase. Also, the antibody tests may help in the diagnosis of COVID-19 in RT-PCR-negative patients who present later during disease course.

Serological antibody tests are fast, robust and easy to perform, but cannot detect the infection in early stage of the disease. There may be an inherent variability of the antibody response due to different genetic makeup of each individual, and cross reactivity to other common coronaviruses may limit the sensitivity and specificity of the antibody test [32]. Presently, the serological tests cannot be used as a definitive tool for determining protective long-term immunity in a recovered patient, as we do not yet have definitive proof of the same.

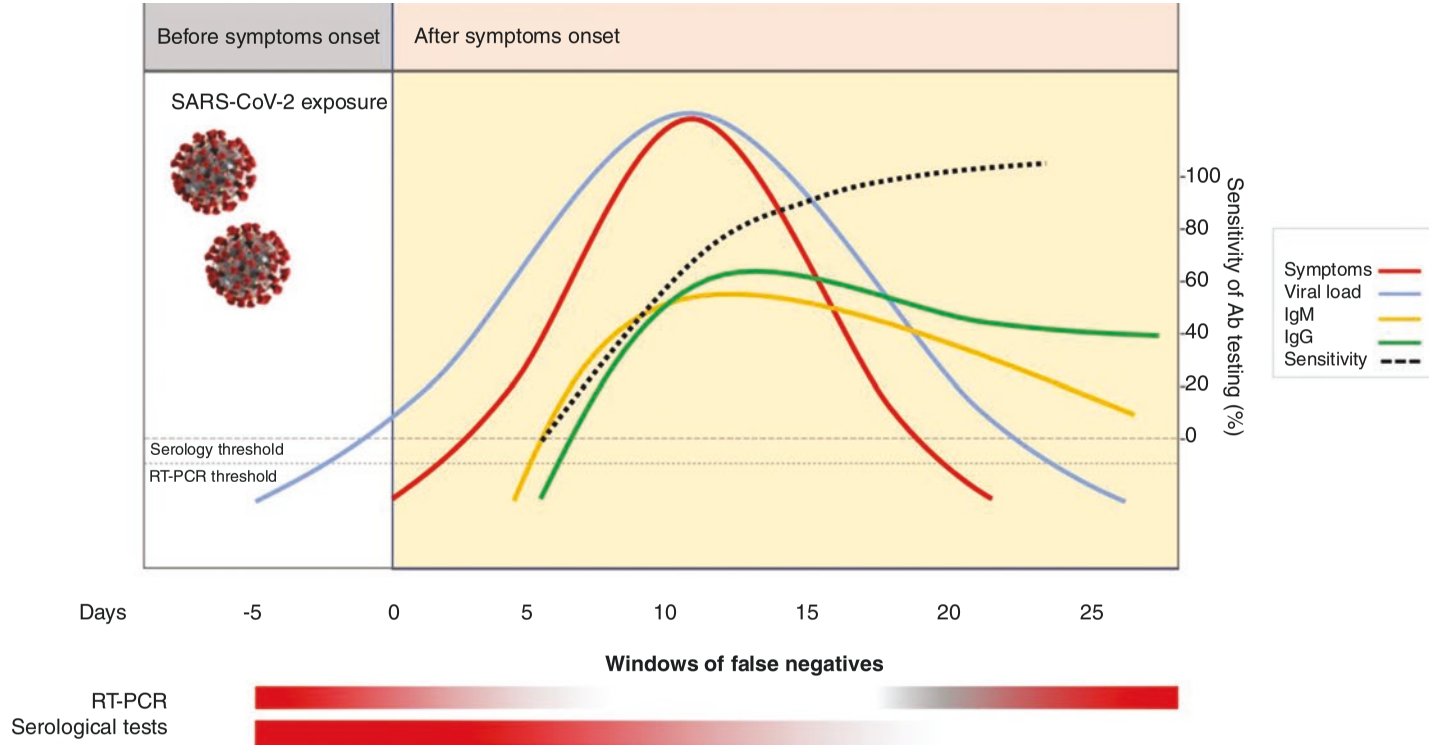


Fig. 4.3 The time relationship between viral load, symptoms and positivity on diagnostic tests. The onset of symptoms (day 0) is usually 5 days after infection (day-5). At this early stage corresponding to the window or asymptomatic period, the viral load could be below the RT-PCR threshold, and the test may give false-negative results. The same is true at the end of the disease, when the patient is recovering. Seroconversion may usually be detectable between 5–7 and 14 days after the onset of symptoms; therefore, in the first phase of the disease, the serological tests are more likely to give false-negative results. The dotted black line in the graph illustrates the sensitivity of the chemiluminescent assay as derived from the data sheet of a commercial test (Abbott Diagnostics, USA). *Ig* immunoglobulin, *RT-PCR* reverse transcription-PCR, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2

The various techniques available for COVID-19 serology tests include the following:

1. Enzyme-Linked Immunosorbent Assay (ELISA).
2. Lateral Flow Immunoassay.
3. Luminescent Immunoassay.
4. Neutralization Assay.
5. Biosensor test.

4.4.1 Enzyme-Linked Immunosorbent Assay (ELISA)

ELISA is a plate-based ligand binding assay technique, to detect the presence of COVID-19 antibodies in a patient. The blood sample is placed inside the microtiter wells of an ELISA plate, which is coated with SARS CoV-2 specific antigens. The antibodies, if present in the sample, passively bind with these specific antigens, and an additional tracer antibody may be used to detect the bound antigen-antibody complex to generate a colorimetric or fluorescent-based readout. This technique needs sophisticated equipment and skilled technicians but can screen large number of specimens (up to 96 samples at a time) in less than 3 h.

A number of IgG/IgM ELISA testing kits have been approved for use under the FDA Emergency Use Authorization (EUA)—examples include the DEIASL019/020 SARS CoV-2 IgG ELISA kit by Creative Diagnostics; EUROIMMUN Anti-SARS-CoV-2 ELISA; KT-1032/33 EDI™ Novel Coronavirus COVID-19 ELISA Kit by Epitome Diagnostics; etc. The Center for Disease Control (CDC) also developed a SARS-CoV-2 serological kit (ELISA based) with a specificity of >99% and sensitivity of 96% [33], but this test awaits permission to be used as a diagnostic test. ELISA antigen tests may be developed in the future to detect current infections.

4.4.2 Lateral Flow Immunoassay (LFIA)

The LFIA rapid detection kits use the principle of immunochromatography, producing fast, qualitative results within 10–30 min without the need for specialized and costly equipment, and typically requires no sample or reagent preparation.

The LFIA kit is essentially a dipstick encased in a cassette, containing the capture reagents (either the viral antigen protein or monoclonal antibodies) immobilized on defined locations on a nitrocellulose membrane, as well as labelled detector antibodies that recognize the same target. A positive result, triggered by the antigen-antibody binding, is visible as a coloured line, much like the regular pregnancy kit. This rapid diagnostic test (RDT) has the potential to be deployed in large-scale serological surveys and can be used as a point-of-care (POC) test or self-test. However, at present, the WHO recommends the use of these tests in research settings only, until evidence supporting use for clinical decision-making is available [34, 35].

Lateral flow assay technology has been used to develop *rapid antigen test kits*, like the *Standard Q COVID-19 Ag* (SD Biosensor) and *COVID-19 Ag Respi-Strip* (Coris Bioconcept), which use nasopharyngeal swabs for sampling. The viral proteins in the swab samples bind to the specific monoclonal antibodies in the reagent strip to yield results in 30 min. These tests detect actively replicating viruses and therefore may be used to identify acute or early infection. In view of their high specificity but relatively low sensitivity, it is recommended that a patient who has tested negative for Covid-19 by rapid antigen test should be tested sequentially by RT-PCR to rule out infection, whereas a positive test should be considered as a true positive.

4.4.3 Luminescent Immunoassay

Luminescent immunoassays are variations of the standard ELISA technique using chemiluminescence or fluorescence.

Chemiluminescence immunoassay (CLIA) is an assay that combines chemiluminescence technique with immunochemical reactions (or immunoassays). CLIA utilizes chemical probes which could generate light emission through chemical reaction to label the antibody. This technique has become popular due to its high sensitivity, wide dynamic range and complete automation to quantitatively measure antibodies in plasma of infected individuals. It does not require long incubations and is therefore faster than the conventional ELISA technique, with a high throughput. *Diazyme DZ-Lite SARS CoV-2 IgG/IgM test* (Diazyme Laboratories) and *Maglumi COVID-19 IgG/IgM test* (Snibe Diagnostics) are few examples of the available CLIA testing kits for Covid-19, that promise high throughput, high clinical sensitivity, rapid detection within 30 min and antibody detection with numerical results.

Fluorescence immunoassay (FIA) is an immunoassay technique in which antigen or antibody is labelled with a fluorescent dye for rapid detection. *Bioeasy nCoV rapid antigen kit* utilizes fluorescence immunochromatography for detecting the SARS CoV-2 antigen.

4.4.4 Neutralization Assay

It is a specialized type of immunoassay which detects only those antibodies that can block virus replication (called neutralizing antibodies), and not all antigen-antibody reactions. This helps in the identification of the virus serotype, as groups of viruses may share common antigens, but only a fraction of these would be targets of neutralizing antibody.

Fluorescence-based neutralization assay is a rapid, high throughput assay that rapidly and reliably measures neutralization of a reporter SARS-CoV-2 by antibodies from patient specimens. The presence of SARS CoV-2 neutralizing antibodies would predict protection from reinfection, thereby helping in large scale

serodiagnosis and vaccine evaluation, and identification of high neutralizing convalescent plasma for therapy. The test, however, needs to be conducted in a biosafety level 3 (BSL-3) containment [36].

4.4.5 Biosensor Test

Biosensors are a promising alternative and a reliable solution to clinical diagnosis and real-time detection of the SARS CoV-2 virus. The biosensor technology, known as localized surface plasmon resonance (LSPR) sensing, detects interactions between molecules on the surface of a constructed metallic nanostructure incorporating DNA probes that recognize specific SARS-CoV-2 RNA sequences, which registers these interactions as a local change in refractive index [37]. This technology is complex and expensive, but is quick, sensitive, automated and real time, and offers tremendous potential for the rapid medical diagnosis of Covid-19.

4.5 Conclusion

The global data reflects the continuing menace of the novel coronavirus SARS CoV-2 across the world, despite preventive and therapeutic advancements. The key to prevent the spread of the virus is to develop better methods for mass screening. While RT-PCR remains the current gold standard for detection of Covid-19, newer molecular tests like isothermal amplification, hybridization microarray and cutting edge CRISPR-based techniques offer faster, cheaper and reliable alternatives. Serological tests like ELISA, lateral flow assays and CLIA help in predicting the course, degree and durability of immune response to the SARS CoV-2 infection, paving way for the development of effective vaccines in the future. These tests may also aid in epidemiological research and will help in confirming if seropositivity equates to immunity. The development of efficient, cost effective point of care laboratory techniques with high sensitivity and specificity, which can be employed on a large scale, is the need of the hour. The validation of these tests across different populations will however be required before they can be routinely used for clinical decision-making.

References

1. Chen J. Pathogenicity and transmissibility of 2019-nCoV-a quick overview and comparison with other emerging viruses. Microbes Infect. 2020;22(2):69–71.
2. Liu T, Hu J, Kang M, et al. Transmission dynamics of 2019 novel coronavirus (2019-nCoV). bioRxiv. 2020:2020.01.25.919787.
3. Chan JF, Kok K, Zhu Z, Chu H, To KK, Yuan S, Yuen K. Genomic characterization of the 2019 novel human pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. Emerg Microb Infect. 2020;9(1):221–36.
4. Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, et al. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. Ann Int Med. 2020;172:577–82.

5. Zhang W, Rong-Hui D, Li B, Zheng XS, Yang X-L, Hu B, et al. Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes. Emerg Microb Infect. 2020;1:386–9.
6. Protocol to investigate non-seasonal influenza and other emerging acute respiratory diseases. Geneva: World Health Organization; 2018. https://www.who.int/influenza/resources/publications/outbreak_investigation_protocol/en/.
7. Ai T, Yang Z, Hou H, Zhan C, Chen C, Lv W, Tao Q, Sun Z, Xia L. Correlation of chest CT and RT-PCR testing in coronavirus disease 2019 (COVID-19) in China: a report of 1014 cases. Radiology. 2020;296:E32–40.
8. Xie X, Zhong Z, Zhao W, Zheng C, Wang F, Liu J. Chest CT for typical 2019-nCoV pneumonia: relationship to negative RT-PCR testing. Radiology. 2020:200343.
9. Bai HX, Hsieh B, Xiong Z, Halsey K, Choi JW, Tran TML, et al. Performance of radiologists in differentiating COVID-19 from viral pneumonia on chest CT. Radiology. 2020;296:E46–54.
10. ACR. ACR Recommendations for the use of Chest Radiography and Computed Tomography (CT) for suspected COVID-19 infection. American College of Radiology. Available at https://www.acr.org/Advocacy-and-Economics/ACR-Position-Statements/Recommendations-for-Chest-Radiography-and-CT-for-Suspected-COVID19-Infection. Accessed 20 March 2020.
11. Corman VM, Landt O, Kaiser M, Molenkamp R, Meijer A, Chu DK. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Euro Surveill. 2020;25(3):2000045.
12. Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, et al. Detection of SARS-CoV-2 in different types of clinical specimens. JAMA. 2020;23:1843–4.
13. To KK, Tsang OT, Leung WS, Tam AR, Wu TC, Lung DC. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. Lancet Infect Dis. 2020;20:565–74.
14. Xiao AT, Tong YX, Zhang S. Profile of RT-PCR for SARS-CoV-2: a preliminary study from 56 COVID-19 patients. Clin Infect Dis. 2020;19:ciaa460.
15. Toms D, Li J, Cai HY. Evaluation of WHO listed Covid-19 QPCR primers and probe in silico with 375 SERS-CoV-2 full genome sequences. medRxiv. 2020;2020.04.22.20075697.
16. World Health Organization. Laboratory testing for coronavirus disease 2019 (COVID-19) in suspected human cases: interim guidance, 2 March 2020. Geneva: World Health Organization; 2020. https://apps.who.int/iris/handle/10665/331329.
17. Wölfel R, Corman VM, Guggemos W, et al. Virological assessment of hospitalized patients with COVID-2019. Nature. 2020;581:465–9.
18. Kumar R, Nagpal S, Kaushik S, et al. COVID-19 diagnostic approaches: different roads to the same destination. Virus Dis. 2020;31:97–105.
19. James AS, Alwneh JI. COVID-19 infection diagnosis: potential impact of isothermal amplification technology to reduce community transmission of SARS-CoV-2. Diagnostics (Basel). 2020;10(6):399.
20. Huang WE, Lim B, Hsu CC, Xiong D, Wu W, Yu Y, et al. RT-LAMP for rapid diagnosis of coronavirus SARS CoV-2. Microb Biotechnol. 2020;13(4):950–61.
21. Gorzalski AJ, Tian H, Laverdure C, Morzunov S, Verma SC, VanHooser S, Pandori MW. High-throughput transcription-mediated amplification on the Hologic panther is a highly sensitive method of detection for SARS-CoV-2. J Clin Virol. 2020;129:104501.
22. Carter LJ, Garner LV, Smoot JW, Li Y, Zhou Q, Saveson CJ, Sasso JM, Gregg AC, Soares DJ, Beskid TR, Jervey SR, Liu C. Assay techniques and test development for COVID-19 diagnosis. ACS Cent Sci. 2020;6(5):591–605.
23. Broughton JP, Deng X, Yu G, Fasching CL, Servellita V, Singh J, Miao X, Streithorst JA, Granados A, Sotomayor-Gonzalez A, Zorn K, Gopez A, Hsu E, Gu W, Miller S, Pan C-Y, Guevara H, Wadford DA, Chen JS, Chiu CY. CRISPR–Cas12-based detection of SARS-CoV-2. Nat Biotechnol. 2020;38:870–4.
24. Chen JS, Ma E, Harrington LB, Da Costa M, Tian X, Palefsky JM, Doudna JA. CRISPR-Cas12a target binding unleashes indiscriminate single-stranded DNase activity. Science. 2018;360(6387):436–9.

25. Goo NI, Kim DE. Rolling circle amplification as isothermal gene amplification in molecular diagnostics. Biochip J. 2016;10:262–71.
26. Chen Q, Li J, Deng Z, Xiong W, Wang Q, Hu YQ. Comprehensive detection and identification of seven animal coronaviruses and human respiratory coronavirus 229E with a microarray hybridization assay. Intervirology. 2010;53(2):95–104.
27. Comprehensive workflow for detecting coronavirus using illumina Benchtop systems – a shotgun metagenomics sequencing workflow for effective detection and characterization of coronavirus strains. Infect Dis Surveill. 2020. www.illumina.com/content/dam/illumina-marketing/documents/products/appnotes/ngs-coronavirus-app-note-1270-2020-001.pdf.
28. Moore SC, Penrice-Randal R, Alruwaili M, Dong X, Pullan ST, Carter DP, et al. Amplicon based MinION sequencing of SARS-CoV-2 and metagenomics characterisation of nasopharyngeal swabs from patients with COVID-19. medRxiv 2020;2020.03.05.20032011.
29. Zhao J, Yuan Q, Wang H, Liu W, Liao X, Su Y, et al. Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019. Clin Infect Dis. 2020; https://doi.org/10.1093/cid/ciaa344.
30. Long QX, Deng HJ, Chen J, Hu J, Liu BZ, Liao P, et al. Antibody responses to SARS-CoV-2 in COVID-19 patients: the perspective application of serological tests in clinical practice. medRxiv. 2020.03.18.20038018.
31. Wölfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Müller MA, et al. Virological assessment of hospitalized patients with COVID-2019. Nature. 2020;581:465–9.
32. Lee CYP, Lin RTP, Renia L, LFP N. Serological approaches for Covid-19: epidemiologic perspective on surveillance and control. Front Immunol. 2020;11:879.
33. Freeman B, Lester S, Mills L, Rasheed MAU, Moye S, Abiona O, et al. Validation of a SARS-CoV-2 spike protein ELISA for use in contact investigations and sero-surveillance. bioRxiv 2020.04.24.057323.
34. World Health Organization. Advice on the use of point-of-care immunodiagnostic tests for COVID-19: scientific brief, 8 April 2020. WHO; 2020.
35. Bastos ML, Tavaziva G, Abidi SK, Campbell JR, Haraoui LP, Johnston JC, et al. Diagnostic accuracy of serological tests for covid-19: systematic review and meta-analysis. BMJ. 2020;370:m2516.
36. Muruato AE, Fontes-Garfias CR, Ren P, Garcia-Blanco MA, Menachery VD, Xie X, et al. A high-throughput neutralizing antibody assay for COVID-19 diagnosis and vaccine evaluation. bioRxiv [Preprint]. 2020;2020.05.21.109546.
37. Qiu G, Gai Z, Tao Y, Schmitt J, Kullack-Ublick GA, Wang J. Dual-functional plasmonic photothermal biosensors for highly accurate severe acute respiratory syndrome coronavirus 2 detection. ACS Nano. 2020;14(5):5268–77.

Therapeutic Approach to Coronavirus Disease

5

Caroline Der-Nigoghossian, Alana Ciolek, and Taylor Chuich

5.1 Introduction to COVID-19 Therapeutics

The global pandemic of coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), was first identified in Wuhan, China, in December 2019. The viral genome was rapidly identified in order to develop diagnostic testing and therapeutic options. SARS-CoV2 is a single-stranded RNA-enveloped virus that uses its surface spike (S) protein to bind host cell's angiotensin converting enzyme 2 (ACE2) receptor in the presence of host cell protease TMPRSS2, a cofactor for virus entry [1]. The virus uses RNA-dependent RNA polymerase to synthesize RNA leading to viral assembly and exocytosis [2].

Drug therapies that could target one or several of the phases of the viral entry and replication processes have been evaluated as potential therapeutics for the treatment of coronavirus disease 2019 (COVID-19). The COVID-19 pandemic has led the scientific community to repurpose different drugs that were previously used for other viral infections such as Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV). In addition, dysregulation of the immune system and consequent cytokine release syndrome have been identified as the main pathophysiological processes associated with COVID-19 [3]. This has led to the evaluation of different immunomodulatory agents to target the inflammatory cascade.

C. Der-Nigoghossian (✉)
Neurosciences Intensive Care Unit, NewYork-Presbyterian Hospital, Columbia University Irving Medical Center, New York, NY, USA
e-mail: cad9105@nyp.org

A. Ciolek · T. Chuich
Cardiothoracic Intensive Care, NewYork-Presbyterian Hospital, Columbia University Irving Medical Center, New York, NY, USA
e-mail: amc9096@nyp.org; tac9114@nyp.org

H. Prabhakar et al. (eds.), *Clinical Synopsis of COVID-19*,
https://doi.org/10.1007/978-981-15-8681-1_5

As of July 2020, 2764 studies are registered on clinicaltrials.gov for COVID-19. In this chapter, we discuss the evidence regarding the use of different therapeutics. Due to the evolving nature of the evidence, we have included drugs that have at least five published and/or undergoing clinical trials evaluating their use in COVID-19. In addition, we summarize the recommendations provided by multiple societies including the Infectious Disease Society of America (IDSA), Society of Critical Care Medicine (SCCM), and the National Institute of Health (NIH) [4–8].

In the following sections, Fig. 5.1 depicts the mechanism of action of therapeutics discussed in this chapter.

Table 5.1 summarizes general information regarding investigational treatments for COVID-19 including dosing, common adverse effects, and pharmacotherapy pearls. Table 5.2 summarizes the recommendations from national guidelines and societies. Finally, due to the rapidly evolving volume of literature, Table 5.3 only summarizes randomized controlled trials of the therapeutic options discussed within the text.

5.2 Antiviral Agents

5.2.1 Favipiravir

Favipiravir is a competitive inhibitor of RNA-dependent RNA polymerase and is approved in Japan for the treatment of influenza (Table 5.1) [9]. It was also shown to decrease mortality in patients with Ebola virus and was effective at preventing Ebola virus infection. An in vitro study showed its effectiveness at inhibiting SARS-CoV2 growth; however, due to the higher EC50 (half maximal effective concentration) compared to influenza, higher than standard doses have been recommended for its use for the treatment of SARS-CoV2 [29].

Two studies have evaluated the efficacy and safety of favipiravir in patients with COVID-19. One was a before-after observational cohort study comparing favipiravir to lopinavir/ritonavir both in combination with inhaled interferon-α1b in patients with mild-moderate disease [30]. Treatment was continued until viral clearance, for up to 14 days. The study showed shorter time to clearance and more improvement in chest imaging in the favipiravir group. The second study was a randomized controlled trial from China of 240 patients who received favipiravir or umifenovir (Table 5.3) [17]. There was no difference between both treatments in the clinical recovery at 7 days. A post hoc analysis showed that patients with moderate disease had a higher clinical recovery at day 7 in the favipravir group (71.4% vs. 55.9%, $p = 0.0199$). More hyperuricemia occurred in the favipiravir group: 13.79% vs. 2.5% ($p = 0.0014$).

The current evidence does not support the use of favipravir for the treatment of COVID-19 patients. The observational study is hypothesis generating, and the randomized controlled trial is only available as a peer-print in MedRxiv since May 2020 and has not been peer reviewed yet. Future randomized controlled trials are needed to evaluate its efficacy and safety in this patient population (Table 5.2).

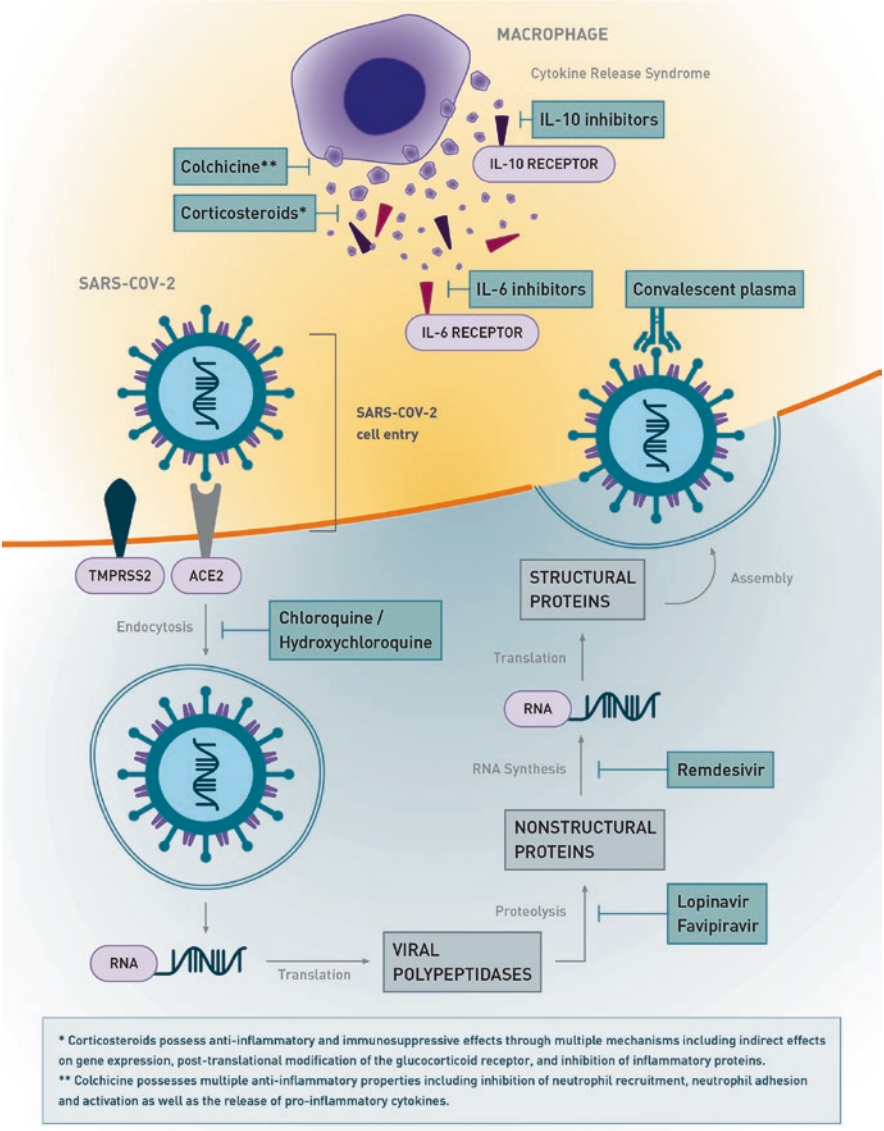


Fig. 5.1 Viral cycle of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) and target of therapeutic agents. *Corticosteroids posses anti-inflammatory and immunosuppressive effects through multiple mechanisms including indirect effects on gene expression, post-translational modification of the glucocorticoid receptor, and inhibition of inflammatory proteins. **Colchicine possesses multiple anti-inflammatory properties including inhibition of neutrophil adhesion and activation as well as the release of pro-inflammatory cytokines

Table 5.1 Summary of investigational treatments for COVID-19 including dosing, common adverse effects, and pharmacotherapy pearls [9–16]

Drug	MOA	Dosing	Pharmacotherapy pearls	Monitoring and adverse events
Favipiravir (Famvir®)	Competitively inhibits RNA-dependent RNA polymerase	Variable dosing based on indication 1600 mg PO BID On day 1 followed by 600 mg twice daily on days 2–14	CYP2C8 and aldehyde oxidase inhibitor	Acute renal failure in patients with baseline renal dysfunction, hyperuricemia, hepatic transaminitis Common ADRs: Headache and nausea Limited data for ADRs at higher doses
Remdesivir	Prodrug nucleotide-analog inhibitor of RNA-dependent RNA polymerases	200 mg IV once on day 1 followed by 100 mg IV daily for 4–9 days	No significant effect on CYP enzymes	Hepatic transaminitis, acute kidney injury
Lopinavir/ritonavir (LPV/r) (Kaletra®)	Lopinavir: Inhibits the enzyme 3-chymotrypsin-like protease ($3CL^{pro}$), disrupting the cleaving and processing of polyproteins translated from the viral RNA Ritonavir: Inhibits CYP3A4 metabolism of lopinavir, leading to increased plasma concentrations	LPV/r 400/100 mg PO twice daily for no more than 10 days	Can be taken with or without food Do not crush (increases systemic exposure)—must use solution in patients who cannot swallow tablets whole Significant drug-drug interactions possible—ritonavir is a strong CYP3A4 inhibitor	GI: Primarily gastrointestinal (diarrhea, nausea, vomiting) Liver: Hepatotoxicity: Hepatic panel Cardiac: Increased serum triglycerides, hyperlipidemia: Lipid panel

Chloroquine Hydroxychloroquine (Plaquenil®) +/− Azithromycin (Zithromax®)	Increases the endosomal pH, inhibiting fusion of SARS-CoV-2 and the host cell membrane Chloroquine inhibits glycosylation of the cellular angiotensin-converting enzyme 2 receptor Azithromycin: Induction of IFN-stimulated genes, attenuating viral replication, enhanced neutrophil activation, attenuation of inflammatory cytokines (IL-6 and IL-8) in epithelial cells and inhibition of fibroblast growth factor in airway smooth muscle cells *[NIH]*	Varies based on study reviewed EUA dosing (revoked): Hydoxychloroquine 800 mg on day 1 then 400 mg for 4–7 days	Avoid concomitant medications that prolong the QTc interval Inhibitor of CYP2D6 and P-glycoprotein	Cardiac: QTc prolongation, TDP, ventricular arrhythmia: Baseline and follow-up ECGs, serum creatinine, electrolytes (potassium and magnesium) GI: Nausea, vomiting diarrhea, hepatitis: Hepatic panel Endocrine: Hypoglycemia: Blood glucose Heme: Hemolysis: CBC Myopathy and rash: Monitor daily clinical review of systems
Interleukin 6 inhibitors Tocilizumab (Actemra®) Sarilumab (Kevzara®) Siltuximab (Sylvant®) Olokizumab (Artlegia®) Clazakizumab *(investigational drug)*	Monoclonal antibodies that inhibit the IL-6 receptor: May potentially mitigate cytokine release syndrome symptoms in severely ill patients	Clinical trial dosing: Tocilizumab 4–8 mg/kg IV once or in divided doses (max 800 mg) Sarilumab 200–400 mg SQ or IV once or in divided doses Siltuximab 11 mg/kg IV once Olokizumab 64 mg SQ once Clazakizumab 12.5–50 mg IV	Elevated IL-6 may downregulate CYP enzymes. Use of tocilizumab may lead to increased metabolism of drugs that are CYP450 substrates	CV: Cholesterol: May increase total cholesterol, LDL and/or HDL: Lipid panel 4–8 weeks after initiation ID: Increased risk of infection: Monitor for infectious symptoms. Hepatitis B reactivation possible Hepatic: Hepatic injury, hepatic transaminitis: Monitor LFTs GI: Monitor for evidence of GI perforation Heme: Neutropenia and thrombocytopenia may occur: Monitor CBC

(continued)

Table 5.1 (continued)

Drug	MOA	Dosing	Pharmacotherapy pearls	Monitoring and adverse events
Corticosteroids	Anti-inflammatory effects of corticosteroids could have a beneficial effect in suppressing the cytokine-related lung injury	Clinical trial dosing: Dexamethasone 6 mg daily for up to 10 days Methylprednisolone dosing varies widely: 40 mg every 12 h for 3 days followed by 20 mg every 12 h for 3 days	Moderate cytochrome 3A4 inducer, which may reduce the concentration and potential efficacy of concomitant medications that are CYP3A4 substrates	Neuro: May cause psychiatric disturbances, including insomnia and euphoria Endo: Hyperglycemia ID: Increased risk of infection. Monitor for infectious symptoms
Anakinra (Kineret®)	Recombinant human interleukin-1 receptor antagonist, inhibiting the activity of proinflammatory cytokines IL-1α and IL-1β	100 mg SQ every 6 h, other reports of 5 mg/kg twice daily Duration variable (7–21 days) based on patient response	Administered subcutaneously Test patients for latent TB prior to initiation	Generally well tolerated Common ADRs include: Headache, nausea, vomiting Serious ADRs: Hypersensitivity reactions/ injection site reactions, infections, neutropenia, reactivation of TB
Colchicine (Colcrys®)	Multiple anti-inflammatory properties including: Inhibits neutrophil recruitment by inhibiting chemotactic factor release Inhibits neutrophil adhesion via inhibiting expression of E-selectin Inhibits neutrophil activation and release on proinflammatory cytokines (IL-1, IL-8, superoxide) Promotes activation of dendritic cells to become antigen presenting cells	Variable based on indication, typically 1–1.5 mg load, then 0.3–0.6 mg PO once to twice daily	Must adjust dose for renal or hepatic dysfunction Hazardous drug—must be handled accordingly Potential for significant drug interactions—P--glycoprotein substrate and metabolized by CYP3A4	GI symptoms, most commonly diarrhea, nausea, vomiting Bone marrow suppression (leukopenia, thrombocytopenia, pancytopenia, aplastic anemia)

Vitamins *Zinc* *Ascorbic acid* *Vitamin D*	Prevent inflammatory cascade by anti-inflammatory and antioxidant activity Fundamental for the structural organization of the epithelial and endothelial barriers; fundamental for phagocytosis and chemotaxis; protection from reactive oxygen species injury Regulation of NK-κB activity	Dosing is not available in the COVID-19 patient population	Zinc: Run drug interaction report to see if concomitant medication administration requires staggered time schedules No significant interactions exist for ascorbic acid or vitamin D	Zinc: Nausea, vomiting, changes in taste Ascorbic acid: Possible nephrolithiasis with large doses Vitamin D: Toxicity can manifest as nausea, vomiting, loss of appetite, weakness, and fatigue

Table 5.2 Summary of current treatment guidelines and guidance recommendations (last updated on July 28th 2020)

Therapies/ guideline recommendations	Remdesivir	Favipravir	Lopinavir/ritonavir	Hydroxychloroquine /chloroquine	Hydroxychloroquine / chloroquine ± azithromycin	Convalescent plasma	Interleukin-6 inhibitors	Colchicine	Corticosteroids	Interleukin -1 inhibitors	Vitamin C	Vitamin D	Zinc
Infectious Disease Society of America	Severe disease								Severe disease				
National Institute of Health	Supplemental oxygen but not HFO, MV, or ECMO								MV or supplemental oxygen				
Society of Critical Care Medicine									MV and ARDS				
Italian Society of Infectious and Tropical Diseases	Severe disease						Severe disease		Severe disease				

Green **recommended,** *Yellow* **recommended in the setting of clinical trial,** *Orange* **not mentioned OR insufficient data to provide recommendation**

Red recommended against except in the setting of a clinical trial

Severe disease defined as $SaO_2 < 94\%$ on room air, supplemental oxygen, mechanical ventilation, or ECMO

Table 5.3 Summary of randomized controlled trials evaluating treatment options for COVID-19

Trial title and design	Patient population	Dosing and duration	Results
Favipiravir			
Favipiravir vs. Arbidol for COVID-19: A Randomized Clinical Trial [17] *Prospective, randomized, controlled, open-label multicenter trial*	$N = 240$ 18 years or older with COVID-19 pneumonia, symptom onset within 12 days	1:1 randomization to umifenovir 200 mg PO TID for 7 days or favipiravir 1600 mg PO BID on day 1 followed by 600 mg PO BID for 10 days	• No difference between both groups in clinical recovery at 7 days (rate ratio: 0.0954; 95% CI −0.0305, 0.2213), use of auxiliary oxygen therapy or noninvasive mechanical ventilation • Favipiravir group had a shorter time to relief of pyrexia (difference 1.7 days, $p < 0.0001$) and cough (difference 1.75 days, $p < 0.0001$) • More hyperuricemia in favipiravir group: 13.79% vs. 2.5% ($p = 0.0014$)
Remdesivir			
Remdesivir in Adults with Severe COVID-19: A Randomised, Double-Blind, Placebo-Controlled Multicentre Trial [18]	$N = 237$ Hospitalized patients with SARS-CoV-2 infection, $SaO_2 \leq 94\%$ on room air, symptom onset within 12 days	2:1 randomization to remdesivir or placebo Remdesivir 200 mg IV once on day 1 followed by 100 mg IV once daily for 9 days	• No difference in time to clinical improvement (HR 1.23, 95% CI 0.87–1.75) • ADRs in 66% of remdesivir group vs. 78% of placebo group
Remdesivir for the treatment of COVID-19—Preliminary Report [19] *Double-blind, placebo-controlled trial*	$N = 1063$ Adult patients with SARS-CoV-2 infection, $SaO_2 \leq 94\%$ on room air or radiologic evidence of PNA or requiring MV or supplemental oxygen	1:1 randomization to remdesivir or placebo Remdesivir 200 mg IV once on day 1 followed by 100 mg IV once daily for 9 days	• Median time to recovery shorter in remdesivir group: 11 (95% CI; 9–12) vs. 15 (95%CI; 13–19) days ($p < 0.001$) • Mortality at 14 days not different between both groups: 7.1% vs. 11.9%, HR 0.70; (95% CI; 0.47–1.04) • Mortality by 14 days not different between both groups; HR 0.70; (95% CI; 0.47–1.04) • Serious ADRs 21.1% vs. 27.0%

(continued)

Table 5.3 (continued)

Trial title and design	Patient population	Dosing and duration	Results
Remdesivir for 5 or 10 days in Patients with Severe COVID-19 [20] *Open-label, randomized controlled phase 3 trial*	$N = 397$ Hospitalized patients with SARS-CoV-2 infection, $SaO_2 \leq 94\%$ on room air and radiologic evidence of PNA	Remdesivir 200 mg IV once on day 1 followed by 100 mg IV once daily 1:1 randomization to 5 or 10 days of therapy	• Patients in the 10-day group had worse clinical status at baseline than patients in the 5 day group • Day 14 clinical improvement: 64% (5-day) vs. 54% (10-day); baseline-adjusted different −6.5% (95% CI, −15.7 to 2.8) • Most common ADRs included nausea (9%), worsening respiratory failure (8%), elevated alanine transferase level (7)% and constipation (7%)
Lopinavir/ritonavir			
A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19 [21] *Open-label, randomized controlled trial*	$N = 199$ Severe disease ($SaO_2 \leq 94\%$ on room air or $PaO_2/FiO_2 < 300$ mmHg)	1:1 randomization: LPV/r 400/100 mg PO every 12 h for 14 days + SOC vs. SOC	• LPV/r not associated with faster time to clinical improvement compared to SOC (HR 1.31; 95% CI 0.95–1.80) • No difference in % of patients with detectable viral RNA at various time points • Modified intention to treat: LPV/r lead to a median time to clinical improvement that was shorter by 1 day vs. SOC • GI ADRs more common with LPV/r vs. SOC

Efficacy and Safety of Lopinavir/Ritonavir or Arbidol in Adult Patients with Mild/Moderate COVID-19: An Exploratory Randomized Controlled Trial [22] *Single-blinded (to patients), randomized controlled trial*	*N* = 86 Mild/moderate disease (mild = mild clinical symptoms with no signs of PNA on imaging; moderate = fever, respiratory symptoms, or PNA on imaging)	2:2:1 randomization: LPV/r 400/100 mg PO every 12 h for 7–14 days vs. umifenovir 200 mg PO every 8 h for 7–14 days vs. SOC	LPV/r vs. umifenovir vs. SOC: • Rate of conversion from positive to negative COVID-19 pharyngeal swab from first day of treatment to day 21: 9.0 ± 5.0 vs. 9.1 ± 4.4 vs. 9.3 ± 5.2 ($p = 0.981$) • Rate of conversion at day 14, rate of antipyresis, rate of cough alleviation, improvement rate of chest computed tomography scan at days 7 and 14, deterioration rate of clinical status from mild/moderate to severe/critical: No difference between groups for any of the outcomes • Adverse effects higher in LPV/r group compared to umifenovir and SOC: 35.5% vs. 14.3% vs. 0%
Hydroxychloroquine			
Effect of High vs. Low Doses of Chloroquine Diphosphate as Adjunctive Therapy for Patients Hospitalized with SARS-COV-2 Infection: A Randomized Clinical Trial [23] *Randomized, double-blind, Phase 2b trial*	*N* = 81 Hospitalized patients with clinical suspicion of COVID-19 • Aged 18 years or older at the time of inclusion • RR > 24 rpm and/or HR > 125 bpm (in the absence of fever), and/or peripheral oxygen saturation < 90% and/or shock	*High dose*: CQ 600 mg BID for 10 days *Low dose*: 450 mg BID for 1 day then 450 mg daily for 4 days • Hospital protocol: Ceftriaxone 1 g BID for 7 days + azithromycin 500 mg QD for 5 days • If influenza suspected, oseltamivir 75 mg BID for 5 days	Low dose vs. high dose CQ: • Viral RNA detection: 77.5% vs. 75.6% • Lethality until day 13: 15% vs. 39% ($p = 0.03$) • QTc interval > 500 ms: 11.1% vs. 18.9%

(continued)

Table 5.3 (continued)

Trial title and design	Patient population	Dosing and duration	Results
Hydroxychloroquine in Patients with Mainly Mild to Moderate Coronavirus Disease 2019: Open Label, Randomized Controlled Trial [24] *Multicenter, open label, randomized controlled trial*	$N = 150$ 18 years or older with ongoing SARS-CoV-2 infection confirmed in upper or lower respiratory tract specimens with RT-PCR	Hydroxychloroquine 1200 mg QD for 3 days followed by 800 mg QD • Total treatment duration: 2 or 3 weeks for patients with mild to moderate or severe disease, respectively) • SOC: Antiviral agents, glucocorticoids and antibiotics	SOC plus hydroxychloroquine vs. SOC • Probability of negative conversion by 28 days: 85.4% vs. 81.3%
Corticosteroids			
Effect of Dexamethasone in Hospitalized Patients with COVID-19: Preliminary Report [25] *Randomized, controlled, open-label, adaptive platform trial*	$N = 6425$ Clinically suspected or laboratory confirmed SARS-CoV-2 infection	Dexamethasone 6 mg QD for 10 days vs. SOC	Dexamethasone vs. SOC • 28 day mortality: 21.6% vs. 24.6% (RR 0.83; 95% CI 0.74–0.92; $p < 0.001$) • Discharged from hospital within 28 days: 64.6% vs. 61.1% (RR 1.11; 95% CI 1.04–1.19; $p = 0.002$)
GLUCOCOVID: A Controlled Trial of Methylprednisolone in Adults Hospitalized with COVID-19 Pneumonia [26] *Partially randomized preference, open-label, controlled, two-arm, parallel-group trial*	$N = 85$ Over 18 years of age with a laboratory confirmed diagnosis of SARS-CoV-2 infection Additional inclusion criteria: • Symptom duration of at least 7 days • Radiological evidence of lung disease in chest X-ray or CT-scan • Moderate-to-severe disease with abnormal gas exchange • Laboratory parameters indicative of hyper-inflammatory state (CRP > 15 mg/dL, D-dimer >800 mg/dL, ferritin >1000 mg/dL, or IL-6 levels >20 pg/mL)	Methylprednisolone 40 mg every 12 h for 3 days then 20 mg every 12 h for 3 days + SOC vs. SOC SOC treatment could include the following: Antibiotics for co-infections, azithromycin, hydroxychloroquine, and/or lopinavir plus ritonavir	Composite endpoint including in-hospital all-cause mortality, escalation to ICU admission, or progression of respiratory insufficiency that required non-invasive ventilation: • Intention-to-treat, age stratified analysis (RR 0.55 95% CI 0.33–0.91; $p = 0.024$) • Per protocol analysis: – Patients aged 72 or less: RR 0.11 (95% CI; 0.01–0.83) – Patients age greater than 72: RR 0.61 (95% CI; 0.32–1.17) – All patients: RR 0.50 (95% CI; 0.27–0.94)

Colchicine			
Effect of Colchicine vs. Standard of Care on Cardiac and Inflammatory Biomarkers and Clinical Outcomes in Patients Hospitalized with Coronavirus Disease 2019: the GRECCO-19 Randomized Clinical Trial [27] *Open-label randomized controlled trial*	$N = 105$ Mild to moderate disease (temperature 37.5 °C or more plus 2 or more of the following: Sustained cough, sore throat, anosmia and/or ageusia, fatigue and/or tiredness, and $SaO_2 < 95\%$ on room air)	SOC only vs. colchicine 1–1.5 mg loading dose PO (1 mg if on concomitant azithromycin) then 0.5 mg PO twice daily (once daily if body weight < 60 kg) until hospital discharge up to a maximum of 21 days	Control vs. colchicine • Biochemical (maximum hs cTn, time for CRP to reach more than three times the upper reference limit): No difference in hs cTn level between groups or CRP • Clinical (time to deterioration by 2 points on a 7-grade clinical status scale): 14.0% vs. 1.8%, OR 0.11 (95% CI 0.01–0.96) • Cumulative event-free 10-day survival: 83% vs. 97% ($p = 0.03$) • Diarrhea: 45.5% vs. 18.0% ($p = 0.003$)
Convalescent plasma			
Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients with Severe and Life-Threatening COVID-19: A Randomized Clinical Trial [28] *Open-label, multicenter, randomized controlled trial*	$N = 103$	Convalescent plasma ($n = 52$) vs. SOC ($n = 51$)	• No difference in clinical improvement within 28 days: 51.9% (CP) vs. 43.1% (SOC), HR 1.40 [95% CI, 0.79–2.49] – Benefit seen in subgroup of patients with severe disease: 91.3% (CP) vs. 68.2% (SOC), HR 2.15 [95% CI; 1.07–4.32] • No difference in 28-day mortality: 15.7% (CP) vs. 24.0% (SOC) ($p = 0.30$) • No difference in time from randomization to discharge: 51.0% (CP) vs. 36.0% (SOC) ($p = 0.12$) • Negative conversion rate of viral PCR at 72 h: 87.2% (CP) vs. 37.5% (SOC) ($p < 0.01$)

ADRs adverse drug reactions, *CRP* C-reactive protein, *CP* convalescent plasma, *CrCl* creatinine clearance, *CQ* chloroquine, *hs cTn* high sensitivity troponin C, *LPV/r* lopinavir/ritonavir, *PNA* pneumonia, *SaO_2* oxygen saturation, *SOC* standard of care

5.2.2 Remdesivir

Remdesivir is an investigational adenosine nucleotide analog that causes premature termination of viral RNA transcription (Table 5.1). It has been shown to have broad-spectrum activity against RNA viruses including Ebola, Marburg, respiratory syncytial virus (RSV), as well as MERS and SARS-CoV. In addition, it showed in vitro activity against SARS-CoV2, which identified it as a promising therapy [29].

Gilead Sciences accepted requests for compassionate use of remdesivir in hospitalized patients with SARS-CoV-2 infection, oxygen saturation (SaO_2) $\leq$ 94% on room air, creatinine clearance (CrCl) > 30 mL/min, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) within five times the upper limit of normal [31]. The drug was administered as a 200 mg intravenous infusion on the first day followed by 100 mg intravenously daily for a total duration of 5 days. In this compassionate use cohort, 57% of patients received mechanical ventilation. Patients were followed up for a mean of 18 days. Out of the patients who were intubated at baseline, 57% were extubated. Overall, 47% of patients were discharged and 13% died.

Following compassionate use, a multicenter, randomized controlled trial from China was published [18]. The trial was terminated early prior to attaining the prespecified sample size. The study showed no statistically significant clinical benefit in the primary endpoint, time to clinical improvement up to day 28. Clinical improvement was defined as a decline of two levels on a 6-point ordinal scale of clinical status (1 = discharged, 6 = death). A few limitations of this trial include low baseline use of mechanical ventilation (7%) and a high rate of corticosteroid use (66%).

A preliminary report of the Adaptive Covid-19 Treatment Trial (ACTT-1) sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), from 60 trial sites in the United States, Europe, Asia, and Latin America, was subsequently published [19]. Based on preliminary data that showed shorter time to recovery in the remdesivir group compared to the placebo group, the data and safety monitoring board recommended early unblinding of the data. A total of 1059 patients were included in this analysis (538 in the remdesivir group and 521 in the placebo group). Patients in the remdesivir group had a median time to recovery of 11 (95% CI; 9–12) days vs. 15 (95% CI; 13–19) days in the placebo group ($p < 0.001$). There was no mortality difference between both groups. A subgroup analysis showed that patients who received remdesivir within 10 days as well as those who received it after 10 days of symptoms onset benefited from the therapy and had a shorter time to recovery. The authors also analyzed time to recovery according to the patients' baseline oxygen requirement. This showed that the benefit of remdesivir on time to recovery decreased as baseline oxygen requirement increased. Patients receiving mechanical ventilation or extracorporeal membrane oxygenation (ECMO) (n = 272) did not have a benefit with remdesivir treatment compared to placebo: RR of recovery = 0.95 (95% CI; 0.64–1.42). This study shed some insight suggesting that even though remdesivir reduced time to recovery in the overall cohort, additional or different therapeutics may be needed in patients with a more severe disease course.

Finally, an open-label phase 3, randomized controlled trial evaluated the efficacy of 5 vs. 10 days of remdesivir therapy [20]. At baseline, patients in the 10-day course had worse clinical status on a 7-point ordinal scale than patients in the 5-day course ($p = 0.02$). There was no difference in the primary outcome, clinical improvement at day 14 between both duration of therapies despite adjustment for baseline clinical status: 64% (5-day) vs. 54% (10-day); baseline-adjusted difference −6.5% (95% CI, −15.7 to 2.8). The most common adverse events reported in this study with remdesivir use included nausea (9%), worsening respiratory failure (8%), elevated alanine transferase level (7%), and constipation (7%).

Based on the results of the ACCT-1 trial, the Food and Drug Administration (FDA) issued an emergency use authorization (EUA) on May 1, 2020, for the use of remdesivir in patients with severe disease [10]. Patients qualified for the EUA if they met all of the following criteria: hospitalized patients with a laboratory confirmed SARS-CoV-2 infection, severe disease with $SaO_2 \leq 94\%$ on room air, requiring oxygen supplementation, mechanical ventilation or ECMO. Clinicians should evaluate the risk/benefit ratio in pregnant patients or patients with renal dysfunction (CrCl <30 mL/min) or hepatic dysfunction. The recommended duration of therapy was a 5-day course except for patients receiving mechanical ventilation or ECMO, suggested to receive a 10-day course of therapy. Multiple guidelines have released recommendations to prioritize the limited supply of remdesivir for patients requiring oxygen support [4, 5] (Table 5.2).

5.2.3 Lopinavir/Ritonavir

Lopinavir is a protease inhibitor used to treat human immunodeficiency virus and has been shown to be effective at inhibiting viral replication in vitro against SARS-CoV [32]. It is given as a fixed dose in combination with ritonavir, which is a potent inhibitor of cytochrome P450 3A4 (CYP3A4), inhibiting the metabolism of lopinavir and effectively increasing plasma concentrations. Specifically, lopinavir inhibits a viral enzyme present in coronaviruses, the enzyme 3-chymotrypsin-like protease (3CLpro), which cleaves and processes polyproteins translated from the viral RNA [33].

There are currently two randomized controlled trials published evaluating the efficacy and safety of lopinavir/ritonavir 400/100 mg two times daily for 7–14 days in patients with COVID-19. Cao and colleagues randomized 199 patients with severe disease in a 1:1 fashion to receive either lopinavir/ritonavir plus standard of care (SOC) vs. SOC alone [21]. The primary endpoint was time to clinical improvement, defined as improvement of two points on a seven-category scale (1 = not hospitalized; 7 = death) or discharge from the hospital, whichever came first. The investigators found that lopinavir/ritonavir was not associated with a more rapid time to clinical improvement compared to SOC (HR 1.31; 95% CI 0.95–1.80). In the modified intention to treat group, however, lopinavir/ritonavir led to a shorter median time to clinical improvement by 1 day compared to SOC. Overall, adverse drug reactions were similar between groups, but gastrointestinal-related adverse

reactions were more common in the lopinavir/ritonavir group, and serious adverse reactions (respiratory failure, acute kidney injury, secondary infection) were more common in the SOC group. Notable limitations include the lack of blinding and use of concurrent pharmacologic agents, which may have confounded results. In the study done by Li and colleagues, 86 patients with mild-to-moderate disease were randomized in a 2:2:1 fashion to receive lopinavir/ritonavir + SOC vs. umifenovir (a fusion inhibitor) + SOC vs. SOC alone [22]. The primary outcome was the rate of conversion from positive to negative COVID-19 pharyngeal swab from the first day of treatment to day 21. The investigators found no difference in any of the primary or secondary outcomes between groups; however adverse reactions were higher in the lopinavir/ritonavir group compared to umifenovir and SOC (35.5% vs. 14.3% vs. 0%, respectively), with diarrhea being the most common adverse drug reaction.

Other published studies that have evaluated the use of lopinavir/ritonavir for patients with COVID-19 were primarily observational and/or descriptive in nature. In a study done by Ye and colleagues, patients with mild disease (no mechanical ventilation) received lopinavir/ritonavir (400/100 mg orally two times daily or 800/200 mg orally once daily for 10 days) plus SOC vs. SOC alone [34]. Investigators found no difference in change in body temperature over 10 days between groups, although the lopinavir/ritonavir group returned to normal body temperature approximately 2.5 days sooner than the control group (4.8 ± 1.94 vs. 7.3 ± 1.53 days, $p = 0.0364$). In addition, the time to a negative viral swab was shorter in the lopinavir/ritonavir group (7.8 ± 3 vs. 12 ± 0.82 days, $p = 0.0219$). In contrast, a study by Zhu and colleagues who compared lopinavir/ritonavir (400/100 mg orally two times daily for 7 days) to umifenovir (0.2 g orally three times daily for 7 days) in patients with mild disease found that the day 14 viral load was undetectable in all patients in the umifenovir group and still detectable in 44.1% of patients in the lopinavir/ritonavir group [35]. Finally, a descriptive study by Wang and colleagues where all patients received lopinavir/ritonavir (no dose disclosed) for 7 days, viral swabs turned negative 4–21 days after diagnosis. In all observational studies, lopinavir/ritonavir was well tolerated [36].

Well-designed, randomized, controlled, double-blind trials assessing the efficacy and safety of lopinavir/ritonavir for use in COVID-19 are lacking. Based on current literature, it appears that lopinavir/ritonavir may not be efficacious in treating COVID-19. Overall, it does not seem that lopinavir/ritonavir decreases time to clinical improvement, and data regarding shortening the time to negative viral swab is conflicting. Due to the open-label or retrospective nature of the available literature, there is a risk for confounding factors that may have influenced the outcomes. For example, not all groups were similar in baseline characteristics (uneven distribution of baseline viral loads) and investigators were not able to control for other treatments patients may have received. In addition, many of these studies were single-center, therefore limiting the external validity. As more studies become available, a definitive conclusion regarding the role of lopinavir/ritonavir in treating patients with COVID-19 will be possible. If utilized, providers must consider drug interactions, gastrointestinal toxicities, and the risk/benefit of use in each patient. In particular, use of lopinavir/ritonavir in patients with COVID-19 may exacerbate hepatotoxicity

and other gastrointestinal toxicities caused by the virus itself. In addition, hepatic transaminitis is a common exclusion criterion for clinical trials on investigational agents (e.g., remdesivir, although not a contraindication for the emergency use authorization); therefore use of Lopinavir/ritonavir may hinder patient access to these trials should adverse reactions occur.

5.2.4 Hydroxychloroquine or Chloroquine with or Without Azithromycin

Hydroxychloroquine or chloroquine has been proposed to increase the endosomal pH, inhibiting fusion of SARS-CoV-2 and the host cell membrane. In addition, chloroquine inhibits glycosylation of the cellular angiotensin-converting enzyme 2 receptor [29]. Both agents have been combined with azithromycin that can induce interferon-stimulated gene that attenuates viral replication, enhance neutrophil activation, attenuate inflammatory cytokines (IL-6 and IL-8) in epithelial cells, and inhibit fibroblast growth factor in airway smooth muscle cell.

A randomized study, CloroCOVID-19, included hospitalized patients with clinical suspicion of COVID-19 with a respiratory rate > 24 rpm and/or a heart rate > 125 bpm and/or peripheral oxygen saturation lower than 90% in ambient air and/or shock [23]. The patients received high-dose chloroquine 600 mg orally twice daily for 10 days or low-dose chloroquine 450 mg twice daily for 1 day then 450 mg daily for 4 days concomitantly with antibiotic therapy and oseltamivir if influenza was suspected. The results in the interim analysis of low-dose vs. high-dose chloroquine included viral RNA detection in 31 of 40 (77.5%) vs. 31 of 41 (75.6%) and lethality until day 13 documented in 6 out of 40 (15%) vs. 16 out of 41 (39%) patients, respectively. Notable adverse events included QTc interval prolongation greater than 500 ms, occurring in 11.1% of patients in the low-dose group vs. 18.9% of patients in the high-dose group. Patients in the high-dose group were older and had a higher incidence of baseline heart disease.

In China, a multicenter, open-label, randomized controlled trial enrolled 150 total patients with ongoing SARS-CoV-2 infection confirmed in upper or lower respiratory tract specimens though RT-PCR [24]. Patients received hydroxychloroquine 1200 mg daily for 3 days followed by a maintenance dose of 800 mg daily for a total treatment duration of 2 or 3 weeks for patients with mild to moderate or severe disease, respectively. All patients received SOC in both groups concomitantly with varying regimens of antiviral agents, antibiotics, and systemic glucocorticoids. The probability of negative conversion by 28 days in the SOC plus hydroxychloroquine group was 85.4% (95% CI 73.8–93.8%), similar to that in the SOC group of 81.3% (95% CI 71.2–89.6%).

In addition to the paucity of data showing positive outcomes, the safety of hydroxychloroquine was assessed with a focus on QTc interval prolongation, particularly when in combination with azithromycin [37]. In a non-critically ill patient population, the combination of hydroxychloroquine 200 mg twice daily with azithromycin 500 mg daily for at least 3 days showed QTc interval prolongation,

particularly in patients with high levels of transaminases [38]. In addition, although not explicitly stated, a mix of ICU and non-ICU patients were given chloroquine/hydroxychloroquine with azithromycin that led to a significantly greater increase in the QTc interval when compared with monotherapy as well as a discontinuation rate of 3.5% due to QTc interval prolongation with no reported cases of TdP in the cohort [39].

The safety and efficacy of hydroxychloroquine or chloroquine combined with azithromycin as well as other investigational therapies have been studied in small retrospective clinical trials, case series, and observational reports that have shown mixed outcomes across a spectrum of illness in the COVID-19 patient population. Although few studies have shown positive outcomes, an overwhelming majority of published data have shown no difference in intubation, probability to negative conversion at a predetermined time point, survival without transfer to the ICU, acute respiratory distress syndrome (ARDS), or overall survival in patients that received treatment with hydroxychloroquine or chloroquine [40–43]. In addition, the FDA revoked the emergency use authorization to use hydroxychloroquine and chloroquine to treat COVID-19 in certain hospitalized patients outside of a clinical trial setting due to lack of benefit [44].

5.3 Immunomodulatory Agents

Cytokines play a pivotal role in the immune response to viral pathogens. This response, however, can become dysregulated, leading to a cytokine release syndrome with downstream complications including end-organ damage such as ARDS. Cytokine release syndrome is a major cause of morbidity in patients infected with SARS-CoV-2. Serum elevations in IL-6 and IL-1 correlate to respiratory failure, ARDS, and adverse clinical outcomes. IL-6 has proinflammatory properties due to the cis- and trans-signaling pathways. In the trans-signaling pathway, high circulating concentrations of IL-6 bind to the soluble form of IL-6 receptor and form the IL-6-sIL-6R-JAK-STAT3 complex that activates cells downstream resulting in a cytokine storm. During the cytokine storm phase, numerous factors including vascular endothelial growth factor, monocyte chemoattractant protein-1, and IL-8 are expressed that contribute to vascular permeability. Consequently, alveolar-capillary permeability to fluid, proteins, and blood cells is increased and respiratory failure occurs [45–48].

5.3.1 Interleukin 6 Inhibitors

Tocilizumab, sarilumab, siltuximab, and olokizumab are IL-6 inhibitors commercially available in different countries, while clazakizumab is undergoing clinical trials. Tocilizumab, the most widely researched IL-6 inhibitor in COVID-19, is a recombinant humanized monoclonal antibody that binds to both membrane-bound and soluble forms of the IL-6 receptor [47, 48].

Chronic administration in patients with rheumatologic diseases such as rheumatoid arthritis can shed light on common adverse reactions that may manifest with short-term administration in the SARS-CoV-2 patient population. Serious and potentially fatal infections, including active tuberculosis, invasive fungal, bacterial, viral, protozoal, and other opportunistic infections, have been reported in chronic therapy, especially in patients treated with concomitant immunosuppressive therapy. Although adverse effects were reported in published literature in the COVID-19 patient population, including infection, many outcomes were limited to short-term endpoints [49].

In a retrospective ICU cohort study, patients with laboratory confirmed severe COVID-19 with elevated C-reactive protein (CRP) levels were administered tocilizumab at a median total dose of 5.7 mg/kg (IQR 4.8–9.5 mg/kg) [50]. Patients also received at least two concomitant investigational antiviral agents. Results obtained on day 1, 3, and 7 showed a decrease in median oral temperature, CRP, number of patients requiring invasive ventilation, and radiological improvement. Twenty-three (92%) patients in the study experienced at least one adverse event, most frequently anemia, ALT rise, and QT prolongation. Due to the patients receiving concomitant investigational therapies, assessing adverse effects could be difficult to ascertain.

In a non-ICU retrospective cohort in patients with COVID-19, tocilizumab was administered at 400 mg with a second dose of 400 mg being administered after 24 h in case of respiratory worsening [51]. The patients enrolled had hyper-inflammation, defined as either CRP $\geq$ 100 mg/L or ferritin >900 ng/mL in the presence of increased LDH, and severe respiratory involvement in the presence of an oxygen saturation $\leq$92% while breathing ambient air or a PaO_2:FiO_2 ratio $\leq$ 300 mmHg. The patients did not receive other anti-inflammatory drugs or glucocorticoids and were not enrolled in other clinical trials. During the 28-day follow-up, 69% of the tocilizumab patients experienced a clinical improvement compared to 61% of the standard treatment group ($p = 0.61$). Mortality was 15% in the tocilizumab group and 33% in the standard treatment group ($p = 0.15$). Between the tocilizumab and standard care group, there were no statistically significant increases in bacterial infections, pulmonary thrombosis, or increases in AST or ALT, although there was a difference in neutropenia reported in 16% of patients in the tocilizumab group ($p = 0.024$) [51].

Patients enrolled in the tocilizumab treatment arm at Michigan Medicine had severe COVID-19 present and required invasive mechanical ventilation. Patients received a dose of 8 mg/kg (maximum 800 mg) once, with additional doses discouraged. Patients in both groups received concomitant therapy with overall rates being 23% hydroxychloroquine, 3% remdesivir, and 25% corticosteroids. Survival probability was significantly higher among tocilizumab treated compared to untreated patients ($p = 0.089$). Patients who received tocilizumab were more than twice as likely to develop superinfection compared to untreated controls (54% vs. 25%; $p < 0.001$), driven primarily by ventilator associated pneumonia, although case fatality rates were similar in infected and uninfected tocilizumab-treated patients [52].

Numerous published case reports and retrospective cohort papers are available to interpret, while many other clinical trials are still enrolling patients. Clinicaltrials.

gov has over 60 registered studies with interleukin-6 inhibitors. When reviewing the available literature, many papers were single arm retrospective reviews with IL-6 inhibitor treatment spanning from ICU to non-ICU patients [53–55]. Given that IL-6 inhibitors were commonly used with concomitant investigational therapies for SARS-CoV-2, one should take into consideration the results from all clinical trials to parse out if the trial result is a cumulative outcome due to a multi-modal treatment approach or due to a single medication given.

5.3.2 Corticosteroids

The use of corticosteroids in patients diagnosed with COVID-19 is controversial given mixed results in the existing literature. Steroids exhibit their anti-inflammatory effects that could have a beneficial effect in suppressing the cytokine-related lung injury in patients with severe COVID-19. Diffuse alveolar damage, inflammatory infiltrates, and microvascular thrombosis are features recognized on autopsy reports [5, 25]. There are three suggested phases of SARS-CoV-2 that include early infection in phase 1, pulmonary involvement with and without hypoxia in phase II, and systemic hyperinflammation in phase III. The viral response phase is thought to occur in stage I with overlap into stage II, while the host inflammatory response phase occurs at the end of stage II into stage III. During the host inflammatory response phase, glucocorticoids have been proposed to play a role [56]. The NIH recommends use of dexamethasone (at a dose of 6 mg/day for up to 10 days) in mechanically ventilated COVID-19 patients and in patients who require supplemental oxygen [5]. In the RECOVERY trial, investigators compared dexamethasone 6 mg daily to SOC in patients with clinically suspected or laboratory confirmed SARS-CoV-2 infection. Overall, the study showed a reduced 28 day mortality ($p < 0.001$) as well as a larger proportion of patients being discharged at 28 days ($p = 0.002$) in the dexamethasone group [25]. Dexamethasone had varying results based upon the level of respiratory support; specifically, there were reduced deaths in patients receiving mechanical ventilation (29% vs. 40.7%, $p < 0.001$) and patients receiving oxygen without invasive mechanical ventilation (21.5% vs. 25%, $p = 0.002$), but there was no difference in mortality in patients not receiving respiratory support (17% vs. 13.2%; $p = 0.14$).

Investigators studied methylprednisolone in varying doses and severity of illness in the SARS-CoV-2 patient population through mostly observational reviews that produced both positive and negative results. In a systematic review, the percentage of patients taking corticosteroids ranged from 7.6 to 44.9% of the cohorts included [57]. Of the four studies reviewed, two studies by Liu et al. and Wang et al. did not show a significant benefit. Wang et al. found that glucocorticoid therapy was associated with a greater risk of ICU admission. In addition, Ling et al. showed that duration of viral RNA detection for oropharyngeal and fecal swabs in the corticosteroids treatment group was longer than that in the non-corticosteroid treatment group. Lastly, in a study published by Wu et al., the administration of methylprednisolone reduced the risk of death in subjects having ARDS for COVID-19. In Spain, patients diagnosed with COVID-19 pneumonia complicated by ARDS and/or

hyperinflammatory syndrome were treated with 1 mg/kg/day methylprednisolone or a steroid pulse with additional investigational therapies at the discretion of the treating physician. Of the various investigational therapies available, the patients in the steroid cohort received statistically more hydroxychloroquine (99.5% vs. 92.5%, $p = 0.001$) and tocilizumab (44.9% vs. 18.5%, $p < 0.001$). Patients received steroid treatment in a median of 10 days after onset of symptoms. In-hospital mortality was lower in patients treated with steroids than in controls (13.9% vs. 23.9%, HR 0.51 [0.27–0.96]). In-hospital mortality was not different between initial regimens of 1 mg/kg/day of methylprednisolone and steroid pulses [58]. Additional retrospective papers have reported similar results including reduced escalation of care from ward to ICU, decreased mortality, decreased ICU length of stay and hospitalization, and decreased inflammatory markers [59, 60].

In the GLUCOCOVID trial, a partially randomized preference, open-label, controlled, parallel-group trial, patients over 18 years of age with confirmed diagnosis of SARS-CoV-2 infection with symptom duration of at least 7 days, radiological evidence of lung disease, moderate-to-severe disease with abnormal gas exchange, and laboratory parameters indicative of hyper-inflammatory state were enrolled [26]. Patients were excluded if they were intubated or mechanically ventilated, were hospitalized in the ICU, or were treated with corticosteroids or immunosuppressive drugs at the time of enrollment. The treatment included methylprednisolone 40 mg every 12 h for 3 days followed by 20 mg every 12 h for 3 days with standard care vs. standard care alone. The composite endpoint, including in-hospital all-cause mortality, escalation to ICU admission, or progression of respiratory insufficiency that required non-invasive ventilation, was reduced in the intention-to-treat, age-stratified analysis (RR 0.55, 95% CI 0.33–0.91, $p = 0.024$). In the per-protocol analysis, RR was 0.11 (0.01–0.82) in patients aged 72 years or less, RR 0.61 (0.32–1.17) in those over 72 years of age, and RR 0.37 (0.19–0.74) in the whole group after age-adjustment by stratification.

5.3.3 Anakinra

Anakinra is an IL-1 antagonist that inhibits the proinflammatory cytokines IL-1α and IL-1β [11]. It is indicated for treatment of rheumatoid arthritis; however, based on its mechanism of action, it was hypothesized that it may benefit patients with COVID-19 with a severe inflammatory component. Anakinra is administered subcutaneously, and although it is generally well-tolerated, severe adverse reactions such as reactivation of tuberculosis (TB), hypersensitivity reactions, secondary infection, and neutropenia are possible.

The data for use of anakinra in patients with COVID-19 is limited to case reports, small case series, and retrospective studies. In the two largest observational studies to date, patients with moderate to severe ARDS (non-invasive mechanical ventilation, not in the ICU) received anakinra in addition to lopinavir/ritonavir and/or HCQ/azithromycin or SOC (including lopinavir/ritonavir and/or HCQ/azithromycin) [12, 61]. In both studies, baseline characteristics were not evenly distributed between groups and

may have affected outcomes. In the study by Cavalli et al., at 21 days, survival was 90% in the anakinra group and 56% in the control group ($p = 0.009$); however there was no difference in mechanical ventilation-free survival or adverse reactions [12]. In the study by Huet et al., admission to ICU for mechanical ventilation or death was significantly lower in the anakinra vs. SOC group (25% vs. 73% (HR 0.22, 95% CI 0.11–0.41)) and results were not affected by multivariate analysis [61]. There were more adverse reactions (elevated LFTs, thromboembolic events) in the anakinra group. Other case reports and case series have reported improvement in inflammatory markers and respiratory status [62–64]. Although results are encouraging, these studies are limited by non-randomized design, uneven distribution of baseline characteristics, and confounders including inter-provider variability in the SOC regimen.

There are currently four studies registered with clinicaltrials.gov assessing the role of anakinra in patients with COVID-19. The results of these randomized controlled trials will be imperative in guiding providers on the most judicious use of this agent, given the paucity of current data does not define a cohort of patients that would benefit most, and expanded use is cost prohibitive and possibly unsafe.

5.3.4 Colchicine

Recently, colchicine has become a drug of interest in treating the inflammatory aspects of COVID-19. Although colchicine's primary mechanism of action is inhibition of the polymerization of microtubules, colchicine also has significant anti-inflammatory properties, particularly on neutrophils. The dosing of colchicine will vary by indication, and the most appropriate dose of colchicine in patients with COVID-19 is yet to be determined. Colchicine commonly causes gastrointestinal symptoms, particularly diarrhea, nausea, and vomiting; however in rare instances, colchicine can cause bone marrow suppression [13, 14].

There is currently only one trial evaluating the role of colchicine in treating the inflammatory aspects of COVID-19. This study by Deftereos and colleagues was an open-label, randomized, controlled trial that assessed colchicine plus SOC vs. SOC alone on various inflammatory markers and clinical outcomes [27]. Patients were enrolled if they had a positive SARS-CoV-2 swab and a temperature ≥37.5 °C plus two or more of the following: sustained cough, sustained sore throat, anosmia and/or ageusia, fatigue and/or tiredness, O_2 sat <95% on room air and did not require ventilator support. Fifty-five patients were randomized to a colchicine loading dose followed by maintenance dosing and SOC and 50 patients received SOC only. The study was stopped early because of slow enrollment and did not meet power; however for the patients that were included, baseline characteristics were similar between groups. The investigators found no significant differences in biochemical outcomes such as CRP or high-sensitivity troponin-C (hs cTn). There was, however, a significant difference in clinical outcomes (time to deterioration, cumulative event-free 10-day survival) favoring the colchicine group. Diarrhea was significantly more frequent in the colchicine group but only caused discontinuation of therapy in two cases and was not associated with electrolyte abnormalities.

There are currently seven studies registered with clinicaltrials.gov assessing colchicine in patients with COVID-19. Currently, data for the use of colchicine in patients with COVID-19 is limited to one small, underpowered, open-label study. In addition, colchicine has never been studied in patients with severe disease requiring intubation and the risk benefit is unknown. Until further information is available, its use cannot be recommended.

5.3.5 Convalescent Plasma

This therapy uses the antibodies from patients recovered from COVID-19 and provides adaptive immunotherapy. It has been shown to be successful in the treatment of other viral infections including SARS, MERS, and H1N1 influenza A [65, 66].

A small prospective observational cohort of 10 patients in China who received a dose of convalescent plasma showed that all patients cleared the viremia and improved within 3 days of administration [67]. This study showed that convalescent plasma could be a promising treatment modality in COVID-19 patients [66].

There is one randomized controlled trial evaluating convalescent plasma, conducted in seven medical centers in Wuhan, China [28]. This study included 103 patients who were randomized to convalescent plasma or standard of care. The study was terminated early due to poor enrollment and therefore has limited power. Most patients (86.4%) were enrolled after 14 days from symptoms onset. The primary outcome evaluated was time to clinical improvement within 28 days, defined as hospital discharge or decrease in 2 points on a 6-point disease severity scale (1 = discharge to 6 = death).

Adverse effects associated with the use of blood products should be considered when deciding whether to administer convalescent plasma. These include transfusion-related lung injury (TRALI), transfusion-associated circulatory overload (TACO), thrombotic events, and transfusion associated infections. A total of 5000 patients who received convalescent plasma as part of the US FDA Expanded Access Program for COVID-19 were analyzed to evaluate the safety. Rate of serious adverse events was <1% [68].

To date, use of convalescent plasma is recommended as part of a clinical trial [4, 5]. More data is needed to evaluate its role in this patient population.

5.3.6 Vitamins and Minerals

Patients with COVID-19 likely have evidence of oxidative stress, characterized by the production of reactive oxygen species and a concomitant deficiency of antioxidants. Given the potential of ascorbic acid, vitamin D, and zinc to influence the immune response, reactive oxygen species, and nitrogen species, these agents may be useful as adjunctive therapy in SARS-CoV-2 infection [69].

Ascorbic acid, also known as vitamin C, functions as an antioxidant by salvaging reactive oxygen species, decreasing the gene expression of proinflammatory

cytokines, and enhancing microbial killing in certain cell types. Although there are currently no published studies assessing the use of ascorbic acid in patients with SARS-CoV-2 infection, high doses of ascorbic acid have been studied in the ARDS and septic shock patient populations [69, 70]. CITRIS-ALI trial suggested that giving intravenous vitamin C 50 mg/kg every 6 h for 96 h did not significantly alter disease severity scores, CRP levels, or thrombomodulin levels in patients with sepsis and ARDS. However, 28-day all-cause mortality was lowered and ICU-free days were shorter with vitamin C use [71]. The VITAMINS trial suggested that a combination of intravenous vitamin C, hydrocortisone, and thiamine did not improve duration of time alive or free from vasopressor administration compared to hydrocortisone alone in a population with septic shock [72]. Randomized controlled trials of vitamin C are registered on the NIH ClinicalTrials.gov website with a wide range in dosing strategies as well as varying concomitant investigational agents.

Zinc has a role in antibody and white blood cell production. A deficiency in zinc can increase proinflammatory cytokine concentrations (IL-1, IL-6, and TNF-alpha) and decrease the production of antibodies. Zinc supplementation may act in a synergistically when co-administered with the standard antiviral therapy. It has been shown that effectiveness of zinc against a number of viral species was best explained through the physical processes, such as viral attachment, infection, and uncoating [73]. Zinc may also stabilize the cell membrane that could help block of the virus entry into the cell. Finally, zinc may also inhibit viral replication by alteration of the proteolytic processing of the replicase polyproteins and RNA-dependent RNA polymerase in rhinoviruses, HCV, and influenza virus and diminish the RNA-synthesizing activity of noroviruses, to which SARS-CoV-2 belongs.

In addition, in vitro studies with vitamin D show immunomodulatory effects, anti-proliferative effects on T cells, modulating expression and secretion of type 1 interferon, and inhibition of proinflammatory cytokine expression. The largest study to date included over 10,000 individuals from 25 high-quality trials, concluded that oral vitamin D_3 supplementation reduced the risk of acute respiratory tract infections with stronger effects in patients with 25-hydroxyvitamin D levels <25 ng/mL [69, 70, 73].

Ascorbic acid, zinc, and vitamin D have biologic plausibility for the prevention and treatment of SARS-CoV-2 and are currently undergoing clinical trial analysis. Unless a patient has a true micronutrient deficiency, additional research is needed before providing doses of these agents above the recommended daily intake.

5.4 Controversial Agents

5.4.1 Renin Angiotensin Aldosterone Inhibitors

One of the key mechanisms responsible for the pathophysiology of COVID-19 is the dysregulation of the renin-angiotensin aldosterone system (RAAS). This is explained by the fact that the SARS-CoV2 spike protein uses the angiotensin converting enzyme 2 as an entry receptor into target cells [1]. Patients with hypertension

have been shown to have more severe disease, which has led to concerning statements that it might be caused by RAAS inhibitor agents such as angiotensin converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs) used to control blood pressure [74, 75]. Concerns regarding their use include the possibility of upregulation of cellular ACE2 expression, thereby increasing viral entry and replication [76]. On the contrary, researchers have described potential benefit of ACEis and ARBs because these agents reduce levels of angiotensin II, which is a potent proinflammatory, pro-oxidative, pro-fibrotic hormone that contributes to the pathophysiology of COVID-19 [77].

Multiple investigators have evaluated the association between the use of ACEis and ARBs and the likelihood of testing positive for COVID-19 and did not find an increased risk [78–80]. Additionally, a meta-analysis of retrospective cohort and case-control studies did not find an association between the use of these agents and the risk of developing severe/lethal COVID-19 disease [81]. The American College of Cardiology, American Heart Association, and Heart Failure Society of America as well as treatment guidelines recommend continuation of ACEis and ARBs in patients prescribed these medications for cardiovascular disease [4, 5].

5.4.2 Non-steroidal Anti-inflammatory Drugs

Initial warning statements were released regarding potential harm with the use of NSAIDs in COVID-19 patients due the risk of reduced antibody production and increased ACE2 expression [82, 83]. Due to the lack of clinical evidence suggesting benefit or harm associated with NSAIDs in COVID-19 patients, the FDA issued a statement regarding their use [84]. The NIH guidelines recommend continuation of NSAIDs in patients prescribed this class of medication. In addition, the panel recommended the use of acetaminophen or NSAIDs as antipyretics in COVID-19 patients [5].

5.5 Summary and Future Research

Aside from the therapeutic options discussed in this text, numerous additional pharmacologic treatment options are being investigated to target the virus itself as well as the downstream inflammatory aspects of the disease. Some of these agents include janus kinase inhibitors (baracitunib, ruxolitinib, tofacitinib), complement pathway inhibitors (ravulizumab, eculizumab), granulocyte-macrophage colony-stimulating factors (lenzilumab, mavrilimumab, sargramostim), ivermectin, famotidine, nitazoxanide, dornase alfa, and anakinra/retinoic acid. This data is paramount in providing insight to healthcare providers on the most safe and effective pharmacologic therapies of this disease and its associated complications.

Non-pharmacologic therapies are also being studied for treatment of COVID-19. In patients with SARS-CoV-induced ARDS in the early 2000s, blood purification strategies such as plasma exchange showed significant cytokine clearance. An

artificial-liver-blood purification system used in patients with severe H7N9 influenza filtered proinflammatory cytokines from the blood of these patients and showed significantly reduced levels of cytokines including TNF-α and various interleukins [85]. Recently, this artificial-liver-blood purification system was trialed in patients with COVID-19 and showed prevention of cytokine storm and adequate clearance of cytokines [86]. In April, the FDA issued four EUAs for blood purification systems, which are designed to filter proinflammatory cytokines from the blood of patients with COVID-19. These emergency use authorizations will facilitate patient access and provide opportunities to assess their safety and efficacy. Mesenchymal stem cell (MSC) therapy is also being investigated to target the inflammatory aspects of COVID-19 primarily due to their immunomodulatory effects. A small case series of seven patients with COVID-19 who were treated with MSC therapy showed improved respiratory function within 2 days of administration [87]. The FDA has granted compassionate use approval for MSC therapy.

The COVID-19 pandemic has globally burdened researchers to swiftly develop, test, assess, and approve or reappraise novel or existing therapies for the treatment of COVID-19. Much of the available literature is limited to case reports, case series, observational studies, or small, open-label studies. Expanded access programs have given patients with limited options access to investigational agents not yet approved by the FDA, European Medicine Agency, and other international equivalents, in the hopes that the benefits will outweigh the risks of treatment. Expert panels are constantly updating national guidelines to be consistent with the most recently published literature and, where data is limited or unavailable, are making recommendations based on expert consensus. Ultimately, until well-designed, large clinical studies are available, a critical assessment of the pros and cons of some of these agents in context of the clinical scenario will be necessary.

References

1. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probably bat origin. Nature. 2020;579:270–3.
2. Chen Y, Liu Q, Guo D. Emerging coronaviruses: genome structure, replication, and pathogenesis. J Med Virol. 2020;92(4):418–23.
3. Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, et al. Extrapulmonary manifestations of COVID-19. Nat Med. 2020;26:1017–32.
4. Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng VCC, et al. Infectious Disease Society of America guidelines on the treatment and management of patients with COVID-19. Clin Infect Dis. 2020;ciaa478. https://doi.org/10.1093/cid/ciaa478. [Epub ahead of print].
5. COVID-19 Treatment Guidelines Panel. Coronavirus disease 2019 (COVID-19) treatment guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed 28 July 2020.
6. 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;48(6):e440–69.
7. Australian guidelines for the clinical care of people with COVID-19 - Australian National COVID-19 Clinical Evidence Taskforce. 2020 Jul 17. [cited 2020 Jul 29]. Available at https://

files.magicapp.org/guideline/b9ed182a-bba7-4887-bcc1-d118aed2d760/published_guideline_4361-14_0.pdf.
8. Italian Society of Infectious and Tropical Diseases. Guidelines for the treatment of people with COVI-19 disease. Edition 2.0, 13 March 2020. [cited 2020 Jul 29]. Available at https://www.acep.org/globalassets/images/italian-guidelines-for-covid-19-google-translate.pdf.pdf.
9. Famvir® (famciclovir) tablets [package insert on the Internet]. East Hanover: Novartis Pharmaceuticals USA, Inc.; 1994 [revised 2016 Sep; cited 2020 Jul 26]. Available at https://www.novartis.us/sites/www.novartis.us/files/Famvir.pdf.
10. US Food and Drug Administration [Internet]. Remdesivir emergency use authorization letter; 2020 [cited 2020 Jul 27]. Available at https://www.fda.gov/media/137564/download.
11. Kineret® (anakinra) injection for subcutaneous use [package insert on the Internet]. Stockholm (SWE): Swedish Orphan Biovitrum AB, 2001 [revised 2018 Jun; cited 2020 Jun 19]. Available at https://www.kineretrx.com/pdf/Full-Prescribing-Information-English.pdf.
12. Cavalli G, De Luca G, Campochiaro C, Della-Tore E, Ripa M, Canetti D, et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respirtatory distress syndrome, and hyperinflmmation: a retrospective cohort study. Lancet Rheumatol. 2020;2(6):e325–31.
13. Colcrys® (colchicine) tablets [package insert on the Internet]. Deerfield: Takeda Pharmaceuticals USA, Inc.,1961 [revised 2020 May; cited 2020 Jun 26]. Available at https://general.takedapharm.com/COLCRYSPI.
14. Leung YY, Hui LLY, Kraus VB. Colchicine – update on mechanisms of action and therapeutic uses. Semin Arthritis Rheum. 2015;45(3):341–50.
15. Baden LR, Rubin EJ. Covid-19 – the search for effective therapy. N Engl J Med. 2020;382(10):1851–2.
16. McCreary EK, Pogue JM. Coronavirus disease 2019 treatment: a review of early and emerging options. Open Forum Infect Dis. 2020;7(4):1–11.
17. Chen C, Huang J, Yin P, Zhang Y, Cheng Z, Wu J, et al. Favipiravir versus arbidol for COVID-19: a randomized clinical trial. medRxiv [Internet]. 2020 [cited 2020 Jul 26]. Available at https://www.medrxiv.org/content/medrxiv/early/2020/04/08/2020.03.17.20037432.full.pdf. https://doi.org/10.1101/2020.03.17.20037432.
18. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 2020;395:1569–78.
19. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Hohmann E, et al. Remdesivir for the treatment of COVID019 – preliminary report. N Engl J Med. 2020; https://doi.org/10.1056/NEJMoa2007764. [Online ahead of print].
20. Goldman JD, Lye DCB, Hui DS, Marks KM, Bruno R, Montejano R, et al. Remdesivir for 5 or 10 days in patients with severe COVID-19. N Engl J Med. 2020; https://doi.org/10.1056/NEJMoa2015301. [Online ahead of print].
21. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe covid-19. N Engl J Med. 2020;382(19):1787–99.
22. Li Y, Xie Z, Lin W, Cai W, Wen C, Guan Y, et al. Efficacy and safety of lopinavir/ritonavir or arbidol in adult patients with mild/moderate COVID-19: an exploratory randomized controlled trial. Medicine. 2020 [cited 2020 Jun 17]. https://doi.org/10.1016/j.medj.2020.04.001. [Epub ahead of print].
23. Borba MG, Val FF, Sampaio VS, Alexandre MA, Melo GC, Brito M, et al. Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: a randomized clinical trial. JAMA Netw Open. 2020;3(4):e208857.
24. Tang W, Cao Z, Han M, Wang Z, Chen J, Sun W, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomized controlled trial. BMJ. 2020;369:m1849.
25. Horby P, Lim WS, Emberson J, Mafham M, Bell J, Linsell L, et al. Effect of dexamethasone in hospitalized patients with COVID-19: a preliminary report. medRxiv [Internet]. 2020 June 22 [cited 2020 June 30]. https://www.medrxiv.org/content/10.1101/2020.06.22.20137273v1. https://doi.org/10.1101/2020.06.22.20137273.

26. Corral L, Bahamonde A, Revillas FA, Gomez-Barquero J, Abadia-Otero J, Garia-Ibarbia C, et al. GLUCOCOVID: a controlled trial of methylprednisolone in adults hospitalized with COVID 19 pneumonia. medRXiv [Internet]. 2020 [cited 2020 Jun 30]. Available at https://www.medrxiv.org/content/10.1101/2020.06.17.20133579v1. https://doi.org/10.1101/2020.06.17.20133579.
27. Deftereos SG, Giannopoulos G, Vrachatis DA, Siasos GD, Giotaki SG, Gargalianos P, et al. Effect of colchicine versus standard of care on cardiac and inflammatory biomarkers and clinical outcomes in patients hospitalized with coronavirus disease 2019: the GRECCO-19 randomized clinical trial. JAMA Netw Open. 2020 [cited 2020 Jun 29]. https://doi.org/10.1001/jamanetworkopen.2020.13136. [Epub ahead of print].
28. Li L, Zhang W, Hu Y, Tong X, Zheng S, Yang J, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: a randomized clinical trial. JAMA. 2020;3:e2010044. https://doi.org/10.1001/jama.2020.10044. [Epub ahead of print].
29. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020 Feb 4;30(3):269–71. https://doi.org/10.1038/s41422-020-0282-0.
30. Cai Q, Yang M, Lui D, Chen J, Shu D, Xia J, et al. Experimental treatment with favipiravir for COVID-19: an open-label control study. Engineering (Beijing). 2020. https://doi.org/10.1016/j.eng.2020.03.007. [Online ahead of print].
31. Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, et al. Compassionate use of Remdesivir for patients with severe COVID-19. N Engl J Med. 2020;382(24):2327–36.
32. Chu CM, Cheng VCCC, Hung IFN, Wong MML, Chan KH, Chan KS, et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. Thorax. 2004;59(3):252–6.
33. Zhang L, Lin D, Sun X, Curth U, Drosten C, Sauerherin L, et al. Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved α-ketoamide inhibitors. Science. 2020;368(6489):409–12.
34. Ye XT, Luo YL, Xia SC, Sun QF, Ding JG, Zhou Y, et al. Clinical efficacy of lopinavir/ritonavir in the treatment of coronavirus disease 2019. Eur Rev Med Pharmacol Sci. 2020;24(6):3390–6.
35. Zhu Z, Lu Z, Xu T, Chen C, Yang G, Zha T, et al. Arbidol monotherapy is superior to lopinavir/ritonavir in treating COIVD-19. J Infect. 2020 Apr 10 [cited 2020 Jun 08]. doi:https://doi.org/10.1016/j.jinf.2020.03.060. [Epub ahead of print].
36. Wang Y, Liu Y, Liu L, Wang X, Luo N, Li L. Clinical outcomes in 55 patients with severe acute respiratory syndrome coronavirus 2 who were asymptomatic at hospital admission in Shenzhen, China. J Infec Dis. 2020;221(11):1770–4.
37. White NJ. Cardiotoxicity of antimalarial drugs. Lancet Infect Dis. 2007 Aug;7(8):549–58.
38. Cipriani A, Zorzi A, Ceccato D, Capone F, Parolin M, Donato F. Arrhythmic profile and 24-hour QT interval variability in COVID-19 patients treated with hydroxychloroquine and azithromycin. Int J Cardiol. 2020;S0167-5273(20)32223-3. Online ahead of print.
39. Saleh M, Gabriels J, Chang D, Kim BS, Mansoor A, Mahmood E, et al. Effect of chloroquine, hydroxychloroquine, and azithromycin on the corrected QT interval in patients with SARS-CoV-2 infection. Circ Arrhythm Electrophysiol. 2020;13(6):e008662.
40. Magagnoli J, Narendran S, Pereira F, Cummings T, Hardin JW Sutton SS, et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with COVID-19. medRxiv [Internet]. 2020 [cited 2020 June 30]. Available at https://www.medrxiv.org/content/medrxiv/early/2020/04/23/2020.04.16.20065920.full.pdf. https://doi.org/10.1101/2020.04.16.20065920.
41. Gautret P, Laugier JC, Parola P, Hoang VT, Meddeb L, Sevestre J, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six day follow up: a pilot observational study. Travel Med Infect Dis. 2020;34:101663.
42. Geleris J, Sun Y, Platt J, Zucker J, Baldwin M, Hripcsak G, et al. Observational study of hydroxychloroquine in hospitalized patients with COVID-19. N Engl J Med. 2020;382(23):2411–8.

43. Mahevas M, Tran VT, Roumier M, Chabrol A, Paule R, Guillaud C, et al. Clinical efficacy of hydroxychloroquine in patients with COVID-19 pneumonia who require oxygen: observational comparative study using routine care data. BMJ. 2020;369:m1844.
44. Food and Drug Administration. FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems [Internet]. [updated 2020 June 15; cited 2020 June 30]. Available at https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or.
45. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the "cytokine storm" in COVID-19. J Infect. 2020;80(6):607–13.
46. Tufan A, Avanoğlu Güler A, Matucci-cerinic M. COVID-19, immune system response, hyperinflammation and repurposing antirheumatic drugs. Turk J Med Sci. 2020;50(3):620–32.
47. Moore JB, June CH. Cytokine release syndrome in severe COVID-19. Science. 2020;368(6490):473–4.
48. Khiali S, Khani E, Entezari-Maleki T. A comprehensive review on tocilizumab in COVID-19 acute respiratory distress syndrome. J Clin Pharmacol. 2020; https://doi.org/10.1002/jcph.1693.
49. Crisafulli S, Isgro V, La Corte L, Atzeni F, Trifiro G. Potential role of anti-interleukin-6 drugs in the treatment of COVID-19: rationale, clinical evidence and risks. BioDrugs. 2020;15:1–8.
50. Alattar R, Ibrahim T, Shaar SH, Abdalla S, Shukri K, Daghfal JN, et al. Tocilizumab for the treatment of severe coronavirus disease 2019. J Med Virol. 2020; https://doi.org/10.1002/jmv.25964.
51. Campochiaro C, Della-Torre E, Cavalli G, De Luca G, Ripa M, Boffini N, et al. Efficacy and safety of tocilizumab in severe COVID-19 patients: a single-center retrospective cohort. Eur J Intern Med. 2020 Jun;76:43–9.
52. Somers EC, Eschenauer GA, Troost JP, Golob JL, Gandi TN, Wang L, et al. Tocilizumab for treatment of mechanically ventilated patients with COVID-19. medRxiv [Internet]. 2020 June 3 [cited 2020 June 30]. Available at https://www.medrxiv.org/content/10.1101/2020.05.29.20117358v1. https://doi.org/10.1101/2020.05.29.20117358.
53. Colaneri M, Bogliolo L, Valsecchi P, Sacchi P, Zuccaro V, Brandolino F, et al. Tocilizumab for treatment of severe COVID-19 patients: preliminary results from SMAtteo COVID19 registry. Microorganisms. 2020;8(5):695.
54. Xu X, Han M, Li T, Sun W, Wang D, Fu B, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci USA. 2020;117(20):10970–5.
55. Toniati P, Piva S, Cattalini M, Garrafa E, Regola F, Castelli F, et al. Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: a single center study of 100 patients in Bescia, Italy. Autoimmune Rev. 2020;19(7):102568.
56. Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: a clinical therapeutic staging proposal. J Heart Lung Transplant. 2020;39(5):405–7.
57. Veronese N, Demuras J, Yang L, Tonelli R, Barbagallo M, Lopalco P, et al. Use of corticosteroids in coronavirus disease 2019 pneumonia: a systematic review of the literature. Front Med. 2020;7:170.
58. Cruz AF, Ruiz-Antoran B, Gomez AM, Lopez, AS, Sanchez PM, Soto GA, et al. Impact of glucocorticoid treatment in SARS-CoV-2 infection mortality: a retrospective controlled cohort study. Antimicrob Agents Chemother. 2020;AAC.01168-20.
59. Fadel R, Morrison AR, Vahia A, Smith ZR, Chaudhry Z, Bhargava P, et al. Early short course corticosteroids in hospitalized patients with COVID-19. Clin Infect Dis. 2020;ciaa601.
60. Selvaraj V, Dapaah-Afriyie K, Finn A, Flanigan TP. Short term dexamethasone in SARS-CoV-2 patients. R I Med J. 2020;103(6):39–43.
61. Huet T, Beaussier H, Voisin O, Jouveshomme S, Dauriat G, Lazareth I, et al. Anakinra for severe forms of COVID-19: a cohort study. Lancet Rheumatol. 2020 May 29 [cited 2020 Jun 22]. https://doi.org/10.1016/S2665-9913(20)30164-8. [Epub ahead of print].

62. Franzetti M, Pozzetti U, Carugati M, Pandolfo A, Molteni C, Faccioli P, et al. Interleukin-1 receptor antagonist anakinra in association with remdesivir in severe coronavirus disease 2019: a case report. Int J Infect Dis. 2020 [cited 2020 Jun 18]. https://doi.org/10.1016/j.ijid.2020.05.050. [Epub ahead of print].
63. Filocamo G, Mangioni D, Tagliabue P, Aliberti S, Costantino G, Minoia F, et al. Use of anakinra in severe COVID-19: a case report. Int J Infec Dis. 2020 [cited 2020 Jun 19]. https://doi.org/10.1016/j.ijid.2020.05.026. [Epub ahead of print].
64. Day JW, Fox TA, Halsey R, Carpenter B, Kottaridis P. Interleukin-1 blockade with anakinra in acute leukaemia patients with severe COVID-19 pneumonia appears safe and may result in clinical improvement. Br J Haematol. 2020 [cited 2020 Jun 19]. https://doi.org/10.1111/bjh.16873. [Epub ahead of print].
65. Soo YO, Cheng Y, Wong R, et al. Retrospective comparison of convalescent plasma with continuing high-dose methylprednisolone treatment in SARS patients. Clin Microbiol Infect. 2004;10(7):676–8. https://doi.org/10.1111/j.1469-0691.2004.00956.x.
66. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, et al., Convalescent Plasma Study Group. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. J Infect Dis 2015;211(1):80–90.
67. Duan K, Lui B, Li C, Zhang H, Yu T, Qu J, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc Natl Acad Sci U S A. 2020 Apr 28;117(17):9490–6.
68. Joyner MJ, Wright RS, Fairweather D, Senefeld JW, Bruno KA, Klassen SA, et al. Early safety indicators of COVID-19 convalescent plasma in 5,000 patients. medRXiv [Internet]. 2020 May 14 [cited 2020 Jul 28]. Available at https://www.medrxiv.org/content/10.1101/2020.05.12.20099879v1.full.pdf, https://doi.org/10.1101/2020.05.12.20099879.
69. Adams KK, Baker WL, Sobieraj DM. Myth busters: dietary supplements and COVID 19. Ann Pharmacother. 2020;12:1060028020928052.
70. Bauer SR, Kapoor A, Rath M, Thomas SA. What is the role of supplementation with ascorbic acid, zinc, vitamin D, or N-acetylcysteine for prevention and treatment of COVID-19? Cleve Clin J Med. 2020. Online ahead of print.
71. Fowler AA III, Truwit JD, Hite RD, Morris PE, DeWilde C, Priday A, et al. Effect of vitamin C infusion on organ failure and biomarkers of inflammation and vascular injury in patients with sepsis and severe acute respiratory failure: the CITRIS-ALI randomized clinical trial. JAMA. 2019 Oct 1;322(13):1261–70.
72. Fujii T, Luethi N, Young PJ, Frei DR, Eastwood GM, French CJ, et al. Effect of vitamin C, hydrocortisone and thiamine versus hydrocortisone alone on time alive and free of vasopressor support among patients with septic shock: the VITAMINS randomized clinical trial. JAMA. 2020;323(5):423–31.
73. Kumar A, Kubota Y, Chernov M, Kasuya H. Potential role of zinc supplementation in prophylaxis and treatment of COVID-19. Med Hypotheses. 2020;144:109848. Online ahead of print.
74. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708–20.
75. Esler M, Esler D. Can angiotensin receptor-blocking drugs perhaps be harmful in the COVID-19 pandemic? J Hypertens. 2020;38(5):781–2.
76. Ferrario CM, Jessup J, Chappell MC, et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. Circulation. 2005;111:2605–10.
77. Kuba K, Imai Y, Rao S, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med. 2005;11:875–9.
78. Reynolds HR, Adhikari S, Pulgarin C, et al. Renin-angiotensin-aldosterone system inhibitors and risk of Covid-19. N Engl J Med. 2020;382:2441–8.
79. Mehta N, Kalra A, Nowacki AS, et al. Association of use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers with testing positive for coronavirus disease 2019 (COVID-19). JAMA Cardiol. 2020;5:e201855. Online ahead of print.

80. Mancia G, Rea F, Ludergnani M, et al. Renin-angiotensin-aldosterone system blockers and the risk of Covid-19. N Engl Med. 2020;382:2431–40.
81. Flacco ME, Martellucci CA, Bravi F, Parruti G, Cappadona R, Mascitelli A, et al. Treatment with ACE inhibitors or ARBs and risk of severe/lethal COVID-19: a meta-analysis. Heart. 2020; https://doi.org/10.1136/heartjnl-2020-317336. [Epub ahead of print]
82. Bancos S, Bernard MP, Topham DJ, Phipps RP. Ibuprofen and other widely used non-steroidal anti-inflammatory drugs inhibit antibody production in human cells. Cell Immunol. 2009;258(1):18–28.
83. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med. 2020;8(4):e21.
84. Food and Drug Administration. FDA advises patients on use of non-steroidal anti-inflammatory drugs (NSAIDs) for COVID-19. 2020. https://www.fda.gov/drugs/drug-safety-and-availability/fda-advises-patients-use-non-steroidal-anti-inflammatory-drugs-nsaids-covid-19. Accessed 28 July 2020.
85. Zhang Y, Yu L, Tang L, Zhu M, Jin Y, Wang Z, et al. A promising anti-cytokine storm targeted therapy for COVID-19: the artificial-liver blood-purification system. Engineering (Beijing). 2020 Mar 20 [cited 2020 Jun 30]. https://doi.org/10.1016/j.eng.2020.03.006. [Epub ahead of print].
86. Xu K, Cai H, Shen Y, Ni Q, Chen Y, Hu S, et al. Management of coronavirus disease-19 (COVID-19): the Zhejiang experience. J Zhejiang Univ (Med Sci). 2020;49(1).
87. Leng Z, Zhu R, Hou W, Feng Y, Yang Y, Han Q, et al. Transplantation of ACE2^{-} mesenchymal stem cells improves the outcome of patients with COVID-19 pneumonia. Aging Dis. 2020;11(2):216–28.

Anesthetic Consideration for Patients with Corona Virus Disease

6

Federico Bilotta, Luca Titi, Francesco De Lazzaro, and Francesco Pugliese

6.1 Preoperative Evaluation

Suspension of elective surgical procedures was one of the first measures to mitigate hospital overload in anticipation of a surge in demand for critical care services during the COVID-19 pandemic [1–3]: many professional societies have released statements on delaying, restricting, and rescheduling non-urgent procedures, to preserve medical resources including healthcare providers, hospital capacities (mostly ICU resources), and personal protective equipment (PPE) [4, 5]. This is an additional effect on healthcare induced by the COVID-19 pandemic and risk/benefit ratio, including consequences related to canceling or postponing the procedure should be considered for each patient.

Patients affected by COVID-19 have higher perioperative morbidity and mortality, due to a high rate of ARDS, cardiac injury, kidney failure, and even deaths observed after surgical procedures [6, 7]. In COVID-19 patients, who underwent elective or emergency surgery, male gender, age > 70 years, presence of comorbidities [American Society of Anesthesiologists (ASA) grades 3–5], and cancer surgery were associated with an increase of pulmonary complications and 30-day mortality [8]. Furthermore, preexist comorbidities—hypertension, chronic obstructive pulmonary disease, diabetes, and cardiovascular disease—increase susceptibility in developing severe COVID-19 [9]. Higher risk to be infected by COVID-19 and poor outcomes were reported also in immunocompromised and oncologic patients caused by respiratory viral infections: indeed conventional coronaviruses are often associated with higher rates of oxygen requirement and

F. Bilotta (✉) · L. Titi · F. De Lazzaro · F. Pugliese
Department of Anesthesiology, Critical Care and Pain Medicine, "Sapienza" University of Rome, Rome, Italy
e-mail: bilotta@tiscali.it.it

H. Prabhakar et al. (eds.), *Clinical Synopsis of COVID-19*,
https://doi.org/10.1007/978-981-15-8681-1_6

mortality. The fatality rate of cancer patients affected by COVID-19 is 5.6%; furthermore, these patients have a greater risk to develop perioperative complications than those without COVID-19 [7, 10].

To increase patients' and healthcare workers' safety, it is essential to include a multimodal screening work up in all patients scheduled for surgery and the procedure should be accomplished before the access to the operating room (OR) [3]. Considering that SARS-CoV-2 mucosal swab testing used to detect COVID-19 has a sensitivity that ranges between 70 and 90%, therefore, it is associated with a potential of non-detecting the virus in up to 30% of infected patients; the ASA suggests to separate patients positive or suspected for SARS-CoV-2 infection from those with a negative swab test. A flowchart given by ASA reports the correct conduct to evaluate patients for elective surgery, in countries where SARS-CoV-2 is present:

- All patients should be screened for signs and symptoms (fever, cough, shortness of breath, chills, muscle pain, headache, sore throat, and/or new loss of taste or smell within the prior 2 weeks) before admission to the hospital. All other patients should undergo nucleic acid amplification testing (including PCR tests) before non-emergent surgery.
- Because false-negative tests may occur, droplet precautions (surgical mask and eye covering) should be used by OR staff.
- For all patients with positive SARS-CoV-2 swab tests, elective surgical procedures should be delayed until the patient is no longer infectious and proven full recovery from COVID-19 infection.

Considering that signs and symptoms referable to COVID-19 infection can be minimal or the infection might be in the incubation phase, it is important to consider that the interval between the preanesthetic consultation and the intervention may evolve into a full disease [11]. It is therefore useful that patients scheduled for surgery complete a "home questionnaire" before the hospital consultation with the anesthesiologist. When the "home questionnaire" is completed, patients should be informed that new onset of signs or symptoms referable to COVID-19 infection should be communicated to the anesthesia team promptly before hospitalization. Temperature monitoring is a key element of pre-hospital evaluation. Although nonspecific, fever is a very common symptom of SARS-CoV-2 infections (75–95%) [9]. The use of telemedicine could be an alternative to face-to-face consultation, as also approved by the World Health Organization. Of course, teleconsultation is carried out using tools that guarantee the security of patient data.

Because SARS-CoV-2 testing has moderate sensitivity, some authors suggested that CT imaging examinations could be a complementary exam to detect indirect signs of virus presence and to isolate patients with typical imaging findings, such as a ground-glass pattern that indicates interstitial rather than alveolar edema [12].

Another possible approach to stratify the clinical conditions of patients with COVID-19 and to evaluate the associated perioperative risk is to use dedicated clinical tools [13]. One study reported a score to measure functional status over time of COVID-19, especially to follow patients after discharge and to evaluate

the respiratory consequences of this syndrome like related COVID-19 pulmonary fibrosis [14]. This scale has six steps ranging from 0 (no symptoms) to 5 (death) and covers the entire range of functional outcomes by focusing on limitations in usual duties/activities either at home or at work/study, as well as changes in lifestyle. Respiratory consequences of COVID patients could be very serious, and, in some patients, lung transplantation was performed as a therapeutic option [15].

Another relevant evaluation to screen patients with increased perioperative risk comes from blood exams of COVID-19 patients. One study found a relationship between blood biomarkers and mortality with an accuracy of 90%: lactic dehydrogenase (LDH), lymphocyte, and high-sensitivity C-reactive protein (hs-CRP). High levels of LDH reflect tissue breakdown occurring in various diseases such as pneumonia and seems to be an important sign to predict COVID-19 stage and prognosis [16].

Mechanisms of cardiac injury in COVID patients remain unknown: myocardial injury, myocarditis, acute coronary syndromes, heart failure, arrhythmias, and venous thromboembolism were reported as serious consequences [17]. Of though, ECG evaluation and cardiac markers before surgery are suggested to evaluate patients, especially for drugs used for COVID-19 like azithromycin and hydroxychloroquine and their rhythms alteration [11].

Preoperative evaluation should be performed by the physicians with self-protection (including medical gowns, medical gloves, eye protection shields, disposable surgical caps, and surgical masks or test-fit N95 or FFP2 masks or respirators), and patients should be received one by one to minimize close contact with the clinician and other individuals [3]. Hand hygiene must be accomplished before and after contact with each patient with 2–3% hydrogen peroxide solution or gel or by washing hands with soap and water.

Patients with suspicious or affected by COVID-19, in whom the surgical procedure cannot be delayed, need to be scheduled in a specific route that includes a dedicated OR and surgical/anesthesiology team [18] (see Chap. 3).

6.2 Operating Room Organization and Self-Protection

In the COVID-19 outbreak, surgery is limited to urgent and emergent procedures [1, 2]. Two separate routes are dedicated to COVID-19 or suspected patients and no-COVID-19 patients with different spaces and teams (Fig. 6.1). This approach reduces the risk of contamination of patients and physicians and improves hospital resources [1, 19]. Caregivers working in OR dedicated to patients affected by COVID-19 must be straightly necessary to reduce the risk of contamination [2, 20]. In OR dedicated for COVID-19 patients, there should be three different ambiances:

- Zone 1 clean: it is a zone necessary to wear the caregivers.
- Zone 2 filter: it is a zone necessary to separate the clean and the dirty zone.
- Zone 3 dirty: it is a zone inside the COVID-19 spaces (wait to bb).

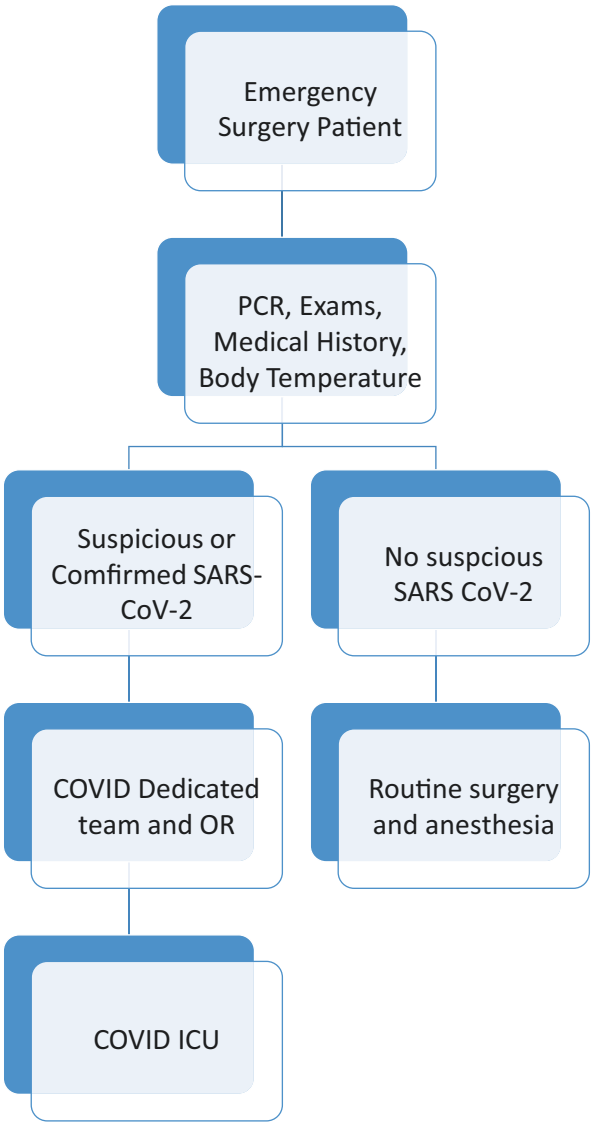


Fig. 6.1 Work up for operating room admission to patients presenting for emergent surgical procedures

The perioperative phase is critical for viral and bacterial transmission, especially during induction and emergence of anesthesia [3, 4, 20]. Viral pathogen survival on environmental surfaces extends for several days and SARS-Cov2 can survive for at least 3 days on a variety of materials commonly used in operating rooms. The multimodal strategy is crucial to remove residual environmental contamination and to reduce intraoperative risk of pathogen transmission events. These include:

(a) Self-protection of patient and caregivers.
(b) Environmental cleaning.

Hand hygiene should be performed with 2–3% hydrogen peroxide solution or gel, or by washing hands with soap and water. Because hand hygiene is not sufficient alone for control of perioperative virus spreading, a double pair of gloves is recommended especially during high-risk maneuvers. Frequency and quality of environmental cleaning are crucial to reduce the overall contamination of the work area: it's suggested to use a top-down approach, spray all surfaces, the anesthesia, and circulating nurse workspace with a quaternary ammonium compound and wait the required time per agent of cleaning. Evidence of the last decade reported that a combination of deep cleaning with surface disinfectants and ultraviolet light (UV-C) is useful to reduce bacterial and viral contamination across a variety of healthcare settings by addressing both surface and air column disinfection; UV-C has been shown to reduce the incidence of both bacterial and viral healthcare-associated infections [5]. Disposable covers should be used whenever possible to reduce equipment contamination.

Some authors especially for aerosol-generating procedures—as recommended by the WHO guidance on COVID-19—reported the role of the negative pressure rooms inside the OR and the anteroom because it has proven to be an effective measure to avoid cross-contamination during the SARS epidemic [6, 7, 21]. Negative pressure rooms are an engineering control created and maintained by a ventilation system that allows extra air to enter the isolated room by differential pressure and be exhausted directly to the outside or be filtered through a high-efficiency particulate air (HEPA) filter directly before recirculation; it aims to prevent the spread of contagious airborne pathogens from room to room and to avoid the accidental release of pathogens into a larger space and open facility, thereby protecting healthcare workers and patients in a hospital setting [21]. If negative pressure rooms are not available—as occurred in a pandemic setting—is suggested to work with engineering to turn off the positive pressure system [4].

Intubation and extubation are the most critical situations with a high risk of aerosolizing of oral droplets: moreover, many barriers were developed to protect personal during these maneuvers (boxes, transparent plastic sheet) (see Airways Management). Before performing an aerosol-generating procedure, healthcare providers within the room should wear fitted respirator masks (N95 respirators, FFP2, or equivalent), as opposed to surgical/medical masks, in addition to other personal protective equipment (gloves, gown, and eye protection). The N95 mask that conforms to United States Federal Drug Agency standards and the FFP2 that conforms to European standards—European Committee for Standards—can block 95–99% of aerosol particles. Before using it is necessary that caregivers test them and verify their integrity. Surgical/medical masks can block large particles, droplets, and

sprays, but are less effective in blocking small particle aerosols (<5 μm) [21, 22]. During the hospitalization, patients should use surgical/medical mask (like caregivers and other personal staff), even when they come to OR.

Eyes protections must be used for every contact with a patient suspected or infected by COVID-19, especially during aerosolizing maneuvers: protect every possible door for this virus is crucial. The gown is recommended to protect caregivers and to reduce the contamination especially during contact with biological fluids [8].

6.3 Airway Management

General anesthesia represents a serious problem in patients affected by COVID-19. Indeed, it is hard to decide to undergo a patient to surgery for imposing biological risk and for higher complication risk.

General anesthesia in COVID-19 patients requires adequate attention on two main issues:

- Airway management.
- Anesthesia management.

Airway management in COVID-19 patients is a complex and debated topic that requires adequate knowledge of guidelines and a defined order of work. Airway manipulation in patients with COVID-19 pneumonia is a serious risk for healthcare providers [18]. Therefore, it is necessary to maximize the use of PPE during aerosol-generating procedures, such as endotracheal intubation, non-invasive ventilation, and high-flow nasal oxygen. The use of N95/FFP2 masks, eye protections, and adopting the double glove technique is recommended [22]. It is strongly recommended to perform rapid sequence intubation with full dose of neuromuscular blockade (aminosteroid neuromuscular blockers such as rocuronium are preferred) to minimize the risk of coughing. The use of video-laryngoscopy, possibly with a separate screen, should be considered and a preloaded bougie or stylet should be routinely adjunct to maximize first-pass success [22, 23]. Any maneuver, which increase aerosolization—including mask ventilation—should be avoided. Unfortunately, hypoxemia is a hallmark of COVID-19 patients requiring tracheal intubation, and apnea should be minimized. Preoxygenation might be partially ineffective and for patients receiving noninvasive ventilation it is important to turn off the ventilator and to depressurize the circuit before proceeding to tracheal intubation [22–24]. However, for ventilation-dependent patients, respiratory assistance should be provided using Mapleson C circuit with a double filter setting [22, 23]. Despite the time-critical nature of airway management in COVID-19 patients, it is recommended to assess airway difficulty and to appropriately plan the most effective approach to avoid unexpected deterioration [24, 25]. It is necessary to assign the most experienced anesthesiologist to perform intubation. Awake fiberoptic

intubation and the use of atomized local anesthetic should be discouraged unless specifically indicated because of the increased risk for virus spreading [26].

Healthcare professional protection is a priority and PPE be available for all providers to ensure droplet/contact isolation. Patients with confirmed or suspected COVID-19 infection should be kept in the OR, transferred to a dedicated ICU or a negative pressure room. In order to ensure high standard of patient-generated aerosolization (removal of 99.97% of 0.3 microns airborne particles) during the transport, it is necessary to place an high-quality heat- and moisture-exchanging filter between the ETT and reservoir bag [22–25]. In extreme conditions, when intubation failed, it is suggested to proceed with early cricothyrotomy independently on saturation values [24, 27]. Finally, a capnography trace or ultrasounds for tube position confirmation should be integrated to the visual and auscultatory confirmation in order to overcome difficulties due to PPE. A dedicated "intubation spots" with disposable flexible video-endoscopic system, monitors, defibrillator, and high-efficiency closed system suction unit and anesthetic medications should be kept available in isolated/negative pressure areas [23, 24, 27].

6.4 General Anesthesia

General anesthesia in COVID-19 patients should ensure adequate depth along with appropriate airway and respiratory management intended to provide necessary ventilation but also to prevent droplets viral spreading. Other types of anesthesia (locoregional, spinal, etc.) can also be considered for specific types of surgery and according patient's individual needs [28–30].

In these patients, anesthesia induction is an especially delicate phase and involves the use of the selection and titration of the most suitable hypnotic drug. In COVID patients, rapid sequence induction is the recommended approach, and this should be accomplished using aminosteroid neuromuscular blocking (rocuronium 1.2 mg/kg). First-choice hypnotic is propofol but associated use a second drug (benzodiazepines, ketamine, etc.) should be evaluated by the attending anesthesiologist in order to minimize the hemodynamic changes [31, 32]. Midazolam has been shown to have important interactions with ritonavir/lopinavir therefore induction with this benzodiazepine may be associated with an increase in its adverse effects [33, 34].

Induction and maintenance of anesthesia also require opioids, and the various pharmacological available drugs (fentanyl, sufentanil, remifentanil) can be used according the individual anesthesiologist experience [33, 35]. The use of fentanyl (at a dose of 3–5 μg/kg) in patients receiving ritonavir/lopinavir may lead to an increase in the adverse effects of the opioid; therefore, in this case remifentanil could be a valid pharmacological alternative [36, 37]. There are no contraindications to the use of halogenates in COVID patients, but special attention should be paid to titrate delivered concentration in hypovolemic, hypotensive, or hemodynamically compromised patients [38, 39]. Often in the first phase of COVID-19, patients have good compliance, poor oxygenation, and without dyspnea. Many authors reported two different

patterns of respiratory disease connected with COVID-19: one with high compliance and a low response to PEEP values and one with low compliance and a high response to PEEP values. Either it should consider widespread micro- and macro-thromboses in the lung (and in other organs) that could compromise oxygenation. So patients who present good compliance could be ventilated with tidal volumes of 7–8 mL/kg (ideal body weight), although, in an advanced stage of the disease, in patients who present low compliance, it is advisable to apply lung-protective strategy with higher PEEP (≤15 cm H_2O) and lower tidal volume (6 mL/kg) [40–42].

6.5 Regional Anesthesia

As previously described, regional anesthesia is not the first choice in COVID patients. However obstetric surgery necessarily requires the execution of a neuraxial procedure as general anesthesia is associated with an unsatisfactory fetal APGAR [43, 44]. Moreover, the general anesthesia drugs (except the curaries) pass the placental filter, reach the fetus and promote a state of fetal distress at birth [43, 45]. COVID-19 patients with hypoxia and concomitant physiologically decreased functional residual capacity from pregnancy will be likely to become more hypoxic, develop further atelectasis with intubation and mechanical ventilation, and possibly require postoperative critical care admission [46, 47].

However, anesthesiologists should take into account the risk of meningitis or encephalitis associated with neuraxial procedures in the context of untreated viremia.

Recent data in the literature do not report cases of post-neuraxial complications in COVID patients after childbirth [48].

Before performing a neuraxial procedure in these patients, it would be advisable to evaluate platelet count given that a third of patients with COVID-19 infection have been reported to have thrombocytopenia compared with 7–12% of patients during pregnancy alone [47, 48]. In pregnant women, a platelet count of 70,000 × 106/L has a low risk for spinal epidural hematoma, and lower levels should be considered in cases such as these with a high risk for respiratory compromise with general anesthesia [47, 48].

It's recommended early epidural placement for parturients with suspected or confirmed COVID-19 to avoid exacerbation of the patient's respiratory symptoms and avoiding the aerosol generation associated with general anesthesia. However, a potential unintended consequence of this recommendation is an increased incidence and severity of intrapartum pyrexia [46–48]. An increased incidence of intrapartum pyrexia during the COVID-19 pandemic, it may increase the risk of adverse neonatal neurological outcome (neonatal encephalopathy, cerebral palsy, and epidural hyperthermia) [49, 50]. The optimal time to site an epidural in a parturient with suspected or confirmed COVID-19 is not therefore as simple as "the earlier the better" [51]. It is imperative that decision be made on a case-by-case basis and must take into account the parturient's respiratory status, the likelihood of progression to emergency cesarean delivery, and the likelihood of prolonged labor.

6.6 Fluid Management and Associated Therapy

In some patients affected by COVID-19, especially recovered in ICU, diarrhea (16.3%) and vomit (8.3%) were the main symptoms; of though fluid management is important for patient scheduled for surgical procedure. The volume depletion that occurred in the first phase of the disease must be replaced to maintain blood pressure and cardiac output especially during intubation and positive pressure ventilation: isotonic fluids must be preferred [53]. In the same way, fluid overload should be avoided for the risk to develop ARDS [21]. Monitoring of the fluid challenge should be performed during surgery to maintain a conservative strategy of fluid therapy.

Despite it is known that albumin could increase endothelial glycocalyx limiting permeability and disruption of this protein [54], it's role remain controversial. Even there is no direct evidence on patients with COVID 19 and the use of albumin, some authors suggest against its routine use especially for the initial resuscitation of patients with COVID 19 and shock based on indirect evidence from critically ill patients in general [21]. Evidence reported that patients recovered in ICU with COVID-19 had less value of albumin with a bad prognosis [52]. Some studies in progress suggest that serum albumin carries antiviral drugs against virus and recommended its use a therapeutic material, stabilizer and deliverer of the drugs [55]. We should consider its cost and limited availability, mostly during a pandemic outbreak, and should be used for a particular situation.

In the COVID-19 outbreak, the number of blood donations has significantly decreased with a consequence limitation of resources. Many societies in the world have elaborated guidelines for blood management and to be safe blood donations; although the transmission of COVID-19 infection through transfusion of blood components is still debated. For these reasons the prevention of anemia especially in COVID-19 is a cornerstone of blood management, obtained with three approaches: optimizing the patient's red cell mass, reducing perioperative blood loss, and enhancing anemia tolerance. In critically ill patients affected by COVID-19, it must be cared with two aspects in the blood management: the higher risk of thrombosis associated with erythropoiesis-stimulating agents and the use of anticoagulant agents with a therapeutic dosage that could increase risk of perioperative blood loss [56, 57]. To guide physicians to correct blood management, some studies reported an individualized goal-directed coagulation and transfusion algorithm in the case of blood loss or bleeding using rotational thromboelastometry.

Some studies reported high rates of thrombotic complications in patients affected by COVID-19, including stroke, acute limb ischemia, and acute coronary syndromes (25–30%), especially in mechanically ventilated patients. The use of prophylactic anticoagulation was supposed not only for antithrombotic effects but also for other mechanisms of action, including anti-inflammatory or antiviral effects. For these reasons all inpatients with COVID-19, in the absence of contraindications, should receive prophylactic antithrombotic and should be undergone to risk stratification for venous thromboembolism (VTE) [58]. The optimal intensity of anticoagulation in patients with COVID-19 remains unknown: prophylactic dosing is the most

widely used but higher intensity of anticoagulation (including intermediate-dose and full-therapeutic anticoagulation) is reported by many authors. It is important to screen the correct risk for thromboembolism (VTE): bilateral lower extremity ultrasound or computed tomography pulmonary angiography should be performed in the pre or postoperative period. Extended pharmacological prophylaxis (up to 45 days) should be considered for patients at high risk of VTE who do not have a high risk of bleeding. Additional studies are required to identify the optimal regimen in various patient groups with COVID-19 risk stratification for VTE should be done for hospitalized patients at the time of discharge.

During the evaluation of patients affected by COVID-19, it must pay attention to any drugs interaction: at this moment even there are no efficacious treatments for COVID-19, many drugs were purposed as rescue therapy. Of these, lopinavir/ritonavir was used in the first phase for SARS experience: its inhibition of cytochrome P450 (CYP) 3A enzymes which are responsible for metabolism in the liver and intestines of various anesthetic drugs like midazolam could decrease themes metabolism increasing serum levels with a high risk of extreme sedation and respiratory depression. Recent studies reported conflicting results for the use of lopinavir/ritonavir but antiretroviral agents could be prospective therapy: it must be cared with the coadministration with these drugs [59–62]. The use of hydroxychloroquine for patients affected by COVID-19 is still debated [63] and its use exposed to many cardiovascular complications, especially older patients. Of though, some authors, based on high risk of interaction with common drugs like anti-diabetic medications, antipsychotics, and antiarrhythmics, such as digoxin and amiodarone, suggested simplifying therapy of older patients to reduce adverse events like QTc prolongation, torsade de pointes, and sudden death [64].

NSAIDs may be associated with worsening of symptoms during respiratory viruses: despite recent alerts, there is no scientific evidence to date linking NSAID use to the aggravation of SARS-CoV-2 infection. In a patient with an established or strongly suspected SARS-CoV-2 infection, the prescription of NSAIDs could be limited, although, in asymptomatic patients, there appears to be no contraindication to their use if their benefit is established.

It is not recommended to discontinue using corticosteroids in patients on long-term therapy. The single intraoperative injection of dexamethasone, at the usual recommended doses, does not appear to present an over-risk in the asymptomatic patient.

6.7 Postoperative Management

Patients who underwent surgery and affected by COVID-19 had a high risk to develop postoperative complications and should be transferred to ICU for monitoring the trend of the disease, in particular cardiologic, renal, and respiratory functions (Fig.6.1). As exposed in Chap. 3, ICU must be dedicated to COVID patients, in a separate route.

Extubation has high risk of aerosolizing of oral droplets and it must be used the airway management recommendations (see section 6.3). Before extubation, it suggested that two layers of wet gauze can be used to cover the patient's nose and mouth to minimize exposure to the patient's secretions. Caregivers must be the straightly necessary during this procedure. After surgery many authors suggested that patients with COVID-19 should be sent to an isolation room in the ICU, bypassing the postanesthesia care unit, or, if is stable after surgery and does not meet the criteria for admission to the ICU, he should be transferred directly back to the negative-pressure ward or isolation ward after extubation in the operating room [3].

SARS-CoV-2 has cytopathic effects on podocytes and proximal straight tubule cells that may cause acute kidney injury(AKI) in patients with COVID-19. Therefore, it is important to pay more attention to the early monitoring of renal function and cautiously handle the urine of COVID-19 patients during surgery and in the postoperative period [65].

At the end of the outbreak, the pandemic is crucial to resume surgical activity gradually for the categories of patients excluded in this phase. It is important to develop a program that ensures the safety and protection of patients and caregivers.

In conclusion, COVID-19 pandemic resulted in extensive changes in the organization of the healthcare system that included reframing perioperative setting. Several measures and dedicated consideration should be implemented to minimize the risk of infection spreading through patients—this includes a formal screening and separated track for those that result to be positive at mucosal swab—and to the healthcare professionals. Furthermore the shortage of blood derivatives induced a profound reconsideration of principles for transfusion. To deliver anesthesia to COVID-19 patients encompasses unique measures that encompass appropriate airway management and specific consideration of the possible pharmacological interactions. Dedicated training and structures play a paramount role in providing optimal clinical care.

References

1. Al-Jabir A, Kerwan A, Nicola M, et al. Impact of the Coronavirus (COVID-19) pandemic on surgical practice - part 1. Int J Surg. 2020;79:168–79.
2. Moletta L, Pierobon ES, Capovilla G, et al. International guidelines and recommendations for surgery during Covid-19 pandemic: a systematic review. Int J Surg. 2020;79:180–8.
3. Chen X, Liu Y, Gong Y, et al. Perioperative management of patients infected with the novel coronavirus. Recommendation from the Joint Task Force of the Chinese Society of Anesthesiology and the Chinese Association of Anesthesiologists. Anesthesiology. 2020;132:1307–16.
4. Rah KH, Platovsky A. Determining urgent/emergent status of gastrointestinal (GI) endoscopic procedures in an ambulatory care setting during the Coronavirus Disease of 2019 (COVID-19) pandemic: additional factors that need to be considered [published online ahead of print, 2020 Apr 8]. Anesth Analg. 2020; https://doi.org/10.1213/ANE.0000000000004861.
5. Krishnamoorthy V, Bartz R, Raghunathan K. Rational perioperative utilisation and management during the COVID-19 pandemic. Br J Anaesth. 2020;125(2):e248–51.
6. ASA and APSF. The ASA and APSF joint statement on perioperative testing for the COVID-19 virus; 29 April 2020.

7. Yeoh CB, Lee KJ, Rieth EF, et al. COVID-19 in the cancer patient. Anesth Analg. 2020;131(1):16–23.
8. COVIDSurg Collaborative. Mortality and pulmonary complications in patients undergoing surgery with perioperative SARS-CoV-2 infection: an international cohort study [published correction appears in Lancet. 2020 Jun 9]. Lancet. 2020;396(10243):27–38.
9. 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 [published correction appears in lancet. 2020 mar 28;395(10229):1038] [published correction appears in lancet. 2020 mar 28;395(10229):1038]. Lancet. 2020;395(10229):1054–62.
10. Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a Nationwide analysis in China. Lancet Oncol. 2020;21(3):335–7.
11. Velly L, Gayat E, Quintard H, et al. Guidelines: anaesthesia in the context of COVID-19 pandemic. Anaesth Crit Care Pain Med. 2020;39(3):395–415.
12. Long C, Xu H, Shen Q, et al. Diagnosis of the coronavirus disease (COVID-19): rRT-PCR or CT? Eur J Radiol. 2020;126:108961.
13. Klok FA, Boon GJAM, Barco S, et al. The post-COVID-19 functional status scale: a tool to measure functional status over time after COVID-19. Eur Respir J. 2020;56(1):2001494.
14. Klok FA, Boon GJAM, Barco S, et al. The post-COVID-19 functional status scale: a tool to measure functional status over time after COVID-19. Eur Respir J. 2020;56(1):2001494.
15. Chen JY, Qiao K, Liu F, et al. Lung transplantation as therapeutic option in acute respiratory distress syndrome for coronavirus disease 2019-related pulmonary fibrosis. Chin Med J. 2020;133(12):1390–6.
16. Yan L, Zhang HT, Goncalves G, et al. An interpretable mortality prediction model for COVID-19 patients. Nat Mach Intell. 2020;2:283–8.
17. Goha A, Mezue K, Edwards P, Nunura F, Baugh D, Madu E. COVID-19 and the heart: an update for clinicians [published online ahead of print, 2020 Jun 12]. Clin Cardiol. 2020; https://doi.org/10.1002/clc.23406.
18. Doll D, Kauf P, Wieferich K, et al. Implications of perioperative team setups for operating room management decisions. Anesth Analg. 2017;124(1):262–9.
19. Zhao S, Ling K, Yan H, et al. Anesthetic management of patients with COVID 19 infections during emergency procedures. J Cardiothorac Vasc Anesth. 2020;20:1125–31.
20. Dexter F, Parra MC, Brown JR, et al. Perioperative COVID-19 defense: an evidence-based approach for optimization of infection control and operating room management. Anesth Analg. 2020;131:37–42.
21. Alhazzani W, Møller 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;48(6):e440–69.
22. Lippi G, Adeli K, Ferrari M, et al. Biosafety measures for preventing infection from COVID-19 in clinical laboratories: IFCC taskforce recommendations. Clin Chem Lab Med. 2020;58(7):1053–62.
23. Sorbello M. Airway management in COVID-19: in the Den of the beast. Anesth Analg. 2020; https://doi.org/10.1213/ANE.0000000000004883.
24. Sorbello M, El-Boghdadly K, Di Giacinto I, Cataldo R, Esposito C, Falcetta S and on behalf of The Società Italiana di Anestesia Analgesia Rianimazione e Terapia Intensiva (SIAARTI) Airway Research Group, and The European Airway Management Society. The Italian coronavirus disease 2019 outbreak: experiences and recommendations from clinical practice. Anaesthesia. 2020. [Epub ahead of print].
25. Cook TM, El-Boghdadly K, McGuire B, McNarry AF, Patel A, Higgs A. Consensus guidelines for managing the airway in patients with COVID-19: guidelines from the difficult airway society, the Association of Anaesthetists the Intensive Care Society, the faculty of intensive care medicine and the royal college of anaesthetists. Anaesthesia 2020. [Epub ahead of print].
26. Greenland JR, Michelow MD, Wang L, London MJ. COVID-19 infection: implications for perioperative and critical care physicians. Anesthesiology. 2020;132(6):1346–61.

27. Sorbello M, Morello G, Pintaudi S, Cataldo R. COVID-19: intubation kit, intubation team or intubation spots? Anesth Analg. 2020; https://doi.org/10.1213/ANE.0000000000004970.
28. Bevilacqua S, Bottari V, Galeotti I. Systematic application of rapid sequence intubation with remifentanil during COVID-19 pandemic [published online ahead of print, 2020 Jul 15]. Semin Cardiothorac Vasc Anesth 2020;1089253220941369. https://doi.org/10.1177/1089253220941369.
29. Yao W, Wang T, Jiang B, et al. Emergency tracheal intubation in 202 patients with COVID-19 in Wuhan, China: lessons learnt and international expert recommendations. Br J Anaesth. 2020;125(1):e28–37.
30. Sorbello M, Di Giacinto I, Corso RM, Cataldo R, Società Italiana di Anestesia analgesia Rianimazione e Terapia Intensiva (SIAARTI) Airway Management Research Group. Prevention is better than the cure, but the cure cannot be worse than the disease: fibreoptic tracheal intubation in COVID-19 patients. Br J Anaesth. 2020;125(1):e187–8.
31. Lv X, Zhou X, Yan J, Jiang J, Jiang H. Propofol inhibits LPS-induced apoptosis in lung epithelial cell line, BEAS-2B. Biomed Pharmacother. 2017;87:180–7.
32. Senthilkumaran S, Koushik M, Sanjay P, Thirumalaikolundusubramanian P. Propofol in COVID 19 - from basic science to clinical impact [published online ahead of print, 2020 Jul 9]. Am J Emerg Med. 2020;S0735-6757(20)30603-3. https://doi.org/10.1016/j.ajem.2020.07.011
33. Cadoni S, Ishaq S, Hassan C, et al. Covid-19 pandemic impact on colonoscopy service and suggestions for managing recovery. Endosc Int Open. 2020;8(7):E985–9.
34. Hughes DA. Acute chloroquine poisoning: a comprehensive experimental toxicology assessment of the role of diazepam [published online ahead of print, 2020 May 15]. Br J Pharmacol. 2020. https://doi.org/10.1111/bph.15101
35. Green TC, Bratberg J, Finnell DS. Opioid use disorder and the COVID 19 pandemic: a call to sustain regulatory easements and further expand access to treatment. Subst Abus. 2020;41(2):147–9.
36. Olkkola KT, Palkama VJ, Neuvonen PJ. Ritonavir's role in reducing fentanyl clearance and prolonging its half-life. Anesthesiology. 1999;91(3):681–5. https://doi.org/10.1097/00000542-199909000-00020.
37. Kharasch ED, Bedynek PS, Walker A, Whittington D, Hoffer C. Mechanism of ritonavir changes in methadone pharmacokinetics and pharmacodynamics: II. Ritonavir effects on CYP3A and P-glycoprotein activities. Clin Pharmacol Ther. 2008;84(4):506–12.
38. Nieuwenhuijs-Moeke GJ, Jainandunsing JS, Struys MMRF. Sevoflurane, a sigh of relief in COVID-19? Br J Anaesth. 2020;125(2):118–21.
39. Orser BA, Wang DS, Lu WY. Sedating ventilated COVID-19 patients with inhalational anesthetic drugs. EBioMedicine. 2020;55:102770. https://doi.org/10.1016/j.ebiom.2020.102770.
40. Marini JJ, Gattinoni L. Management of COVID-19 respiratory distress [published online ahead of print, 2020 Apr 24]. JAMA. 2020. https://doi.org/10.1001/jama.2020.6825.
41. Gattinoni L, Chiumello D, Caironi P, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? Intensive Care Med. 2020;46(6):1099–102.
42. Gattinoni L, Meissner K, Marini JJ. The baby lung and the COVID-19 era. Intensive Care Med. 2020;46(7):1438–40.
43. Edipoglu IS, Celik F, Marangoz EC, Orcan GH. Effect of anaesthetic technique on neonatal morbidity in emergency caesarean section for foetal distress. PLoS One. 2018;13(11):e0207388.
44. Kavak ZN, Başgül A, Ceyhan N. Short-term outcome of newborn infants: spinal versus general anesthesia for elective cesarean section. A prospective randomized study. Eur J Obstet Gynecol Reprod Biol. 2001;100(1):50–4.
45. Ong BY, Cohen MM, Palahniuk RJ. Anesthesia for cesarean section--effects on neonates. Anesth Analg. 1989;68(3):270–5.
46. Bauer ME, Chiware R, Pancaro C. Neuraxial procedures in COVID-19 positive parturients: a review of current reports [published online ahead of print, 2020 Mar 26]. Anesth Analg. 2020; https://doi.org/10.1213/ANE.0000000000004831.

47. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins, Turrentine M. ACOG practice bulletin no. 207: thrombocytopenia in pregnancy. Obstet Gynecol. 2019;133:e181–93.
48. Lee LO, Bateman BT, Kheterpal S, et al. Multicenter Perioperative Outcomes Group Investigators. Risk of epidural hematoma after neuraxial techniques in thrombocytopenic parturients: a report from the multicenter perioperative outcomes group. Anesthesiology. 2017;126:1053–63.
49. Breslin N, Baptiste C, Miller R, et al. Coronavirus disease 2019 in pregnancy: early lessons. Am J Obstet Gynecol MFM. 2020;2(2):100111. https://doi.org/10.1016/j.ajogmf.2020.100111.
50. Bauer ME, Chiware R, Pancaro C. Neuraxial procedures in COVID-19 positive parturients: a review of current reports. Anesth Analg. 2020; https://doi.org/10.1213/ANE.0000000000004831.
51. Chen R, Zhang Y, Huang L. Safety and efficacy of different anesthetic regimens for parturients with COVID-19 undergoing cesarean delivery: a case series of 17 patients. Can J Anaesth. 2020;67:655–63.
52. 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;323(11):1061–9.
53. Berlin DA, Gulick RM, Martinez FJ. Severe Covid-19 [published online ahead of print, 2020 May 15]. N Engl J Med. 2020; https://doi.org/10.1056/NEJMcp2009575.
54. Alphonsus CS, Rodseth RN. The endothelial glycocalyx: a review of the vascular barrier. Anaesthesia. 2014;69(7):777–84.
55. Mishra PM, Uversky VN, Nandi CK. Serum albumin-mediated strategy for the effective targeting of SARS-CoV-2. Med Hypotheses. 2020;140:109790.
56. Baron DM, Franchini M, Goobie SM. Patient blood management during the COVID–19 pandemic: a narrative review. Anaesthesia. 2020;75(8):1105–13.
57. Bikdeli B, Madhavan MV, Gupta A, et al. Pharmacological agents targeting thromboinflammation in COVID-19: review and implications for future research. Thromb Haemost. 2020;120(7):1004–24. https://doi.org/10.1055/s-0040-1713152.
58. Twu SJ, Chen TJ, Chen CJ, et al. Control measures for severe acute respiratory syndrome (SARS) in Taiwan. Emerg Infect Dis. 2017;9:718–20.
59. William Endersby RV, Ching Yee Ho E, Spencer AO, et al. Barrier devices for reducing aerosol and droplet transmission in Coronavirus disease 2019 patients: advantages, disadvantages, and alternative solutions. Anesth Analg. 2020; https://doi.org/10.1213/ANE.0000000000004953.
60. Coccolini F, Perrone G, Chiarugi M, et al. Surgery in COVID-19 patients: operational directives. World J Emerg Surg. 2020;15:25.
61. Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. N Engl J Med. 2020;382:1787–99.
62. Brackett CC. Severe prolonged sedation associated with coadministration of protease inhibitors and intravenous midazolam during bronchoscopy: a commentary. Pharmacotherapy. 2013;33(5):e85–6.
63. The Lancet Editors. Expression of concern: Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. Lancet. 2020;395(10240):e102. https://doi.org/10.1016/S0140-6736(20)31290-3.
64. Ross SB, Wilson MG, Papillon-Ferland L, et al. COVID-SAFER: deprescribing guidance for hydroxychloroquine drug interactions in older adults [published online ahead of print, 2020 May 22]. J Am Geriatr Soc. 2020; https://doi.org/10.1111/jgs.16623.
65. Pan XW, Xu D, Zhang H. Identification of a potential mechanism of acute kidney injury during the COVID-19 outbreak: a study based on single-cell transcriptome analysis. Intensive Care Med. 2020;46(6):1114–6.

Intensive Care Management of Corona Virus Disease

7

F. Alessandri, G. Giordano, E. Magnanimi, and F. Bilotta

7.1 Structural and Functional Features of COVID-19 ICU

7.1.1 Structural Characteristics

Given the severe morbidity and mortality of the disease, the COVID-19 outbreak represents a major public health problem not only for clinical physician but also for those who had to set up a healthcare strategy aiming to optimize patient's assistance [1]. The sudden and unpredicted spreading of COVID-19 prevented to organize an adequate response system to face on the overcrowding of patients in emergency departments (ED) and ICU [2]. An exceptional number of patients accessed healthcare facilities, imposing unprecedented intra-hospital organizational efforts, in the context of a dynamic and ever-evolving situation.

COVID-19 surge led to a rapid increase ICU beds capability; this has been pursued reallocating spaces in previously existing medical and/or surgical ICUs (including the reconversion of operating rooms, coronary care units, stroke units, recovery areas into critical care units) and with new dedicated facilities [3, 4]. In order to limit the in-hospital spreading of the infection it is necessary—when possible—to use negative pressure airborne isolation rooms in dedicated ICUs [3]. However, during the pandemic surge, available spaces with these characteristics have been rapidly saturated [3]. Structural partition of ICUs spaces should include "clean" and "contaminated" areas, to be kept separated by a double filter zone [4, 5]. For ICU admission of suspected COVID-19 patients, it has also been described the use of isolated positions as "buffer zone" while waiting for swab results [5]. "Clean areas" should be dedicated to activities that don't imply a direct contact with

F. Alessandri · G. Giordano · E. Magnanimi · F. Bilotta (✉)
Department of Anesthesiology, Critical Care and Pain medicine, "Sapienza" University of Rome, Rome, Italy
e-mail: bilotta@tiscali.it.it

H. Prabhakar et al. (eds.), *Clinical Synopsis of COVID-19*,
https://doi.org/10.1007/978-981-15-8681-1_7

patients, such as briefings and clinical discussions, planning of ordinary activities at the beginning of the turn-shift, resting of personnel while rotating, fulfilling of bureaucratic tasks, etc. [4] Clean areas should also include appropriate "filter zone" for personal protection equipment (PPE) donning before entering the contaminated areas [5]. Efficient communication between the clean and contaminated areas is fundamental and might also be facilitated by the use of intercom and new technologies such as smartphones [4, 5]. Access to contaminated areas should be selectively limited to patient's care at the bedside [4–6].

7.1.2 Equipment (Ventilators/Monitors/Devices)

Separation of "clean" and "contaminated" areas along with the increase of ICU beds imposes a comparable expansion of equipment availability: ventilators, monitors, and a growing supply of disposable devices [3–6]. In setting up a system of diversified routes and increasing resources, the placement of resources follows two different needs: machinery for each patient and machinery for common use in the contaminated space. In the first case, in order to meet the unprecedented demand for mechanical ventilators, the use of anesthesia machines in critical care settings has become a frequently adopted solution [6]. In this scenario, in March of 2020, the US Food and Drug Administration allowed the off-label use of anesthesia machines for ICU purposes; furthermore, the Anesthesia Patient Safety Foundation and the American Society of Anesthesiologists released dedicated guidelines. Furthermore, several other alternatives were used as emergency transport ventilators, magnetic resonance imaging compatible ventilators, and a last option alternative technique (as prolonged manual ventilation, NIV for invasive ventilation, veterinary ventilators).

In order to warrant a common equipment for all COVID-19 patients, the ultrasound machine and other necessary devices, including fiberbronchoscopes, videolaryngoscopes, point-of-care arterial blood gas and coagulation analyses, as well as transport ventilator and emergency cart with defibrillator, should be included in the contaminated area [5].

In order to limit the access of healthcare providers to the "contaminated" area, it has been suggested to use a centralized monitoring system in the clean zone [4, 5].

7.1.3 Human Resources

Structural hospital's changes have been accompanied by reallocation of internal human resources (intensivists, anesthesiologists, emergency doctors, pneumologists, infection diseases specialists, nurses, and other healthcare providers) and by hiring new healthcare personnel [3, 6]. In most of the cases, when routine hospital activities were reduced or suspended, anesthesiologist, pulmonologists, and non-critical care nurses were employed to fill ICU rotation [3, 6]. Recommendations were released in order to reduce the risk for personnel exposure [3, 4, 6]. It is

important that staff undergo proper training in donning and doffing of PPE; the use of visual aids, checklists, and trained observers to assist in safely doffing PPE is also suggested [6]. Moreover, it is recommended to minimize the permanence of staff personnel in the "contaminated area" [4–6].

ICU organization	
ICU beds increase	Reorganizing spaces in previously existing medical and/or surgical ICUs; building new facilities
	Reconversion of operating rooms, coronary care units, stroke units, recovery areas
	In case of lack of mechanical ventilators, the use of anesthesia machines in critical care settings is suggested; the use of different alternatives was also suggested
	The use of a single ventilator to support multiple patients is not recommended
Staff management	In case of expected surge, suspend, or reduce regular activity
	Recruit and educate staff from other wards
Reducing in-hospital spreading of the infection	If available, the use of isolation ICUs, with negative pressure airborne infectious isolation rooms, is recommended
	The creation of cohort ICUs for COVID-19 patients can maximize the containment
	ICU units should be divided into clean and contaminated isolated areas, separated by a double filter zone
	The use of a "buffer zone" for suspected COVID-19 patients is described
	Programme infected waste disposal
Reducing the risk for personnel exposure	The staff must undergo a proper training in donning and doffing of PPE
	The use of visual aids, checklists, and trained observers to assist in safely doffing PPE is suggested
	Minimize staff permanence in contaminated areas by reducing the number of personnel and ensuring rotation of the staff

7.2 Criteria for COVID-19 ICU Admission

Out of the infected COVID-19 patients, about 5% develop critical illness, including severe pneumonia, respiratory failure and acute respiratory distress syndrome (ARDS), septic shock, coagulopathy, rhabdomyolysis, and multiorgan—cardiac, kidney, and liver—dysfunction or failure; the majority of them require invasive mechanical ventilation and advanced ventilatory support including prone position, curarization, or extracorporeal membrane oxygenation (ECMO) [7–9]. According to the most recent interpretation, the possible underlying mechanism can be attributed to altered immune system response that leads to a cytokine release syndrome and subsequent multiorgan failure [7, 10, 11].

Several characteristics have been associated to a higher rate of developing COVID-19-related critical illness and death: advanced age, comorbidities

(including cardiovascular and cerebrovascular diseases, diabetes, kidney disease, obesity), higher Sequential Organ Failure Assessment (SOFA) score, severity of presenting symptoms (dyspnea, anorexia), plasmatic levels of D-dimer, troponin I, lactate dehydrogenase (LDH), lymphocytes, platelets, inflammation-related marker levels (high sensitivity C-reactive protein, erythrocyte sedimentation rate, and ferritin), cytokine (i.e., IL-2R, IL-6, IL-10, and TNF-α) [12–14]. Reported mortality in mechanically ventilated patients ranges between 12 and 97% depending on severity of ICU admission criteria and on the reported phase of the pandemic [13, 15–19].

Early recognition of COVID-19 patients who require intensive care is of utmost importance especially considering the surge during pandemic that run critical care management capabilities to an edge [20]. To standardize the criteria for ICU admission, several severity scores have been used. In some cases previously developed and purposely modified indicators were adopted; some centers tested new and dedicated scores. Among the used available scores are quick-SOFA (qSOFA); confusion, rate of respiration, and blood pressure (CRB) score; confusion, urea nitrogen, rate of respiration, blood pressure (CURB-65) score; CRB-65 score; National Early Warning Score (NEWS); Adjusted National Early Warning Score (ANEWS); VitalPAC-Early Warning Score (ViEWS). The COVID-GRAM is a newly developed clinical risk score. The qSOFA score that ranges from 0 to 3 was developed in 2016 as a bedside tool that identifies patients at greater risk for a poor outcome outside the ICU, and it is based on three clinical variables: altered mental status—evaluated with Glasgow coma scale—the respiratory rate, and blood pressure values. The CRB score is based on the same variables of the qSOFA (with "confusion assessment" to evaluate the altered mental status), and it turns to be a simplified version of the CURB-65 score that was firstly introduced in 2003 in order to stratify patients with community-acquired pneumonia, and, in addition to the variables that are evaluated by the CRB score, it considers urea nitrogen values and also age when ≥65. The CRB-65 does not evaluate urea nitrogen levels. The CRB score ranges from 0 to 3, the CURB-65 score ranges from 0 to 5, and the CRB-65 ranges from 0 to 4. Predictive value in identifying patients who require intensive respiratory or vasopressor support was retrospectively tested in this setting by evaluating a cohort of 116 cases and suggesting an higher performance for CRB-65 and CURB-65 scores. The CRB-65 score, when a cut-off value of 2 is applied, had a sensitivity of 64% and specificity of 93.4%; the CURB-65 score, when a cut-off value of 2 is applied, had a sensitivity of 80% and specificity of 87.9%; the CRB score, when a cut-off value of 1 is applied, had a sensitivity of 72% and specificity of 79.1%; the qSOFA score, when a cut-off value of 1 is applied, had a sensitivity of 80% and specificity of 47.3% [21]. The NEWS was originally developed in 2012 and further implemented in 2017 (i.e., NEWS2) in order to improve the detection of patients in with acute illness at risk for clinical deterioration and includes several parameters: respiration rate, oxygen saturation, systolic blood pressure, pulse rate, level of consciousness and new confusion, and temperature, plus a weighting score for supplemental oxygen. A maximum score of 3 is associated to each of the parameters, and four trigger levels, that should determine the urgency of the clinical response, are recommended: low score (1–4), nurse assessment, a single red score (a score of 3 in any one parameter), urgent review by a

ward doctor; medium score (5 or 6), urgent review by a ward doctor; and high score (≥7), emergency assessment by a critical care team. The Royal College of Physicians (RCP), United Kingdom, recommends the use of NEWS2 when managing patients with COVID-19. The predictive value of NEWS2 for ICU admission in COVID-19 patients was retrospectively tested in a cohort of 71 patients: a NEWS2 ≥ 5 showed sensitivity of 89%, specificity of 66%, and accuracy of 75%; a NEWS2 ≥ 7 showed sensitivity of 63%, specificity of 98%, and accuracy of 84%; the AUROC curve was 0.90 [22]. The Adjusted National Early Warning Score (ANEWS) is a modified version of the NEWS2 that includes also age and comorbidities and has been proposed as a tool for early recognition and escalation of treatment in hospitalized COVID-19 patients. The ANEWS ranges from 0 to 24: a score ≥ 5 is related to a medium clinical risk and is considered a key threshold for urgent response [20]. The VitalPAC-Early Warning Score (ViEWS) was described in 2010 and is very similar to the NEWS2, including the same variables with a slightly different scoring system and ranging from 0 to 21. Some authors propose the use of a modified version of the ViEWS (that did not include a central nervous system evaluation) for the early identification of COVID-19 patients requiring ICU admission. A modified-ViEWS ≥7 showed sensitivity of 87–94% and specificity of 78–93%; the AUROC curve was 0.88–0.98 [23].

The COVID-GRAM is a score designed to predict the course of hospitalized COVID-19 patients, based on a development cohort of 1590 patients and a validation cohort of 710 patients [24]. It includes ten variables: chest X-rays abnormality, age, hemoptysis, dyspnea, unconsciousness, number of comorbidities, cancer history, neutrophil-to-lymphocyte ratio, lactate dehydrogenase, and direct bilirubin. The selected comorbidities include chronic obstructive pulmonary disease, hypertension, diabetes, coronary heart disease, chronic kidney disease, cancer, cerebral vascular disease, hepatitis B, and immunodeficiency. This score can be achieved by an online calculation tool that predicts the probability for critical-ill events (including invasive ventilation, ICU admission, and death), identifying three risk groups: low-risk group (0.7%); medium-risk group (7.3%); and high-risk group (59.3%). Accuracy of this risk score is 0.88, based on AUCs in both the development and validation cohorts.

Test	Clinical variables	Performance
qSOFA	– Altered mental status (GCS < 15) – Respiratory rate > 22 – Systolic BP ≤ 100	– Cut-off value of 1: Sensitivity = 80%, specificity = 47.3%
CRB	– Altered mental status (confusion) – Respiratory rate ≥ 30 – Systolic BP < 90 mmHg or diastolic BP ≤ 60 mmHg	– Cut-off value of 1: Sensitivity = 72%, specificity = 79.1%
CRB-65	– Altered mental status (confusion) – Respiratory rate ≥ 30 – Systolic BP < 90 mmHg or diastolic BP ≤ 60 mmHg – Age ≥ 65 years	– Cut-off value of 2: Sensitivity = 64%, specificity = 93.4%

(continued)

Test	Clinical variables	Performance
CURB-65	– Altered mental status (confusion) – BUN >19 mg/dL (>7 mmol/L) – Respiratory rate ≥ 30 – Systolic BP < 90 mmHg or diastolic BP ≤ 60 mmHg – Age ≥ 65 years	– Cut-off value of 2: Sensitivity = 80%, specificity = 87.9%
NEWS2	– Respiratory rate – Hypercapnic respiratory failure – Room air or supplemental O_2 – Temperature – Systolic BP – Pulse – Consciousness (AVPU)	– Cut-off ≥5: Sensitivity = 89%, specificity = 66%, accuracy = 75% – Cut-off ≥7: Sensitivity = 63%, specificity = 98%, accuracy = 84%
ANEWS	– Age ≥ 65 years – Comorbidities (DM, HTN, COPD, CKD, malignant tumors) – Respiratory rate – Oxygen saturation – Room air or supplemental O_2 – Temperature – Systolic BP – Pulse – Consciousness (AVPU)	– Not tested in COVID-19 patients
Modified-ViEWS	– Pulse – Respiratory rate – Systolic BP – Temperature – Oxygen saturation – Room air or supplemental O_2	– Cut-off value ≥7: Sensitivity from 87 to 94%, specificity from 78 to 93%
COVID-GRAM	– Chest X-ray abnormality – Age – Hemoptysis – Dyspnea – Unconsciousness – Number of comorbidities[a] – Cancer history – Neutrophil-to-lymphocyte ratio – Lactate dehydrogenase – Direct bilirubin	– Accuracy = 88%

qSOFA quick Sequential [sepsis-related] Organ Failure Assessment, *GCS* Glasgow Coma Scale, *BP* blood pressure, *BUN* blood urea nitrogen, *NEWS* National Early Warning Score, *AVPU* alert, voice, pain, unresponsive, *ANEWS* Adjusted National Early Warning Score, *DM*, diabetes mellitus, *HTN* hypertension, *COPD* chronic obstructive pulmonary disease, *CKD* chronic kidney disease, *ViEWS* VitalPAC-Early Warning Score

[a]Chronic obstructive pulmonary disease, hypertension, diabetes, coronary heart disease, chronic kidney disease, cancer, cerebral vascular disease, hepatitis B, and immunodeficiency

7.3 Respiratory Support

The respiratory system is commonly involved in COVID-19 patients, and the spectrum of disease expression can variously range from asymptomatic hypoxemia to severe acute respiratory distress syndrome (ARDS) [7, 19] The optimal noninvasive respiratory support as well as intubation timing and settings is debated. To date, few data are available on the efficacy of noninvasive and invasive respiratory support in COVID19 patients [25]. The reported available evidence and related recommendations are mostly based on patients affected by different types of acute respiratory failure (ARF) and on different pandemic contexts such as severe acute respiratory syndrome (SARS), influenza A H1N1, and Middle East respiratory syndrome (MERS) [25, 26].

7.3.1 Noninvasive Respiratory Support

The high-flow through nasal cannula (HFNC) allows to deliver up to 100% of inspiratory fraction of oxygen (FiO_2), a flow up to 60 L/min, a positive end-expiratory pressure (PEEP) up to 8 cmH_2O and CO_2 wash out from the upper airways dead space. Compared with other noninvasive strategies such as NIV, the HFNC is more acceptable for patients and associates with higher compliance; moreover, the effect of heat and humidified oxygen minimizes mucosal injury, improves secretion clearance, and reduces transpulmonary driving pressure [26]. The use of HFNC has been proposed also with the adding prone positioning and in combination with NIV in sequential application [26].

Avoiding of hyperoxemia is a recommended priority [27, 28]. Guidelines released in March, 2020, by the Surviving Sepsis Campaign (SSC) COVID-19 subcommittee, suggest to start conventional oxygen therapy when peripheral oxygen saturation (SpO_2) drops <92% and recommended it for $SpO_2 < 90\%$ [27]. According to the SSC panel, when treating acute hypoxemic respiratory failure not responding to oxygen therapy, HFNC should be preferred over NIV because of lower mortality and reduced need for subsequent endotracheal intubation, as reported in some subsets of non-COVID-19 patients [27]. Furthermore, HFNC should be preferred because of the possible reduced risk for nosocomial infection spreading to healthcare providers [27]. On the other hand, the NHS guidelines advise against the use of HFNC in COVID-19 patients because of concerns on potential of aerosolization related to this treatment [28, 29]. This concern is disproportionate considering the evidence of comparable viral aerosols and droplet dispersion of HFNC and standard oxygen masks [29]. Data on the efficacy of HFNC on improving oxygenation and reducing respiratory rate in hypoxemic COVID-19 patients are increasing but are mainly derived from small clusters of patients in observational studies. HFNC failure was seen in 61% of patients with PaO_2/FiO_2 ratio < 200 mmHg, and NIV was

used as rescue therapy. HFNC use has been also reported in series of patients from the USA, Italy, and other countries [13, 14, 16–18, 26, 30, 31]. Interestingly, in a cohort of 84 patients in Italy, it has been reported that the use of HFNC in a regular ward, together with other measures aimed to rise the intensity of care, reduced the need for ICU admission [30].

The use of mechanical ventilators together with dedicated interfaces (including facial masks and helmets) allows the application of continuous positive airway pressure (CPAP) and eventually of a pressure support (PS) at patient's bedside through a noninvasive approach (i.e., NIV). Alternatively, some devices can administrate CPAP, but not PS, with specific flow drivers connected to an oxygen source. The use of NIV has been proposed also with the adding of prone positioning [26]. In patients under NIV, there is the risk that high inspiratory efforts could lead to large tidal volumes (V_t) that are independently associated with NIV failure [26].

According to the SSC panel, a trial of NIV is suggested if HFNC is not available, and there is no urgent indication for endotracheal intubation, but the application of CPAP is not mentioned; on the contrary, others (e.g., NHS guidelines) stated that, for some patients, CPAP or NIV could represent the "appropriate ceiling of treatment" [27, 28]. Also the use of CPAP and NIV has been considered at high risk for aerosolization and transmission among healthcare personnel [27]. Considering the higher potential of facial masks, the application of a CPAP or NIV through the helmet would be a safer option [26].

The use of CPAP and NIV in COVID-19 patients has been reported in studies from China and other countries [13, 14, 16–18, 26, 31, 32]. A management strategy proposal, based on the experience with >70 COVID-19 patients, suggests to start with helmet-CPAP support when PaO_2/FiO_2 ratio < 250 mmHg or respiratory rate ≥ 30/min and to consider the use of NIV with PS in case of presence of hypercapnia [32]. In a retrospective study on 52 patients in China, 56% of patients were treated with NIV with a high rate of noninvasive support failure and need for intubation [13, 25].

In a study of 15 COVID-19 patients receiving NIV and prone position (PP), all patients had improvement in SpO_2 and PaO_2/FiO_2 during pronation and in 12 (80%) the improvement was maintained after [33].

7.3.2 Invasive Mechanical Ventilation

Whenever noninvasive support is not enough and the patient shows symptoms and signs of respiratory fatigue along with impairment of gas exchanges, endotracheal intubation and invasive mechanical ventilation are mandatory. Acute refractory hypoxemia and bilateral infiltrates at the chest imaging, not completely explained by cardiac failure, are clinical features comparable with ARDS despite high respiratory compliance, and plateau pressures (P_{plat}) < 30 mmHg are not consistent in all cases; however pulmonary microembolism, the intrapulmonary shunt, lung

perfusion dysregulation, and hypoxic vasoconstriction mechanism play an important role in the pathogenesis of respiratory failure in COVID-19. Some authors hypnotized two different phenotypes to describe the respiratory mechanic of COVID-19: the Type L is a low-elastance, low ventilation-to-perfusion (VA/*Q*) ratio, low lung weight, and low lung recruitability, while the Type H is a high elastance due to increased edema, high right to left shunt, and high lung weight associated with a high lung recruitability [34]. However, these could be two different stage of severity more than two real phenotypes, and respiratory treatment should be titrated to the different recruitability and respiratory system compliance.

The Type L patients can be ventilated with volumes greater than 6 mL/kg (up to 8–9 mL/kg), as the high compliance results in tolerable strain without the risk of ventilator induced lung injury (VILI). The PEEP should be reduced to 8–10 cmH_2O, given that the recruitability is low and the risk of hemodynamic failure increases at higher levels. Type H patients should be treated as severe ARDS; low tidal volume ventilation (4–8 mL/kg of predicted body weight) is strongly recommended and preferred over higher tidal volumes. Plateau pressure (P_{Plat}) has to be limited to 30 cmH_2O. Oxygenation has to guarantee a $SpO_2 > 92–95\%$ optimizing FiO_2 and PEEP. The "best PEEP" is the value that allow the lower driving pressure and consequently the best compliance, but in a condition of well-preserved lung mechanics, the target should be the optimal oxygenation and the best pulmonary perfusion, so it has to be considered the hemodynamic impairment due to high level of PEEP. In COVID-19 patients undergoing MV, there is no advantage attributed to different MV modes, and pressure modes are comparable to the volume modes.

7.3.3 Prone Position

Based on the evidence on PP usefulness as adjunct to invasive ventilation support in moderate-severe ARDS patients with $PaO_2/FiO_2 < 150$ mmHg, it has been introduced in the treatment of COVID-19 patients [35]. In ARDS, 12–16 h of MV in prone position improves several parameters: dorsal lung recruitment, end-expiratory lung volume, and chest wall elastance increase, alveolar shunt decreases, and tidal volume along with ventilation/perfusion mismatch (*V*/*Q*) [35]. In COVID-19 patients, that present Type H pattern of respiratory mechanic and predominant basilar consolidation to include PP is especially effective [34]. Considering the context of limited human resources availability that characterizes the workload of ICU healthcare professionals in COVID-19 surge, long-term clinical benefits of this strategy have been questioned (five guidelines). Further concerns have been raised in consideration of the specific training necessary to appropriately deliver PP and prevent associated complications (i.e., pressure sores, vascular line and endotracheal tube displacement, facial edema, corneal abrasions, brachial plexus injury, etc.) [36].

7.3.4 Extracorporeal Membrane Oxygenation (ECMO)

Extracorporeal membrane oxygenation (ECMO) should be considered for COVID-19 patients with refractory hypoxemia when all other rescue therapy failed in improving oxygenation. The ECMO should can be considered in presence of one of the following criteria: (1) PaO_2/FiO_2 < 50 mmHg for >3 h; (2) PaO_2/FiO_2 < 80 mmHg for >6 h; and (3) pH < 7.25 with $PaCO_2$ > 60 mmHg for >6 h with a respiratory rate up to 35 breaths per minute, adjusted for plateau pressure > 30 cmH_2O [37]. The complexity of ECMO requires a well-qualified ICU team to deliver care to these critically ill patients, and therefore the use of ECMO should be limited to expert and high-volume centers. ECMO mortality rates vary widely across ECMO centers, and experience in COVID-19 outbreak is still limited.

7.3.5 Tracheostomy

The weaning process from MV in COVID-19 patients remains poorly described, and the latest guidelines did not provide any specific recommendation. Several studies showed the relationship between the timing of tracheostomy and the prognosis of patients, comparing early tracheostomy with late tracheostomy or prolonged intubation and assessing the influence of timing of tracheostomy on mortality, duration of MV, ICU stay, and other clinical outcomes. Although there are no evidence-based guidelines on the timing to perform a tracheostomy in MV patients, early tracheostomy (within 10 days from translaryngeal intubation) should be preferred to late tracheostomy when MV is expected to last >21 days [38]. To accomplish early tracheostomy associates with several advantages, including shortening duration of sedation and vasopressor infusion, increased patient comfort, oral feeding, interactive communication, and nursing care [38]. Furthermore, early tracheostomy might decrease the incidence of ventilator-associated pneumonia (VAP), duration of MV, and length of ICU stay. In COVID-19 patients, some authors suggest an *"earlier than usual"* tracheostomy along with weaning with NIV in order to improve patient-ventilator interaction, early weaning from MV, and ICU discharge [39]. This could also contribute to optimize ventilators availability in a context of limited resources.

7.3.6 Lung Ultrasound

Bedside lung ultrasonography is gaining popularity in the ICU and permits timely assessment of pleural and lung conditions, such as consolidation, effusions, and prompt detection of pneumothorax. In COVID-19 pneumonia and ARDS patients, most of the lesions are distributed peripherally in the lung, which facilitates detection by lung ultrasound [40]. The most common findings in patients with severe respiratory involvement have recently been reported by some authors: separated or confluent B-lines (100%), consolidation (64%), and pleural line abnormalities

(100%). Bilateral involvement was always observed with predominant distribution in the posterior part of the lungs. Composition B-lines and areas of consolidation showed parallel changes with the clinical severity with a peak at the second week.

Respiratory support	
Noninvasive respiratory support	Avoiding of hyperoxemia is recommended
	Starting conventional oxygen therapy is suggested when peripheral oxygen saturation drops <92% and recommended for SpO_2 < 90%
	The SSC panel suggests to prefer HFNC over NIV when treating acute hypoxemic respiratory failure not responding to oxygen therapy
	NHS guidelines advise against the use of HFNC in COVID19 patients
	The SSC panel suggests a trial of NIV if HFNC is not available and there is no urgent indication for endotracheal intubation
	NHS guidelines: For some patients, CPAP or NIV could represent the "appropriate ceiling of treatment"
Invasive mechanical ventilation	Endotracheal intubation and invasive mechanical ventilation is mandatory if noninvasive support is not enough and the patient shows symptoms and signs of respiratory fatigue along with impairment of gas exchanges
	The type L patients can be ventilated with volumes greater than 6 mL/kg (up to 8–9 mL/kg); the PEEP should be reduced to 8–10 cmH_2O
	Type H patients should be treated as severe ARDS
	There is no advantage attributed to different MV modes
Prone position	Prone position can be useful especially in type H pattern of respiratory mechanic
ECMO	Should be considered for COVID19 patients with refractory hypoxemia despite all other rescue therapy took in place to improve oxygenation
Tracheostomy	Early tracheostomy should be preferred to late tracheostomy

SSC surviving sepsis campaign, *HFNC* high-flow nasal cannula, *NIV* noninvasive ventilation, *NHS* National Health Service, *ARDS* acute respiratory distress syndrome

7.4 Management of Hemodynamic Failure

7.4.1 Shock

Prevalence of hemodynamic failure in COVID-19 patients is extremely variable in both hospitalized and in ICU patients, ranging from 1 to 35% [9, 12–15, 17, 18, 27, 31]. In these patients, the pathophysiology of shock and organs hypoperfusion is multifactorial: patients often present at hospital admission with severe dehydration and hypovolemia, after several days of hyperthermia and gastrointestinal symptoms, including severe diarrhea [41, 42]. Distributive shock is probably the main mechanism for acute circulatory failure, and the magnitude of the "cytokine storm" is directly involved in the severity of the clinical presentation [10]. Nevertheless, growing evidence highlights that acute myocardial injury, cardiomyopathy, and

venous and pulmonary embolism also contribute to worsen hemodynamic stability [8, 43]. Therefore, in COVID-19 patients, a combination of hypovolemic, distributive, cardiogenic, and obstructive shock mechanisms are variously involved in different phases of the disease.

7.4.2 Fluid Therapy and Vasopressors

Fluid therapy is a key point in restoring perfusion in patients with hypovolemic shock along with fluid resuscitation strategy. In COVID-19 patients, fluid infusion should aim to maintain organ perfusion to avoid fluid overload ("keeping lungs dry") [42]. Recommendations from SSC COVID-19 panel, based on the evidence available for general management of fluid therapy in sepsis and septic shock, suggest initial conservative approach with buffered/balanced crystalloids and advise against the use of colloids (i.e., hydroxyethyl starch, gelatins, dextrans) [27]. In advanced phase of management, when patients present a reliable restored hemodynamic stability, optimal fluid management include de-escalation strategy associated with active fluid removal through the renal replacement therapy aim to pursue daily negative fluid balance [41].

Rapid variability of fluid volume status of these patients, ranging from hypovolemia to severe fluid overload, imposes a reliable monitoring [44]. According to SSC COVID-19 panel, monitoring recommends to include preferentially dynamic rather than static parameters and clinical measurements (including skin temperature, capillary refilling time, and/or serum lactate) to assess fluid responsiveness and guide fluid resuscitation [27]. Dynamic parameters include stroke volume variation (SVV), pulse pressure variation (PPV), passive leg raise test, and fluid challenge. Static parameters include central venous pressure (CVP) and mean arterial pressure (MAP). Dynamic parameters can be easily obtained by minimally invasive technologies that use arterial waveform variation analysis and transpulmonary thermodilution to estimate cardiac output, volumetric parameters, and fluid responsiveness.

Point-of-care ultrasound (POCUS) is useful tool to guide fluid management since integrates information from scanning different organs as proposed by "Tri-POCUS" approach that combines the use of lung ultrasound (LUS), focused cardiac ultrasound (FoCUS), and venous Doppler ultrasound [44].

The use of pulmonary artery catheter (PAC) in COVID-19 critically ill patients provides valuable information on hemodynamic status, especially in those affected by pulmonary hypertension associated with right-heart dysfunction, but no firm evidence prove benefits with this approach [45].

Norepinephrine infusion is the first-choice vasopressor to treat hypotension and achieve target mean arterial pressure (MAP) of 60–65 mmHg; vasopressin is suggested as adjunct, in order to reduce the dose of norepinephrine [27]. Dobutamine should be preferred in patients with cardiac dysfunction and persistent hypoperfusion. In case of refractory shock, low-dose corticosteroid therapy ("shock-reversal") is suggested.

7.4.3 Basic and Advanced Life Support in COVID-19 Adult Patients

The American Heart Association (AHA) released specific guidelines for basic and advanced life support in patients with suspected or confirmed COVID-19 [46]. The unique perspective of these guidelines is the attention to reduce the exposure of healthcare providers that include ventilation strategies associated lower aerosolization and to consider appropriateness of beginning and continuing resuscitation maneuvers. Despite evidence on aerosolization and virus spreading during chest compressions and defibrillation is very limited, the World Health Organization listed cardiopulmonary resuscitation (CPR) as an aerosol-generating procedure. The strategies proposed to reduce providers' exposure include PPE donning by all providers of the team before entering the scene; limiting the personnel in the room; considering the use of mechanical CPR devices to replace manual chest compressions; and communicating COVID-19 status to any new provider [46]. A more rapid switching of the rescuers (e.g., 1 min) is suggested to cope with the damage or the loss of PPE such as mask slipping and to limit the fatigue caused by the CPR wearing PPE [47]. Other measures to minimize aerosolization include using high-efficiency particulate filter (HEPA) adjunct to any ventilation circuit; rapid intubation and increase of a first-pass success likelihood expertise of the provider, device such as video laryngoscopy if available and pausing chest compressions for intubation); using a bag-mask device with HEPA filter and tight seal before intubation or considering passive oxygenation with non-rebreathing face mask, covered by surgical mask; if intubation is delayed, considering the use of manual ventilation with supraglottic airway or bag-mask device with HEPA filter covered by surgical mask; and minimizing disconnection of the "close-circuit" [46]. Considering the poor survival rates of COVID-19 patients, who require intubation and invasive ventilation, the appropriateness of beginning resuscitation maneuvers should include to share with the patient or next of kin the expected results after CPR and to implement specific policies for CPR discontinuation [13, 17, 46].

7.4.4 Acute Kidney Injury (AKI) and Continuous Renal Replacement Therapy (CRRT)

While in mild-moderate COVID-19 infection, acute kidney injury (AKI) is relatively infrequent (5%), but proteinuria and hematuria are frequently detected (44%, 27%). Changes in serum creatinine (SCr) and/or blood urea nitrogen (BUN) occur in up to 13% of patient's [48, 49]. In these patients, AKI is associated to an higher risk of in-hospital death. In severe COVID-19 patients, AKI complicates about 37% and is the first extrapulmonary complication (29%), and 14–25% of patients leads to temporary CRRT. In this case, mortality raise up to 80%: Kdigo stage 1 was in 47% of patients, Kdigo stage 2 in 22% of patients, and Kdigo stage 3 in 31% [13].

In ICU, several predisposing factors such as older age, diabetes mellitus, cardiovascular disease, black race, chronic arterial hypertension, and need for ventilation and vasopressor medications increase the risk to develop AKI in COVID-19 critical patients. Right ventricular dysfunction or left ventricular failure get worsen the renal function. The SARS-Cov2 directly induces mitochondrial dysfunction, acute tubular necrosis, glomerulopathy, and protein leakage in Bowman's capsule through angiotensin-converting enzyme (ACE)-2-depending pathway. A dysregulation of the immune host response, lymphopenia, and cytokine storm contributes to endothelium damage. Other contributing factors for AKI in COVID-19 patients are rhabdomyolyses, macrophage activation syndrome, and microemboli and microthrombi caused by hypercoagulopathy.

There are no specific treatments for AKI in ICU, and current clinical management of COVID-19 patients affected by renal impairment follows general indications of the KDIGO guidelines: to avoid nephrotoxins, regular monitoring of serum creatinine and urine output, and hemodynamic monitoring. Several evidence demonstrate the kidney protective effect of a reduction in tidal volume up to 6 mL/kg of PBW. Fluid balance has to be maintained according to volume responsiveness and tolerance assessment, in order to restore normal volume status and to avoid fluid overload, right ventricular overload, pulmonary edema, congestion, and subsequent AKI. When oliguria persists or fluid overload impairs renal function, despite all conservative treatments, patients should undergo CRRT.

Hemodynamic management	
Avoid fluid overload	Initial conservative approach with buffered/balanced crystalloids is suggested
	Recommendation against using hydroxyethyl starch, gelatins, dextrans and the routine use of albumin
	Consider the use of a deresuscitation or de-escalation strategy, also with active fluid removal through the use of renal replacement therapy
Hemodynamic monitoring	Use dynamic parameters together with clinical measurements for fluid responsiveness assessment and to guide fluid resuscitation
	Point-of-care ultrasound assessment has been proposed
	Both the use of minimally invasive technologies and pulmonary artery catheter are options
Vasopressors use	Target a medium artery pressure of 60–65 mmHg
	Norepinephrine is first-line vasoactive agent; vasopressin or epinephrine are second-line agents
	Combined strategy with norepinephrine and vasopressin is suggested in order to reduce the dose of norepinephrine
	Dobutamine is the inotrope of choice in case of cardiac dysfunction and persistent hypoperfusion
	Low-dose corticosteroid ("shock-reversal") is suggested in case of refractory shock

Basic and advanced life support	
Reduce providers exposure	All providers should don personal protective equipment before entering the scene
	Limit the personnel in the room
	Consider the use of mechanical CPR devices
	Communicate COVID-19 status to any new provider
	A rapid switching of the rescuers (e.g., 1 min) is suggested to limit fatigue, damage to PPE, and slipping of the face mask
Lower aerosolization risk	Use high-efficiency particulate (HEPA) filter
	Early intubation and maximization of likelihood of a first-pass success
	Use a bag-mask device with HEPA filter and tight seal before intubation or consider passive oxygenation with non-rebreathing face mask, covered by surgical mask
	Consider the use of manual ventilation with supraglottic airway or bag-mask device with HEPA filter covered by surgical mask
Consider the appropriateness of resuscitation	Address goals of care with COVID-19 patients or proxy in anticipation
	Implementation of policies to guide front-line providers
Out-of-hospital cardiac arrest	Consider bystanders CPR with a face mask covering the mouth and nose of the rescuer and/or victim
	Consider the use of an automated external defibrillator
In-hospital cardiac arrest	Prearrest management should include a close monitoring for signs and symptoms of clinical deterioration
	Patients at risk for cardiac arrest should be moved into negative pressure room/unit or at least door must be closed
	Intubated patients at the time of cardiac arrest should be maintained on a mechanical ventilator
AKI and CRRT	AKI is common in severe COVID-19 patients
	Predisposing factors in ICU are older age, diabetes mellitus, cardiovascular disease, black race, hypertension, need for ventilation and vasopressor medications, right ventricular dysfunction, or left ventricular failure
	The current clinical management follows the general indications of the KDIGO guidelines
	Early treatment seems to improve outcomes

AKI acute kidney injury, *CRRT* continuous renal replacement therapy

7.5 Adjuvant Therapies

7.5.1 Coagulation

The relevance of COVID-19 coagulopathy has been suggested by the presence of a hypercoagulable state that, along with immobilization and vascular damage, increases the risk of thromboembolic complications and death. Critical COVID-19

patients are characterized by high concentrations of proinflammatory cytokines (i.e., TNF-α, IL1, and IL-6) and chemokines, which subsequently initiates coagulation activation and thrombin generation, while SARS-Cov2 infection is also associated with the activation of fibrinolytic system. The increase in D-dimer, platelet count, and prolongation of the prothrombin time is the most typical finding in coagulopathy of COVID-19 patients that result in higher death rate.

Post-mortem findings from COVID-19 patients show typical microvascular platelet-rich thrombotic depositions in small vessels of the lungs and other organs; however, there are no signs of hemolysis or schistocytes in the blood film [50]. In critical COVID-19 patients, the rate of thromboembolic complications ranges between 5 and 15%, and pulmonary embolism is often involved. Tests to monitor critical COVID-19 patients should include prothrombin time, fibrinogen, platelet count, and D-dimers. The use of viscoelastic tests is still debated. In these patients, despite the use of standard thromboprophylaxis with low molecular-weight heparin (LMWH) or unfractionated heparin (UFH), prevalence of thrombotic events is unusually high: hence "aggressive" pharmacological thromboprophylaxis should be considered when multiple risk factors for thromboembolism are present.

7.5.2 Co-Infections and Antibiotics Use in COVID-19 ICU Patients

Co-infections in COVID-19 patients can be caused by bacteria, viruses, and fungus and predispose to higher mortality [51–53]. Among hospitalized COVID-19 patients, antibiotics' use ranges from 71 to 100% of patients; the co-infection rate in non-survivors ranges between 4.8 and 50% [51, 52]. Incidence of bacterial co-infection in ICU patients is higher than in non COVID-19 with bloodstream detected in 25% after 15 days and 50% after 30 days [53, 54]. Overall, most frequent reported bacteria are *Mycoplasma pneumonia*, *Pseudomonas aeruginosa*, and *Haemophilus influenzae* [52, 53]. Other reported bacteria include *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Chlamydia pneumonia*, *Legionella pneumophila*, *Acinetobacter baumannii*, and *Clostridioides difficile* [52, 53]. Respiratory syncytial virus and influenza A are the most common viral co-infections, along with other coronaviruses, rhinovirus/enterovirus, parainfluenza, metapneumovirus, influenza B virus, and human immunodeficiency virus [52, 53]. Several risk factors associated with severe COVID-19—including ICU admission, corticosteroid therapy, intubation and MV, underlying respiratory disease, cytokine storm—are related to an increase of invasive fungal infections [51]. Up to date, different pulmonary fungal co-infections have been reported in COVID-19 patients, including *Aspergillus flavus* and *A. fumigatus* and *Candida glabrata* and *C. albicans,* but data are scarce, considering the difficulty of the diagnosis [51]. Of note, high rates of candidemia (6, 9%) have been reported in a subset of COVID-19 patients treated with tocilizumab [51].

Unfortunately, routine laboratory findings or imaging studies alone cannot discriminate bacterial co-infection from COVID-19 [52]. Respiratory symptoms as well as sepsis and septic shock are common and are virtually present in all severe cases [18]. A strict clinical and laboratory monitoring is mandatory for an early diagnosis of co-infections in order to promptly start appropriate therapy [27, 54]. SARS-CoV-2 has been recently incorporated into preexisting syndromic multiplex panels; therefore the risk to under-diagnose co-infections in COVID-19 patients could be effectively reduced [52].

Prophylactic interventions released by national authorities must be taken into account in order to lower the incidence of co-infections, particularly for VAP: appropriate sterile insertion of vascular catheters, with daily reminder to remove catheter if no longer needed; oral intubation is preferable to nasal intubation in adolescents and adults; keep patient in semi-recumbent position (head of bed elevation 30–45°); use a closed suctioning system; periodically drain and discard condensate in circuit tubing; use of a new ventilator circuit for each patient; once patient is mechanically ventilated, change circuit if it is soiled or damaged, however, not routinely; and change heat moisture exchanger when it malfunctions, soiled, or every 5–7 days [27, 52]. Optimal antimicrobials stewardship in the COVID-19 pandemic is debated; a ratio between the risk of patients' clinical deterioration and the concern about antimicrobial resistance must be considered [52, 53]. Several antibiotics showed a synergic effect on virus clearance: teicoplanin was found to effectively prevent the entry of Ebola virus, MERS, and SARS-Cov1 and is a promising agent for the prophylaxis and treatment of SARS-CoV2 infection [42, 52, 55]. Azithromycin showed in vitro activity against different viruses and has been found useful in preventing severe respiratory tract infections [42]. Fluoroquinolones have been proposed as an adjunct treatment in COVID-19 patients because of their in vitro antiviral activity and immunomodulatory properties, favorable pharmacokinetics, and safety profile [56].

7.5.3 Steroids

Although the use of systemic corticosteroids is controversial in patients with ARDS and beside the potential effect as a "shock reversal" therapy, their use has been suggested in critical COVID-19 patients in order to attenuate the hyper-inflammatory response and the "cytokine storm" [11]. Nevertheless, the potential adverse effects include the risk of delaying virus clearance, secondary bacterial infections, and osteonecrosis of the femoral head [11]. Preliminary findings of the RECOVERY trial released that the use of dexamethasone reduced deaths by one-third in ventilated patients and by one-fifth in other patients receiving only oxygen. There was no benefit among those patients who did not require respiratory support [57].

Associated therapy	
Coagulation	A more aggressive thromboprophylaxis using LMWH or UFH could be considered on an individual basis
Co-infections and antibiotics use	Prophylactic interventions must be taken in order to lower the incidence of co-infections
	Empiric treatment of co-infections in COVID-19 patients should be started as soon as they are suspected, and appropriate de-escalation should be performed on the basis of microbiologic results and clinical judgment
Steroids	Potential adverse effects
	According to preliminary results of the RECOVERY trial, dexamethasone reduced deaths by one-third in ventilated patients and by one-fifth in other patients receiving oxygen only

LMWH low-molecular-weight heparin, *UFH* unfractionated heparin

7.6 Communication Strategies in the ICU at the Time of COVID-19 Pandemic

The surge of COVID-19 pandemic has posed unique challenge in communication management, in particular in ICU setting. The need for social distancing and access limitations to hospital delivered according to public health policy have induced several forms of psychological discomfort in patients, relatives, and healthcare providers. Furthermore, there were other important factors that affected communication: uncommon clinical scenario, increased workload, and need for PPE [58, 59]. Effective communication is a cornerstone of high-quality medical care and humanization of hospitalization process is part of the treatment [60].

There is no consistent literature on ICU communication issues at the time of complete isolation, and most of the guidelines available refer to other settings, still providing inspiring principles to be carefully adapted to this challenging and evolving situation.

7.6.1 Basic Principles: Honesty, Punctuality, Accountability, Trust

First contact (phone call) with patient's relatives should take place at the time of admission in the ICU consistently delivered at least once a day and more frequently should clinical conditions worsen. Communication should be punctual, informative, and honest. It is of the utmost importance to identify clearly both who is responsible for the call (a doctor who knows the patient directly) and who will receive clinical information (a selected family member): the same doctor—whenever possible—should be involved, to ensure continuity, avoid repetition, and build trust. Patient dignity, autonomy, and ethical principles are pivotal in a pandemic as in any other

condition. Transparency about available resources, criteria for ICU access, and allocation policy should be carefully discussed with both patient and relatives, and when patient is not suitable for intensive care treatment, it is important to clarify alternative goals of care.

7.6.2 Content of the Communication

Clinical content of the communication should be clear, simple, and tailored to the level of comprehension of the person. An effective communication may also help collecting previous medical history and reconstruct values of the patient and treatment directives, when present. The communicator should cover all aspects involved in patient care: actual clinical condition, therapeutic options, and goals. Information should be given gradually (i.e., "small packets"). The communicator can select the amount of information to be given in a step-by-step manner to ensure full understanding, but omitting is not recommended. Medical staff should also encourage questions and give time for listening. When asked for prognostic evaluation of the case ("how long will it last?", "when will this happen?") it is important to be transparent also about uncertainty and possible clinical scenarios of an almost unknown disease.

7.6.3 Checklist for Communication

Healthcare workers are used to follow checklists for a lot of standard procedures (e.g., airway management, surgery, transfusions), yet they are not confident with checking themselves for effective communication. Structured communication strategies (maps, checklists) can effectively guide healthcare providers throughout the process.

7.6.4 Videocalls and Other Communication Strategies

There are several communication tools available: phone and videocalls with medical staff, videocalls with patient, emails and text messages. It is important to choose the most suitable tool for patients and relatives. Videocalls can promote closeness by visual contact and reduce anxiety and stress in the awake patient and should be encouraged by doctors and nurses. When planning for a videocall adequate preparation of patient and family is desirable, especially in the presence of tracheostomy, swelling, tubes, and monitors. Video calling is not recommended for patients who are conscious but uncooperative. Family conferences with doctors have also been widely used.

7.6.5 Communication at the End of Life and Grief

Should patient's condition deteriorates, prompt, close communication with family must be established. To prepare families for the loss at the time of complete isolation is very hard. Physical nearness and end-of-life rituals are essential for grief elaboration in normal conditions, yet often they are not feasible because of sanitary reasons during a pandemic. There is no receipt, but a combination of significant interventions may help: allowing for direct calls on the ward, leaving an email address, and keeping yourself accountable as a team around the patient. Family must receive reassurance about pain and distress relief, sedation, and continuous presence of healthcare staff around their loved one even when withholding/withdrawal of disproportioned treatment. After communication of death, psychological and religious/spiritual support should be offered.

Due to the dramatic nature of pandemic and the huge workloads, healthcare providers must take into serious account the importance of their own emotional and psychological well-being, improve communication between members of the team, share their emotions, and learn to seek for help and consultation to prevent moral distress and burnout.

Communication strategies	
Basic principles	Honesty, punctuality, accountability, trust
Content	Clear, simple, free of technicism and adjusted to the level of comprehension of the person. It is important to be transparent also about uncertainty and possible clinical scenarios of an almost unknown disease
Checklist	Can guide healthcare workers throughout the process of communication
Alternative communication tools	Phone and videocalls with medical staff, videocalls with patient, emails and text messages
Communication at the end of life and grief	Allowing for direct calls on the ward, leaving an email address and keeping yourself accountable as a team around the patient
	Reassure about pain and distress relief, sedation, and continuous presence of healthcare staff
Basic principles	Honesty, punctuality, accountability, trust
Content	Clear, simple, free of technicism, and adjusted to the level of comprehension of the person. It is important to be transparent also about uncertainty and possible clinical scenarios of an almost unknown disease
Checklist	Can guide healthcare workers throughout the process of communication
Alternative communication tools	Phone and videocalls with medical staff, videocalls with patient, emails and text messages
Communication at the end of life and grief	Allowing for direct calls on the ward, leaving an email address and keeping yourself accountable as a team around the patient
	Reassure about pain and distress relief, sedation and continuous presence of healthcare staff

References

1. Pan A, Liu L, Wang C, et al. Association of Public Health Interventions with the epidemiology of the COVID-19 outbreak in Wuhan, China. JAMA. 2020;323(19):1–9.
2. Remuzzi A, Remuzzi G. COVID-19 and Italy: what next? Lancet. 2020;395:1225–8.
3. Goh KJ, Wong J, Tien JC, et al. Preparing your intensive care unit for the COVID-19 pandemic: practical considerations and strategies. Crit Care. 2020;24:215.
4. Vargas M, De Marco G, De Simone S, et al. Logistic and organizational aspects of a dedicated intensive care unit for COVID-19 patients. Crit Care. 2020;24:237.
5. Mojoli F, Mongodi S, Grugnetti G, et al. Setup of a dedicated coronavirus intensive care unit: logistical aspects. Anesthesiology. 2020;133:244–6.
6. Aziz S, Arabi YM, Alhazzani W, et al. Managing ICU surge during the COVID-19 crisis: rapid guidelines [published online ahead of print, 2020 Jun 8]. Intensive Care Med. 2020;46:1303–25.
7. Berlin DA, Gulick RM, Martinez FJ. Severe Covid-19 [published online ahead of print, 2020 May 15]. N Engl J Med. 2020; https://doi.org/10.1056/NEJMcp2009575.
8. Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol. 2020;27:1–8. (Epub ahead of print).
9. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497–506.
10. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395:1033–4.
11. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the 'cytokine Storm' in COVID-19. J Infect. 2020;80:607–13.
12. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China [published online ahead of print, 2020 Feb 7]. JAMA. 2020;323(11):1061–9.
13. Yang X, Yu Y, Xu J. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8(5):475–81.
14. Grasselli G, Zangrillo A, Zanella A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. JAMA. 2020;323:1574–81.
15. Zhou F, Yu T, Du R. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395:1054–62.
16. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2015;30:994–7.
17. Bhatraju PK, Ghassemieh BJ, Nichols M, et al. Covid-19 in critically ill patients in the Seattle region - case series. N Engl J Med. 2020;382:2012–22.
18. Arentz M, Yim E, Klaff L, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington state. JAMA. 2020;323:1612–4.
19. Richardson S, Hirsch JS, Narasimhan M, et al. and the Northwell COVID-19 Research Consortium. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA. 2020;323:2052–9.
20. Kumar A, Kumar N, Kumar A, Kumar A. COVID-19 pandemic and the need for objective criteria for ICU admissions [published online ahead of print, 2020 Jun 1]. J Clin Anesth. 2020;66:109945.
21. Su Y, Tu GW, Ju MJ, et al. Comparison of CRB-65 and quick sepsis-related organ failure assessment for predicting the need for intensive respiratory or vasopressor support in patients with COVID-19 [published online ahead of print, 2020 May 7]. J Infect. 2020;S0163-4453(20)30281-4.

22. Gidari A, De Socio GV, Sabbatini S, Francisci D. Predictive value of National Early Warning Score 2 (NEWS2) for intensive care unit admission in patients with SARS-CoV-2 infection [published online ahead of print, 2020 Jun 25]. Infect Dis (Lond). 2020;52:698–704.
23. Meylan S, Akrour R, Regina J, Bart PA, Dami F, Calandra T. An Early Warning Score to predict ICU admission in COVID-19 positive patients [published online ahead of print, 2020 May 28]. J Infect. 2020;S0163-4453(20)30324-8.
24. Liang W, Liang H, Ou L, et al. Development and validation of a Clinical Risk Score to predict the occurrence of critical illness in hospitalized patients with COVID-19 [published online ahead of print, 2020 May 12]. JAMA Intern Med. 2020;180:1–9.
25. Robba C, Battaglini D, et al. Distinct phenotypes require distinct respiratory management strategies in severe COVID-19 [published online ahead of print, 2020 May 10]. Respir Physiol Neurobiol. 2020;279:103455.
26. Winck JC, Ambrosino N. COVID-19 pandemic and non invasive respiratory management: every Goliath needs a David. An evidence based evaluation of problems [published online ahead of print, 2020 Apr 27]. Pulmonology. 2020;S2531-0437(20)30093-3.
27. Alhazzani W, Møller MH, Arabi YM, et al. Surviving sepsis campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19) [published online ahead of print, 2020 Mar 27]. Crit Care Med. 2020; https://doi.org/10.1097/CCM.0000000000004363.
28. https://www.england.nhs.uk/coronavirus/secondary-care/other-resources/specialty-guides/#adult-critical-care. Accessed 28 July 2020.
29. Li J, Fink JB, Ehrmann S. High-flow nasal cannula for COVID-19 patients: low risk of bio-aerosol dispersion. Eur Respir J. 2020;55(5):2000892. Published 2020 May 14. https://doi.org/10.1183/13993003.00892-2020.
30. Lagi F, Piccica M, Graziani L, et al. Early experience of an infectious and tropical diseases unit during the coronavirus disease (COVID-19) pandemic, Florence, Italy, February to March 2020. Euro Surveill. 2020;25(17):2000556.
31. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ. 2020;368:m1091.
32. Radovanovic D, Rizzi M, Pini S, Saad M, Chiumello DA, Santus P. Helmet CPAP to treat acute hypoxemic respiratory failure in patients with COVID-19: a management strategy proposal. J Clin Med. 2020;9:1191.
33. 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;323(22):2338–40.
34. Marini JJ, Gattinoni L. Management of COVID-19 respiratory distress. JAMA. 2020;323(22):2329–30.
35. Guérin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med. 2013;368:2159–68.
36. Pugliese F, Babetto C, Alessandri F, Ranieri VM. Prone positioning for ARDS: still misunderstood and misused. J Thorac Dis. 2018;10:S2079–82.
37. Brodie D, Slutsky AS, Combes A. Extracorporeal life support for adults with respiratory failure and related indications: a review. JAMA. 2019;322:557–68.
38. Freeman BD. Tracheostomy update: when and how. Crit Care Clin. 2017;33:311–22.
39. Price S, Singh S, Ledot S, Bianchi P, Hind M, Tavazzi G, Vranckx P. Respiratory management in severe acute respiratory syndrome coronavirus 2 infection. Eur Heart J Acute Cardiovasc Care. 2020;9(3):229–38.
40. Pan F, Ye T, Sun P, et al. Time course of lung changes on chest CT during recovery from 2019 novel coronavirus (COVID-19) pneumonia. Radiology. 2020;295:715–21.
41. Kazory A, Ronco C, McCullough PA. SARS-CoV-2 (COVID-19) and intravascular volume management strategies in the critically ill. Proc (Bayl Univ Med Cent). 2020;0:1–6.
42. Alessandri F, Bilotta F, Ceccarelli G, Ruberto F, Araimo F, Imperiale C, Pugliese F. Clinical management of critical COVID-19 patients: insights from the literature and “on the field”. J Neuroanaesthesiol Crit Care 2020;07(02):54–61.

43. Boukhris M, Hillani A, Moroni F, et al. Cardiovascular implications of the COVID-19 pandemic: a global perspective [published online ahead of print, 2020 May 16]. Can J Cardiol. 2020;36(7):1068–80. https://doi.org/10.1016/j.cjca.2020.05.018.
44. Koratala A, Ronco C, Kazory A. Need for objective assessment of volume status in critically ill patients with COVID-19: the tri-POCUS approach [published online ahead of print, 2020 May 27]. Cardiorenal Med. 2020;10:209–16.
45. Rozental O, Thalappillil R, White RS, Kumar SR, Tam CW. Hemodynamic monitoring options in COVID-19 [published online ahead of print, 2020 May 6]. J Cardiothorac Vasc Anesth. 2020;S1053-0770(20)30409-2.
46. Edelson DP, Sasson C, Chan PS, et al. Interim Guidance for Basic and Advanced Life Support in Adults, Children, and Neonates With Suspected or Confirmed COVID-19: From the Emergency Cardiovascular Care Committee and Get With the Guidelines®-Resuscitation Adult and Pediatric Task Forces of the American Heart Association in Collaboration with the American Academy of Pediatrics, American Association for Respiratory Care, American College of Emergency Physicians, The Society of Critical Care Anesthesiologists, and American Society of Anesthesiologists: Supporting Organizations: American Association of Critical Care Nurses and National EMS Physicians [published online ahead of print, 2020 Apr 9]. Circulation. 2020; https://doi.org/10.1161/CIRCULATIONAHA.120.047463.
47. Shao F, Sun P, Tang Z. Cardiopulmonary resuscitation of inpatients with severe COVID-19 pneumonia: The Wuhan experience [published online ahead of print, 2020 May 11]. Resuscitation. 2020;152:95–6.
48. Ronco C, Reis T, Husain-Syed F. Management of acute kidney injury in patients with COVID-19. Lancet Respir Med. 2020;8(7):738–42.
49. Hirsch JS, Ng JH, Ross DW, Sharma P, Shah HH, Barnett RL, et al. Acute kidney injury in patients hospitalized with COVID-19. Kidney Int. 2020;98(1):209–18.
50. Joly BS, Siguret V, Veyradier A. Understanding pathophysiology of hemostasis disorders in critically ill patients with COVID-19. Intensive Care Med. 2020;46(8):1603–6.
51. Antinori S, Galimberti L, Milazzo L, Ridolfo AL. Bacterial and fungal infections among patients with SARS-CoV-2 pneumonia. Infez Med. 2020;28:29–36.
52. Lai CC, Wang CY, Hsueh PR. Co-infections among patients with COVID-19: the need for combination therapy with non-anti-SARS-CoV-2 agents? [published online ahead of print, 2020 May 23]. J Microbiol Immunol Infect. 2020;S1684-1182(20)30127-4.
53. Lansbury L, Lim B, Baskaran V, Lim WS. Co-infections in people with COVID-19: a systematic review and meta-analysis [published online ahead of print, 2020 May 27]. J Infect. 2020;S0163-4453(20)30323-6.
54. Giacobbe DR, Battaglini D, Ball L, et al. Bloodstream infections in critically ill patients with COVID-19 [published online ahead of print, 2020 Jun 14]. Eur J Clin Investig. 2020;e13319.
55. Ceccarelli G, Alessandri F, d'Ettorre G, et al. Is teicoplanin a complementary treatment option for COVID-19? The question remains [published online ahead of print, 2020 May 23]. Int J Antimicrob Agents. 2020;56:106029.
56. Karampela I, Dalamaga M. Could respiratory fluoroquinolones, levofloxacin and moxifloxacin, prove to be beneficial as an adjunct treatment in COVID-19? [published online ahead of print, 2020 Jun 6]. Arch Med Res. 2020;S0188-4409(20)30924-3.
57. https://www.recoverytrial.net/news/low-cost-dexamethasone-reduces-death-by-up-to-one-third-in-hospitalised-patients-with-severe-respiratory-complications-of-covid-19. Accessed 28 July 2020.
58. Marra A, Buonanno P, Vargas M, et al. How COVID-19 pandemic changed our communication with families: losing nonverbal cues. Crit Care. 2020;24:297.
59. Shen X, Zou X, Zhong X, et al. Psychological stress of ICU nurses in the time of COVID-19. Crit Care. 2020;24(1):200.
60. Vincent JL. Communication in the ICU. Intensive Care Med. 1997;23:1093–8.

Complications of Corona Virus Disease

8

Cristiane Tavares, Rachel Emy Straus Takahashi, and Carlos Viana Poyares Jardim

8.1 Introduction

The coronavirus disease of 2019 (COVID-19), characterized as a pandemic by the World Health Organization in March 2020, has infected over 30.3 million people and caused 948,147 deaths globally, 134,935 of them in Brazil, as of September 18, 2020 [1]. It can lead to severe pulmonary disease, including pneumonia and acute respiratory distress syndrome (ARDS), and many extrapulmonary complications. These include thrombotic events and cardiovascular, neurological, renal, endocrine, hepatic, and gastrointestinal manifestations, as well as musculoskeletal, ocular, and dermatological symptoms [2]. In this chapter, we will overview some of these complications, reported until now, and some treatment-related and possible long-term sequelae.

8.2 COVID-19-Related Pulmonary Complications

Undoubtedly, the foremost feared complication related to COVID-19 is the development of respiratory failure due to lung involvement. Since the beginning of the pandemic, it has been evident that the mortality was directly related to a viral

C. Tavares (✉)
Department of Anesthesiology, Surgical Sciences and Perioperative Medicine, Hospital das Clinicas, University of São Paulo Medical School, Sao Paulo, Brazil

R. E. S. Takahashi
Department and Institute of Psychiatry, Hospital das Clinicas, Faculty of Medicine of University of Sao Paulo, Sao Paulo, Brazil

C. V. P. Jardim
Pulmonary Circulation Unit, Pulmonary Division, Heart Institute, University of São Paulo Medical School, Sao Paulo, Brazil

H. Prabhakar et al. (eds.), *Clinical Synopsis of COVID-19*,
https://doi.org/10.1007/978-981-15-8681-1_8

pneumonia that leads to severe hypoxemia, often requiring invasive mechanical ventilation that is, in many occasions, irresponsive to standard ventilatory strategies. The distinctive acute respiratory distress syndrome (ARDS) related to COVID-19 occurs in roughly up to 20% of hospitalized patients [3].

The first cohorts provided a clinical picture of patients being admitted to the hospital with clinical and radiological features of pneumonia, with somehow rapid deterioration, i.e., with severe hypoxemia in the context of an inflammatory syndrome. From the beginning, a clear pattern of ground-glass opacifications on lung CT scans was evident in most patients, ranging from mild to severe extensions. From the clinical standpoint, patients often presented cough and dyspnea, a clear and unequivocal sign of pulmonary involvement. Patients may present a progressive dyspnea or sudden deterioration of the ability to tolerate exercise, depending on the extension and rate of inflammation that varies from each individual. Cough is usually dry and persistent [4]. We have also learned that those patients with pre-existing lung conditions, such as COPD, or smoking habit are at a higher risk for increased mortality [5].

From pathology case series, lung involvement is characterized by distinctive features both from the epithelial and vascular standpoints. Diffuse alveolar damage and/or hyaline membranes, along with desquamation and/or reactive hyperplasia of pneumocytes, are present in most of 70% of analyzed specimens. On the vascular front, presence of capillary congestion, microthrombi deposition, and alveolar hemorrhage was the most frequent findings. Interstitial and fibrotic findings, such as fibrosis of fibroblast hyperplasia, are also present in roughly 33% of the specimens [6]. Nevertheless, we must consider that most analyses are from autopsies, i.e., neither from mild nor moderate or even severe cases of living patients, since lung biopsies are not used to gauge patient management, providing a possible severity bias for these findings.

From the specific pulmonary circulation standpoint, it is acknowledged that the incidence of venous thromboembolism (VTE) is frequent and higher than expected when compared to other viral syndromes such as influenza infection [7]. However, there are no specific recommendations so far for the use of routine screening or use of full anticoagulation as a routine use in the absence of a definite VTE diagnosis [8]. As it will be discussed further in this chapter, thrombotic complications are rather common in COVID-19, and there is an evolving and exciting field of research in this particular realm.

Finally, the last particular aspect of COVID-19 pulmonary complications may be explored by the mechanical ventilation standpoint. From previous ARDS studies, this condition is defined as a severe hypoxemia with low respiratory system compliance. However, in many COVID-19 ARDS cases, despite the ARDS hypoxemia criterion, lung mechanics is somehow preserved, with patients showing normal or near-normal lung compliance, leading to an interesting discussion on the existence of different COVID-19 phenotypes [9]. For this reason, mechanical ventilation needs special attention from healthcare providers to support patients in the way they need and not necessarily in the way guidelines suggest we should treat the so far "standard" ARDS.

In the lungs, air meets blood. In the context of a rather new clinical condition, we were able to understand in a very short period of time that SARS-CoV-2 damages the lungs in distinctive ways, causing at the same time epithelial and endothelial impairments that in conjunction will be responsible for a great deal of early mortality for COVID-19 patients. We still need more laboratorial, clinical, and pathological data to understand how to support our patients through the most critical phase of the disease.

8.3 COVID-19-Related Extrapulmonary Complications

Direct viral toxicity, endothelial cell damage, immune response impairment, and dysregulation of the renin-angiotensin-aldosterone system seem to be related to these complications [10]. SARS-CoV-2 has a spike protein surface unit with a high binding affinity to the human receptor angiotensin-converting enzyme 2 (ACE2). These receptors are highly expressed in many tissues in humans, such as airway epithelia and lung parenchyma, which may be responsible for the pulmonary manifestations, and also in the cardiovascular tissue, central nervous system, kidney cells, small intestine, and vascular endothelium throughout the body, which account for the many extrapulmonary manifestations of this disease [11].

8.3.1 Hematological

Endothelial cell damage caused by ACE-2-mediated entry of SARS-CoV-2 leads to subsequent inflammation and generates a prothrombotic milieu. Therefore, infection-mediated endothelial injury (with elevated levels of von Willebrand factor) and "endothelialitis" (inflammation of the endothelium, characterized by the presence of activated neutrophils and macrophages) occur in multiple vascular beds. Excessive production of thrombin, diminished fibrinolysis, and activated complement pathways, all lead to thrombo-inflammation, microthrombi deposition, and microvascular dysfunction [12].

Platelet-neutrophil cross-communication and macrophage activation cause an inflammatory response, with release of cytokines, and production of neutrophil extracellular traps (NETs). NETs further damage the endothelium and activate extrinsic and intrinsic coagulation pathways [13]. Hypoxia-mediated hyperviscosity and upregulation of the HIF-1 (hypoxia-inducible factor1) signaling, along with direct coronavirus-mediated effects, cause an imbalance of pro- and anticoagulant pathways [14].

Patients with the severe presentation of COVID-19 have an overactivation of their innate immunity and T cell lymphodepletion, with dysregulation of the immune response and cytokine release syndrome (cytokine storm), characterized by high-grade fever, hypotension, and multi-organ dysfunction [2].

High rates of thrombotic events occur because of hypoxia, inflammation, and direct viral-mediated effects. Besides, the increased expression of ACE2 in

endothelial cells after infection with SARS-CoV-2 may perpetuate this vicious cycle of "endothelialitis," endothelial activation, and microvascular dysfunction [15].

Autopsy studies have shown high rates of microvascular and macrovascular thrombosis, especially in the pulmonary circulation. Thrombosis is found either in arterial or venous sites as well as in invasive catheters or extracorporeal circuits [2].

Other reported hematological complications are immune thrombocytopenia, autoimmune hemolytic anemia, and disseminated intravascular coagulation [16].

8.3.2 Cardiovascular

The pathophysiology of cardiac complications related to COVID-19 is probably multifactorial. ACE2 receptors are hyper-expressed in the cardiovascular tissue, including cardiac myocytes, fibroblasts, and endothelial cells, which points to a direct viral injury. Other possible mechanisms are endothelial cell damage and systemic inflammatory response syndrome with cytokine storm [16].

Acute heart failure may be the initial presentation of the disease in 23% of patients, and cardiomyopathy is present in up to 33% [5]. Many patients seek medical care because of cardiovascular symptoms, from mild chest pain without ejection fraction compromise to severe cardiovascular collapse that may require extracorporeal membrane oxygenation (ECMO). Echocardiography findings vary from regional wall motion abnormalities to global hypokinesis with or without pericardial effusion [17]. Electrocardiogram usually shows low-voltage QRS complexes in the limb leads; ST segment elevations in leads I, II, aVL, and V2–V6; and PR elevation and ST depressions in aVR [17]. It is currently unknown if heart failure is due to a new cardiomyopathy or exacerbation of previously undiagnosed heart failure [18].

Chronic cardiovascular diseases with a reduced cardiac reserve may become unstable in the setting of this viral infection due to an imbalance caused by an increase in metabolic demand [19]. This imbalance, summed to an accentuated inflammatory response and myocardial damage, increases the risk of acute coronary events, heart failure, and arrhythmias [20].

Moreover, acute "cor pulmonale" may occur due to elevated pulmonary vascular pressures secondary to ARDS, pulmonary thromboembolism, or potentially virus-mediated injury to vascular endothelial and smooth muscle tissue [2].

Elevated troponin levels as a sign of myocardial injury occur in 7–17% of hospitalized patients and up to 22–31% of those admitted to the intensive care unit (ICU). Myocardial mononuclear infiltrates leading to myocarditis have been identified on the autopsy of patients with high viral loads. Indeed, one study suggested that up to 7% of COVID-19 related deaths were due to myocarditis [21].

Acute coronary syndromes may be due to severe systemic inflammation and hypercoagulability and should be differentiated from acute myocarditis [18]. Moreover, patients with pre-existing coronary artery disease may develop a supply-demand mismatch in the setting of severe hypoxia and hemodynamic instability, which can lead to myocardial ischemia [2].

Patients can refer palpitations in 7% of cases [22]. Many arrhythmias have been reported, most commonly sinus tachycardia, due to multiple and simultaneous reasons, like fever, hypoxia, anxiety, and hypoperfusion [23]. Hypoxemia can also trigger atrial fibrillation, especially in elderly patients. It can become persistent even after the correction of the pulmonary conditions [20]. Another critical issue is the finding of prolonged QTc (corrected QT > 500 ms), which was reported in 6% of 4250 patients with COVID-19 in a multicenter New York city cohort at the time of admission to the hospital [24]. There is a report of new-onset atrial fibrillation, heart block, and ventricular arrhythmias in up to 17% of hospitalized patients and in 44% of those under intensive care [19].

Even after hospital discharge, we should consider that myocardial injury might result in atrial or ventricular fibrosis, the substrate for subsequent cardiac arrhythmias. Future studies may assess the extent of myocardial scar using magnetic resonance or other methods, in order to identify long-term cardiac complications in patients recovered from COVID-19 [20].

8.3.3 Neurological

A high proportion of patients with SARS-Cov-2 develop neurological symptoms. Data series from Wuhan, China, found neurological abnormalities in 36.4% of hospitalized patients [25]. Many of these manifestations have an early onset, suggesting that direct involvement of the nervous system by the virus is an essential factor.

The physiopathology of neurological injury seems to be heterogeneous and multifactorial. Besides direct viral neuroinvasion, autoimmune factors, inflammation ("cytokine storm"), drug side effects, metabolic disturbances, and critical care neuropathy may be involved [26].

Viral neuroinvasion can occur through the olfactory nerve or by leukocyte migration across the blood-brain barrier, infecting the vascular endothelium. It has also been described transsynaptic transfer between infected neurons [11].

ACE2 receptors are highly expressed in the ventrolateral medulla and the nucleus of the tractus solitarius, both areas involved in respiratory cycle regulation, as well as in the ventricles, olfactory bulb, middle temporal gyrus, posterior cingulate cortex, and substantia nigra [11].

Once the virus establishes in the brain, there is evidence that it can disseminate along some neurotransmitter pathways, such as the serotonergic dorsal raphe system or by hematogenous route, through the Virchow-Robin spaces [27].

Symptoms like headache, anosmia, and ageusia are very common. Other neurological findings are impairment of consciousness, seizures, and stroke [11].

Anosmia is the absence of the sense of smell, whereas ageusia is the loss of taste. Both conditions may occur in isolation or be associated with a structural damage to the nervous system and are more frequent in patients with SARS-CoV-2 compared to other upper airway infections. Recovery is variable but usually occurs after 2 or 3 weeks. Follow-up reassessment will be needed to determine if these symptoms are transient findings or permanent sequelae of SARS-CoV-2 infection [28].

Headache is reported in up to 34% of patients. In most of these cases, it is a non-specific symptom, without features suggestive of meningeal irritation [26]. An observational study with 138 patients with COVID-19 showed that, on admission, 69.6% of patients reported fatigue, 34.8% had myalgia, and 6.5% complained of headache [19]. However, patients with refractory or persistent headache should be investigated for meningoencephalitis and cerebral venous thrombosis [26].

Data from a retrospective study with 214 patients showed 36.4% of nervous system-associated manifestations, divided into three subgroups: central nervous system (CNS), peripheral nervous system, and skeletal-related injury. CNS involvement was present in 53 patients (24.8%), with the report of the following signs and symptoms: dizziness (n = 36; 16.8%), headache (n = 28; 13.1%), impaired consciousness (n = 16; 7.5%), acute cerebrovascular disease (n = 6; 2.8%), ataxia (n = 1; 0.5%), and seizure (n = 1; 0.5%). The definition of impaired consciousness by the authors was very broad, since it included any change in level or content of consciousness [25].

Possible mechanisms are direct viral infection and damage to the cerebral parenchyma, toxic-metabolic encephalopathy, seizures, or even demyelinating disease [11].

There is a case report of a middle-aged female with COVID-19 who presented with cough, fever, and altered mental status and, after 3 days, had the diagnosis of necrotizing hemorrhagic encephalitis. MRI showed hemorrhagic lesions within the bilateral thalami, medial temporal lobes, and sub-insular regions [29]. In another case report, a 24-year-old man initially complained of headaches, generalized fatigue, and fever. Later, he developed generalized seizures and altered mental status that progressed to impaired consciousness. Clinical and laboratory evidence was suggestive of a viral meningoencephalitis, and SARS-CoV-2 was detected in the CSF through an RT-PCR analysis. A brain MRI revealed changes in the right wall of the lateral ventricle, the right mesial temporal lobe, and hippocampus, probably due to meningitis. Interestingly, the nasopharyngeal swab specimen for RT-PCR of this patient was negative for SARS-CoV-2, raising awareness of COVID-19 possible independent mechanisms of neuropathogenesis [30].

Despite postulated mechanisms of neuronal colonization and clinical reports, more robust evidence for the association between COVID-19 and encephalitis is needed [27]. Other possible mechanisms for encephalic compromise are hypoxic injury, toxic-metabolic encephalopathy, and vascular damage to the endothelium [26].

Toxic-metabolic encephalopathy may be triggered by numerous toxic-metabolic derangements, including cytokine storm, severe inflammation, sepsis, and renal dysfunction [11].

As previously mentioned, seizures can also lead to consciousness impairment. Subclinical seizures are reported in up to 10% of patients with critical illnesses. There is a case report of a patient with no history of epilepsy who had multiple apparent tonic-clonic seizures. Indeed, if this patient had no formerly undiagnosed seizure disorder, it may represent a clue to a direct effect of SARS-CoV-2 in the CNS [28].

Experimental models performed in susceptible strains of mice inoculated with the coronavirus JHMV strain resulted in an acute encephalomyelitis followed by a chronic demyelinating disease. Despite evidence showing the persistence of CoV RNA in the nervous system after the acute phase of infection, more clinical research is required to evaluate the risk of developing demyelinating diseases chronically [27].

Acute autoimmune polyneuropathy is also a concern, since it was already postulated to be triggered by other kinds of coronavirus infection. As found in case report publications, most of these patients were observed in a critically ill context. Therefore, critically ill polyneuropathy (CIP), prolonged neuromuscular blockade, vitamin deficiencies, electrolyte disturbances, and drug-related neuromuscular disorders should be included in the differential diagnosis [28].

Guillain-Barré syndrome (GBS) has also been reported as expected, since it occurs in association with many viral diseases. Until now, to our knowledge, 12 cases were described. Some of them required mechanical ventilation, and the interval for the development of the symptoms was around 10 days. Clinical features included paresthesia and progressive, flaccid quadriparesis. CSF study showed albuminocytologic dissociation. The most commonly observed subtype was acute inflammatory demyelinating polyneuropathy, and immunoglobulin was the treatment of choice in all these reports [31].

Strokes have also been reported more frequently, specially in younger patients, which points toward a possible association to COVID-19. Evidence of occlusion of large vessels treated with endovascular therapy was documented in all of them [31].

However, it can be only an association without causality, since both conditions share similar risk factors, such as systemic hypertension, diabetes, and atherosclerosis. Moreover, these patients are more prone to develop hypotension and cardiac arrhythmias, which can potentially lead to hypoperfusion, embolic mechanisms of stroke, and large vessel occlusion [32]. Data from an observational study showed acute cardiac injury in 7.2%, arrhythmia in 16.7%, and shock in 8.7% of 138 hospitalized patients [19]. Another observational study showed an incidence of 23% of heart failure, 20% of septic shock, 19% of coagulopathy, and 17% of acute cardiac injury [5]. All of them are factors that can potentially predispose patients to stroke. Hopefully, future research will discover if there are specific viral factors responsible for hypercoagulability, arteritis, and endothelial dysfunction, which can lead to ischemic stroke or brain bleeding in these patients [27].

Neurological injury caused by SARS-CoV-2 may lead to an impairment in respiratory regulation, with consequent breathing-related sleep disorders. In this scenario, long-term worsening of sleep quality may occur, as well as neurocognitive and neuropsychiatric impairment [33]. Patients can also develop posterior reversible encephalopathy syndrome, which causes headache, confusion, seizures, and visual loss [34].

Psychosis, neurocognitive disorders, and other psychiatric disorders (personality change, catatonia, mania, anxiety or depression, chronic fatigue syndrome, and post-traumatic stress disorder) have also been reported, especially in younger

patients [27]. Although many case reports described neurological complications, it is still unknown whether there is a direct viral damage to the central nervous system or if these complications occur due to secondary mechanisms [11]. Future longitudinal studies with patients recovered from COVID-19 will be needed to understand the natural history of this disease and monitor for potential neurologic sequelae, as well as psychological and psychiatric long-term complications.

8.3.4 Renal

Acute renal dysfunction in COVID-19 was initially reported in about 15% of the patients, with a high mortality rate of 60–90%. Higher rates of acute kidney injury (AKI) were furtherly reported in other studies, like the one in New York City with nearly 5500 patients. They found it in 37% of all patients, and 14% of them required dialysis. It was an early finding since one third were diagnosed within 24 h of admission to the hospital [35]. These rates are much higher compared to those reported during the SARS-CoV epidemic [36].

Hematuria has been reported in nearly 50% and proteinuria in up to 87% of critically ill patients with COVID-19. Hyperkalemia and acidosis are also common, even among patients without AKI [2].

Several possible mechanisms may be related to AKI, including direct viral infection of renal cells, microvascular dysfunction, and cytokine storm. Histopathological findings include lymphocytic "endothelialitis" in the kidney and viral inclusion particles in glomerular capillary endothelial cells [10].

8.3.5 Endocrine

SARS-CoV-2 may directly attack the endocrine glands, causing disorders that worsen prognosis of these patients, but there are still few studies regarding it.

Besides worsening glycemic control in diabetic patients, ongoing data has shown that coronavirus increases the rate of hyperglycemia and ketosis in patients with no previous diagnosis of diabetes. Ketoacidosis coexisting with COVID-19 is particularly hazardous to treat, because of the risk of pulmonary fluid accumulation [37].

Mild pancreatic injury has been reported in 17% of patients in one case series. It was defined as elevated serum amylase or lipase [19]. The possible mechanisms are either a direct viral effect or an exaggerated immune response that occurs in some patients [28].

There is a possibility that SARS-CoV-2 can directly affect thyroid tissue. Therefore, thyroid function should be monitored, especially in patients complaining of neck or ear pain, since thyrotoxicosis can worsen cardiovascular conditions [28, 37].

Adrenal gland aggression has not been reported yet, but it may hypothetically occur due to a thrombotic event. This could lead to an acute adrenal insufficiency with impaired hormone production with refractory hypotension. The prompt

recognition of this condition is necessary to allow adequate replacement therapy in order to avoid shock and impaired reaction to severe respiratory distress [38].

8.3.6 Hepatic and Gastrointestinal

Mild to moderate liver injury, with elevated aminotransferases, hypoproteinemia, and prothrombin time prolongation, has been reported [39]. Differently from SARS, COVID-19 seems to cause hepatotoxicity through direct damage to intrahepatic bile ducts instead of hepatocytes [5].

A study taken in Shanghai Public Health Clinical Center reported abnormal liver function in more than one third of patients. Their degree of hepatic dysfunction had direct correlation with the length of hospitalization [40]. It seems that cholangiocytes (the lining epithelial cells in bile duct) are directly damaged. These cells have a high expression of ACE2 receptors, which determines viral cellular tropism [28].

Abdominal pain, diarrhea, inappetence, nausea, and vomiting are also reported in patients with COVID-19 [41]. Recent bioinformatics analysis showed that ACE2 receptors are also expressed in the upper esophagus, stratified epithelial cells, and absorptive enterocytes from the ileum and colon, which can be an evidence for enteric infectivity [39]. The clinical relevance of the persistence of the virus on stool is not yet defined. It is speculated that it may lead to re-admission of patients that were discharged after the resolution of pulmonary symptoms and possibly a fecal-oral route transmission [42].

8.3.7 Others (Musculoskeletal, Ophthalmological, Dermatological)

Musculoskeletal pain may occur in up to 34% of patients during their illness, and elevated creatinine kinase (CK) levels are present in 14–33%. Rhabdomyolysis has also been reported, with myoglobin levels >12,000 μg/L and CK levels >11,000 U/Ls [19].

Regarding dermatological features, there are many described lesions. These findings are mostly due to diffuse microvascular thrombosis and viral exanthem and may include maculopapular rash, urticaria, vesicular rash, petechia, purpura, chilblains, livedo racemosa, and distal ischemia. The most common is maculopapular eruptions, urticaria, or the acral vasculopathic rashes (pseudo-chilblains, pernio-like lesions) recognized as the "COVID toe." There are also dermatosis treatment-related drug reactions, like the generalized pustular rash due to hydroxychloroquine. Lastly, there is a concern that many pre-existing chronic dermatoses may worsen due to circumstances like stress and delayed or interrupted treatment. Besides, physical and environmental and behavioral issues such as wearing masks and latex gloves, frequent washing, and disinfectants could possibly lead to dermatological complications [43].

Ocular manifestations may resemble a common viral infection of the ocular surface, with conjunctival hyperemia and watery discharge. They were reported in up to 31.6% of patients and more commonly in those with severe disease [44]. SARS-CoV-2 has been isolated from conjunctival swabs in patients with ocular symptoms for as many as 27 days after symptom onset [28].

8.4 Long-Term Complications

- Since COVID-19 was first reported on December 31, 2019, we still don't have much knowledge about its sequelae and long-term outcomes. Complications can be related to the disease itself, the combination of the disease with previous comorbidities that the patients may present, and also the treatment, including the hospitalization, medications, and invasive procedures.
- In the Table 8.1, we list some of the complications directly related to COVID-19 infection and their possible long-term outcomes.
- Subacute cardiac complications are beginning to appear. In a recent cohort study, cardiac involvement was revealed by magnetic resonance in 78%, and ongoing myocardial inflammation was present in 60% of patients that had already recovered from COVID-19 with complete resolution of respiratory symptoms and negative results on a swab test at the end of the isolation period [45].
- The long-term impact of COVID-19 is still under investigation, and little is known about how the immune system recovers after infection. There is compelling evidence of persistent viral shedding in nasopharyngeal secretions and also in stool for more than 2 weeks after resolution of symptoms [46].

Table 8.1 COVID-19 complications

	Clinical manifestations	Possible chronic complications
Pulmonary	Acute pneumonia ARDS Pulmonary embolism	Pulmonary fibrosis Chronic respiratory insufficiency
Hematologic	Arterial thrombotic complications: Acute limb and mesenteric ischemia Venous thrombotic complications: Deep vein thrombosis Catheter-related thrombosis Cytokine release syndrome: High-grade fevers, hypotension, multi-organ dysfunction	Limb amputation Chronic venous insufficiency

(continued)

Table 8.1 (continued)

	Clinical manifestations	Possible chronic complications
Cardiovascular	Myocardial ischemia and myocardial infarction Myocarditis Arrhythmia: Atrial fibrillation and flutter, sinus tachycardia, and bradycardia, QTc prolongation Cardiomyopathy: Biventricular, isolated right or left ventricular dysfunction	Myocardial fibrosis Arrhythmias Chronic cardiac insufficiency
Neurologic	Headache, dizziness Anosmia, ageusia Stroke Encephalopathy, encephalitis, Guillain-Barré syndrome, acute hemorrhagic necrotizing encephalopathy	Chronic anosmia and ageusia Neurologic deficits Posterior reversible encephalopathy syndrome Cognitive impairment Chronic neuropathy Chronic neuropathic and non-neuropathic pain Breathing-sleep disorders
Neuropsychiatric	Altered mental status New-onset psychosis Dementia-like syndrome Affective disorders	Chronic anxiety and affective disorders
Renal	Acute kidney injury Electrolyte abnormalities Proteinuria Hematuria Metabolic acidosis Clotting of extracorporeal circuits used for RRT	Chronic renal insufficiency
Endocrine	Hyperglycemia and ketoacidosis, even in patients without the previous diagnosis of diabetes	Diabetes Other endocrine diseases
Hepatic and gastrointestinal	Nausea and/or vomiting, diarrhea, abdominal pain Elevated hepatic transaminases and bilirubins, low serum albumin	Chronic hepatic insufficiency
General manifestations	Anorexia, myalgias, fatigue	Chronic fatigue and musculoskeletal pain
Ophthalmological	Conjunctivitis	Chronic conjunctivitis
Dermatological	Petechiae, livedo reticularis, erythematous rash, urticaria, vesicles, pernio-like lesions	Chronic dermatosis

- In relation to the interaction between the disease and comorbidities, it is important to emphasize that the most frequent comorbidities are hypertension (55%), coronary artery disease, stroke (32%), and diabetes (31%). Patients with COVID-19 are less likely to have the following chronic illnesses: liver diseases (9%), chronic obstructive pulmonary disease (7%), malignancy (6%), chronic renal failure (4%), gastrointestinal diseases (3%), central nervous system diseases (<1%), and immunodeficiency (1%) [47]. Therefore, survivors requiring prolonged rehabilitation are more likely to be older and to have a pre-existing cardiovascular and cerebrovascular disease, which may influence their rehabilitation and outcomes [34].

8.4.1 Treatment-Related Complications

8.4.1.1 Medications

- Medications under study include antivirals (e.g., remdesivir, ribavirin, lopinavir/ritonavir, favipiravir), antimalarials (e.g., chloroquine, hydroxychloroquine), azithromycin, corticosteroids, and biologics (tocilizumab) [48]. They may interfere with other frequently used drugs, like antihypertensives, antiarrhythmics, anticoagulants, antiplatelets, and statins, causing significant pharmacokinetics and pharmacodynamical interactions.
- Many antiviral drugs can cause cardiac insufficiency, arrhythmia, or other cardiovascular disorders [49]. Remdesivir is a polymerase inhibitor of viral RNA and showed in vitro effect against SARS-CoV-2. However, it may cause neurological and cardiovascular adverse effects that are still under investigation [50]. Lopinavir/ritonavir may cause QT and PR prolongation [51].
- Chloroquine and hydroxychloroquine have been used even without clinical benefit evidence and may be responsible for cardiotoxicity, prolonged QT intervals, and also electrolyte and acid-basic intracellular abnormalities [52]. They can also lower the seizure threshold; cause irritability, peripheral neuropathy, and neuromyopathy, and even be associated with psychosis [11].
- Tocilizumab is a monoclonal antibody to the IL-6 receptor and may attenuate the "cytokine storm." However, it may cause neurological adverse effects, like headache, dizziness, and multifocal cerebral thrombotic microangiopathy [11].
- Osteonecrosis of the femoral head and osteoporosis may be a concern in patients treated with high doses of corticosteroids, since many patients recovered from SARS developed it [53]. Patients using supraphysiological doses of corticosteroids are also more prone to develop metabolic and cardiovascular complications (hypertension, obesity, and diabetes) [54].

8.4.1.2 ICU-Related Complications

Early complications related to ICU admissions are acute respiratory distress syndrome (ARDS) and sepsis, multi-organ failure, acute kidney injury, and cardiac injury [47]. Other important concerns are secondary bacterial and fungal infections.

A recent prospective multicentered study has found an incidence of 27.7% of invasive pulmonary aspergillosis among intubated patients with COVID-19 [55].

- Other complications related to prolonged mechanical ventilation are tracheal stenosis, heterotopic ossification, muscle contractures with associated myofascial pain, adhesive capsulitis, decubitus ulcers, hoarseness, tooth loss, sensorineural hearing loss, tinnitus, brachial plexus injuries, and entrapment neuropathies (peroneal and ulnar) [56]. Since COVID-19 patients have higher rates of thrombotic events, they are more prone to develop catheter-related thrombosis. It can occur in either the arterial or venous catheter and also inside extracorporeal circuits [2].
- Prone positioning (PP) is a supplementary strategy to improve oxygenation in patients with acute respiratory distress (ARDS). It has been used in up to 28% of patients admitted to ICU with COVID-19 [57]. Some related complications are transient desaturation, transient hypotension, accidental extubation, and catheter displacing. Besides increased intracranial and intraocular pressure, compression of nerves and pressure ulcers can occur accordingly to the duration of staying prone. A recent study [58] found pressure ulcer incidence in prone positioning of 14% in the following locations: 5% face and chin, 6% face/cheekbones, 6% thorax, 1% trochanter, and 5% other sites. Pressure ulcers occur due to a pressure applied to a specific area over a period of time. This continued pressure leads to tissue ischemia, in addition to an impairment of nutrition and oxygen supply [59].

8.4.1.3 Post-ICU Discharge Syndrome

- Post-intensive care syndrome is characterized by a reduced pulmonary function (restrictive pattern), diminished inspiratory muscle strength, poor knee extension, reduced upper extremity and grip strength, and low functional capacity. Improvement occurs over a year or more [60].
- Critical illness polyneuropathy (CIP) and critical illness myopathy (CIM) may occur after COVID-19 and cause weakness, loss of function and quality of life, as well as poor endurance that may persist for up to 2 years or longer. CIP is characterized by a generalized and symmetrical weakness due to a mixed sensorimotor neuropathy that leads to axonal degeneration. It can be difficult wean from mechanical ventilation, since diaphragmatic weakness may also be present. Other clinical findings are distal weakness (more significant than proximal) and sensory loss, atrophy, and decreased or absent deep tendon reflexes. The incidence of CIP is dependent on the patient population, diagnostic criteria, and timing of the examination. Long-term sequelae may be pain, loss of range of motion, fatigue, incontinence, dysphagia, anxiety, depression, post-traumatic stress disorder (PTSD), and cognitive impairment [60].
- Critical illness myopathy (CIM) is a non-necrotizing diffuse myopathy with fatty degeneration, fiber atrophy, and fibrosis. It may occur in up to 50% of patients under mechanical ventilation for more than 7 days and is likely to be underdiagnosed because of the lack of early and accurate diagnostic tools, since a muscle

biopsy is necessary for definite diagnosis. The clinical presentation is similar to CIP, but sensory is well preserved, and weakness is more proximally located. The physiopathology of this syndrome includes extended periods of immobilization, sepsis, and exposure to corticosteroids. Cranial nerves and facial muscles are usually preserved in both syndromes, and recovery is faster than from neuropathies. There is no correlation between these features and any residual loss of pulmonary function [61].

8.5 Other Possible Long-Term Complications

- Cognitive impairment is also a concern in critically ill patients. In one study of patients with respiratory failure or shock, after ICU admission, median global cognition scores (measured by a neuropsychological battery of tests) were significantly lower than the age-adjusted population mean. Among these patients, 26% had scored 2 SD below the population mean, similar to scores for patients with mild Alzheimer's disease. Repeated testing after 12 months showed no recovery, raising the concern that cognitive impairment can persist [62]. Indeed, cognitive impairment can be present in 70–100% of patients at discharge; 46–80% still have it 1 year later, and 20% still have it after 5 years. All components of cognition may be affected, including attention, visual-spatial abilities, memory, executive function, and working memory.
- In research regarding ICU admissions for ARDS, many adverse psychological impacts have been reported. Even after 2 years, post-traumatic stress disorder PTSD (22–24%), depression (26–33%), and general anxiety (38–44%) were prevalent [56]. Risk factors were premorbid psychiatric illness, younger age, female sex, unemployment, alcohol use, and greater use of opioid sedation. Family members may also suffer from PTSD, anxiety, and depression, and they may have difficulty managing their new caregiver roles.
- Further research will be needed to assess the impact on the mental health of COVID-19 pandemic for the whole society, related to its socioeconomic effects and the quarantine experience, as well as for healthcare professionals who worked in the front line.

References

1. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis. 2020;20(5):533–4.
2. Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, et al. Extrapulmonary manifestations of COVID-19. Nat Med. 2020;26(7):1017–32.
3. Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ. 2020;369:m1966.

4. Stokes EK, Zambrano LD, Anderson KN, Marder EP, Raz KM, El Burai FS, et al. Coronavirus disease 2019 case surveillance - United States, January 22-May 30, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(24):759–65.
5. 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;395(10229):1054–62.
6. Polak SB, Van Gool IC, Cohen D, von der Thüsen JH, van Paassen J. A systematic review of pathological findings in COVID-19: a pathophysiological timeline and possible mechanisms of disease progression [published online ahead of print, 2020 Jun 22]. Mod Pathol. 2020;1–11. https://doi.org/10.1038/s41379-020-0603-3.
7. Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMP, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res. 2020;191:145–7.
8. Orsi FA, De Paula EV, Santos FO, et al. Guidance on diagnosis, prevention and treatment of thromboembolic complications in COVID-19: a position paper of the Brazilian Society of Thrombosis and Hemostasis and the Thrombosis and Hemostasis Committee of the Brazilian Association of Hematology, Hemotherapy and Cellular Therapy [published online ahead of print, 2020 Jun 13]. Hematol Transfus Cell Ther. 2020;S2531–1379(20)30070–5. https://doi.org/10.1016/j.htct.2020.06.001.
9. 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 Med. 2020;46(6):1099–102.
10. Sanie MS, Rastegarian A, Kalani N, Radmehr M, Mortezaie M. A comparison between pregabalin and melatonin for controlling Extracorporeal Shock Wave Lithotripsy (ESWL) pain. J Res Med Dent Sci. 2017;5(6):101–6.
11. Zubair AS, McAlpine LS, Gardin T, Farhadian S, Kuruvilla DE, Spudich S. Neuropathogenesis and neurologic manifestations of the coronaviruses in the age of coronavirus disease 2019: a review. JAMA Neurol. 2020; https://doi.org/10.1001/jamaneurol.2020.2065.
12. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet. 2020;395(10234):1417–8.
13. Zuo Y, Zuo M, Yalavarthi S, et al. Neutrophil extracellular traps and thrombosis in COVID-19. Preprint. medRxiv. 2020;2020.04.30.20086736. Published 2020. https://doi.org/10.1101/2020.04.30.20086736.
14. Giannis D, Ziogas IA, Gianni P. Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past. J Clin Virol. 2020;127:104362.
15. Poissy J, Goutay J, Caplan M, Parmentier E, Duburcq T, Lassalle F, et al. Pulmonary embolism in patients with COVID-19: awareness of an increased prevalence. Circulation. 2020;142(2):184–6.
16. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708–20.
17. Bangalore S, Sharma A, Slotwiner A, Yatskar L, Harari R, Shah B, et al. ST-segment elevation in patients with Covid-19 - a case series. N Engl J Med. 2020;382(25):2478–80.
18. Long B, Brady WJ, Koyfman A, Gottlieb M. Cardiovascular complications in COVID-19. Am J Emerg Med. 2020;38(7):1504–7.
19. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323:1061–9.
20. Kochi AN, Tagliari AP, Forleo GB, Fassini GM, Tondo C. Cardiac and arrhythmic complications in patients with COVID-19. J Cardiovasc Electrophysiol. 2020;31(5):1003–8.
21. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020;46(5):846–8.

22. Liu K, Fang YY, Deng Y, Liu W, Wang MF, Ma JP, et al. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. Chin Med J. 2020;133(9):1025–31.
23. Driggin E, Madhavan MV, Bikdeli B, Chuich T, Laracy J, Biondi-Zoccai G, et al. Cardiovascular considerations for patients, health care workers, and health systems during the COVID-19 pandemic. J Am Coll Cardiol. 2020;75(18):2352–71.
24. 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;323:2052–9.
25. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol. 2020;77(6):1–9.
26. Munhoz RP, Pedroso JL, Nascimento FA, Almeida SM, Barsottini OGP, Cardoso FEC, et al. Neurological complications in patients with SARS-CoV-2 infection: a systematic review. Arq Neuropsiquiatr. 2020;78(5):290–300.
27. Montalvan V, Lee J, Bueso T, De Toledo J, Rivas K. Neurological manifestations of COVID-19 and other coronavirus infections: a systematic review. Clin Neurol Neurosurg. 2020;194:105921.
28. Gulati A, Pomeranz C, Qamar Z, Thomas S, Frisch D, George G, et al. A comprehensive review of manifestations of novel coronaviruses in the context of deadly COVID-19 global pandemic. Am J Med Sci. 2020;360(1):5–34.
29. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19-associated acute hemorrhagic necrotizing encephalopathy: imaging features. Radiology. 2020;296(2):E119–E20.
30. Moriguchi T, Harii N, Goto J, Harada D, Sugawara H, Takamino J, et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. Int J Infect Dis. 2020;94:55–8.
31. Alberti P, Beretta S, Piatti M, Karantzoulis A, Piatti ML, Santoro P, et al. Guillain-Barré syndrome related to COVID-19 infection. Neurol Neuroimmunol Neuroinflamm. 2020;7(4):e741.
32. Avula A, Nalleballe K, Narula N, Sapozhnikov S, Dandu V, Toom S, et al. COVID-19 presenting as stroke. Brain Behav Immun. 2020;87:115–9.
33. Vitti-Ruela BV, Dokkedal-Silva V, Rosa DS, Tufik S, Andersen ML. Possible sequelae in post-SARS-CoV-2 patients: effects on sleep and general health condition. Sleep Breath 2020.
34. Sheehy LM. Considerations for postacute rehabilitation for survivors of COVID-19. JMIR Public Health Surveill. 2020;6(2):e19462.
35. Hirsch JS, Ng JH, Ross DW, Sharma P, Shah HH, Barnett RL, et al. Acute kidney injury in patients hospitalized with COVID-19. Kidney Int. 2020;98(1):209–18.
36. Chu KH, Tsang WK, Tang CS, Lam MF, Lai FM, To KF, et al. Acute renal impairment in coronavirus-associated severe acute respiratory syndrome. Kidney Int. 2005;67(2):698–705.
37. Marazuela M, Giustina A, Puig-Domingo M. Endocrine and metabolic aspects of the COVID-19 pandemic. Rev Endocr Metab Disord 2020.
38. Bellastella G, Maiorino MI, Esposito K. Endocrine complications of COVID-19: what happens to the thyroid and adrenal glands? J Endocrinol Investig. 2020;43(8):1169–70.
39. Gu J, Han B, Wang J. COVID-19: gastrointestinal manifestations and potential fecal-oral transmission. Gastroenterology. 2020;158(6):1518–9.
40. Fan Z, Chen L, Li J, Cheng X, Yang J, Tian C, et al. Clinical features of COVID-19-related liver functional abnormality. Clin Gastroenterol Hepatol. 2020;18(7):1561–6.
41. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497–506.
42. Wang X, Zhou Y, Jiang N, Zhou Q, Ma WL. Persistence of intestinal SARS-CoV-2 infection in patients with COVID-19 leads to re-admission after pneumonia resolved. Int J Infect Dis. 2020;95:433–5.
43. Seirafianpour F, Sodagar S, Mohammad AP, Panahi P, Mozafarpoor S, Almasi S, et al. sCutaneous manifestations and considerations in COVID-19 pandemic: a systematic review. Dermatol Ther. 2020.
44. Wu P, Duan F, Luo C, Liu Q, Qu X, Liang L, et al. Characteristics of ocular findings of patients with coronavirus disease 2019 (COVID-19) in Hubei Province, China. JAMA Ophthalmol. 2020;138(5):575–8.

45. Puntmann VO, Carerj ML, Wieters I, Fahim M, Arendt C, Hoffmann J, et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). JAMA Cardiol Published online July 27, 2020. https://doi.org/10.1001/jamacardio.2020.3557.
46. Hartman WR, Hess AS, Connor JP. Persistent viral RNA shedding after COVID-19 symptom resolution in older convalescent plasma donors. Transfusion. 2020.
47. Kakodkar P, Kaka N, Baig MN. A comprehensive literature review on the clinical presentation, and management of the pandemic coronavirus disease 2019 (COVID-19). Cureus. 2020;12(4):e7560.
48. Elfiky AA. Anti-HCV, nucleotide inhibitors, repurposing against COVID-19. Life Sci. 2020;248:117477.
49. Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. Nat Rev Cardiol. 2020;17(5):259–60.
50. Davis JS, Ferreira D, Denholm JT, Tong SY. Clinical trials for the prevention and treatment of COVID-19: current state of play. Med J Aust. 2020;213(2):86–93.
51. Chavez S, Long B, Koyfman A, Liang SY. Coronavirus disease (COVID-19): a primer for emergency physicians. Am J Emerg Med. 2020.
52. Tönnesmann E, Kandolf R, Lewalter T. Chloroquine cardiomyopathy - a review of the literature. Immunopharmacol Immunotoxicol. 2013;35(3):434–42.
53. Zhang B, Zhang S. Corticosteroids-induced osteonecrosis in COVID-19: a call for caution. J Bone Miner Res. 2020; https://doi.org/10.1002/jbmr.4136.
54. Almeida MQ, Mendonca BB. Adrenal insufficiency and glucocorticoid use during the COVID-19 pandemic. Clinics (Sao Paulo). 2020;75:e2022.
55. Bartoletti M, Pascale R, Cricca M, Rinaldi M, Maccaro A, Bussini L, et al. Epidemiology of invasive pulmonary aspergillosis among COVID-19 intubated patients: a prospective study. Clin Infect Dis. 2020; https://doi.org/10.1093/cid/ciaa1065.
56. Herridge MS, Moss M, Hough CL, Hopkins RO, Rice TW, Bienvenu OJ, et al. Recovery and outcomes after the acute respiratory distress syndrome (ARDS) in patients and their family caregivers. Intensive Care Med. 2016;42(5):725–38.
57. Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, et al. Covid-19 in critically ill patients in the Seattle region - case series. N Engl J Med. 2020;382(21):2012–22.
58. Lucchini A, Bambi S, Mattiussi E, Elli S, Villa L, Bondi H, et al. Prone position in acute respiratory distress syndrome patients: a retrospective analysis of complications. Dimens Crit Care Nurs. 2020;39(1):39–46.
59. Gebhardt KS. Pressure-ulcer prevention. Part 3. Prevention strategies. Nurs Times. 2002;98(13):37–40.
60. Ohtake PJ, Lee AC, Scott JC, Hinman RS, Ali NA, Hinkson CR, et al. Physical impairments associated with post-intensive care syndrome: systematic review based on the World Health Organization's international classification of functioning, Disability and Health Framework. Phys Ther. 2018;98(8):631–45.
61. Z'Graggen WJ, Tankisi H. Critical illness myopathy. J Clin Neurophysiol. 2020;37(3):200–4.
62. Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, et al. Long-term cognitive impairment after critical illness. N Engl J Med. 2013;369(14):1306–16.

Psychosocial Issues Related to Corona Virus Disease

9

Aman Mahajan and Charu Mahajan

9.1 Introduction

Coronavirus disease 2019 (COVID-19) was declared a pandemic by the World Health Organization (WHO) on March 11, 2020. This is the first time the WHO called an outbreak a pandemic since H1N1 in 2009. The serious health risk which it has posed is nothing which has been seen in the last 100 years since the Spanish flu of 1917. COVID-19 has spread to more than 184 countries. While affecting physical health has been its major issue, the psychosocial perspective is equally important. Due to COVID-19's high mortality rate in comparison to seasonal flu, lack of pharmacological interventions, and easy transmission, various strategies to prevent spread of virus have been implemented [1, 2]. The global mass quarantine of this kind, for an infectious disease, is unique in the history of mankind. With widespread lockdown, social distancing norms, shutdown of schools, work from home orders, people stuck away from their loved ones, and financial crisis; life has been extremely challenging for people of all strata. This has significantly increased the psychosocial burden among people across the globe.

9.1.1 Psychosocial Issues Related to Corona Virus Disease

9.1.1.1 Corona Virus Disease and Effect on General Population

This infectious illness has brought about rapid change in everyday lives. The impositions like shelter in place, stay at home orders, and social distancing have led

A. Mahajan (✉)
Rogers Behavioral Health, Brown Deer, Wisconsin, USA

C. Mahajan
Neuroanaesthesiology and Critical Care, All India Institute of Medical Sciences, New Delhi, Delhi, India

H. Prabhakar et al. (eds.), *Clinical Synopsis of COVID-19*,
https://doi.org/10.1007/978-981-15-8681-1_9

to increased stress. In the initial days, there was an increased anxiety in relation to availability of essential items leading to rationing. This could amount to panic, paranoia, depression, and hoarding. Unknown nature of infection with no available cure and fear of contraction and transmission to loved ones have been a significant source of distress. This has been evident on surveys which noted that about 53.8–33.2% of the respondents had some degree of psychological impact in the initial phase of pandemic [3, 4]. Younger age, female sex, and those with comorbidity were more prone to have increased psychological burden [3].

The loneliness that quarantine and isolation have set in has been tried to be overcome by involving oneself into social networks. The lack of in-person contact with different family members and relatives has been substituted with technology. Vague and improper information through media during early phase of pandemic did rounds all over the world. The coronavirus "infodemic" of misinformation may propagate fear and panic which can spread quite fast causing public health disaster [5]. At the same time, memes to disrupt the precautionary measures by taking disease too lightly can be hazardous. Few people may become paranoid and practice repeated sanitization to the extent of developing obsessive-compulsive disease [6].

Another challenge is that with schools now closed, parents have to provide care to children at home. It is more so ever trying for parents who have to do daily chores in addition to doing official work from home. In this hour of need, parents face dual challenge of balancing and performing the duties and parenting role.

Many people have been infected over these last few months and several have died. While being affected with infection, the need for quarantine and staying away from family has added to the anxiety level. Some of families have been grief stricken to hear about their loved ones passing away and being unable to see them for the last time. The inability to go through the natural mourning process for family members may likely lead to increased adjustment disorders, prolonged grief, and posttraumatic stress disorder.

In addition to all these, economic recession has also hit hard. With millions of people filing for unemployment claims and nearly every other person affected by drop in earnings, the stress level has further increased due to financial crisis. Loss of job can lead to increased depression, anxiety, distress and low self-esteem, substance abuse, and even suicide rate. This can result in inability to pay for housing and increased incidence of homelessness. Financial crisis may lead to increased stress among couples. There has been rise in the frequency of incidents of domestic violence during the quarantine [7, 8]. Social isolation, depression, financial crisis, alcoholism, and lack of social support have led to increase in conflict. Such marital conflicts are extremely bad for the mental health of family as a whole and may result in separation.

Elderly population may be more susceptible than other ages, to develop serious illness if they contract COVID-19 infection. Aging is associated with decreased immunity, chronic illnesses, and comorbidities, making them vulnerable. This can be an immense source of anxiety and stress for them [9]. Due to increased risk of infection, it is more important for them to practice social distancing. This can lead to limited interactions with caregivers, compromised care, and increased feelings of loneliness. The cognitive decline if present may make it challenging for them to

understand the situation and practice protective measures. It was likely for them to be distressed in case of limited supply of essentials or medicines at home during lockdown period. The limited access to medical facilities with strict stay at home order could worsen their ailments. Moreover, being technically unaware of how to put Internet services to a good use is a big disadvantage for elderly people. Being away from their children or losing a close one may lead to exaggerated emotional lability and depression.

9.1.2 Corona Virus Disease and Healthcare Workers

COVID-19 disease has also led to unprecedented psychological stress on frontline health workers. The healthcare workers (HCW) form an especially high-risk group exposed to infection with thousands being infected and sacrificing health to battle this virus. Any pandemic or epidemic illness like COVID-19 or Middle East respiratory syndrome coronavirus (MERS-CoV) imposes a significant level of stress and anxiety on frontline healthcare workers caring for infected individuals. There is risk of contracting infection and in turn transmitting infection to families or close associates. This reinforces importance of providing them with adequate infection prevention and control measures so that anxiety can be allayed to some extent and they are able to work better [10].

The shortage of personal protective equipment for health workers in initial days of pandemic had increased concerns. About 9% of the people affected in Italy are HCW [11]. A lot of frontline healthcare workers have to face worst-case scenarios of being exposed to high viral load of COVID-19 infection, putting them at high risk. They are left with making painstaking decisions leading to urgency of making or reviewing their wills/power of attorney and life insurance policies. With the progressive nature of illness in few cases, this raises concern for foreign healthcare workers in the United States whose family is in native country. The professional responsibilities of working in difficult conditions in hospitals, self-isolating themselves after catering to positive patients, along with concern for one's own health and loved ones, have subjected HCW to significant stress and anxiety. In addition, various HCW have to deal with psychological distress of losing patients. There is further lack of treatment availability and unpredictability of the nature of the virus. It is all more important that organizations are implementing appropriate strategies to support the mental well-being of their staff. The sudden surge of cases is likely to invoke feeling of fear, anxiety, and extreme stress. There is risk of burnout and fear of incompetence due to unpredictability of the disease progression [12]. The exhaustion and fatigue at workplace can stress them immensely compromising their physical and mental well-being. The additional financial burden by curtailment of salaries along with increased workload has placed them in a stressful situation. Few HCW may even develop posttraumatic stress disorder, years after epidemic [13].

There have been incidences of increased marginalization and stigmatization against medical communities. At-risk groups include staff who have to face increased marginalization and victimization with some being blamed even for the

etiology and onset of the infection. Previous research indicates that frontline healthcare staff may experience both self and social stigma [14]. While the HCW have been celebrated as heroes at places, there are several reports of violence against them in various countries [15]. This has been quite disheartening and is a major area of concern and worry.

In addition, the personal responsibilities of HCW still remains the same as any other person, and they are supposed to fulfill them too.

9.1.3 Corona Virus Disease and Children

Children who are wistfully the most vulnerable group need special attention during these times. With closure of schools and playgrounds and social distancing, children have been forced to stay at home. This has led to lack of social support, increased loneliness, isolation, and disruption of social functioning. Parents are facing dual challenge of performing professional duties and balancing it with parenting role. The inability of parents to cope can lead to domino effect on kids. Restrictions like social distancing and closure of schools have made children turn toward electronic media, both for the purpose of learning and entertainment. While it is irreplaceable in day-to-day lives, few exposed ones may become addicted to Internet resulting in difficulty in re-adaptation later, after the crisis is over [16]. The risk of exposure to harmful content, cyberbulling, and online gaming and gambling is the serious harmful effects of screen time. Pre-existing socioeconomic and geographical differences accentuate the digital divide, i.e., educational facilities depend upon Internet connection, speed, and devices. Moreover, less educated and poor parents may be unable to assist their children during online education [17].

It is always difficult to have conversation in relation to public health emergencies like this. This can cause a lot of distress among children and adolescents leading to them asking questions about their own safety and safety of immediate family members. It is all more important that one is providing reassurance and giving accurate information as social media can give mixed information making them more confused. The disturbing news and images on media can have a long-lasting impact on their minds [18]. This has been extremely worrying for children who are concerned for their own as well as loved one's safety.

Small children affected by COVID-19 disease may need institutional care or quarantine, and staying away from family may be unbearable for them. Loss of parents due to illness can lead to kids ending up in foster care and social isolation. Such children may suffer loneliness, intense grief, and adversity. This can significantly impact their sense of security and safety, leading to long-term emotional problems due to failure to resolve the loss of loved one. This can lead to children switching school, living with a different parent, or even working to support their family. Such children are likely to have a posttraumatic stress disorders and development of somatic diseases in later life. The child's natural stress response may become dysregulated in response to extreme stress at a young age. This results in persistent elevation of proinflammatory cytokines and cortisol resulting in development of

somatic disorders. There can be development of diabetes, asthma, decreased immunity leading to recurrent infections, sleep disturbances, cognitive disturbances, and other negative health outcomes [19].

The stress of parents directly affects children. This is an important implication for children of HCW [20]. Financial hardship has badly affected children, causing a possible surge in school dropout. Financial crisis and marital conflicts can increase stress among parents leading to ineffective parenting and risk of physical and emotional abuse of children [21]. This can significantly impact the education of children leading to repeating a grade and getting lower grades, and for high school graduates, it can affect their future prospects. The school and situations have also been affected causing increased stress to children. It had led to postponement of various examinations. All this can lead to increased risk of mental illness and behavioral and psychological problems. Lack of coping skills can lead to increased substance abuse and even self-harm behaviors.

9.2 Signs and Symptoms

Historically Great Depression in the early 1930s was the greatest economic recession of the modern world that was associated with significant increase in depressive symptoms and other mental health problems. As a result, there was an increase in incidence of suicide [22, 23]. Similarly, an increase in rate of depression, anxiety, substance abuse, and posttraumatic stress disorder (PTSD) following natural disasters, such as earthquakes, tsunamis, hurricanes, or floods, has been observed [24].

Viral infections may infect the central nervous system resulting in neuropsychiatric disorders.

Though the exact pathogenesis is not known, the cerebrovascular prothrombotic state, brain hypoxia, inflammation, and immunological response may play a significant role [25]. The social factors may have an added effect on the development of psychiatric consequences.

There are many concerns about the COVID-19 disease that with passage of time will become more clear, and psychological effects are one of these. Other epidemics like polio, HIV, Ebola, MRSA, and SARS were not as widespread as this one, implicating lesser psychosocial impact. Past studies indicate effect of quarantine during SARS 2003 pandemic on mental health resulting in high rates of depression (31.2%) and anxiety (28.9%) [26]. Also, elevated levels of anxiety were observed during the 2009 H1N1 pandemic as well [27]. The stay at home orders and perceived impact of COVID-19 on daily life have been seen to be independently associated with severe psychological outcomes. The implementation of stay at home orders has led to significant social, psychological, and economic impact. This has led to increased anxiety, depression, and PTSD. There were concerns about increased perception of risk for self-harm to one's physical financial and social health resulting in increased anxiety. There are also concerns about increased feelings of loneliness and social isolation. Studies have found association between sex and psychological outcomes [2]. However, there was limited data about the long-term associations.

The psychological impact of quarantine is wide-ranging and substantial and can be long-lasting [28]. The income level was inversely associated with anxiety, loneliness, and financial worries and directly associated with perceived social support. The individuals with lower incomes may be particularly at risk for negative psychological outcomes of COVID-19.

A recent systematic review of 3559 patients admitted to hospital for SARS or MERS studied the psychiatric and neuropsychiatric presentations associated with severe coronavirus infections [25]. These included studies involving patients having SARS-CoV (2068 cases), MERS-CoV (515 cases), and SARS-CoV-2 (976 cases) infection. There was high incidence of depressed mood (32.6%), anxiety (35.7%), impaired memory (34.1%), insomnia (41.9%), impaired concentration (38.2%), and confusion (27.9%). The others include emotional lability, euphoria, aggression, irritability, persecutory ideas, suicidality, and auditory or visual hallucinations. So, while symptoms associated with delirium are common in acute stage, a high incidence of anxiety, fatigue, and posttraumatic stress disorder was seen in post-illness stage of previous coronavirus epidemics. The female sex was found to be significantly associated with development of psychiatric symptoms. However, the long-term psychological effects of coronavirus infection are still unknown. The patients having mild disease have not been studied, and true incidence might be more than what is known. In another systematic review by Luo et al., the prevalence of anxiety and depression was highest among patients with pre-existing conditions and COVID-19 infection (56% [39–73%] and 55% [48–62%], respectively), and it was similar between healthcare workers and the general public [29].

The HCW are likely to suffer psychological burden. It has been seen that medical health workers with an organic disease are more likely to suffer psychological burden like anxiety, depression, insomnia, and OCD [30, 31]. The female HCW, pregnant HCW, and older HCW form a high risk group [32]. The death prospects of sick COVID-19 patients can affect HCW tremendously leading to depression. Fear is common among HCW but still less than general population because of better health literacy [32]. PTSD symptoms usually manifest months after the traumatic experience. Though it may be too early to be evident for COVID-19 pandemic, cases have been proven for other coronavirus diseases.

Psychiatric patients may suffer worsening of their symptoms. People having increased health anxiety can avoid getting medical care due to fear of infection. This may potentially cause further increase risk of getting infected with COVID-19 if they have pre-existing physical health issues [33].

Loades et al. highlighted that children and adolescents are more likely to have high rates of depression and anxiety during periods of social isolation and loneliness [34]. In terms of emotions, it can make one more anxious, depressed, feel guilty and angry, poorly motivated, and feel overwhelmed easily. It's more important to monitor signs of stress as small changes in behavior like increased or decreased energy levels, use of illicit drugs, increased irritability, crying spells, increased anxiety, blaming other people, and anhedonia. The stress can also cause somatic symptoms like stomachache, diarrhea, eating disorders, and headache. It may also lead to

worsening of mental health conditions and chronic health problems [35]. PTSD may be commonly seen in children as well as adults who undergo immense grief and distress. One needs to closely monitor for increased anxiety, intrusive thoughts, sleep disturbances, mood changes, and separation anxiety. This can spiral down to children being depressed, having low self-worth, feeling inadequate, and having poor self-esteem. Children can start blaming themselves for parent's conflict and separation leading to increased feelings of guilt, anger, and low self-esteem. Lack of stable environment at home can significantly impact school performance, concentration, and behaviors. COVID-19 has led to children having increased fear and anxiety about their own health and health of loved ones. This can lead to worsening of mental health conditions and chronic health problems. Moreover relatives or acquaintances infected with COVID-19 are also risk factor for increasing the anxiety of college students [34]. Stay at home and social distancing have led to increase in feeling of loneliness which can lead to increased alcohol use and suicide risk [36, 37]. Suicidal ideation is another major mental health risk among adolescents. While suicide is the tenth leading cause of death overall, it is the second leading cause of death among adolescence ages 12–17. Existing mental illness among adolescents may be exacerbated by social isolation and school closure. Table 9.1 summarizes the common symptoms seen and the risk factors involved.

Table 9.1 Symptoms and risk factors [25, 29–31, 38]

Symptoms	Risk factors
General population	Female sex
Depressed mood	Healthcare worker
Anxiety	Previous chronic physical illness
Fear	Death of relative due to SARS
Insomnia	Lack of psychological preparedness
Impaired concentration	Having high risks of contracting COVID-19
Confusion	Having lower socioeconomic status
Emotional lability	Social isolation
Euphoria	Unsteady family
Aggression	Higher social media exposure
Irritability	
Persecutory ideas	
Suicidality	
Auditory or visual hallucinations	
COVID-19 patients	Chronic illness
Anxiety	Longer period of quarantine
Panic	Lack of adequate information
Mood disorder	
Depression	
Loneliness	
PTSD	

(continued)

Table 9.1 (continued)

Symptoms	Risk factors
HCW Depressed mood Anxiety Fear Insomnia Burnout Obsessive-compulsive symptoms Feeling of stigmatization Increased substance dependence PTSD	Nurses working in front line with direct contact with COVID-19 patients Having organic disease Working in the hardest-hit area Need to be quarantined and away from family
Children Loneliness Anxiety Boredom Irritability Impaired concentration Excessive crying Clinginess Addiction Somatic disorders	Longer periods of quarantine Excessive social media exposure Lack of adequate information Unstable family Loss of a loved one

9.3 Interventions

While the psychosocial impact has been felt all across different places and persons, it has been seen that few factors also protect against greater psychological distress. These include family support, having sufficient local medical resources, having highly efficient health systems and effective prevention and control measures against the epidemic, having up-to-date and accurate health information, and taking precautionary measures (e.g., hand hygiene, wearing masks). Because of lack of pharmacological interventions, public health interventions like social distancing and stay at home orders are important to reduce the spread of infection in the community. This distancing from people can lead to loneliness leading to psychological problems. This highlights the importance of social connection and social support [39]. There is increased risk of adverse mental health outcomes among patients with pre-existing mental disorders. Such patients may need to increase frequency of contact and help from mental health providers. People who have lost their loved ones may need more emotional support. It is important that telemental health services are available to vulnerable individuals in community. There is also need for increased online psychological therapies and self-help programs. Through these people should be encouraged to maintain regular sleep, do physical exercise, remain socially connected, and learn how to manage stress and coping strategies

and prevention of addictions [39]. People should not feel alone, and a telephonic support line can be provided with social networking to allay loneliness [40]. This holds special importance for the quarantined people and the elderly strata. As a society, help should be readily given to those in need while maintaining physical distance. Communication with family members who are staying distant by means of video call can be extremely helpful for allaying isolation. There is increased need for primary care mental health surveillance through routine screening for various mental illnesses and greater availability of services to enable larger number of affected individuals to receive treatment. For people having suicidal ideation, it is important to maintain social connection with them. Telephone-based outreach and caring letter intervention have been seen to reduce the suicide rate. The provision of telemental health treatment should be put in use effectively [41].

Various national healthcare systems of different countries have been pushed to limits. Healthcare professionals are vulnerable to adverse mental health consequences. There is need for increased emotional and physical support and flexible working hours during these times.

Both health professionals and general public are under increased stress and need psychological crisis intervention which may play a very important role to prevent long-term negative mental health consequences. Various mental health organizations have compiled educational articles and videos for general public and mental health professionals to help mitigate the effect of COVID-19 on mental health. A digital support package has been developed in the United Kingdom (UK) which includes evidence-based guidance, support, and signposting relating to psychosocial well-being for UK healthcare employees [41]. It outlines the steps that team leaders can take like providing psychologically safe spaces for staff along with guidance on reducing social stigma and improving peer and family support. It also includes advice from various mental health professionals on learning how to manage emotions and promote self-care [42].

It is of utmost importance to attend children's physical, mental, and emotional well-being. At this time of need, the children and adolescents are looking up to adults on how to respond.

We should provide children with reassurance, make them feel safe, and at the same time gradually build resilience. There is need for educating parents about how to balance work as well as to take care of children at home. Constant media coverage can also lead to increased stress and anxiety. This reinforces importance of facts being reported effectively in the media. Any uncertainty and inaccuracy can lead to feelings of increased anxiety. The parents can provide support by explaining the facts, limiting exposure to news coverage, having regular routine, and being a role model [43]. Prospective longitudinal studies have concluded heightened stress response during and in the immediate aftermath of threatening event can lead to adverse physical and mental health outcomes over time [44]. Intervention programs should be implemented by local government agencies to serve children and their caregivers. These should focus on improving parenting skills, being more understanding and responsive to their needs, protecting them from negative experiences,

assisting them in their problems, and mentoring them. Skill building opportunities and cognitively based compassion training for older children help to build self-esteem, self-efficiency and for their future targets [45].

The WHO Department of Mental Health and Substance have issued a series of messages with an aim to support mental and psychosocial well-being of population [46].

For the general population, the key messages are:

- Stigma should not be attached to people who contract the COVID-19 infection. They should be provided with support and treated with compassion.
- One should minimize watching, reading, or listening to news about disease that makes one feel distressed and anxious. The information should be seeked only from trusted sources which will help to eliminate misinformation and rumors. Getting facts right helps in minimizing fear.
- It is the responsibility to protect oneself but we should also be supportive to others. Solidarity in community can help fight COVID-19 together.
- People who have recovered from the disease can willingly share their experience in the community. Positive news can uplift the morale of the others and minimize fear.
- HCW and others who are supporting COVID-19 patients should be applauded for their effort in saving lives.
- Older adults who are in isolation or quarantine may become more stressed and anxious and experience mood disorders. They should be provided with practical and emotional help by their families and health staff.
- Older adults should be informed of ways to protect themselves from infection in a clear, concise, respectful, and patient way. Family members should help them to practice protective measures.
- Elderly people should have access to medications that they are using for chronic health conditions. Their social contacts should provide assistance if required.
- Physical exercise should be performed at home to maintain mobility.
- Regular schedules should be followed for daily chores and hobbies. Regular contact with family and loved ones is essential.
- Similarly, for the HCW and the managers in health facilities, WHO has issued certain messages as under.
- It is likely to feel under pressure in the current situation, but this does not mean that one is weak. Managing one's mental and psychosocial well-being is as important as managing the physical health.
- Useful coping strategies are sufficient rest and respite during work or between shifts, healthy eating habits, engaging in physical activity, and staying connected with family and friends. Use of tobacco, alcohol, or other drugs should be totally avoided. Any activity that de-stresses one should be used.
- Few HCW may face social stigma due to the fear and misinformation. The best way is to stay connected to your loved ones and share your experiences with your colleagues, manager. or other whom one trusts.

- People with intellectual, cognitive, and psychosocial disabilities may need understandable ways other than written information to make them aware.
- One should provide support to people affected by COVID-19 especially those who require mental or psychosocial support and direct them to available resources. Even health staff and their managers may face stress and need mental support at times. All should be aware where and how to access mental health and psychosocial support services.
- The managers in health facilities should ensure protection of their staff from chronic stress and poor mental health by focusing on long-term occupational capacity.
- Staff should be updated with accurate information, and good quality communication should be ensured. Provide support to workers by rotating them from higher-stress to lower-stress work areas. They should be allowed to work in pairs to feel more stress free and secure. Work breaks and flexible work schedule may be followed for those who are affected by a stressful event. Social support among colleagues should be encouraged.
- All responders, health staff, volunteers, social leaders, and social workers should be able to provide basic emotional support to affected people.
- Urgent neurological and mental health complaints should be managed within emergency or general healthcare facilities and should be adequately staffed.
- All essential psychotropic medications should be made available at all levels of health care.

For the caregivers of children, the important points to remember are:

- We should help children find positive ways to express their emotions, so that they can feel relieved. This can be done in the form of playing, drawing, etc.
- Children should not be separated from their parents and family as far as possible. If, for any reason, child is separated (quarantine, etc.), regular contact by telephonic or video calls with parents should be ensured.
- A routine at home should be followed which should include time for learning, playing, physical exercise, etc.
- Honest and age-appropriate communication about COVID-19 will help to ease their anxiety. Adults should set themselves as mentor and lead by example.

The pandemic has changed the world around us, and time will unfold what holds for us in the future. In the meantime, it is our duty to extend help to each other and maintain solidarity and harmony. Government should earnestly develop prevention and counselling models for the vulnerable section of society. Psychological resilience will help mankind to survive and flourish in future.

References

1. Linton M, Kobayashi T, Yang Y, Hayashi K, Akhmetzhanov AR, Jung S, Yuan B, Kinoshita R, Nishiura H. Incubation period and other epidemiological characteristics of 2019 novel coronavirus infections with right truncation: a statistical analysis of publicly available case data. J Clin Med. 2020;9:538.
2. Tull MT, Edmonds KA, Scamaldo KM, Richmond JR, Rose JP, Gratz KL. Psychological outcomes associated with stay-at-home orders and the perceived impact of COVID-19 on daily life. Psychiatry Res. 2020;289:113098.
3. Wang C, Pan R, Wan X, Tan Y, Xu L, Ho CS, et al. Immediate psychological responses and associated factors during the initial stage of the 2019 coronavirus disease (COVID-19) epidemic among the general population in China. Int J Environ Res Public Health. 2020;17:1729. PMID: 32155789.
4. Varshney M, Parel JT, Raizada N, Sarin SK. Initial psychological impact of COVID-19 and its correlates in Indian community: an online (FEEL-COVID) survey. PLoS One. 2020;15(5):e0233874.
5. Rovetta A, Bhagavathula AS. COVID-19-related web search behaviors and infodemic attitudes in Italy: infodemiological study. JMIR Public Health Surveill. 2020;6(2):e19374. Published 2020 May 5. https://doi.org/10.2196/19374.
6. Li W, Yang Y, Liu ZH, Zhao YJ, Zhang Q, Zhang L, et al. Progression of mental health services during the COVID-19 outbreak in China. Int J Biol Sci. 2020;16:1732–8.
7. Mazza M, Marano G, Lai C, Janiri L, Sani G. Danger in danger: interpersonal violence during COVID-19 quarantine [published online ahead of print, 2020 Apr 30]. Psychiatry Res. 2020;289:113046.
8. Boserup B, McKenney M, Elkbuli A. Alarming trends in US domestic violence during the COVID-19 pandemic [published online ahead of print, 2020 Apr 28]. Am J Emerg Med. 2020; S0735-6757(20)30307-7.
9. Forlenza OV, Stella F; LIM-27 Psychogeriatric Clinic HCFMUSP. Impact of SARS-CoV-2 pandemic on mental health in the elderly: perspective from a psychogeriatric clinic at a tertiary hospital in São Paulo, Brazil [published online ahead of print, 2020 Jun 11]. Int Psychogeriatr. 2020;1–5. https://doi.org/10.1017/S1041610220001180.
10. Temsah M-H, Al-Sohime F, Alamro N, Al-Eyadhy A, Al-Hasan K, Jamal A. The psychological impact of COVID-19 pandemic on healthcare workers in MERS-CoV endemic country. J Infect Public Health. 2020;13(6):877–82.
11. Felice C, Di Tanna GL, Zanus G, Grossi U. Impact of COVID-19 outbreak on healthcare workers in Italy: results from a national E-survey. J Community Health. 2020;45(4):675–83.
12. Willan J, King AJ, et al. Challenges for NHS hospitals during COVID–19 epidemic. BMJ. 2020;368:m1117.
13. Wu P, Fang Y, Guan Z, Fan B, Kong J, Yao Z, et al. The psychological impact of the SARS epidemic on hospital employees in China: exposure, risk, perception, and altruistic acceptance of risk. Can J Psychiatr. 2009;54:302–11.
14. Park JS, et al. Mental health of nurses working at goal meant–designated hospital during a MERS-CoV outbreak cross–section study. Arch Psychiatry Nurs. 2018;32(1):2–6.
15. McKay D, Heisler M, Mishori R, Catton H, Kloiber O. Attacks against health-care personnel must stop, especially as the world fights COVID-19. Lancet. 2020;395(10239):1743–5. https://doi.org/10.1016/S0140-6736(20)31191-0.
16. King DL, Delfabbro PH, Billieux J, Potenza MN. Problematic online gaming and the COVID-19 pandemic [published online ahead of print, 2020 Apr 29]. J Behav Addict. 2020; https://doi.org/10.1556/2006.2020.00016.
17. Dosi G, Fanti L, Virgilito ME. Unequal societies in usual times, unjust societies in pandemic ones. J Ind Bus Econ. 2020;47:1–19. https://doi.org/10.1007/s40812-020-00173-8.

18. Jiao WY, Wang LN, Liu J, et al. Behavioral and emotional disorders in children during the COVID-19 epidemic. J Pediatr. 2020;S0022-3476(20)30336-X. https://doi.org/10.1016/j.jpeds.2020.03.013. Epub ahead of print. PMID: 32248989; PMCID: PMC7127630.
19. Oh DL, Jerman P, Silverio Marques S, et al. Systematic review of pediatric health outcomes associated with childhood adversity. BMC Pediatr. 2018;18:83.
20. Mahajan C, Kapoor I, Prabhakar H. Psychological effects of Corona Virus Disease (COVID 19) on children of health care workers [published online ahead of print, 2020 Jun 1]. Anesth Analg. 2020; https://doi.org/10.1213/ANE.0000000000005034.
21. Green P. Risks to children and young people during covid-19 pandemic. BMJ. 2020;369:m19669. https://doi.org/10.1136/bmj/m1669.
22. Chaves C, Castellanos T, Abrams M, Vazquez C. The impact of economic recessions on depression and individual and social well-being: the case of Spain (2006-2013). Soc Psychiatry Psychiatr Epidemiol. 2018;53:977–86.
23. Tapia Granados JA, Christine PJ, Ionides EL, et al. Cardiovascular risk factors, depression, and alcohol consumption during joblessness and during recessions among young adults in CARDIA. Am J Epidemiol. 2018;187:2339–45.
24. Beaglehole B, Mulder RT, Frampton CM, et al. Psychological distress and psychiatric disorder after natural disasters: systematic review and meta-analysis. Br J Psychiatry. 2018;213:716–22.
25. Rogers JP, et al. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. Lancet Psychiatry. 2020;7(7):611–27.
26. Hawryluck L, Gold WL, Robinson S, Pogorski S, Galea S, Styra R. SARS control and psychological effects of quarantine, Toronto, Canada. Emerg Infect Dis. 2004;10:1206–12.
27. Wheaton MG, Abramovich JS, et al. Psychological predictors of anxiety in response to the H1 N1 (swine flu) Pandemic. Cogn Ther Res. 2012;36:210–8.
28. Brooks SK, et al. The psychological impact of quarantine and how to reduce it: rapid review of the evidence. Lancet. 2020;395(10227):912–20.
29. Luo M, Guo L, Yu M, Jiang W, Wang H. The psychological and mental impact of coronavirus disease 2019 (COVID-19) on medical staff and general public - a systematic review and meta-analysis [published online ahead of print, 2020 Jun 7]. Psychiatry Res. 2020;291:113190. https://doi.org/10.1016/j.psychres.2020.113190.
30. Zhang WR, Wang K, Yin L, et al. Mental health and psychosocial problems of medical health workers during the COVID-19 epidemic in China. Psychother Psychosom. 2020;89(4):242–50. https://doi.org/10.1159/000507639.
31. Vindegaard N, Benros ME. COVID-19 pandemic and mental health consequences: Systematic review of the current evidence [published online ahead of print, 2020 May 30]. Brain Behav Immun. 2020;S0889-1591(20)30954-5. https://doi.org/10.1016/j.bbi.2020.05.048.
32. Salazar de Pablo G, Vaquerizo-Serrano J, Catalan A, et al. Impact of coronavirus syndromes on physical and mental health of health care workers: systematic review and meta-analysis [published online ahead of print, 2020 Jun 25]. J Affect Disord. 2020;275:48–57. https://doi.org/10.1016/j.jad.2020.06.022.
33. Asmundson GJ, Taylor S. How health anxiety influences responses to viral outbreaks like COVID-19: what all decision-makers, health authorities, and health care professionals need to know. J Anxiety Disord. 2020;71:102211. https://doi.org/10.1016/j.janxdis.2020.102211.
34. Loades ME, Chatburn E, Higson-Sweeney N, Reynolds S, Shafran R, Brigden A, Linney C, et al. Rapid systematic review: the impact of social isolation and loneliness on the mental health of children adolescents in context of COVID-19. J Am Acad Child Adolesc Psychiatry. 2020.
35. Cao W, et al. The psychological impact of COVID-19 epidemic on college students in China. Psychiatry Res. 2020;287:112934.
36. Åkerlind I, Hörnquist JO. Loneliness and alcohol abuse: a review of evidences of an interplay. Soc Sci Med. 1992;34:405–14.

37. Calati R, Ferrari C, Brittner M, Oasi O, Olié E, Carvalho AF, Courtet P. Suicidal thoughts and behaviors and social isolation: a narrative review of the literature. J Affect Disord. 2019;245:653–67.
38. Dubey S, Biswas P, Ghosh R, Chatterji S, Dubey MJ, et al. Psychosocial impact of COVID-19. Diabetes Metab Syndr. 2020;14:779–88.
39. Chevance D, Gourion N, Hoertel P-M, Llorca P, Thomas R, Bocher M-R, Moro V, Laprévote H, et al. Ensuring mental health care during SARS-CoV-2 epidemic in France: a narrative review. L'Encéphale. 2020;46(3):193–201.
40. Courtet P, Olié E, Debien C, Vaiva G. Keep socially (but not physically) connected and carry on: preventing suicide in the age of COVID-19. J Clin Psychiatry. 2020;81:20com13370.
41. Reger MA, Stanley IH, Joiner TE. Suicide mortality and coronavirus disease 2019-a perfect storm? JAMA Psychiatry. 2020; https://doi.org/10.1001/jamapsychiatry.2020.1060. Published online April 10, 2020.
42. Blake H, et al. Mitigating the psychological impact of COVID-19 on healthcare workers: a digital learning package. Int J Environ Rest Public Health. 2020;17(9):2997.
43. Dalton L, Rapa E, Stein A. Protecting the psychological health of children through effective communication about COVID-19. Lancet Child Adolesc Health. 2020;4(5):346–7. https://doi.org/10.1016/S2352-4642(20)30097-3. Epub 2020 Mar 31.
44. Garfin DR, Thompson R, Holman EA. Mental and physical health effects of acute stress following traumatic events: a systematic review. J Psychosom Res. 2018;112:107–13.
45. Purewal Boparai SK, Au V, Koita K, et al. Ameliorating the biological impacts of childhood adversity: a review of intervention programs. Child Abuse Negl. 2018;81:82–105.
46. who.int/docs/default-source/coronaviruse/mental-health-considerations.pdf.

Trauma Care and Coronavirus Disease

10

Cedric P. Van Dijck, Abhijit V. Lele, and Rajen Nathwani

10.1 Introduction

The impact of the novel coronavirus (SARS-nCoV-2) on trauma care extends far beyond the direct consequences of an infection in an individual. The presence of this contagious disease in our society presents unprecedented challenges for healthcare systems, impacting the care for trauma patients on a system-wide level. The COVID-19 pandemic demands unseen system-wide measures by healthcare authorities to protect the public from this disease. Societal measures and restrictions change the epidemiology of trauma, prompting trauma care networks to adjust their operation. Ensuring continued access to trauma care aside navigating the local healthcare response to an expanding number of COVID-19 patients demands additional resources and updated standard protocols. On an individual level, all emergent admissions to trauma hospitals are to be considered cases to keep healthcare workers safe. Lastly, a trauma in a patient with COVID-19 can present with unique challenges.

10.2 Epidemiology of Trauma Amidst the COVID-19 Pandemic

The worldwide community spread of COVID-19 in 2020 was met by unprecedented measures to protect the public in many countries. National and regional authorities across the globe implemented directives to limit the spread of the virus. Actions ranging from social distancing to stay-at-home orders profoundly influence daily

C. P. Van Dijck · A. V. Lele (✉) · R. Nathwani
Department of Anesthesiology and Pain Medicine, Harborview Medical Center, University of Washington, Seattle, WA, USA
e-mail: abhijit2@uw.edu

H. Prabhakar et al. (eds.), *Clinical Synopsis of COVID-19*,
https://doi.org/10.1007/978-981-15-8681-1_10

interactions in society. These actions affect the epidemiology of many conditions and societal problems, including injury.

Various states and countries implementing stay-at-home orders saw a significant decline in trauma admissions to major trauma centers during the time the orders were active. The state of Washington implemented stay-at-home orders early March 2020, resulting in a decrease in trauma admissions, without significant changes in trauma severity in the months following this order at Harborview Medical Center, which is the only level 1 pediatric, and adult trauma center in the Pacific Northwest. Admissions increased again with the progressive lessening of societal measures to limit spread, including the lifting of the statewide stay-at-home order at the end of May (Table 10.1: Harborview Medical Center Trauma Census and Injury Severity).

Decreased social interactions result in less road traffic and fewer mass gatherings, ultimately reducing the sheer number of opportunities for an individual to sustain an injury. Many European countries have seen traffic volume decline between 50 and 75% compared to the 5-year monthly average from the years preceding the 2020 COVID-19 pandemic [1]. France and Spain have reported 40–70% fewer fatalities due to road accidents compared to the monthly average for the same months from 2014 to 2019. This observation occurred despite a concurrent increase in speeding offenses caught by automated cameras in the same countries. In the United States, a similar rise in speeding offenses was reported in several states with stay-at-home orders by the Governors Highway Safety Association, an organization assessing the safety of the US highway network [2]. New York City has seen the number of speeding offenses in April caught by automated cameras doubled compared to the year before, despite being one of the epicenters of the US COVID-19 epidemic. Los Angeles has seen a 30% increase in speeding offenses prompting city management to make changes to the timing of pedestrian and traffic signals to improve safety. Minnesota saw an increase in both car crashes and fatalities in April of 2020 compared to the averages in April of 2019. Massachusetts reported doubling of roadside fatalities in April of 2020 compared to 2019, despite a decrease in overall motor vehicle crashes. Nevada and Rhode Island reported an increase in pedestrian deaths

Table 10.1 Harborview Medical Center trauma census and injury severity

	2015–2019	2020	Decline (%)
March counts	482	410	−15
March ISS	11.6	10.6	−8
April counts	466	321	−31
April ISS	11.5	12	+4
May counts	577	526	−9
May ISS	12.1	12.3	+2
Overall counts	1525	1257	−18
Overall ISS	11.7	11.5	−2

Overview of the number of trauma admissions during the months where a stay-at-home order was active in the State of Washington (March 18–May 31) compared to the 5-year average of the preceding years for the same month. *ISS* Injury Severity Score

after being hit by motor vehicles. These data show an overall change in the behavior of motorists due to the societal consequences of the COVID-19 pandemic, leading to altered epidemiology of roadside trauma.

COVID-19 profoundly impacts society, both due to the burden of disease and due to the measures taken by the governments to contain the epidemic within their territory. Many families and individuals see their financial, social, and healthcare situation jeopardized. These increased stressors combined with stay-at-home orders seem to lead to an increase in domestic violence. According to United Nations Women, reports of violence against women and girls have increased parallel to the implementation of statewide lockdown orders in various nations in Asia, Europe, North America, and South America [3]. In the United States, though hard to quantify with only data from a limited time period available, there have been fewer reports of child abuse despite hospitals subjectively reporting increased severity of injuries in children suffering domestic abuse who are being admitted. Authorities closing schools and daycare centers as part of their efforts to reduce the spread of the epidemic should be aware that this limits opportunities for external providers and family members to notice warning signs prompting concerns of child abuse. In many countries taking society-wide measures, such as stay-at-home orders, accessibility of services helping victims of domestic violence may be severely reduced. Healthcare providers involved in primary and/or trauma care should be aware of these changes in the epidemiology of domestic violence and make efforts to prevent and identify cases. Institutional policies may need to be adapted to ascertain the safety of suspected victims of domestic violence with access to safe-houses, psycho-social, judicial, and protective services potentially being more restricted due to lockdown measures taken by local authorities.

With the overall decline in interpersonal contacts seen with national and regional stay-at-home orders, non-domestic interpersonal violence has overall decreased in most countries. However, some countries have reported an increase in violence against healthcare workers, mostly in healthcare systems that have been overwhelmed by COVID-19 patients, thus reducing the availability of immediate care to those seeking it. Hospitals need to be aware of this and may need to adjust staffing and security to avoid escalation of verbal violence to physical violence, potentially leading to injury of essential healthcare workers.

In summary, most regions globally have seen a decline in the trauma census. A reduction in traffic volume has not led to a decrease in fatalities everywhere, as some areas report increased speeding and reckless driving on less busy roads. Lockdown orders have led to an increase in domestic violence in many countries. Trauma hospitals need to be aware of these changes in the epidemiology of trauma resulting from the COVID-19 pandemic, and the different measures authorities have taken to limit the spread of the virus. Staffing and institutional policies may need to be updated to accommodate victims of interpersonal violence with access to support services potentially being more limited.

10.3 Trauma Care During a Pandemic

Trauma management during the pandemic involves adequately treating non-elective patients while minimizing risk and exposure to the healthcare workforce. While trauma numbers and caseload will vary during the pandemic, ultimately, trauma will continue to bring patients into a health system that is already stressed by the rising COVID-19 workload. Given that most Level 1 trauma centers are also the regional referral center for other specialties, often with the largest quota of intensive care unit (ICU) beds, these centers have often become overwhelmed during the COVID-19 pandemic, and it is at times challenging to sustain historical trauma center operations. Staff have needed to be redeployed to care for COVID-19 patients, and non-critical trauma center functions such as trauma outreach and prevention, research activities, administrative meetings, and educational courses have been halted. As such, the Medical Director and Program Manager for the trauma services should be actively involved with hospital planning and development of ICU triage, surge capability and capacity, cross-training of ICU providers, and protection of all hospital staff [4]. Specific data points for critical trauma center functions (e.g., operating room, ICU, emergency department, blood bank, radiology, and surgical availability) should be reviewed daily by the trauma leadership [5]. Triaging of patients to the center with the highest trauma center designation may need periodic re-examination and prioritization of high acuity injuries only, with the diversion of minor trauma at peripheral sites with telemedicine guidance from the major trauma center.

All staff should be trained in the usage of adequate personal protective equipment (PPE) (Levels 1–3 and their respective indications; see Table 10.2). With an increasing demand for PPE, correctly using the appropriate level of protection is essential.

Table 10.2 Levels of PPE with clinical applications (Gong et al. Anesthesia Considerations and Infection Precautions for Trauma and Acute Care Cases During the Coronavirus Disease 2019 Pandemic: Recommendations from a Task Force of the Chinese Society of Anesthesiology. Anesth Analg ePub)

	Level 1	Level 2	Level 3
Work clothing	+	+	+
Fluid resistant gown		+	+
Latex/nitrile gloves	Depending on activity	+	+
Surgical facemask	+		
>95% efficiency particle filter respirator ((K)N95, FFP2 and above)		+	+
Goggles/face shield	Depending on activity	+	+
Application	Low exposure risk clinical work: e.g., imaging technicians	Moderate to high risk of exposure clinical work: e.g., Emergency dept. triage nurse	Aerosolizing procedures: e.g., intubation

Systems should be in place to decontaminate and recycle PPE, such as powered air-purifying respirators (PAPR) and N95 masks. COVID-19-positive patients should be treated to minimize the aerosol spread and fomite production with scrupulous hand hygiene, universal masking in place, and adequate decontamination of areas.

10.3.1 Prehospital Measures

For paramedic and emergency medical services (EMS) responders, given the proximity to patients and other members of the public, all patients should be presumed COVID-19 positive. Therefore, prehospital providers should wear a minimum of Level 2 protection in communities where COVID-19 is prevalent. Screening based on symptoms and examination findings of febrile respiratory illness is not sensitive enough for the diagnosis of COVID-19 in the prehospital setting [6]. Therefore, emergency call takers and dispatchers cannot reliably triage patients into risk categories to minimize PPE use by prehospital providers. If possible, minimizing the number of staff being exposed will reduce PPE usage and decrease risk. In EMS systems that operates a tiered-response system, only the first crew to arrive should enter the scene and assess the need for extra personnel to minimize entry and exposure by other providers. Air medical services should assess the flammability of different types of PPE and introduce procedures to don and doff PPE at appropriate times to minimize fire hazards. Surgical masks should be applied to patients before moving them from a scene to the hospital and where able patients should undertake hand hygiene. Severely hypoxic patients may need to be intubated in the field before transfer (see recommendations below). All equipment used on these patients should either be discarded or appropriately sterilized. EMS crews may be requested to obtain nasal COVID-19 reverse transcriptase-polymerase chain reaction (RT-PCR) swabs in deceased patients to track COVID-19 mortality accurately. While myocardial infarction and stroke admissions seem to have decreased during the acute pandemic stage, it is not clear yet if there is delayed or no self-presentation of certain trauma patients in the emergency department.

10.3.2 Hospital Trauma Bay

Potential COVID-19 patients requiring emergent intubation should follow a strict protocol that ensured that the most experienced airway practitioner instruments the airway. Elective intubation in the ED to minimize exposure during the transportation is often appropriate.

Many institutions' emergency departments have become overwhelmed during the pandemic as the rate of influx of new patients outpaced the ability of the institution to open appropriate beds (general ward, operating room (OR), or the ICU). Overall, managing COVID-19 patients under investigation (PUI) slows down patient movement with an added layer of complexity with all areas of management. Therefore, managing patients expeditiously will avoid the ED from becoming overwhelmed.

10.3.3 COVID-19 Triage/Rule out

To enable adequate precautions and appropriate management within the hospital system, patients need to be triaged as to the likelihood of COVID-19 status as rapidly as possible. Over and under triaging, both pose risks for the patient and the healthcare system. Triage has been managed in different ways depending on community prevalence of COVID-19, healthcare resources, availability, and rapidity of RT-PCR testing and imaging.

Screening can be based on symptoms obtained at the time entry into ED, whereby all patients are asked about exposure to COVID-19 patients, and if they are experiencing fever, cough, shortness of breath, or diarrhea. Any patient screening positive is given a surgical mask, cohort into a separate area, and treated as presumed positive until further testing is done. This, however, may overburden the system as well as miss asymptomatic carriers. Many trauma patients, especially those with severe illnesses and those with neurotrauma, are not able to provide a reliable history.

Triage has been based on whether the patient has a fever >100 F and/or bilateral infiltrates on chest X-ray, in which case they are presumed COVID-19 positive. Lung ultrasound is relatively sensitive for pneumonitis and so, while not specific for COVID-19, has been used in ED to triage patients. Given that most severe trauma patients undergo some form of point of care ultrasound/extended focused assessment with sonography in trauma (FAST) scan, this method could be used. Lung contusions may make this harder and require adequate operator training. Many trauma patients undergo computed tomography (CT) scans, which will cover the thorax. Patchy ground-glass opacities in multiple bilateral pulmonary lobules with peripheral distribution are typical COVID-19 CT chest features, and therefore CT has been used to triage patient COVID-19 status. Caution is warranted; however, as viral pneumonia and aspiration of gastric contents and blood that often occurs in trauma, patients may present with similar radiological findings on CT chest [7]. There are several documented cases of picking up asymptomatic COVID-19 patients in trauma via CT scan [8, 9].

Nasopharyngeal RT-PCR swabs are presumed to be the gold standard for detecting the presence of COVID-19 viral disease, and the availability of testing with rapid turnaround is essential to utilize healthcare resources adequately. However, false-negative rates are significantly high at times, and ideally, RT-PCR should not be used alone, and the clinical and epidemiologic situation should be carefully considered. If the pre-test probability is high, the patient should be treated as COVID-19 positive with further imaging and repeating RT-PCR testing, including testing an endotracheal aspirate in intubated patients. Whenever possible, endotracheal sampling should be preferred over nasopharyngeal sampling [10].

10.3.4 Transport of the Patient

Effective communication and coordination between staff with peer-to-peer sign out and completion of documentation is imperative before any patient movement.

Ideally, hospitals should have designated COVID-19 pathways and elevators for patient transfer.

Non-intubated PUI and COVID-19-positive patients should be transported wearing a surgical mask and should proceed directly to the OR and not via a preoperative holding area. Any staff moving these patients should wear a minimum of Level 2 PPE and should help with patient positioning in the OR before departing from the OR to minimize exposure of further staff and conserve PPE. The handover of the patient should be clear and concise. A doffing of PPE area for transfer staff in the OR suite should be identified, and further PPE supplies (including scrubs) should be available for these non-OR staff.

10.4 Surgical Interventions (Fig. 10.1)

Elective surgeries should ideally be postponed until necessary [11]. This will reduce unnecessary patient traffic in the hospital and decrease the introduction and spread of disease between symptomatic and asymptomatic patients and also the healthcare staff. Also, reducing surgeries allows planning for surge capability, saves resources, including hospital beds and PPE, as well as preserving the health of the surgical team. There is also increasing evidence that COVID-19 patients undergoing general anesthesia are at increased risk of post-op pulmonary complications. The drawbacks of postponing surgeries may lead to more prolonged ICU or hospital length of stays, as out of hospital discharges to skilled nursing facilities, or rehabilitation centers may be dependent on a negative COVID-19 test at the time of anticipated discharge.

Hospital policies and care pathways for managing patients in the operating room with known or suspected COVID-19 infection must be developed, thereby preventing delays in critical operative interventions for unstable patients (see Fig. 10.1). For urgent cases, delay to surgery should not compromise care; cases should preferentially be performed at times of day when staffing and resources are optimal; and after RT-PCR or CT, scan results are available. Patients' symptoms inconsistent with with COVID-19, or no radiologic findings, or have a negative RT-PCR test, should be managed in the OR with standard operating room precautions, thereby preserving resources in COVID-19-negative cases. Anesthesiologists may use N95/FFP2-3 masks in these patients, if available.

Where possible, ORs should be explicitly designated for suspected and confirmed COVID-19 patients. Collocating these rooms away from high traffic areas optimizes patient flow and resource utilization and decreases disease spread. The operating room should conform to negative pressure airflow. The negative pressure system should be turned on half an hour before the patient is moved in. The operation should be performed when the negative pressure reaches −5 kPa or lower. If this is not possible, a high-frequency air exchange (≥25 cycles/h) is preferred. Ideally, these ORs should have their ventilation system with an integrated high-efficiency particulate air (HEPA) filter. Traffic and flow of contaminated air can be minimized by locking all doors to the OR during surgery. There should be only one possible route for entry/exit. Warning signs should be placed outside the OR. PPE should

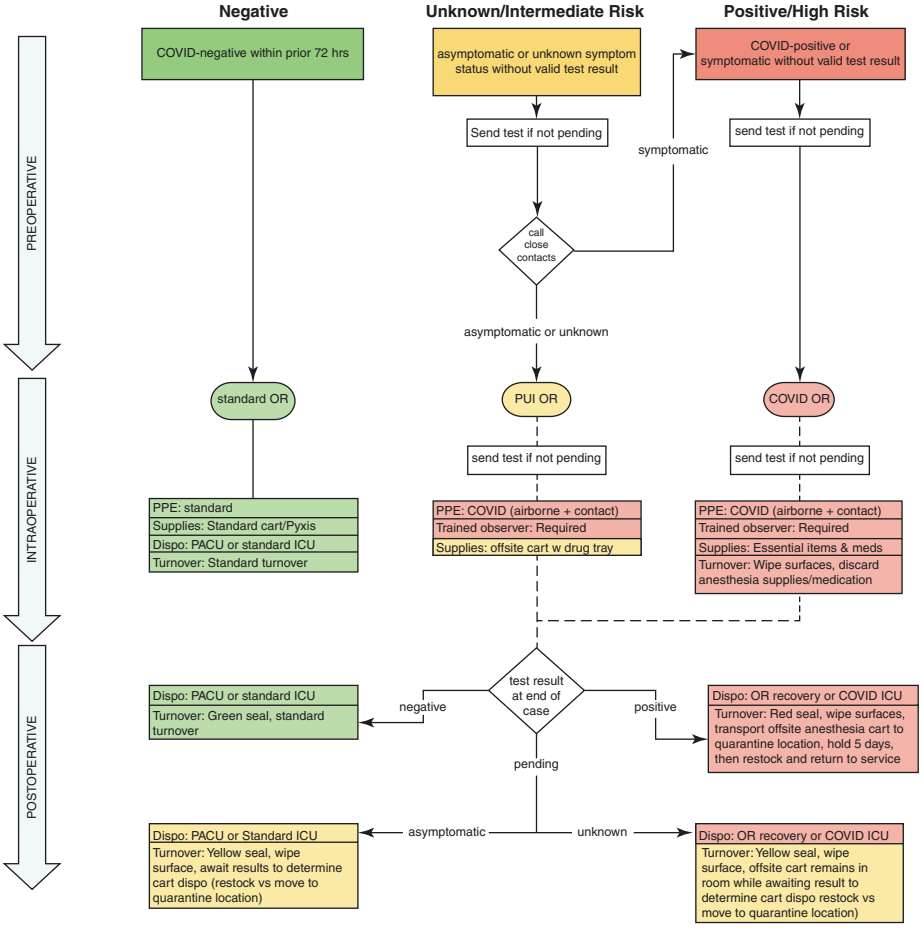


Fig. 10.1 Example of workflow pattern for emergent patients at Harborview Medical Center during the COVID-19 pandemic

be readily available with designated areas for donning/doffing. If an anteroom is not available, a taped off area should be marked for these activities just outside of the OR door. Instructional posters on appropriate procedures should be prominently displayed. Surgical staff should be limited to essential personnel to conserve PPE. One should avoid flux of multiple professionals into the room. Doffing of PPE should be undertaken with the guidance of another person. N95 masks and PAPR hood should undergo specific recycling and storage to conserve PPE.

Deploying senior practitioners where possible may enable more efficient case turnover. The pandemic has required rewriting of practitioner work schedules, and while surgical volume may be decreased, in house and on-call staffing requirements may have increased. A 12-h work shift for staff may reduce PPE usage in certain areas.

Before proceeding with surgery, there should be a huddle between anesthesia, surgical, and nursing/allied health teams. The decision to proceed should be based on a likely risk-benefit ratio. It is preferred that patients proceeding to OR should have consideration to code status and for those with anticipated poor prognosis. "Do Not Resuscitate" status should be considered preoperatively, to limit the possibility of cardiopulmonary resuscitation (CPR) in the OR.

All instruments and supplies having disposable alternatives should be used. Anesthesia carts (with adequate medication stock), ventilators, cautery, laparoscopic towers, tables, and all essential equipment should be limited to use in the designated COVID-19 room. It is reasonable to remove unnecessary devices from the OR before surgery. Personal items such as pagers, phones, and pens should not be brought into the OR. Disposable pens should be provided in the room. All disposables should be discarded at the end of the case. Necessary devices, such as computers, anesthesia machines, and telephones, should be covered with disposable plastic wrap.

A "runner" should remain available by phone to service the room and limit entrance and egress during the case. Equipment and medication exchanges can be performed using a material exchange cart placed immediately outside of the room or in the anteroom or via a dual access port.

Communication, while one is in PPE in the OR, is a challenge, especially as non-verbal communication is lost. Using closed-loop verbal communication and speaking slowly, deliberately, is vital. The use of handheld radios, telephones, and writing down instructions to enable communication with the outside of the OR has all been used.

Minimizing cross-contamination in the OR requires scrupulous practice. Ideally, the hands of the patient should be cleaned before coming to the OR, and the patient adequately sanitized peri-op. Regular hand hygiene with alcohol-based hand gel on gloves is recommended. Areas should be regularly wiped down regularly using a quaternary ammonium compound with alcohol. Closed intravenous systems for drug administration should be the norm. Blood samples of COVID-19 patients should be stored in double bags and labeled with a warning sign of "COVID-19."

It is advisable to limit the number of OR personnel in the room during intubation. Those actively involved with the intubation attempt should wear Level 3 PPE. The patient should be optimally positioned and pre-oxygenated with a well-fitting mask with a good seal and a closed breathing system. Noninvasive ventilation systems and high flow nasal cannulas have variable reports as to their propensity to form aerosols and thus are not recommended for routine intubation. Before induction of anesthesia, a HEPA filter should be connected to the patient end of the breathing circuit. The other of the filter should be connected between the expiratory limb and the anesthetic machine. Equipment should be prepared to reduce the need for circuit disconnections. Disposable equipment should be used where available.

Double gloves should be used routinely during intubation, and the top layer removed following intubation to limit further contamination. To shorten intubation time and maximize the "first-pass success" rate, intubation should be performed by experienced staff.

To enable rapid airway control, a rapid sequence induction should be undertaken. Ideally, the patient should not be bag-mask ventilated to decrease the risk of aerosol formation. However, should the patient be hypoxic, low tidal volume breaths with adequate PEEP are useful. A video laryngoscope is recommended as the first intubation plan because a PAPR hood or goggles may hamper vision during direct laryngoscopy. A video laryngoscope also keeps the intubator farther from the patient's airway during intubation. However, ultimately, the practitioner should use the intubation method they are most familiar with and comfortable with. Severe hypoxia from COVID-19, as well as lung trauma, may require lung-protective ventilation with adequate PEEP, tidal volumes, and plateau pressures. Recruitment maneuvers intraop to minimize atelectasis may be needed.

The patient should be in a deep plane of anesthesia with an adequate neuromuscular block before the intubation attempts to avoid the patient coughing. The cuff of the endotracheal tube should be inflated before attempting ventilation. For any circuit disconnects, the patient should be pre-oxygenated with 100% oxygen, adequately sedated and paralyzed, the anesthetic gas flow stopped, and the circuit is broken on the machine side of the HEPA filter. If required, the endotracheal tube can also be clamped—this may be necessary if the HEPA filter itself needs to be exchanged. The closed system in line suction can be attached to the circuit to avoid circuit disconnects once the patient is intubated.

Use of supraglottic airway devices such as the laryngeal mask airway (LMA) is not advisable as the first line for airway management due to the risk of gas leakage around the LMA. However, this may be the only airway adjunct available in the prehospital care setting. For difficult airways, standard operating guidelines should be followed. However, it should be noted that there is an increased risk of an aerosol generation with awake fiberoptic intubations, and this is not recommended in COVID-19-positive patients.

Which induction agents to use in trauma patients depend on practitioner familiarity as well as the hemodynamic status of the patient. However, while the data is sparse, etomidate may pose an increased risk to COVID-19-positive trauma patients due to the immunosuppressive side effects of etomidate. COVID-19 can cause immune dysfunction and immunosuppression with the potential of severe infection and multi-organ dysfunction syndrome post-trauma [12]. Thus, emergency surgery should follow the principles of damage control. Surgical manipulation should be minimized, and surgical duration should be shortened. If laparoscopic surgery is being performed, a smoke evacuator attached to a HEPA filtration device must be used during and at the end of the case to facilitate the release of pneumoperitoneum. Use smoke evacuators/filtration device in all cases requiring electrocautery, laser, or ultrasonic scalpels, to limit exposure to aerosols. Closed suction systems such as the Neptune system (Stryker Corporation, Michigan, USA) are ideally suited for this.

In suspected or confirmed COVID-19, the choice of anesthetic technique should be based on the patient's overall clinical status, trauma condition, and adapted to the surgical treatment. Regional anesthesia is preferred if it can meet the needs imposed by surgical technique and surgeon preference. Patients receiving regional anesthesia

can use oxygen through a nasal cannula, with a surgical mask on top. Neuraxial techniques may cause translocation of the virus into the central nervous system. Coagulopathy from COVID-19, as well as trauma-induced, should be considered.

SARS-nCoV-2 has the propensity to cause cardiac, renal, and coagulation dysfunction. Therefore, serial perioperative monitoring of cardiac and renal biomarker tests is advisable, and advanced cardiac output monitoring/echocardiography considered in unstable patients. Patients should be maintained in a euvolemic state, mainly to minimize secondary lung and renal injury [13]. Coagulation status should be monitored by regular emergency hemorrhage panels or point of care viscoelastic testing and blood gas analysis intraoperatively in trauma patients.

Extubation can be undertaken in the OR or ICU, depending on resources and time. Essential staff only should be present in the OR during extubation, and level 3 PPE should be utilized for those extubating. A technique targeting smooth emergence with minimal coughing is preferable. When possible, the patient should be recovered in the operating room until they can be transferred to an isolation room on the ward or in the intensive care unit. After extubating, the patient will need to remain in the OR for approximately 30 min to allow adequate air exchanges to occur and make sure the patient is sufficiently recovered from the anesthetic. Nasal prongs for oxygenation of the patient with a surgical face mask on top should be used. Venturi masks and high flow systems should be avoided, given their potential to aerosolize viral particles.

Non-operating room anesthetic areas for COVID-19-positive trauma patients, such as interventional radiology, should ideally be organized in the same way as OR suites.

Terminal cleaning of all surfaces should be performed after each operation, following hospital guidelines. This will typically mean that OR turnaround time is increased and other ORs should be available to continue operating. Human coronaviruses can be efficiently inactivated by surface disinfection procedures with 62–71% ethanol, 0.5% hydrogen peroxide, or 0.1% sodium hypochlorite within 1 min. Surfaces should be wiped down and left to dry [14]. The room can then be sterilized with UV-C for at least 30 min or a hydrogen peroxide vaporizer. If the hospital has the capacity, items such as anesthesia carts can be quarantined for at least 60 h (to ensure natural viral particle breakdown) before reuse. This strategy minimizes waste and enables more equipment and medication to be kept in the OR during the case.

With elective procedures canceled in most hospitals, there is an ever-increasing backlog of surgical cases. Governments, professional bodies, and hospitals are therefore keen to move from a position of curtailment to reopening elective surgery. This, however, requires a low prevalence of SARS-nCoV-2 in the community with easy access to testing and ensuring there are adequate hospital and ICU beds, OR provisions, PPE, trained staff, and other medical supplies. The affect COVID-19 may have on access to safe surgery in low and middle-income countries, and for homeless persons, migrants and refugees are particularly worrisome.

10.4.1 Blood Products

While the cancelation of elective surgery and transplants have decreased blood usage in many areas, community social distancing policies, public fear of donation and disease transmission, and closing of blood donation centers may lead to a decrease in the regional blood availability. Specific blood donation campaigns have been employed to increase public donation during the pandemic, and there is no data to suggest that SARS-nCoV-2 can be transmitted via blood transfusion. Hospital blood stocks should be monitored daily, and restrictive transfusion strategies enforced where appropriate. While cell savers can be used in the OR, this often involves another member of staff being present with the risk and cost that this entails.

10.4.2 ICU

COVID-19 has placed an enormous strain on ICU services worldwide, and therefore ICU capacity, especially for trauma patients, should be monitored daily. The availability of monitors, ventilators, and oxygen supply has often been in critical short supply. COVID-19 positive patients are usually collocated geographically, and so this may often require patients under the trauma service being spread across the hospital site. In hospitals where extra ICU beds have rapidly been increased with urgent up-training of nursing and allied health staff to care for COVID-19 patients, it should be remembered that trauma patients who are also COVID-19 positive will require the most highly skilled nursing staff.

When transferring patients to and from ICU, ideally, hospital transport pathways designated for COVID-19-positive patients should be used. Clear communication and handoff between OR and ICU staff should occur before the movement of the patient. To minimize ventilator circuit disconnects, healthcare worker exposure, PPE usage, and patient movement to and from ICU, medical therapy should be pre-planned, and any imaging or therapy requirements undertaken in a single move.

Trauma patients may return to the OR for multiple surgeries. Therefore, their COVID-19 status based on symptoms and radiological changes should be continuously monitored, and RT-PCR ideally repeated every 72 h until the requirement for surgery has passed. Hospital visitors should be kept to a minimum, and logs should be kept as to which healthcare workers have been in contact with which patients to enable contact tracing should there be a change in positive COVID-19 status.

10.4.3 Rehabilitation and Out-Patient Services

These services have been particularly affected during the SARS-nCoV-2 pandemic, with many services stopping or moving onto telemedicine/online platforms. Every effort should be made to continue this provision as good patient outcomes in trauma are dependent on ongoing rehabilitation, psychiatric, family health, and out-patient services.

10.5 COVID-19 in the Injured Patient

With an essential share of COVID-19 infections occurring asymptomatically, sustaining trauma while being infected with the novel coronavirus is a risk of unknown magnitude.

Publications assessing the risks of trauma and general anesthesia or surgery in infected individuals are mostly lacking. Trauma patients may need emergent surgery for their injuries. Undergoing general anesthesia while being COVID-19 positive may carry the risk of exacerbation of the pulmonary disease. Currently, no substantial evidence on simultaneous COVID-19 and (poly)trauma exists; however, a large case series provided insight into the correlation of emergent surgery in COVID-19-positive patients and postoperative outcomes [4, 15]. This report pooled outcomes from various COVID-19 patients undergoing different elective and emergent procedures in a single database. Though no control group was used, the authors noted a higher number of postoperative respiratory complications (50.1%), as well as higher mortality than what would be reasonably expected for a similar non-infected cohort. About 10% of the cases in this database were trauma patients, but no conclusions were drawn specifically to this population.

Both general anesthesia requiring intubation with mechanical ventilation and direct injury to the airway, chest or lungs, can worsen the existing underlying pulmonary disease. This is no different for patients who may have a subclinical or asymptomatic SARS-nCoV-2 infection. Both blunt and penetrating trauma to the chest can induce inflammatory changes that may exacerbate an underlying viral infection, thus resulting in a higher risk of adverse respiratory outcomes, such as prolonged mechanical ventilation, ventilator-assisted pneumonia, lung injury, or ARDS. Currently, no evidence suggests trauma patients with COVID-19 benefit from a mechanical ventilation strategy that is different than for non-trauma patients with COVID-19. Trauma may limit clinicians in treatment options for COVID-19 patients. For instance, injury to the spine may preclude the possibility of elevating the head of the bed or placing the patient in a prone position. Patients with chest trauma may have a more limited reserve and require intubation earlier on. Hypoxia and hypercarbia may be less tolerated in patients with significant injury or resulting systemic inflammation. Permissive hypercapnia may not be feasible in a patient with metabolic acidosis following systemic inflammation after polytrauma. Efforts should be made to optimize homeostasis in trauma patients with COVID-19: Increasing hypercarbia worsens acidosis, contributing to systemic inflammation, coagulation, and enzymatic dysfunction and decreased effectiveness of catecholamines.

A more proactive approach to diagnose complications in critically ill trauma patients with COVID-19 is warranted. The threshold to admit COVID-19 patients with concomitant (poly)trauma should be lower than for trauma patients without significant comorbidities, especially in patients with systemic inflammation, chest trauma, or lung injury.

Conflicting reports have been published on the incidence of venous thromboembolism in patients hospitalized with COVID-19. Some institutions have

liberalized their recommendations for venous thromboembolism (VTE) prophylaxis for COVID-19 patients in comparison to non-COVID-19 patients [16, 17]. Other ICUs have started screening patients using ultrasound or have increased their screening frequency. Orthopedic trauma with subsequent immobilization and systemic inflammation both contribute to the risk of developing deep venous thrombi. Trauma patients may be at increased risk of bleeding, or they may have an injury where bleeding significantly increases the risk for an adverse outcome, such as traumatic brain injury patients. Currently, there is too little evidence to support altering the dosing regimen of VTE prophylaxis in inpatients as well as in outpatients who require immobilization for orthopedic injuries. Due to the low risk associated with increased screening efforts, heightened vigilance for the development of VTE in hospitalized trauma patients with concomitant COVID-19 infection may be warranted. Many health systems have standardized the use of tranexamic acid in hemorrhaging trauma patients. The administration of this product may pose a higher risk of thrombo-embolic events in COVID-19 trauma patients due to the possible pro-thrombotic state associated with this disease. With the lack of evidence surrounding tranexamic acid use in COVID-19 trauma patients, the decision to use tranexamic acid in severe trauma should be made on a case by case basis. The use of perioperative sequential compression devices (SCD) is advisable if there are no other contraindications.

Multiple reports describe processes of microthrombosis, intrapulmonary hemorrhage, or diffuse intravascular coagulation to be involved in the COVID-19 pathophysiology [7, 18]. Severe injury leads to activation and, ultimately, depletion of coagulation factors. Increased vigilance over the performance of the patients' coagulative function is to be recommended in polytraumatized patients or patients who receive multiple transfusions for trauma while being infected with SARS-nCoV-2. The viral illness may lead to the consumption of coagulation factors beyond the time of achieving surgical and biochemical hemorrhage control for the patients' injury, translating into a need for a more extended period of vigilance over the patients' coagulation parameters than would be otherwise expected for an injured patient.

Patients who leave the hospital after prolonged ICU stays recovering from COVID-19 have decreased strength, balance, and increased osteopenia. This puts patients at risk of more severe injury with falls and minor trauma. Providers involved in the discharge of these patients should educate patients about the implications of prolonged hospitalization and make efforts to prevent injuries during the rehabilitation phase. Physical therapy can help reduce fall risk, increase stability and muscle strength, and reduce osteopenia.

10.6 Conclusion

The 2020 COVID-19 pandemic affects many facets of society and healthcare provision, including the care available to trauma patients. Hospitals and providers should make efforts to anticipate the altered epidemiology of trauma that results mostly from societal measures to limit the spread of the virus.

The presence of a pandemic poses specific challenges to healthcare systems necessitating adaptation of routines and protocols to protect healthcare workers and contain viral spread within healthcare facilities. Separating patient flows upon hospital admissions, even for urgent admissions, is of utmost importance. This implies changes are needed to routine workflow in every phase of care, from the prehospital to the hospital phase and to discharge.

Healthcare providers involved in the care of trauma patients should be educated on the pathophysiology of COVID-19 and potential complex interactions on various organ systems. Some pathophysiological processes associated with SARS-nCoV-2 may increase the disease burden of trauma in (poly)traumatized patients.

More research and more data are needed to draw conclusions on the epidemiology of trauma, the interplay of COVID-19, and pathophysiologic processes in the traumatized patient and to design optimal guidelines for preparing the healthcare system to deal with different patient flows as well as for direct patient care.

10.7 Summary Points

- The number of trauma patients presenting to the hospital has been affected by the COVID-19 pandemic.
- Trauma services should presume that all patients are positive for SARS-nCoV-2 until they have been adequately triaged.
- Triage is based on patient symptoms, radiology, and RT-PCR testing.
- COVID-19 is a multisystem disorder and may exacerbate the effects of polytrauma.
- Renal and cardiac dysfunction should be monitored perioperatively.
- Hypoxia and hypercarbia may not be well tolerated in acidotic trauma patients.
- COVID-19 patients may be at risk of pro-thrombotic complications.

References

1. European Transportation Safety Council, Brussels, Belgium: COVID-19: Huge drop in traffic in Europe, but impact on road deaths unclear. ePub 7 April 2020.
2. Governors Highway Safety Association, Washington District of Columbia, United States of America: Traffic Safety Community Urges Safer Driving During Coronavirus Pandemic. ePub 16 April 2020.
3. United Nations Women, New York City, United States of America. COVID-19 and ending violence against women and girls. ePub May 2020.
4. American College of Surgeons Committee on Trauma. Maintaining trauma center access and care during the COVID-19 pandemic: guidance document for trauma directors. https://www.facs.org/quality-programs/trauma/maintaining-access. Accessed on 20.09.2020.
5. Bank M, O'Neill P, Prince J, Simon R, Teperman S, Winchell R. Early report from the Greater New York Chapter of the American College of Surgeons Committee on Trauma on the COVID-19 crisis. https://www.facs.org/-/media/files/covid19/nyc_chapter_acs_cot_covid19_crisis.ashx. Accessed on 20.09.2020.

6. Yang B, Barnard L, Emert J, Drucker C, Schwarz L, Counts C, et al. Clinical characteristics of patients with coronavirus disease 2019 (COVID-19) receiving emergency medical services in King County, Washington. JAMA Netw Open. 2020;3(7):e2014549.
7. Zarei F, Reza J, Sefidbakht S, Iranpour P, Haghighi R. Aspiration pneumonia or COVID-19 infection: a diagnostic challenge. Acad Radiol. 2020;27(7):P1046.
8. Oran DP, Topol EJ. Prevalence of asymptomatic SARS-CoV-2 Infection; a narrative review. Ann Intern Med. 2020; https://doi.org/10.7326/M20-3012.
9. Samsami M, Bagherpour J, Nematihonar B, Tahmasbi H. COVID-19 pneumonia in asymptomatic trauma patients; report of 8 cases. Arch Acad Emerg Med. 2020;8(1):e46.
10. https://www.covid19treatmentguidelines.nih.gov/critical-care/laboratory-diagnosis.
11. Coimbra R, Edwards S, Kurihara H, Bass GA, Balogh Z, Tilsed J. European Society of Trauma and Emergency Surgery (ESTES) recommendations for trauma and emergency surgery preparation during times of COVID-19 infection. Eur J Trauma Emerg Surg. 2020;17:1–6.
12. Zaim S, Chong J, Sankaranarayanam V, Harky A. COVID-19 and multiorgan response. Curr Probl Cardiol. 2020;00:100618.
13. Gong Y, Cao X, Mei W, Wang J, Shen L, Wang S, et al. Anesthesia considerations and infection precautions for trauma and acute care cases during the coronavirus disease 2019 pandemic: recommendations from a Task Force of the Chinese Society of Anesthesiology. Anesth Analg. 2020;131(2):326–34.
14. Dexter F, Parra M, Brown J, Loftus R. Perioperative COVID-19 defense: an evidence based approach for optimization of infection control and operating room management. Anesth Analg. 2020;131(7):37–42.
15. COVIDSurg Collaborators. Mortality and pulmonary complications in patients undergoing surgery with perioperative SARS-CoV-2 infection: an international cohort study. Lancet. 2020;396(10243):27–38.
16. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(2020):497–506.
17. Maldonado E, Tao D, Mackey K. Antithrombotic strategies in COVID-19 disease: a systematic review. J Gen Intern Med. 2020;17:1–9. ePub ahead of print.
18. Abou-Ismail MY, Diamond A, Kapoor S, Arafah Y, Nayak L. The hypercoagulable state in COVID-19: incidence, pathophysiology and management. Thromb Res. 2020;194:101–15.

Pregnant Patients and COVID-19

11

Vibha Mahendra and Shobana Murugan

11.1 Introduction

Management of COVID-19 disease in pregnancy poses unique challenges, as it requires consideration of maternal physiologic changes, fetal and placental physiology, and a multidisciplinary approach to decision-making, particularly in patients with severe or critical disease. Though the majority of pregnant patients who test positive for SARS-CoV-2 remain asymptomatic or have mild disease and recover without undergoing delivery [1], a significant number develop critical illness and may have prolonged and complex disease courses [2].

The prevalence of SARS-CoV-2 infection in pregnant women approximates the overall population prevalence. Based on data from the H1N1 influenza and SARS pandemics during which pregnant women were at a higher risk of infection and had worse clinical outcomes [3, 4], it was anticipated that parturients during the SARS-CoV-2 outbreak would follow similar patterns.

Current studies, however, have found that pregnant women have similar rates of infection with SARS-CoV-2 and clinical courses and outcomes when compared with reproductive-aged non-pregnant women [5, 6]. In a systematic review of 538 pregnancies from China, Italy, and the United States, 15% of patients met criteria for severe disease, and only 1.4% were considered critical. This is in contrast to the SARS, H1N1, and MERS pandemics, during which pregnant women suffered disproportionately from critical respiratory disease and mortality [4, 7].

V. Mahendra
University of Southern California, Keck School of Medicine, Los Angeles, CA, USA

S. Murugan (✉)
University of Texas Medical Branch Health, Galveston, TX, USA

H. Prabhakar et al. (eds.), *Clinical Synopsis of COVID-19*,
https://doi.org/10.1007/978-981-15-8681-1_11

11.2 Background

11.2.1 Epidemiology in the Obstetric Population

Since April 2020, universal SARS-Cov-2 testing of pregnant women and their companions has been widely implemented [8] in obstetric clinics, triage, and labor and delivery in many hospitals in the United States and has aided in recognizing symptomatic as well as asymptomatic carriers. In one New York hospital at the peak of the pandemic, 15% of asymptomatic maternity patients tested positive for SARS-CoV-2 infection despite having screened negative with a telephone screening tool, and 58% of their asymptomatic, screen-negative support persons also tested positive for SARS-CoV-2 infection [9].

Prevalence differs between endemic regions and non-endemic regions. A second hospital in New York City reported a 13.5% prevalence of asymptomatic infection in women presenting for childbirth [8]. In comparison, the prevalence of positive SARS-CoV-2 test results among asymptomatic patients was much lower (<3%) in a pregnant population outside of the highly endemic region of New York City [10].

No large population studies exist on maternal mortality related to COVID-19 disease, but several maternal deaths from cardiopulmonary complications and multiorgan failure have been reported, often in women with no underlying medical conditions [11–13]. There is no evidence, however, that the maternal mortality rate is higher than that of the general population.

11.2.2 Patient Characteristics

Pregnant patients with symptoms of SARS-CoV-2 are most commonly (65%) infected in the third trimester [5, 14–17]. In a review of 195 parturients from China, Italy, and the United States, 66% of these women delivered at or after 37 + 0 weeks gestational age (wga), 26% delivered between 28 + 0 and 36 + 6 wga, and only 9% delivered earlier than 28 + 0 wga [18]. The average time to delivery after onset of severe or critical COVID-19 disease was 13 days [14, 19].

As of July 2020, maternal fatality rates remain low but may be underreported. Risk factors for development of respiratory and multiorgan failure are yet to be determined, but it has been suggested that increased pregestational BMI, abnormal heart and respiratory rates on admission, and underlying cardiopulmonary comorbidities are associated with severe disease [16].

11.3 COVID-19 Disease Manifestations in Pregnancy

The most common clinical manifestations of COVID-19 disease in pregnancy are fever and cough (>65%) and less often dyspnea, sore throat, and myalgia (<10%). Laboratory findings include a modest increase in liver enzymes, lymphopenia, and thrombocytopenia [20]. Severe or critical COVID-19 disease in pregnancy typically

Table 11.1 NIH classification system for disease severity [21]

Asymptomatic	Mild	Moderate	Severe	Critical
+ SARS-CoV-2 test, no symptoms	Any signs or symptoms (fever, cough, malaise, headache, myalgia, sore throat) without shortness of breath or abnormal chest imaging	Evidence of lower respiratory disease by clinical assessment or imaging and a saturation of oxygen (SaO_2) >93% on room air at sea level	Respiratory frequency > 30 breaths per minute, $SaO_2 \leq 93\%$ on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300, or lung infiltrates >50%	Respiratory failure, septic shock, and/or multiple organ dysfunction

begins with the onset of hypoxemic respiratory failure followed by acute respiratory distress syndrome (ARDS) and may progress to multiorgan dysfunction; most commonly this includes renal failure, thromboembolic disease, cardiovascular complications, inflammatory complications, secondary infections, and neurologic sequelae.

Disease severity in pregnancy is determined according to the same NIH classification system used in non-pregnant individuals. Disease severity categories are asymptomatic, mild, moderate, severe, and critical (see Table 11.1) [21].

The American College of Obstetricians and Gynecologists (ACOG) supports the use of telehealth platforms whenever possible to reduce patient and physician exposures while providing pregnancy care, particularly in patients with uncomplicated pregnancies. Telehealth interventions including remote antenatal blood pressure and glucose monitoring, symptom monitoring, and SMS/text messaging, among other interventions, have been shown to be non-inferior when compared to in-person visits in low-risk populations [22]. In-person visits should be reserved for high-risk patients and those for whom face-to-face evaluation is required per obstetric and maternal fetal medicine guidelines.

In accordance with guidelines from the Society for Maternal-Fetal Medicine, pregnant women with mild COVID-19 disease plus comorbidities (particularly any cardiopulmonary pathology) should be observed in a medical facility, and those with moderate to critical disease should be hospitalized. Pregnant women with severe to critical disease should be cared for at a high-acuity hospital with an intensive care unit, as well as obstetric and neonatal care teams [23].

11.4 Management of COVID-19 Disease in Pregnancy

11.4.1 Maternal Hemodynamic Goals

Uteroplacental blood flow increases from 50 mL/min up to 1 L/min or more at term, is not autoregulated, and depends on maintenance of maternal mean arterial pressure (MAP) ≥ 65 mmHg. Strategies to maintain adequate MAP include judicious volume resuscitation, vasopressor support, and left uterine displacement to relieve aortocaval compression.

11.4.2 Vasopressor Choice in Pregnancy

Commonly used vasopressors in pregnancy are phenylephrine, ephedrine, and norepinephrine. Norepinephrine, the vasopressor of choice in septic shock, has gained favor in obstetric management, particularly in the setting of hypotension during cesarean delivery [24]. Norepinephrine's safety profile is well established in pregnancy, but FHR monitoring should be considered if there is concern over uteroplacental perfusion. Phenylephrine and ephedrine can be used safely in pregnancy but have limited potency in critical illness. Epinephrine and dopamine are more arrhythmogenic than norepinephrine, but they, along with dobutamine, may also be used safely during pregnancy, as determined by the overall clinical status.

Vasopressin is structurally similar to oxytocin and may result in activation of uterine V1A and oxytocin receptors [25]. It should be used with extreme caution and in conjunction with uterine tocodynamometry and FHR monitoring due to the risk of inducing uterine contractions.

11.4.3 ARDS Management in Pregnancy

ARDS management principles must be adapted to accommodate the physiologic changes of pregnancy. Hypoxia and acidosis are poorly tolerated by both mother and fetus; even healthy parturients can tolerate only brief periods of hypoxia due to pregnancy-associated diaphragmatic elevation up to 4 cm, decreased functional residual capacity (FRC), increased oxygen consumption, and susceptibility to pulmonary edema. Maternal PaO_2 is elevated at 100–105 mmHg due to increased alveolar ventilation, and maternal SpO_2 must remain >95% ($PaO_2 > 70$ mmHg) to ensure sufficient fetal oxygenation.

Early treatment for hypoxia is recommended. Noninvasive options include HFNC and prone positioning (self-proning in less severe disease), but the risks of aspiration, aerosolization of viral particles, and compression of the gravid abdomen should be considered. Proning in pregnancy is challenging but, if done correctly, is highly effective at reducing diaphragmatic and aortocaval compression. Special considerations include NPO status and avoiding compression of the gravid abdomen with pillows, padding, or a RotoProne® (or similar) bed. Right or left lateral displacement are also safe positions in pregnancy; a minimum lateral tilt between 30° and 45° is needed to achieve an appreciable increase in caval diameter [26].

Intubation and mechanical ventilation are reserved for critical cases of hypoxemic respiratory failure. Application of high positive end expiratory pressure (PEEP) should be used cautiously in pregnant women, as the reduction in preload and cardiac output may be detrimental to uteroplacental flow. Neuromuscular blockade with cisatracurium is safe in pregnancy and should be considered in patients with PaO_2/FiO_2 ratio < 150. Inhaled nitric oxide (iNO), a selective pulmonary vasodilator, may be used if the potential benefit to the mother outweighs the risks to the fetus.

Increased minute ventilation in normal pregnancy creates a respiratory alkalosis ($PaCO_2$ of 27–32 mmHg), compensated by a reduction in serum bicarbonate to approximately 20 meq/L. This reduction in total buffering capacity decreases the parturient's ability to tolerate acidosis [27]. Hypercapnia creates an unfavorable transplacental CO_2 gradient for removal of fetal metabolic waste, causing fetal acidemia. Therefore, permissive hypercapnia, a strategy to limit tidal volumes and reduce lung injury in ARDS, should be used cautiously in pregnancy, and maternal $PaCO_2$ should be kept well below 60 mmHg. Due to decreased chest wall compliance during pregnancy, plateau pressures $\leq$35 cm H_2O may be tolerated. Excessive hyperventilation and alkalosis should also be avoided, as hypocarbia results in uterine artery vasoconstriction and reduction of uteroplacental blood flow.

11.4.4 Extracorporeal Life Support (ECLS)/Extracorporeal Membrane Oxygenator (ECMO)

The use of ECMO for refractory ARDS during the SARS-CoV-2 pandemic is based on data from prior global pandemics that showed improvements in mortality in young patients afflicted with severe pulmonary disease [28, 29]. Pregnant women with critical COVID-19 disease represent an ideal group of patients who may benefit from ECLS due to their relative youth and lack of comorbidities when compared to the general population.

ARDS is the most common indication for initiation of ECLS in pregnancy [30]. Parturients on ECMO for ARDS demonstrate a survival rate of 80% (more favorable than the general population, with similar rates of complications), while fetal survival is approximately 65%. Maternal risk of complications such as bleeding and neurologic morbidity (hemiparesis, limb weakness) should be considered when initiating ECLS.

11.4.5 Thromboembolic Disease

The elevated risk of venous thromboembolism during normal pregnancy places parturients with COVID-19 disease at an even higher risk of thromboembolic complications. Generally in pregnancy, low-molecular-weight heparin (LMWH) is preferred over unfractionated heparin (UFH) [31]. However, due to its short half-life and reversibility with protamine sulfate, UFH is favored in severe or critically ill parturients, as they are at greater risk for unpredictable delivery timing and neuraxial placement, as well as postpartum hemorrhage [32]. UFH and LWMH do not cross the placenta, but alcohol-free preparations should be used in pregnancy.

11.5 Antenatal Considerations

11.5.1 Fetal Monitoring and Interventions

Antenatal maternal hypoxia has been shown to alter fetal cardiovascular growth and function, cause fetal neurologic deficits and fetal growth restriction (FGR), and increase risk for postnatal complications [33]. In patients with critical respiratory disease, decisions around fetal heart rate monitoring and frequency of monitoring should depend on the gestational age of the fetus, desires of the patient, and feasibility and safety of intervention [34].

In cases of fetal distress, the common practice of maternal supplemental oxygen therapy for fetal resuscitation should be abandoned, as it has no proven fetal benefit and may result in aerosolization of maternal respiratory secretions. Other maneuvers such as lateral positioning and hemodynamic support are appropriate alternatives.

11.5.2 Corticosteroids, Pregnancy Category B

Betamethasone or dexamethasone are administered in pregnancies at risk of preterm delivery to reduce neonatal complications and mortality. The RECOVERY trial reports a reduction in mortality in non-pregnant hospitalized patients with severe and critical COVID-19 who received daily dexamethasone [35]. As of July 27, 2020, ACOG recommends administration of antenatal steroids to patients who require supplemental oxygen or mechanical ventilation and are in the early (24w0d–33w6d) or late preterm period (34w0d–36w6d) [23] as indicated for fetal benefit.

11.5.3 Intrapartum Fever

The differential diagnosis for intrapartum fever (intraamniotic infection, respiratory tract infection, urinary tract infection, drug/neuraxial related, DVT) should be expanded to include COVID-19 disease, particularly when the patient has respiratory symptoms and decreased oxygenation.

11.5.4 Preterm Labor

In women with known or suspected COVID-19, the preferred tocolytic is nifedipine. Nifedipine is a suitable alterative to indomethacin, which is subject to the theoretical yet unproven risk of NSAID use in COVID-19 disease, and to beta-sympathomimetics (i.e., terbutaline), which are associated with high rates of maternal tachyarrhythmias.

Magnesium sulfate should be administered on a case-by-case basis for maternal seizure prophylaxis and/or fetal neuroprotection due to the risks of pulmonary edema and neuromuscular weakness, particularly respiratory weakness. Serum magnesium levels may be drawn in patients who are unable to participate in clinical assessments aimed at recognizing signs and symptoms of magnesium toxicity.

11.5.5 Nutrition and Glucose Control

Many intensive care units utilize a caloric calculation of 25 kcal/kg/day of ideal body weight. An extra 300 kcal/day should be added during pregnancy (500 kcal/day in multiple gestation). No current guidelines exist for glucose control in critically ill parturients, but a target glucose level between 70 and 140 mg/dL has been suggested to avoid fetal complications associated with hyperglycemia.

11.6 Timing and Mode of Delivery

Greater than 90% of infected mothers recover from COVID-19 disease without undergoing delivery [36–40]. Data related to the timing of delivery in women with acute respiratory distress syndrome (ARDS) is limited, and there is much debate surrounding the topic of therapeutic delivery to improve maternal outcome in ARDS. It has been suggested that delivery of the fetus may improve maternal respiratory status by improving FRC and pulmonary mechanics and reducing metabolic stress [41, 42]. Decisions regarding delivery in this setting should be made based on a case-by-case basis by a multidisciplinary team including intensivists, obstetricians/maternal fetal medicine specialists, neonatologists, and obstetric anesthesiologists.

Cesarean delivery should be based on obstetric (fetal or maternal) indications and not COVID-19 status alone. Early in the SARS-CoV-2 pandemic, the majority of pregnancies (>90%) were delivered via cesarean section due to limited understanding of the risks of vertical transmission of disease as well as a desire to control the timing of delivery and prevent emergent intubations that would increase the risk of exposure for healthcare workers [43]. ACOG Committee Opinion 761 states that in the absence of maternal or fetal indications for cesarean delivery, a plan for vaginal delivery is safe and appropriate and should be recommended [44]. Vaginal delivery is preferred in asymptomatic, mild, or moderate disease, to reduce the risk of hemorrhage, infection, and thromboembolic disease associated with cesarean delivery [38, 44], while cesarean delivery may be favored in a severe or critically ill parturient who is unable to tolerate or participate in labor.

11.7 Safety of Common Therapies for COVID-19 Disease in Pregnancy (Table 11.2)

11.7.1 Convalescent Plasma

Early studies suggest a possible clinical benefit to administering ABO-compatible convalescent plasma, a high antibody titer plasma pooled from donors previously infected with SARS-CoV-2. Though pregnant women are excluded from ongoing RCTs for COVID-19, convalescent plasma was successfully used for eight pregnant Ebola patients [45], without any serious adverse maternal or fetal reactions. Potential complications include transfusion-related reactions and immunosuppression.

11.8 Uterotonics and Postpartum Hemorrhage (PPH)

Four uterotonic medications are available in the United States for the management of postpartum hemorrhage (PPH): oxytocin, carboprost (prostaglandin F2α), methylergonovine, and misoprostol (prostaglandin E_1). Early administration of oxytocin and mechanical tamponade are preferred first-line treatments for PPH in severe or critical COVID-19 disease due to the significant risk of bronchospasm with administration of carboprost and pulmonary vasoconstriction with methylergonovine. Standardized recommendations have not been established, but given these risks, avoidance of carboprost and methylergonovine may be prudent in severe or critical COVID-19 disease. Due to thromboembolic risk, tranexamic acid should be administered with extreme caution and only in patients without renal insufficiency and neurologic or thromboembolic disease.

11.9 Anesthetic Management

The pre-anesthetic evaluation is an important component of management of all pregnant women on labor and delivery, but special considerations must be observed in COVID-19 disease.

1. *Airway evaluation:* A thorough evaluation should be performed while observing institutional practices around personal protective equipment (PPE). Endotracheal intubation can be challenging in pregnancy due to edema of the upper airway and difficult to perform with the increased breast volume. Airway exam may worsen as labor progresses and should be reassessed just prior to cesarean delivery if indicated [46]. Pregnant women are at high risk for aspiration due to increased intraabdominal pressure and impaired gastric emptying and should be pre-medicated with gastric prophylaxis prior to any procedure.
2. *Cardiopulmonary evaluation*: All COVID-19 positive patients should have a physical exam focused on cardiopulmonary status. If found to be hypoxic with or without dyspnea, obtain a blood gas and chest X-ray, and consider CT of the

Table 11.2 Safety of investigational therapies for COVID 19 disease in pregnancy

Therapy	Original indication	Indication for use in COVID-19	Mechanism of action	Pregnancy safety category	Dosing	Available study data	Placental/ breastmilk transfer	Common adverse effects	Contraindications
Remdesivir	Hepatitis C, filoviruses (Ebola, Marburg)	Severe or critical disease respiratory disease	Adenosine nucleoside analogue that interferes with viral RNA production	C	200 mg IV as a single dose on day 1, followed by 100 mg IV once daily × 4 days (may extend to 10 days total if no improvement). IV infusion over 30 to 120 min	Pregnant women excluded from RCTs. Faster time to recovery and a non-statistically significant trend toward lower 14-day mortality[a]	No data. Its small molecular weight and high protein-binding rate suggest it may cross the placenta	Transaminitis, infusion reaction, impaired metabolism in renal insufficiency	Use with caution in patients with liver dysfunction
Ritonavir/ lopinavir	HIV	Currently not recommended based on early studies showing a lack of benefit and significant side effects	Protease inhibitors	C	Lopinavir 400 mg/ ritonavir 100 mg PO (tablet) twice daily	Pregnant women excluded from RCTs. The first randomized, open-label, controlled study to be published reported lopinavir-ritonavir treatment did not significantly accelerate clinical improvement, reduce mortality, or diminish throat viral RNA detectability in patients with serious COVID-19	Poor placental transfer due to strong protein binding for protease inhibitors	Diarrhea, abdominal pain, altered liver enzymes	Tablets are recommended; avoid use of the oral solution in pregnancy

(continued)

Table 11.2 (continued)

Therapy	Original indication	Indication for use in COVID-19	Mechanism of action	Pregnancy safety category	Dosing	Available study data	Placental/ breastmilk transfer	Common adverse effects	Contraindications
Unfractionated heparin	Venous thromboembolism (VTE) prophylaxis, multiple uses	VTE prophylaxis or treatment in severe or critical disease	Enzymatic activation of antithrombin III	C	Prophylactic: 5000/7500/10,000 units SC every 8 h, depending if first/second/third trimester; therapeutic: Heparin drip titrated to anti-Xa levels	Pregnant women excluded from RCTs. A study of 449 COVID-19 patients found that deep vein thrombosis (DVT) prophylaxis decreased 28-day mortality by 20% in patients with a D-dimer ≥3000 ng/mL or a sepsis-induced coagulopathy score ≥ 4 without increasing rates of major bleeding[b]	No placental transfer, large molecular weight; avoid preparations containing alcohol	Heparin-induced thrombocytopenia (HIT), bleeding	Hypersensitivity reaction, history of HIT

Dexamethasone	Pregnancies at risk for preterm delivery ± maternal benefit in COVID-19	Dexamethasone should be administered to patients in the early and late preterm period (24w0d–33w6d or 34wod–36w6d) who require supplemental oxygen or mechanical ventilation	Induce the production of surfactant proteins and lipid synthesis, decrease fetal lung fluid, and alter preterm responses to oxidative stress	B	6 mg IM or IV q12 h × 4 doses for FLM. Consider extending course for maternal benefit based on results of RECOVERY trial	Pregnant women excluded from RCTs. The RECOVERY trial reports a reduction in mortality in non-pregnant hospitalized patients with severe and critical COVID-19 who received daily dexamethasone[c]	High placental/breastmilk transfer	Transient hyperglycemia and neutrophilia, neuropsychiatric symptoms	Use with caution in uncontrolled maternal hyperglycemia, neuropsychiatric conditions, adrenal suppression and immunosuppression
Betamethasone	Pregnancies at risk for preterm delivery	Dexamethasone should be administered to patients in the early and late preterm period (24w0d–33w6d or 34wod–36w6d) who require supplemental oxygen or mechanical ventilation	Induce the production of surfactant proteins and lipid synthesis, decrease fetal lung fluid, alter preterm responses to oxidative stress	B	12 mg IM or IV q24 h × 2 doses for fetal lung maturation	No studies currently on betamethasone but expected to behave similarly to dexamethasone	High placental/breastmilk transfer	Transient hyperglycemia and neutrophilia, neuropsychiatric symptoms	Use with caution in uncontrolled maternal hyperglycemia, neuropsychiatric conditions, adrenal suppression and immunosuppression

(continued)

Table 11.2 (continued)

Therapy	Original indication	Indication for use in COVID-19	Mechanism of action	Pregnancy safety category	Dosing	Available study data	Placental/ breastmilk transfer	Common adverse effects	Contraindications
Tocilizumab	Rheumatoid arthritis, juvenile idiopathic arthritis, giant cell arthritis	Patients with moderate to severe COVID-19 disease, uncertain effect on patients already on mechanical ventilation	Monoclonal anti-IL-6 antibody, leads to a reduction in cytokine and acute phase reactant production	C	IV: Limited data available; dosing used in clinical trials commonly 8 mg/kg (maximum 800 mg/dose) as a single dose; may repeat dose in 8–12 h if signs/symptoms worsen or do not improve	Pregnant women excluded from RCTs. Safety and efficacy have not been established; early retrospective cohort data suggests treatment with tocilizumab might reduce the risk of invasive mechanical ventilation or death in patients with severe COVID-19 pneumonia	Significant placental and breastmilk transfer, though there does not seem to be an increased risk for congenital anomalies	Elevated LFTs, infusion reaction, increased serum cholesterol	Hypersensitivity

[a]Tang N, Bai H, Chen X, Gong J, Li D, Sun Z.. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020;18(5):1094-1099. https://doi.org/10.1111/jth.14817

[b]Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 — Preliminary Report. N Engl J Med. 2020. https://doi.org/10.1056/nejmoa2007764

[c]Horby P, Lim WS, Emberson J, et al. Dexamethasone for COVID-19-Preliminary Report Effect of Dexamethasone in Hospitalized Patients with COVID-19-Preliminary Report RECOVERY Collaborative Group*. medRxiv. 2020. https://doi.org/10.1101/2020.06.22.20137273

chest or transthoracic echocardiography to rule out other cardiopulmonary pathology.
3. Evaluate labs, particularly complete blood count, chemistry panel, coagulation factors (including anti-Xa level if on heparin), and fibrinogen (>350 mg/dL in pregnancy).
4. Access/hemodynamic monitoring:
   (a) Mild disease: adequate IV access for blood, resuscitation, and uterotonics.
   (b) Moderate disease: adequate IV access, consider arterial line.
   (c) Severe-critical disease: adequate IV access, arterial line for frequent blood sampling.

11.9.1 Neuraxial Anesthesia

Neuraxial is preferred for both vaginal delivery and cesarean section. Spinal anesthesia/dural puncture is considered safe as there have been no documented adverse complications related to CNS transmission of viral particles, and COVID-19 disease is not a contraindication [47]. However, the accompanying abrupt drop in preload may not be tolerated in seriously ill women.

Decision to proceed with neuraxial may be complicated by thrombocytopenia and concurrent use of anticoagulants. Common practice is to avoid neuraxial in patients with platelet counts <70,000/μL, though different practitioners may use different cutoffs. Thrombocytopenia secondary to COVID-19 disease is rarely <70,000/μL, so other causes should be considered if platelet count becomes critically low. Early labor epidurals are encouraged because the block provided by the in situ catheter may be extended for cesarean delivery in an urgent or emergent situation. These patients should be evaluated regularly to ensure early recognition of epidural failure and allow the provider to troubleshoot or replace the catheter in a controlled manner. The risk of general anesthesia (aspiration, difficult airway management, uterine atony, low neonatal APGARS) is greater than the theoretical risk of causing meningitis/encephalitis from neuraxial procedures; therefore, neuraxial procedures may be performed in parturients with COVID-19 unless otherwise contraindicated or logistically prohibited. In the setting of COVID-19 disease, many patients started on anticoagulation with either LMWH or UFH. Anticoagulation guildelines from the American Society of Regional Anesthesia (ASRA) [48] should be followed when considering neuraxial procedures or catheter removals.

Other analgesics such as nitrous oxide for labor analgesia should be suspended in the absence of sufficient data about cleaning, filtering, and potential aerosolization of nitrous oxide systems. Similarly, IV patient-controlled opiate analgesics should be avoided due to risk of respiratory depression and potential need for emergent airway procedures.

During labor with neuraxial, maternal heart rate, maternal pulse oximetry with plethysmography, and fetal heart rate should be continuously monitored. Additional monitors should be applied on a case-by-case basis.

11.9.2 General Anesthesia for Cesarean Delivery

General endotracheal anesthesia (GETA) may be required if patient is already intubated or hemodynamically unstable or in cases of emergent cesarean delivery (fetal or maternal distress) without in situ epidural catheter. Intubation of SARS-CoV-2-positive patients is associated with a high risk of transmission to healthcare providers. Providers should don full PPE and decrease risk of transmission by performing rapid sequence induction after adequate preoxygenation and intubate with a video laryngoscope to facilitate placement while reducing aerosolization of respiratory secretions. Pregnant women have reduced FRC and therefore minimal apneic time despite adequate preoxygenation. Intubation may be challenging due to airway edema or presence of large breasts. COVID-19 patients with hypoxia concomitant with the physiologically decreased FRC from pregnancy will likely become more hypoxic, develop further atelectasis with intubation and mechanical ventilation, and possibly require postoperative critical care admission [47]. Providers should also be aware of the decrease in mean alveolar concentration (MAC) and mean local anesthetic concentration (MLAC) requirements in pregnancy and adjust anesthetic depth accordingly.

11.10 Conclusions

Management of obstetric patients who test positive for SARS-CoV-2 ranges from outpatient care of asymptomatic or mildly symptomatic patients to inpatient management of those with moderate to critical illness. Inpatients are best managed by a multidisciplinary team including obstetricians/maternal fetal medicine specialists, anesthesiologists, neonatologists, intensivists, and nurses with obstetric and ICU training. Care teams should meet early and frequently to determine optimal delivery timing, mode of delivery, anesthetic options, and hemodynamic goals, with special attention to contingency plans for maternal instability, fetal distress, and postpartum hemorrhage.

References

1. 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;323(13). https://doi.org/10.1001/jama.2020.2648.
2. Huntley BJF, Huntley ES, Di Mascio D, Chen T, Berghella V, Chauhan SP. Rates of maternal and perinatal mortality and vertical transmission in pregnancies complicated by severe acute respiratory syndrome coronavirus 2 (SARS-Co-V-2) infection. Obstet Gynecol. 2020; https://doi.org/10.1097/aog.0000000000004010.
3. Creanga AA, Johnson TF, Graitcer SB, et al. Severity of 2009 pandemic influenza a (H1N1) virus infection in pregnant women. Obstet Gynecol. 2010; https://doi.org/10.1097/AOG.0b013e3181d57947.

4. Jamieson DJ, Honein MA, Rasmussen SA, et al. H1N1 2009 influenza virus infection during pregnancy in the USA. Lancet. 2009; https://doi.org/10.1016/S0140-6736(09)61304-0.
5. Qiancheng X, Jian S, Lingling P, et al. Coronavirus disease 2019 in pregnancy. Int J Infect Dis. 2020;95:376–83. https://doi.org/10.1016/j.ijid.2020.04.065.
6. Rasmussen SA, Smulian JC, Lednicky JA, Wen TS, Jamieson DJ. Coronavirus disease 2019 (COVID-19) and pregnancy: what obstetricians need to know. Am J Obstet Gynecol. 2020; https://doi.org/10.1016/j.ajog.2020.02.017.
7. Schwartz DA, Graham AL. Potential maternal and infant outcomes from coronavirus 2019-NCOV (SARS-CoV-2) infecting pregnant women: lessons from SARS, MERS, and other human coronavirus infections. Viruses. 2020;12(2):1–16. https://doi.org/10.3390/v12020194.
8. Sutton D, Fuchs K, D'Alton M, Goffman D. Universal screening for SARS-CoV-2 in women admitted for delivery. N Engl J Med. 2020;382(22):2163–4. https://doi.org/10.1056/nejmc2009316.
9. Bianco A, Buckley AB, Overbey J, et al. Testing of patients and support persons for coronavirus disease 2019 (COVID-19) infection before scheduled deliveries. Obstet Gynecol. 2020;136(2):283–7. https://doi.org/10.1097/AOG.0000000000003985.
10. Campbell KH, Tornatore JM, Lawrence KE, et al. Prevalence of SARS-CoV-2 among patients admitted for childbirth in Southern Connecticut. JAMA. 2020;323(24):2520–2. https://doi.org/10.1001/jama.2020.8904.
11. Hantoushzadeh S, Shamshirsaz AA, Aleyasin A, et al. Maternal death due to COVID-19 disease. Am J Obstet Gynecol. 2020;223(1):109.e1–109.e16. https://doi.org/10.1016/j.ajog.2020.04.030.
12. Dphil MK, Mbchb NS, Gale C, Knight M. Characteristics and outcomes of pregnant women hospitalised with confirmed SARS-CoV-2 infection in the UK a national cohort study using the UK Obstetric Surveillance System (UKOSS). medrxiv. 2020; https://doi.org/10.1101/2020.05.08.20089268.
13. Karami P, Naghavi M, Feyzi A, et al. Mortality of a pregnant patient diagnosed with COVID-19: a case report with clinical, radiological, and histopathological findings. Travel Med Infect Dis. 2020; https://doi.org/10.1016/j.tmaid.2020.101665.
14. Chen H, Guo J, Wang C, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet. 2020;395(10226):809–15. https://doi.org/10.1016/S0140-6736(20)30360-3.
15. Liu Y, Chen H, Tang K, Guo Y. Clinical manifestations and outcome of SARS-CoV-2 infection during pregnancy. J Infect. 2020; https://doi.org/10.1016/j.jinf.2020.02.028.
16. Savasi VM, Parisi F, Patanè L, et al. Clinical findings and disease severity in hospitalized pregnant women with coronavirus disease 2019 (COVID-19). Obstet Gynecol. 2020;136(2):252–8. https://doi.org/10.1097/AOG.0000000000003979.
17. Chen L, Li Q, Zheng D, et al. Clinical characteristics of pregnant women with Covid-19 in Wuhan, China. N Engl J Med. 2020;382:e100. https://doi.org/10.1056/nejmc2009226.
18. Yan J, Guo J, Fan C, et al. Coronavirus disease 2019 in pregnant women: a report based on 116 cases. Am J Obstet Gynecol. 2020;223(1):111.e1–14. https://doi.org/10.1016/j.ajog.2020.04.014.
19. Mullins E, Evans D, Viner RM, O'Brien P, Morris E. Coronavirus in pregnancy and delivery: rapid review. Ultrasound Obstet Gynecol. 2020;55(5):586–92. https://doi.org/10.1002/uog.22014.
20. Elshafeey F, Magdi R, Hindi N, et al. A systematic scoping review of COVID-19 during pregnancy and childbirth. Int J Gynecol Obstet. 2020;150:47–52. https://doi.org/10.1002/ijgo.13182.
21. Treatment Guidelines. Coronavirus disease 2019 (COVID-19) treatment guidelines. 2019. Disponible en: https://covid19treatmentguidelines.nih.gov/.
22. Denicola N. Implementing telehealth in practice. Obstet Gynecol. 2020;135(2):e73–9. https://doi.org/10.1097/AOG.0000000000003671.

23. Miller E. Management considerations for pregnant patients with COVID-19. Soc Matern Fetal Med. 2020. https://s3.amazonaws.com/cdn.smfm.org/media/2415/SMFM_COVID_Management_of_COVID_pos_preg_patients_7-2-20.PDF_.pdf.
24. Singh PM, Singh NP, Reschke M, Ngan Kee WD, Palanisamy A, Monks DT. Vasopressor drugs for the prevention and treatment of hypotension during neuraxial anaesthesia for Caesarean delivery: a Bayesian network meta-analysis of fetal and maternal outcomes. Br J Anaesth. 2020; https://doi.org/10.1016/j.bja.2019.09.045.
25. Akerlund M. Vasopressin and oxytocin in normal reproduction and in the pathophysiology of preterm labour and primary dysmenorrhoea. Development of receptor antagonists for therapeutic use in these conditions. Rocz Akad Med w Białymstoku. 2004;49:18–21.
26. Higuchi H, Takagi S, Zhang K, Furui I, Ozaki M. Effect of lateral tilt angle on the volume of the abdominal aorta and inferior vena cava in pregnant and nonpregnant women determined by magnetic resonance imaging. Anesthesiology. 2015;122:286–93. https://doi.org/10.1097/ALN.0000000000000553.
27. Dayal P, Murata Y, Takamura H. Antepartum and postpartum acid-base changes in maternal blood in normal and complicated pregnancies. BJOG. 1972;79:612–24. https://doi.org/10.1111/j.1471-0528.1972.tb14210.x.
28. Alshahrani MS, Sindi A, Alshamsi F, et al. Extracorporeal membrane oxygenation for severe Middle East respiratory syndrome coronavirus. Ann Intensive Care. 2018;8:3. https://doi.org/10.1186/s13613-017-0350-x.
29. Sukhal S, Sethi J, Ganesh M, Villablanca P, Malhotra A, Ramakrishna H. Extracorporeal membrane oxygenation in severe influenza infection with respiratory failure: A systematic review and meta-analysis. Ann Card Anaesth. 2017; https://doi.org/10.4103/0971-9784.197820.
30. Naoum EE, Chalupka A, Haft J, et al. Extracorporeal life support in pregnancy: a systematic review. J Am Heart Assoc. 2020;9:e016072. https://doi.org/10.1161/JAHA.119.016072.
31. Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos A-M, Vandvik PO. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physician Evidence-Based Clinical Practice Guidelines Online Only Articles: VTE, Thrombophilia, Antithrombotic Therapy, and Pregnancy. Chest. 2012;141(2):2012. https://doi.org/10.1378/chest.11-2300.
32. Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost. 2020;18(5):1023–6. https://doi.org/10.1111/jth.14810.
33. McCullough RE, Reeves JT, Liljegren RL. Fetal growth retardation and increased infant mortality at high altitude. Arch Environ Health. 1977;32(1):36–9. https://doi.org/10.1080/00039896.1977.10667251.
34. ACOG Practice Bulletin No. 211: critical care in pregnancy. Obstet Gynecol. 2019. https://doi.org/10.1097/AOG.0000000000003241
35. Horby P, Lim WS, Emberson J, et al. Dexamethasone for COVID-19-preliminary report effect of dexamethasone in hospitalized patients with COVID-19-preliminary report RECOVERY Collaborative Group*. medRxiv. 2020. doi:https://doi.org/10.1101/2020.06.22.20137273
36. Wu Z, McGoogan JM. Characteristics of and important lessons from the Coronavirus Disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020; https://doi.org/10.1001/jama.2020.2648.
37. Di Mascio D, Khalil A, Saccone G, et al. Outcome of coronavirus spectrum infections (SARS, MERS, COVID-19) during pregnancy: a systematic review and meta-analysis. Am J Obstet Gynecol MFM. 2020;2:100107. https://doi.org/10.1016/j.ajogmf.2020.100107.
38. Martínez-Perez O, Vouga M, Cruz Melguizo S, et al. Association between mode of delivery among pregnant women with COVID-19 and maternal and neonatal outcomes in Spain. JAMA. 2020; https://doi.org/10.1001/jama.2020.10125.
39. Schwartz DA. An analysis of 38 pregnant women with COVID-19, their newborn infants, and maternal-fetal transmission of SARS-CoV-2: maternal coronavirus infections and pregnancy outcomes. Arch Pathol Lab Med. 2020; https://doi.org/10.5858/arpa.2020-0901-SA.

40. Khan S, Jun L, Nawsherwan, et al. Association of COVID-19 with pregnancy outcomes in health-care workers and general women. Clin Microbiol Infect. 2020; https://doi.org/10.1016/j.cmi.2020.03.034.
41. Hung C, Hu H, Chang C, Huang C, Kao K. Outcomes of early delivery in pregnant patients with acute respiratory distress syndrome. Crit Care. 2012;16:P112. https://doi.org/10.1186/cc10719.
42. Daily WH, Katz ARTA, et al. Beneficial effect of delivery in a patient with adult respiratory distress syndrome. Anesthesiology. 1990;72(2):383–6.
43. Goyal P. Correspondence clinical characteristics of Covid-19 in China. NEJM. 2020;100(1):1–3. https://doi.org/10.1056/NEJMc2005203.
44. Porter TF. ACOG Committee Opinion #761. Obstet Gynecol. 2019;133(1):73–6. https://doi.org/10.1097/00006250-200601000-00051.
45. Van Griensven J, Edwards T, De Lamballerie X, et al. Evaluation of convalescent plasma for Ebola virus disease in Guinea. N Engl J Med. 2016; https://doi.org/10.1056/NEJMoa1511812.
46. Kodali BS, Chandrasekhar S, Bulich LN, Topulos GP, Datta S. Airway changes during labor and delivery. Anesthesiology. 2008;108(3):357–62. https://doi.org/10.1097/01.ogx.0000318139.07057.6e.
47. Bauer ME, Chiware R, Pancaro C. Neuraxial procedures in COVID-19 positive parturients: a review of current reports. Anesth Analg. 2020; https://doi.org/10.1213/ANE.0000000000004831.
48. Horlocker TT, Vandermeuelen E, Kopp SL, Gogarten W, Leffert LR, Benzon HT. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Fourth Edition). 2018;43. https://doi.org/10.1097/AAP.0000000000000763

Pediatric Patients and COVID-19

12

Malini Mahendra, Vibha Mahendra,
and Shobana Murugan

12.1 Introduction

The Novel Coronavirus Disease (COVID-19) the World Health Organization (WHO) declared a worldwide pandemic on March 11, 2020 [1]. Although the burden of COVID-19 has fallen largely on adults, there are unique pediatric considerations that clinicians should be aware of. In this section, we will review the impact of COVID-19 on the pediatric population, common disease presentation, physiology, anesthetic considerations, and critical care management of the illness.

12.2 Background

12.2.1 Epidemiology

The SARS CoV2 epidemic was first reported in Wuhan, China, in November 2019. The Chinese Center for Disease Control Chinese Center for Disease Control reported 2% of confirmed COVID cases were in patients <19 years of age. No deaths in children <9 years of age [2]. Similar findings were reported in the Italian outbreak [3]. The United States also reported similar findings with only 1.7% of COVID-19 cases in pediatric patients with a case fatality rate of 0.1%. However, the

M. Mahendra
Division of Pediatric and Critical Care Medicine and Philip R. Lee Institute for Health Policy Studies, University of California, San Francisco, CA, USA

V. Mahendra
University of Southern California, Keck School of Medicine, Los Angeles, CA, USA

S. Murugan (✉)
University of Texas Medical Branch Health, Galveston, TX, USA

H. Prabhakar et al. (eds.), *Clinical Synopsis of COVID-19*,
https://doi.org/10.1007/978-981-15-8681-1_12

incidence of COVID-19 in pediatric patients with chronic illness is unknown. Additionally, like in adults, majority (57%) of cases were male and 91% of cases occurred after exposure at home or in the community [4]. Of pediatric patients with COVID-19, the hospitalization admission rate ranged between 5.7 and 20%. With 15% admitted to an ICU. Children aged <1 year accounted for the highest percentage (15–62%) of hospitalization among pediatric patients with COVID-19 [4]. Although nearly 5% of adults with COVID-19 require admission to the ICU, a case series suggested that 0.6% of pediatric patients had disease progression to acute respiratory distress syndrome or multiple organ dysfunction [5, 6]. The true incidence of the disease is unknown as some studies have reported that up to 10% of children are asymptomatic [7, 8].

12.2.2 Presentation of Symptoms

Case series have reported that the majority of neonatal and pediatric patients have been transmitted from infected family members [7]. Pediatric patients most frequently presented with fever, cough, and shortness of breath. The frequency of reported symptoms in pediatrics was less than what has been reported in adults [4].

A minority of patients who are critically ill have presented with a hyperinflammatory shock that has been described as the pediatric multisystem inflammatory syndrome associated with COVID-19. The literature has commented on the similarity in presentation of this syndrome to Kawasaki disease. In a cohort of eight patients identified in the United Kingdom, patients presented with unrelenting fever, rash, conjunctivitis, peripheral edema, extremity pain, and significant GI symptoms. Interestingly, all patients initially tested negative for COVID [9]. Most children in this case series did not present with respiratory symptoms but did require mechanical ventilation for hemodynamic support. All patients progressed to warm, vasoplegic shock. Common echocardiographic findings were echo bright coronary vessels, with one patient progressing to development of a giant coronary aneurysm. One patient suffered arrhythmias that required support with ECLS. The patient ultimately diedfrom a cerebrovascular infarct.

12.2.3 Special Considerations: Pediatric

There is a growing body of literature that has suggested that the general pediatric population has been less severely affected by COVID-19 than adults. There are several hypotheses that have been proposed to explain this observation. Recent studies have proposed a correlation between the severity of COVID-19 disease with viral load or the duration of viral shedding [8, 10]. Differences in clinical presentation may be related to the differential expression of ACE2 receptors because SARS CoV2 is known to enter cells by binding to the ACE2 receptor. Data show that there is differential expression of the ACE2 receptor in the population: (1) ACE2 receptors are expressed more in adults than children; (2) there is increased expression of

the ACE2 receptor in neonates compared to older children; and (3) circulating levels of ACE2 are higher in males than females. This differential expression may explain part of the reason why COVID-19 is more present in adults, males, and neonates [8].

Children also seem to have a different immune response to the SARS CoV2 virus than adults. Robustness of the immune response may decrease with age. With aging, T-cell distribution shifts from having naïve T cells to a population of mostly memory and effector T cells. This is associated with loss of co-stimulatory molecules that may increase susceptibility to infection [8]. Neonates also may be more susceptible to the SARS CoV2 virus because their immune response is skewed more to the Th2 rather than the pro-inflammatory Th1 response. When compared to younger macaques and mice, aging macaques and mice infected with SARS CoV2 had a more robust pro-inflammatory response associated with worse lung pathology. Because severe COVID-19 infection is associated with a massive proinflammatory response, cytokine storm, and multiorgan failure, it is proposed that differences in inflammatory response between the pediatric and adult patient may also contribute to differences in disease presentation [8].

12.2.4 Special Considerations: Neonatal

Although transmission of the SARS CoV2 virus is thought to occur primarily through respiratory droplets, there is concern that vertical transmission of the virus exists. There has been a case report of a neonate who tested positive via RT PCR at 16 h of life [11]. IgM antibodies have also been detected in the placenta, suggesting transplacental passage of the virus is possible. Testing is recommended for all neonates born to women with confirmed or suspected COVID-19 regardless of symptoms in the neonate via RT-PCR. Serologic testing is not recommended at this time to diagnose an acute infection in the neonate. Testing should occur at 24 h of life. If initial testing is negative or not available, testing should be repeated at 48 h of age [12].

Postnatally, the AAP, ACOG, and Chinese experts have recommended separation of the newborn from COVID-19-positive mothers. However, the CDC recommends that the decision to separate and to breast feed the infant be a shared decision with the mother. If the decision is made to room in with the baby, mothers should wear facemask and practice social distancing as appropriate.

12.3 Anesthetic Consideration

Transmission of aerosolized particles places anesthesiologists at high risk for transmission of the virus. Recorded rates of COVID-19 in healthcare workers range from 3 to 14% [13]. Precautions taken while caring for COVID-19-positive adults should also be applied to the pediatric patient. Because parents may not be able to accompany the child into the operating room, strong consideration should be given to premedicating the child to reduce crying and screaming (which may increase spread

of the virus) [13]. Because the pediatric patient is at increased risk for tube dislodgement or obstruction while intubation and laryngospasm after extubation, effort should be taken to minimize the need to re-intubate patients [13].

12.4 Critical Care Management

Early data has suggested that around 15% of COVID-19 pediatric patients had critical illness (defined as requiring mechanical ventilation or having ARDS, shock, systemic inflammatory response syndrome, or multiorgan failure) [14]. Seventy-three percent of patients presented with respiratory symptoms, but the remainder of patients presented with other symptoms (circulatory collapse, seizures, vaso-occlusive crisis of sickle cell, and DKA). Over 90% of patients admitted to the ICU had at least one comorbidity, with the most common comorbidity being long-term dependence on technological support. Over 1/3 of these patients required mechanical ventilation. Thirteen percent of patients required extracorporeal therapies. Reported case fatality rate was 4.2% at time of the report [14].

Therapeutic management strategies stems from knowledge gained from treatment of other infectious diseases [15]. Treatment of critical illness has been largely supportive (nutrition, fluids, supplemental oxygen) [7]. Although the WHO and CDC do not recommend any specific treatment strategies in children because novel therapies have not been shown clear benefit, pediatric intensivists have used targeted therapy to COVID-19. The most common therapy received was hydroxychloroquine as a single agent. Azithromycin, remdisivir, and convalescent plasma were also used [14]. At the time of writing, there are no published guidelines on how to manage multisystem inflammatory syndrome. However, clinicians have used intravenous immunoglobulin, corticosteroids, and biologics such as infliximab and anakinra to treat patients [16].

12.5 Conclusion

Most pediatric patients infected with SARS CoV2 present with mild symptoms. A minority of patients become critically ill and develop pediatric multisystem inflammatory syndrome. Differences in gene expression and the inflammatory response in neonatal and pediatric patients may explain differences in COVID-19 disease presentation. Supportive care is the recommended management strategy for patients with COVID-19 infections. No novel therapeutic strategies in children have been recommended as there is no clear evidence that there is benefit from use. Anesthetic management of the COVID-19-positive pediatric patient is similar to what has been described in the adult anesthetic literature.

References

1. 5/26/2020 A. World Health Organization-COVID19 situation report-126 [Internet]. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200525-covid-19-sitrep-126.pdf?sfvrsn=887dbd66_2.
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;323(13).
3. Livingston E, Bucher K. Coronavirus Disease 2019 (COVID-19) in Italy. JAMA. 2020;323(14):1335. https://doi.org/10.1001/jama.2020.4344.
4. Coronavirus Disease 2019 in Children — United States, February 12–April 2, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(422–426).
5. Lambert V, Matthews A, MacDonell R, Fitzsimons J. Paediatric early warning systems for detecting and responding to clinical deterioration in children: a systematic review. BMJ Open [Internet]. 2017;7(3). Available from: https://search.proquest.com/docview/1876695481.
6. Ong JSM, Tosoni A, Kim Y, Kissoon N, Bs MB, Frcp C, et al. Coronavirus disease 2019 in critically ill children: a narrative review of the literature. Pediatr Crit Care Med. 2020;21:662–6.
7. Zimmerman P, Curtis N. Coronavirus infections in children including COVID-19 an overview of the epidemiology, clinical features, diagnosis, treatment and prevention options in children. Pediatr Infect Dis J. 2020;39(5):355–68.
8. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology : a review. Clin Imunol. 2020;215:108427.
9. Riphagen S, Gomez X, Gonzalez-martinez C, Wilkinson N, Theocharis P. Correspondence hyperinflammatory shock in children during COVID-19 : PCR screening of asymptomatic health- hospital. Lancet. 2020;395(10237):1607–8. https://doi.org/10.1016/S0140-6736(20)31094-1.
10. Yang L, Yan L-M, Wan L, Xiang T-X, Le A, Liu J-M, Peiris M, Leo LM, Poon WZ. Viral dynamics in mild and severe cases of COVID-19. Lancet Infect Dis. 2020;20:656–7.
11. Amatya S, Corr TE, Gandhi CK, Glass KM, Kresch MJ, Mujsce DJ, et al. Management of newborns exposed to mothers with confirmed or suspected COVID-19. J Perinatol. 2020;40(7):987–96. https://doi.org/10.1038/s41372-020-0695-0.
12. Evaluation and management considerations for neonates at risk for COVID-19. CDC [Internet]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/caring-for-newborns.html.
13. Lee-Archer P, Von Ungern-sternberg BS. Pediatric anesthetic implications of COVID-19 — a review of current literature. Paediatr Anaesth. 2020;(April):1–6.
14. Shekerdemian LS, Mahmood NR, Wolfe KK, et al. Characteristics and Outcomes of Children With Coronavirus Disease 2019 (COVID-19) Infection Admitted to US and Canadian Pediatric Intensive Care Units. JAMA Pediatr. 2020;174(9):868–873. https://doi.org/10.1001/jamapediatrics.2020.1948.
15. Castagnoli R, Votto M, Licari A, et al. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Children and Adolescents: A Systematic Review [published online ahead of print, 2020 Apr 22]. JAMA Pediatr. 2020. https://doi.org/10.1001/jamapediatrics.2020.1467.
16. Viner RMWE. Kawasaki-like disease : emerging complication during the COVID-19 pandemic. Lancet. 2020;6736(20):1741–3.

Geriatric Patients and COVID-19

13

Shobana Murugan and Jayanth Rajan

13.1 Introduction

The CDC reports that, as of July 26, 2020, there are over 16.3 million cases of the novel coronavirus in the United States and that the death toll is nearly 645,000 [1]. Although information regarding risk factors, pathophysiology, treatments, and protective measures remains controversial, analysis of patient demographics suggests that older patients are particularly vulnerable to COVID-19: in China, where the disease first emerged, coronavirus deaths in those aged 60 and older constituted 80% of the total number of deaths [2]; in Italy, the median age of death due to COVID-19 is reported as 78.5 [3, 4]; an examination of COVID-19 cases in the United States between February 12 and March 16 reports that adverse outcomes most frequently occur in adults aged over 85 years [2]. The correlation between adverse outcomes and advanced age demonstrates the need to develop efficient guidelines to provide palliative care for older and vulnerable populations while protecting healthcare workers.

13.1.1 Background

To develop these guidelines in a targeted and specific manner, it is necessary to consider the nuances in the pathophysiology and clinical manifestations of COVID-19 in the context of geriatric patients. Current literature suggests that the incubation period of COVID-19 is 2–14 days [5] with a median of 5.1 days [6], and

S. Murugan (✉)
University of Texas Medical Branch Health, Galveston, TX, USA

J. Rajan
Lake Erie College of Osteopathic Medicine, Erie, PA, USA

H. Prabhakar et al. (eds.), *Clinical Synopsis of COVID-19*,
https://doi.org/10.1007/978-981-15-8681-1_13

the most common symptoms include fever, cough, shortness of breath, and fatigue [7]. In older adults, because the fever response is attenuated and because other symptoms are concurrent with age-related disorders, diagnosis can be more challenging [6]. Moreover, age-related disorders may directly contribute to the vulnerability of geriatric patients to COVID-19. Cases of COVID-19 in older adults are also unique because healthcare providers must consider the impact of medications for age-related disorders upon pathogenicity and virulence [6]. Special precautions must be taken for older patients residing in nursing facilities to prevent rapid transmission to other residents who may be at high risk of severe outcomes [8]. Finally, differential clinical features of COVID-19 in older patients warrant the development of treatment guidelines specific to geriatric patients [9]. By considering the unique aspects of COVID-19 in older patients, in this subsection we outline the clinical and anesthetic considerations, potential complications, and critical care management of geriatric patients.

13.2 Clinical Considerations

13.2.1 Diagnosis and Clinical Presentation

Several clinical features indicate coronavirus infection in the older adult. Although fever is one of the most common symptoms of COVID-19, the definition of fever must be modified to account for the attenuated fever response in older adults. High et al. proposed that for residents of long-term care facilities, a single oral temperature >100 °F, multiple oral temperatures >99 °F, and a >2 °F increase in temperature compared to baseline are suitable definitions of fever [6, 10]. In addition to typical symptoms such as cough and dyspnea, atypical symptoms such as confusion, sore throat, chills, and rhinorrhea may also occur. Godaert et al. suggest, based on experience in a short-stay geriatric unit for suspected COVID-19 cases, that some atypical symptoms may present more frequently in older adults [11]. Both typical and atypical symptoms reportedly take longer to present in older patients [12]. In consideration of clinical presentation and duration of incubation period, a low threshold for suspicion and frequent testing should be employed [6]. Management of these typical and atypical symptoms is summarized in the Sect. 13.2.4 of this chapter. Older individuals are more likely to present with higher pneumonia severity index, more acute respiratory distress syndrome, and acute organ dysfunction [9]. Furthermore, lung lesions appear particularly severe in older patients. Tomographic findings show a more extensive bilateral ground-glass pattern of lung involvement, peripheric ground-glass opacity and consolidation, and interlobular septal, subpleural line, and pleural thickening. Alveolar and interstitial involvement are twice more intense than in younger adults [13]. Laboratory findings in older patients indicate lower lymphocyte ratios and lower C-reactive protein levels compared with younger patients [9]. A summary of differential clinical features of COVID-19 between older and younger patients is provided below in Table 13.1.

Table 13.1 Differential clinical characteristics of COVID-19 in older adults compared to younger patients

Clinical feature	Presentation in older patients compared to younger patients	References
Pneumonia severity index	Older adults present with higher pneumonia severity index	[9]
Lung CT	Lung lesions are more severe in older patients In older adults, there is more extensive ground-glass pattern of lung involvement, peripheric ground-glass opacity Interlobular septal, subpleural line, and pleural line thickening compared to younger patients More intense alveolar and interstitial involvement in older adults	[13]
Laboratory findings	Lower lymphocyte ratio in older adults Lower C-reactive protein in older adults	[9]

13.2.2 Frailty and COVID-19 Outcomes

The COPE study, COVID-19 in Older People, in *The Lancet* assessed the effect of frailty on outcomes in people of all ages with COVID-19. Frailty increases mortality, earlier death, and longer hospital stays in hospital-admitted patients affected with COVID-19. The importance of this study is that frailty assessment rather than age is important in determining admission, triage, and resource allocation [14]. Age-related physiological changes may contribute to the frailty of older patients; these physiological changes are provided in Table 13.2.

13.2.3 Anesthetic Considerations

13.2.3.1 Perioperative Anesthesiologic Evaluation

Protecting hospital personnel and patients during perioperative anesthesiologic evaluation is imperative, and a general protocol is provided in Table 13.3.

In a scientific brief published on July 9, 2020, the World Health Organization implicates airborne transmission as one possible modality by which COVID-19 spreads—particularly in the context of aerosol-generating medical procedures (AGMPs) [16]. Provided below is a list of anesthesiologic procedures considered AGMPs:

- Manual mask ventilation [17]
- Endotracheal intubation [17]
- Extubation [17]
- Non-invasive ventilation such as BiPAP or CPAP [17]
- Bronchoscopy [17]
- Open airway suctioning [17]
- Processes which induce coughing and sputum generation [17]
- Tracheostomy [17]
- Cardiopulmonary resuscitation [17]

Table 13.2 Systemic physiological changes associated with advanced age [15]

	Clinical findings
Cardiopulmonary system	Systolic hypertension
	Increased afterload
	Left ventricular hypertrophy
	Decreased cardiac output
	Diastolic dysfunction
	Depressed baroreceptor function
	Decreased heart rate
	Increased incidence of arrhythmia, particularly atrial fibrillation
	Compromised small airway patency
	Increased closing capacity
	Chronic airway obstruction
	Increased shunting and dead space
	Micro-aspiration and concomitant chronic pulmonary inflammation
	Decreased ventilatory response to hypoxemia and hypercarbia
	Presence of pulmonary diseases such as COPD, pneumonia, and sleep apnea
Renal system	Decline (50%) of functioning nephrons by age 80
	Glomerular filtration rate reduces by 1–1.5% per year
	Reduced creatinine clearance
	Impaired electrolyte handling and ability to dilute/concentrate urine
	Increased risk of dehydration and sodium depletion
	Increased retention of drugs and drug metabolites
Hepatic system	Decreased liver mass and hepatic blood flow decreases (10% per decade)
	Decreased hepatic metabolism of drugs especially phase 1 reactions
	Altered pharmacokinetics of drugs
	Increased plasma concentration of water-soluble drugs
	Decreased plasma concentration of lipid-soluble drugs
	Cognitive, sensory, motor, and autonomic function impairments
Nervous system	Reduction in brain mass and neuronal size
	Decreased dendritic tree complexity and decreased number of synapses
	Decreased production of neurotransmitters, neurotransmitter receptors
	Impaired autonomic nervous system function
	Impaired thermoregulation
	Decreased baroreceptor sensitivity
	Increased susceptibility to dehydration
	Increased prevalence of central nervous system disorders in older patients such as cerebral atherosclerosis, Parkinson's disease, Alzheimer's disease, dementia, and depression
	Increased risk of delirium
Endocrine system	Potential for hormonal deficiency (insulin, thyroxine, growth hormone, aldosterone, testosterone)
	Potential for endocrine disorders such as diabetes, hypothyroidism, osteoporosis, impotence, and impaired electrolyte homeostasis

Table 13.3 General protocol for perioperative anesthesia evaluation during the COVID-19 pandemic

	Protocol	Notes
Prior to preoperative anesthesia evaluation	Utilize appropriate personal protective equipment	• White medical gowns • Medical gloves • Eye protection shields • Disposable surgical caps • Surgical masks or test-fit N95 masks or respirator
	Ensure patients practice good social distancing	• Patients should enter the consulting room one by one • Patients should minimize contact with the clinician and other individuals
	Screen patients prior to evaluation	• Measure patient body temperature with electronic ear thermometer • If body temperature is greater 37.3 °C, the infection control officer should be notified
During preoperative anesthesia evaluation	Conduct a thorough examination for COVID-19	• Take a detailed history • Conduct a thorough physical examination • Conduct a chest examination
	Practice good hand hygiene	• Wash hands with soap and water for at least 20 s • Or utilize hydrogen peroxide solution/gel
After preoperative anesthesia evaluation	Report suspected COVID-19 cases	• Maintain low threshold for suspicion of COVID-19 • Report suspected infection to the infection control officer
	Apply decontamination protocols	• Decontaminate the consulting room at the end of the shift • Wipe potentially contaminated surfaces (floor, furniture, equipment) with 2–3% hydrogen peroxide

The list above is not extensive and new information may identify additional AGMPs germane to anesthesia. In addition, surgical societies cite procedures that are potentially aerosol-generating, including oral and upper airway procedures and surgeries, upper GI endoscopies including ERCP (endoscopic retrograde cholangiopancreatography), and laparoscopies. It is uncertain whether aerosols generated from some procedures may be infectious, such as nebulizer administration and high-flow O_2 delivery.

13.2.3.2 General Anesthesia

While conclusive evidence indicating the use of particular airway techniques is not available, heuristics and clinical experience can be utilized to intuit the risk

associated with anesthetic choices. For instance, at low pressures, LMA seals the airway, thus protecting healthcare personnel; however, at high pressures, a complete seal may not be maintained, and a resultant leak may allow for the generation of aerosols. Another suggestion is that, in general, fiber-optic intubation is *not* advised. If difficult airway or cannot ventilate situation is anticipated, video laryngoscope, LMA for cannot intubate, and difficult airway cart and algorithm should be ready.

COVID-19 Airway Management and Anesthesia Recommendations

- *RSI* (rapid sequence induction) or a modified version of RSI with small tidal volumes must be used during induction [18].
- *Video laryngoscope should be used for intubation* and a high-quality heat- and moisture-exchanging filter (>99.97% rejection of airborne particles >0.3 μm) placed in between the facemask and breathing circuit or between the facemask and reservoir bag [18].
- *Monitored anesthesia care* cases with low fresh gas flow rate and spontaneous ventilation are permissible; note, during jaw lift and positive pressure administration, the likelihood of coronavirus transmission to the anesthesiologist increases. Risk is further increased to healthcare personnel if AGMPs (such as upper endoscopy and bronchoscopy) are conducted; accordingly, appropriate PPE must be donned for these procedures [17]. It is also important to recognize that transition from MAC to tracheal intubation augments risk to the anesthesiologist which could be why local experts report the use of endotracheal anesthetics instead of MAC when there is high prevalence of COVID-19 cases in the community [17].

13.2.3.3 Regional Anesthesia

To circumvent the risk associated with AGMPs, Uppal et al. provide a comprehensive review on the guidelines for providing regional anesthesia for suspected or confirmed COVID-19 patients [19]. Uppal et al. first recommend decreasing clinical load and testing and triaging patients adequately prior to anesthesia to ensure optimal allocation of hospital resources. Next, neuraxial anesthesia and peripheral nerve blocks should be encouraged for hospital procedures; however, because intraoperative conversion to general anesthesia is undesirable, anesthetic considerations and options should be thoroughly investigated and planned. Once anesthetic considerations are evaluated, regional anesthesia should be conducted in an operating room or isolation room to prevent the spread of disease to other healthcare providers and patients. To prevent fomite-based transmission of COVID-19, all non-essential items should be removed from the patient's room. Since neuraxial anesthesia and peripheral nerve blocks are considered non-aerosol-generating procedures, contact and droplet precautions can be used; however, evidence suggests that the use of airborne precautions for spinal anesthesia reduces risk of transmission. Importantly,

the anesthesiologist must be prepared with the appropriate PPE in case there is an emergent need to convert to general anesthesia. Modulating the flow rate of oxygen delivery and considering an appropriate oxygen delivery device can reduce risk of disease transmission while ensuring oxygen saturation. Considerations for neuraxial anesthesia include testing for the presence of thrombocytopenia, adequate dosing, and post-dural puncture headache; these considerations are enumerated, delineated, and discussed by Uppal et al. Considerations for peripheral nerve blocks include utilizing appropriate PPE (blocks performed in the head and neck area may indicate airborne precautions) and minimizing systemic toxicity; these factors are discussed in detail by Uppal et al. Patient monitoring must be thorough to eliminate the need for intra-operative conversion to general anesthesia; the use of a viral filter for the monitoring of gas samples is recommended [19]. The article by Uppal et al. utilized for our discussion of regional anesthesia is provided below and should be read for a more detailed review of these key points.

13.2.4 Treatment

Triaging patients is one of the first key steps in treatment; appropriate triage can allocate resources efficiently and provide targeted care. Triage of older patients is predicated on the presence of comorbidities, frailty of patients, and resource availability. Triage of older patients residing in congregate senior living facilities also involves isolating the patient from other residents or transporting the patient to an appropriate facility [20]. Mantha et al. propose a modified 6-min walk test for triaging but do not recommend its use for patients aged over 70 years old as they may already qualify for emergent care [21]. The recent NICE guideline of frailty assessment of older adults upon admission to hospital, irrespective of age and COVID-19 status, is recommended to efficiently utilize available resources [22].

Because of reports of asymptomatic and pre-symptomatic disease transmission, patients admitted to the hospital for non-COVID-19-related surgical procedures must also be triaged; essentially, all surgical procedures must be planned and approached systematically to protect OR personnel. The general protective procedures for conducting surgeries during this pandemic are provided in Fig. 13.1.

As no anti-viral therapeutics against COVID-19 have been conclusively established, treatment is primarily supportive. Several pharmacological agents and treatments are utilized to ameliorate symptoms of COVID-19, such as paracetamol for fever, codeine for cough, and ventilation for respiratory distress [3]. For older patients presenting with atypical symptoms, drugs such as haloperidol and metoclopramide can be used to treat delirium/confusion and nausea, respectively [3]. Another important consideration for geriatric patients is appropriate dosing of

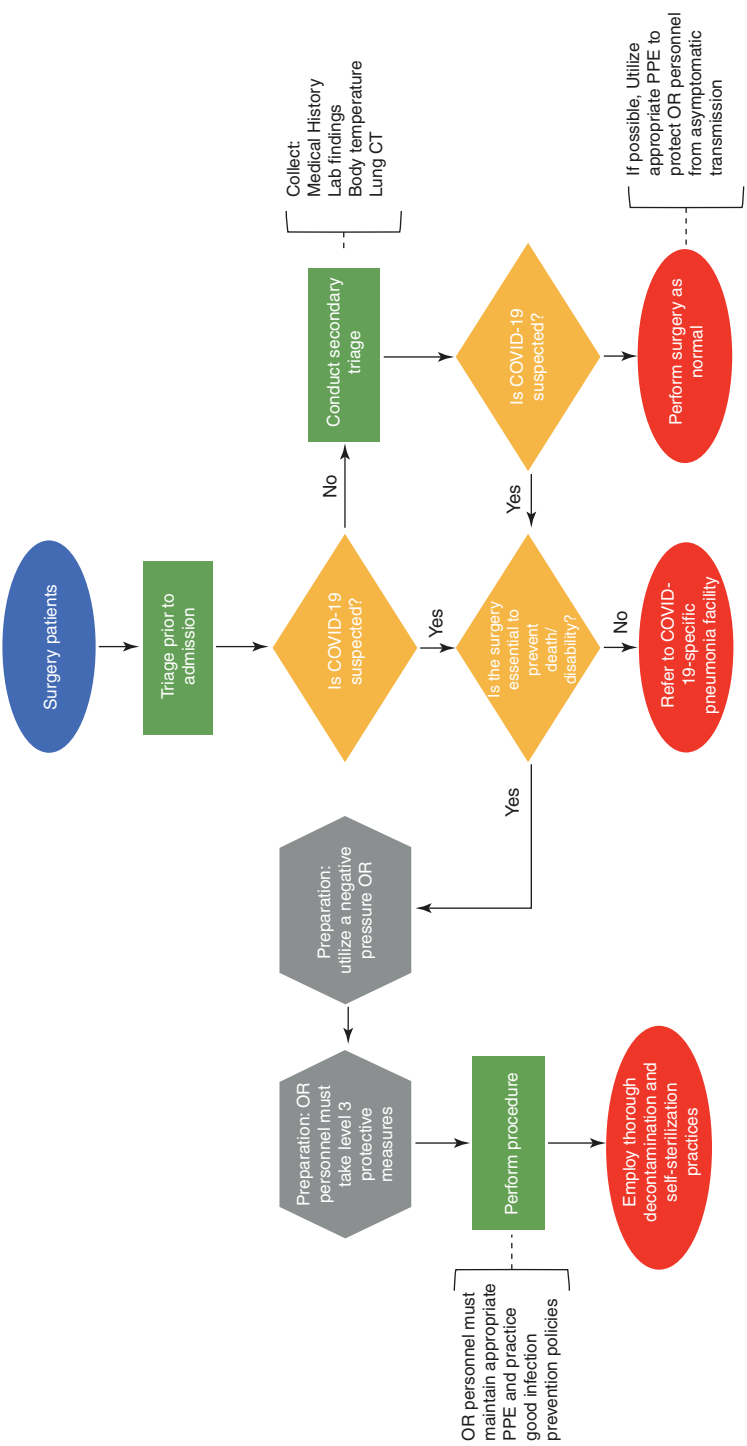


Fig. 13.1 Flowsheet demonstrating the protocol for surgery patients during the COVID-19 pandemic. (Modified from Zhao et al. [23])

Table 13.4 Common typical and atypical symptoms along with presentation, clinical relevance, and treatment in geriatric COVID-19 patients

	Symptom	Presentation in geriatric patients	Clinical relevance	Treatment	Source
Typical symptoms	Fever	Attenuated fever response	Define fever as: 1. Single oral temperature >100 °F 2. Multiple oral temperatures >99 °F 3. >2 °F increase from baseline	Paracetamol Metamizole	[3, 6, 10]
	Cough	May be conflated with age-related comorbidities	Low threshold of suspicion for COVID-19 Frequent testing for rapid diagnosis, triaging, and isolation	Codeine	[3, 6]
	Dyspnea			Oxygen therapy	[3, 6]
Atypical symptoms	Nausea	May be conflated with age-related comorbidities and may be more common in older patients		Metoclopramide Domperidone	[3, 6]
	Delirium			Haloperidol Midazolam	[3, 6]
	Fatigue			NA	[6, 11]
	Fall			NA	[6, 11]

medications; typically, potentially due to age-related changes in renal and hepatic metabolism, older patients are more sensitive to analgesics such as midazolam [3, 24, 25]. Information regarding treatment of common symptoms is summarized in Table 13.4.

13.2.5 Recent Advances in the Treatment of Coronavirus

Several candidate pharmacological treatments to attenuate the severity of COVID-19 are currently being investigated. As severe outcomes following COVID-19 are more frequently reported in older patients, this developing research should be continuously reviewed by healthcare providers treating geriatric COVID-19 patients.

Zhang and Yap reported in 2004 that a combination of lopinavir and ritonavir, which is used to treat HIV (human immunodeficiency virus), demonstrates weak in vitro activity against severe acute respiratory syndrome-associated coronavirus (SARS-CoV) [26]. Accordingly, Cao et al. explicate the efficacy of lopinavir/ritonavir combination in patients (median age, 58 years; IQR, 49–68 years) with COVID-19 was not significantly different from standard care in terms of time to clinical improvement in critically ill patients, mortality in critically ill patients, and viral load and detectability [27]. Cao et al. explain that their results do not necessarily indicate that lopinavir/ritonavir is ineffective. Dalerba et al., Kunz, and Havlichek suggest that experimental parameters, such as delayed administration of lopinavir/

ritonavir and primary outcome measures may obfuscate the efficacy of lopinavir/ritonavir [28]. In another study, COVID-19 patients (median age, 52 years; IQR, 42–62 years) treated with lopinavir/ritonavir along with ribavirin and interferon beta-1b displayed significantly decreased time from onset of infection to negative nasopharyngeal swab and improved secondary clinical outcomes such as sequential organ failure assessment score [29]. These data suggest that more studies to assess the efficacy and clinical use of lopinavir/ritonavir combination for COVID-19 in elderly patients are required.

The non-selective cyclooxygenase inhibitor, indomethacin [30], was shown by Xu et al. to possess anti-viral properties against SARS-CoV-2 pseudovirus in vitro and canine coronavirus [31]. More testing is needed to confirm the utility of indomethacin for COVID-19, keeping in mind that advanced age may contraindicate indomethacin due to harmful side effects [30, 32].

Remdesivir, an anti-viral RNA-dependent RNA polymerase inhibitor, is postulated by Cao et al. to be a putative treatment for COVID-19; the severity of illness in animal models of SARS-CoV and Middle East respiratory syndrome-related coronavirus was attenuated through treatment with remdesivir [33]. In a randomized control trial, COVID-19 patients (median age, 65 years; IQR, 56–71 years) treated with remdesivir displayed numerically shorter time to clinical improvement compared with the placebo group; however, the difference between the treatment and placebo group was not statistically significant [34]. Similar results are reported for 28-day mortality, duration of mechanical ventilation, and viral load [34].

A more recent randomized control trial by Biegel et al. reports that the remdesivir group had shorter time to recovery and numerically lower mortality (not statistically significant) compared with the placebo group; in this study, the mean patient age is 58.9 ± 15 years [35].

Dexamethasone is the latest candidate treatment for COVID-19 and is reported to decrease the mortality of COVID-19 patients on ventilators by one-third [36]. Additional studies regarding the efficacy of dexamethasone as a pharmacotherapy will certainly be published; it is important to consider the most recent and accurate literature regarding its usage for COVID-19. Moreover, data on age of COVID-19 patients treated with dexamethasone must be examined in determining its utility in geriatric patients.

A summary of promising treatments for COVID-19 is provided in Table 13.5.

13.2.6 Outcomes

Adverse outcomes refer to death due to COVID-19 and complications such as acute kidney injury, acute respiratory distress syndrome, and secondary infection. Several

Table 13.5 Candidate pharmacotherapies for COVID-19 along with their biological effects, reported clinical outcomes, advantages, and disadvantages

Therapy	Biological effects	Reported clinical outcomes	Advantages	Disadvantages	References
Lopinavir/ritonavir	Type 1 aspartate protease inhibitor	Similar to placebo in one study but improved outcomes in another when administered with interferon beta-1b and ribavirin	Some results demonstrating improved outcomes	Inconsistent outcomes reported	[25, 28]
Indomethacin	Cyclooxygenase inhibitor	NA	In vitro and in vivo evidence suggests a potential use for COVID-19	Lack of randomized clinical trials Side effects including gastritis, renal dysfunction, and platelet dysfunction which could be deleterious to geriatric COVID-19 patients	[30–32]
Remdesivir	RNA-dependent RNA polymerase inhibitor	Reports suggest numerically or statistically significant shorter time to recovery; numerically reduced mortality rate	May potentially reduce mortality and time to clinical recovery—more evidence is needed	In short supply	[34–36]
Dexamethasone	Anti-inflammatory corticosteroid	NA	Widely available and inexpensive	Lack of randomized clinical trials	[36]

factors contribute to the selective vulnerability of older patients to COVID-19. Age-dependent comorbidities, such as cerebrovascular disease, COPD, and cardiovascular disease, disrupt cardiopulmonary function and impose physiological stresses that may therefore lead to more severe outcomes following COVID-19 [37]. Additionally, medications used to treat comorbidities may also exacerbate SARS-CoV-2 infections. The most controversial of these are the use of ACE inhibitors (ACEIs) and aldosterone receptor blockers (ARBs) for diabetes and hypertension; reports differ on whether the role of ACEIs/ARBs in the renin-angiotensin-aldosterone system (RAAS) is beneficial or detrimental in COVID-19 [38]. A schematic of RAAS is provided in Fig. 13.2. The controversial role of ACEIs/ARBs in COVID-19 is portrayed in Fig. 13.3.

In the absence of conclusive evidence, as of March 17, 2020, the American Heart Association, the Heart Failure Society of America, and the American College of Cardiology recommend the continued use of ACEIs and ARBs for patients with prescriptions unless otherwise stated by personal physicians [39]. More research is needed to conclusively state the effects of ACEIs/ARBs and drugs, such as corticosteroids, for other age-related disorders. Age-related immunological changes such as decreased production of naïve T and B cells, attenuated lymphocyte proliferation and activity, and ultimately a blunted immune response further contribute to the vulnerability of geriatric patients to COVID-19 [6].

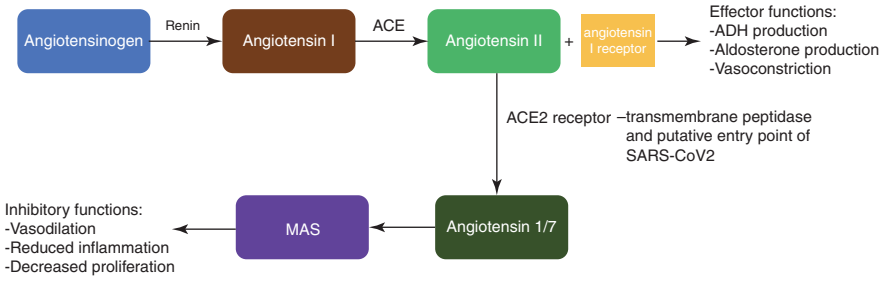


Fig. 13.2 Schematic depiction of RAAS [38]

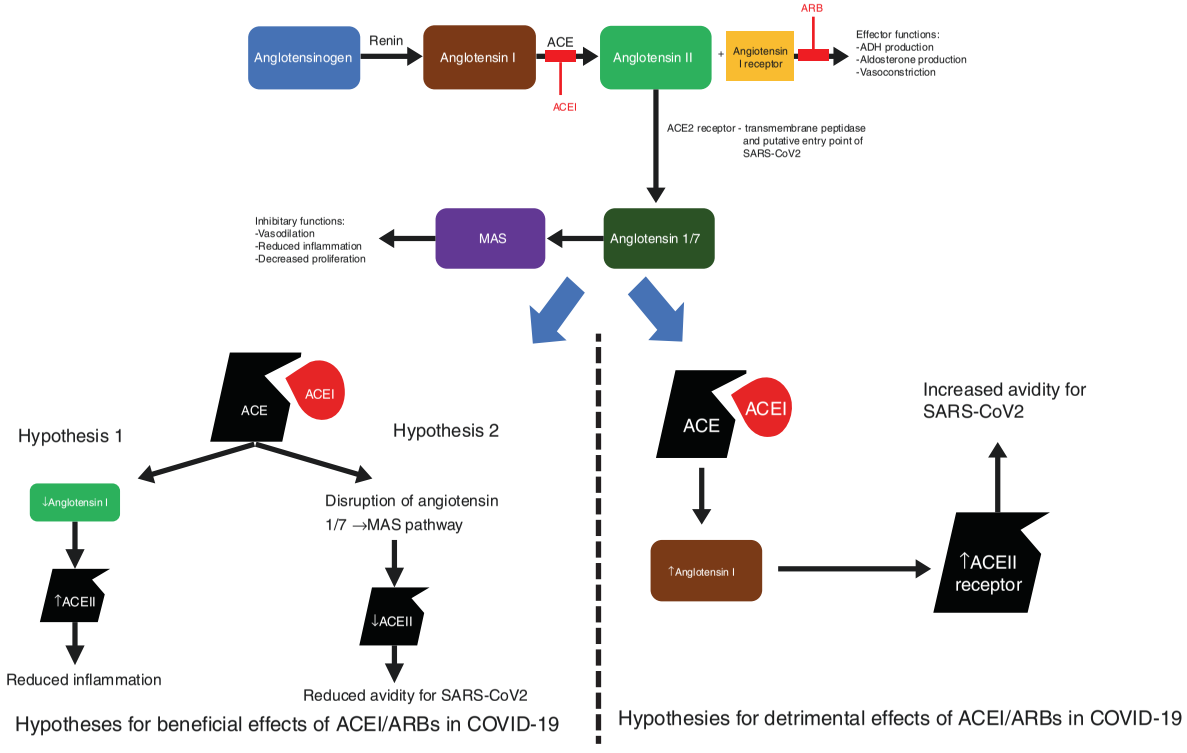


Fig. 13.3 Contrasting hypotheses suggest both beneficial and detrimental effects of ACEI and ARBs in COVID-19 [38]

References

1. CDC. Coronavirus Disease 2019 (COVID-19) in the U.S. Centers for Disease Control and Prevention; 14 July 2020. Available from https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/cases-in-us.html. Accessed 20 July 2020.
2. CDCMMWR. Severe outcomes among patients with coronavirus disease 2019 (COVID-19) — United States, February 12–March 16, 2020. MMWR Morb Mortal Wkly Rep. 2020;69 https://doi.org/10.15585/mmwr.mm6912e2.
3. Kunz R, Minder M. COVID-19 pandemic: palliative care for elderly and frail patients at home and in residential and nursing homes. Swiss Medical Weekly. 2020;150(1314) https://doi.org/10.4414/smw.2020.20235.
4. Report-COVID-2019_20_marzo_eng.pdf. [Online]. Available from https://www.epicentro.iss.it/coronavirus/bollettino/Report-COVID-2019_20_marzo_eng.pdf. Accessed 20 July 2020
5. Kolifarhood G, et al. Epidemiological and clinical aspects of COVID-19; a narrative review. Arch Acad Emerg Med. 2020;8(1). Available from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7117787/. Accessed 20 July 2020.
6. Nikolich-Zugich J, Knox KS, Rios CT, Natt B, Bhattacharya D, Fain MJ. SARS-CoV-2 and COVID-19 in older adults: what we may expect regarding pathogenesis, immune responses, and outcomes. GeroScience. 2020:1–10. https://doi.org/10.1007/s11357-020-00186-0.
7. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun. 2020;109:102433. https://doi.org/10.1016/j.jaut.2020.102433.
8. Kimball A, et al. Asymptomatic and presymptomatic SARS-CoV-2 infections in residents of a long-term care skilled nursing facility — King County, Washington, March 2020. MMWR Morb Mortal Wkly Rep. 2020;69(13):377–81. https://doi.org/10.15585/mmwr.mm6913e1.
9. Liu K, Chen Y, Lin R, Han K. Clinical features of COVID-19 in elderly patients: a comparison with young and middle-aged patients. J Infect. 2020;80(6):e14–8. https://doi.org/10.1016/j.jinf.2020.03.005.
10. High KP, et al. Clinical practice guideline for the evaluation of fever and infection in older adult residents of long-term care facilities: 2008 update by the Infectious Diseases Society of America. Clin Infect Dis. 2009;48(2):149–71. https://doi.org/10.1086/595683.
11. Godaert L, Proye E, Demoustier-Tampere D, Coulibaly PS, Hequet F, Dramé M. Clinical characteristics of older patients: the experience of a geriatric short-stay unit dedicated to patients with COVID-19 in France. J Infect. 2020;81(1):e93–4. https://doi.org/10.1016/j.jinf.2020.04.009.
12. Kong T. Longer incubation period of coronavirus disease 2019 (COVID-19) in older adults. Aging Med. 2020;3(2):102–9. https://doi.org/10.1002/agm2.12114.
13. Zhu T, Wang Y, Zhou S, Zhang N, Xia L. A comparative study of chest computed tomography features in young and older adults with corona virus disease (COVID-19). J Thorac Imaging. 2020;35(4):W97. https://doi.org/10.1097/RTI.0000000000000513.
14. Hewitt J, et al. The effect of frailty on survival in patients with COVID-19 (COPE): a multicentre, European, observational cohort study. Lancet Public Health. 2020. p. S2468266720301468. https://doi.org/10.1016/S2468-2667(20)30146-8.
15. Bittner E, Vassallo S, Wiener-Kronish J. Geriatric issues in anesthesia. Clinical Pain Advisor. 19 Jan 2019. https://www.clinicalpainadvisor.com/home/decision-support-in-medicine/anesthesiology/geriatric-issues-in-anesthesia/. Accessed 20 July 2020.
16. Transmission of SARS-CoV-2: implications for infection prevention precautions. https://www.who.int/news-room/commentaries/detail/transmission-of-sars-cov-2-implications-for-infection-prevention-precautions. Accessed 20 July 2020.
17. COVID-19 and anesthesia FAQ. Anesthesia Patient Safety Foundation. https://www.apsf.org/covid-19-and-anesthesia-faq/. Accessed 20 July 2020.

18. Zucco L, Levy N, Ketchandji D, Aziz M, Ramachandran SK. Recommendations for airway management in a patient with suspected coronavirus (2019-nCoV) infection. https://www.apsf.org/news-updates/perioperative-considerations-for-the-2019-novel-coronavirus-covid-19/ Accessed on 20.09.2020.
19. Uppal V, Sondekoppam RV, Landau R, El-Boghdadly K, Narouze S, Kalagara HKP. Neuraxial anaesthesia and peripheral nerve blocks during the COVID-19 pandemic: a literature review and practice recommendations. Anaesthesia. 2020; https://doi.org/10.1111/anae.15105.
20. Malone ML, et al. COVID-19 in older adults: key points for emergency department providers. https://gedcollaborative.com/article/covid-19-in-older-adults-key-points-for-emergency-department-providers/ Accessed on 20.09.2020.
21. Mantha S, Tripuraneni SL, Roizen MF, Fleisher LA. Proposed modifications in the 6-minute walk test for potential application in patients with mild COVID-19: a step to optimize triage guidelines. Anesth Anal. 2020;131(2):398–402. https://doi.org/10.1213/ANE.0000000000004986.
22. NICE publishes first rapid COVID-19 guidelines | News and features | News. NICE. https://www.nice.org.uk/news/article/nice-publishes-first-rapid-covid-19-guidelines. Accessed 20 July 2020.
23. Zhao S, et al. Anesthetic management of patients with COVID 19 infections during emergency procedures. J Cardiothorac Vasc Anesth. 2020;34(5):1125–31. https://doi.org/10.1053/j.jvca.2020.02.039.
24. Cavalieri TA. Managing pain in geriatric patients. J Am Osteopath Assoc. 2007;107(suppl_4):ES10–6. Available from https://jaoa.org/article.aspx?articleid=2093506. Accessed 20 July 2020.
25. Chauhan M, Carter E, Rood P. Intravenous midazolam dose ranges in older patients sedated for oral surgery--a preliminary retrospective cohort study. Br Dent J. 2014;216(5):E12. https://doi.org/10.1038/sj.bdj.2014.197.
26. Zhang XW, Yap YL. Old drugs as lead compounds for a new disease? Binding analysis of SARS coronavirus main proteinase with HIV, psychotic and parasite drugs. Bioorg Med Chem. 2004;12(10):2517–21. https://doi.org/10.1016/j.bmc.2004.03.035.
27. Cao B, et al. A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. N Engl J Med. 2020;382(19):1787–99. https://doi.org/10.1056/NEJMoa2001282.
28. A trial of lopinavir–ritonavir in Covid-19. N Engl J Med. 2020;382(21):e68. https://doi.org/10.1056/NEJMc2008043.
29. Hung IF-N, et al. Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. Lancet. 2020;395(10238):1695–704. https://doi.org/10.1016/S0140-6736(20)31042-4.
30. Marinella MA. Indomethacin and resveratrol as potential treatment adjuncts for SARS-CoV-2/COVID-19. Int J Clin Pract. 2020;74(9):e13535. https://doi.org/10.1111/ijcp.13535.
31. Xu T, Gao X, Wu Z, Selinger DW, Zhou Z. Indomethacin has a potent antiviral activity against SARS CoV-2 in vitro and canine coronavirus in vivo. Microbiology, preprint, 2020. https://doi.org/10.1101/2020.04.01.017624.
32. Indomethacin (oral route) before using - Mayo Clinic. https://www.mayoclinic.org/drugs-supplements/indomethacin-oral-route/before-using/drg-20069700. Accessed 20 July 2020.
33. Cao Y, Deng Q, Dai S. Remdesivir for severe acute respiratory syndrome coronavirus 2 causing COVID-19: An evaluation of the evidence. Travel Med Infect Dis. 2020;35:101647. https://doi.org/10.1016/j.tmaid.2020.101647.
34. Wang Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 2020;395(10236):1569–78. https://doi.org/10.1016/S0140-6736(20)31022-9.
35. Beigel JH, et al. Remdesivir for the treatment of Covid-19 — preliminary report. N Engl J Med. 2020; https://doi.org/10.1056/NEJMoa2007764.

36. Ledford H. Coronavirus breakthrough: dexamethasone is first drug shown to save lives. Nature. 2020;582(7813):469. https://doi.org/10.1038/d41586-020-01824-5.
37. Wang L, et al. Coronavirus disease 2019 in elderly patients: characteristics and prognostic factors based on 4-week follow-up. J Infect. 2020;80(6):639–45. https://doi.org/10.1016/j.jinf.2020.03.019.
38. Rico-Mesa JS, White A, Anderson AS. Outcomes in patients with COVID-19 infection taking ACEI/ARB. Curr Cardiol Rep. 2020;22(5) https://doi.org/10.1007/s11886-020-01291-4.
39. Patients taking ACE-i and ARBs who contract COVID-19 should continue treatment, unless otherwise advised by their physician. American Heart Association. https://newsroom.heart.org/news/patients-taking-ace-i-and-arbs-who-contract-covid-19-should-continue-treatment-unless-otherwise-advised-by-their-physician. Accessed 20 July 2020.

Control of Spread of Coronavirus Disease

14

Gentle Sunder Shrestha and Saurabh Pradhan

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes the disease COVID-19 has been declared as pandemic by the World Health Organization (WHO) and has spread to more than 200 countries around the world. Despite stringent and desperate measures to control the spread, such as whole country lockdown for weeks to months, more than 14 million people have been affected till date, and more than hundred thousands of people are getting infected each day [1]. The medical world was unprepared for the unprecedented threat that has caused the loss of so many lives and long-lasting repercussions on worldwide economy. However, with knowledge about the disease gradually increasing, measures to stop the spread are being implemented. In this chapter we discuss about what the current evidences recommend regarding prevention of spread of SARS-CoV-2.

14.1 Transmission of Coronavirus

The mode of transmission has major implications in prevention of spread of a disease. The close genetic similarity of SARS-CoV-2 to bat coronaviruses suggests a zoonotic origin with a spillover to humans in late 2019. Human-to-human transmission was confirmed on January 2020 [2], but confusion remains regarding the mode of transmission, with droplets and aerosols both being attributed.

Viral particles can spread through encapsulation in globs of mucus, saliva, and water. Dissemination of such particles may depend on various factors but primarily on the size of the globs. Bigger globs fall to the ground within a short distance before they can evaporate, forming droplets [3]. Smaller globs evaporate and form

G. S. Shrestha (✉) · S. Pradhan
Department of Anaesthesiology, Tribhuvan University Teaching Hospital, Kathmandu, Nepal

H. Prabhakar et al. (eds.), *Clinical Synopsis of COVID-19*,
https://doi.org/10.1007/978-981-15-8681-1_14

respiratory nuclei or aerosols, which can suspend in the air and drift farther away than the droplets. Though the distinction between droplets and aerosols is a gray area, there is general agreement that particles with a diameter of 5 μm or less are aerosols, whereas particles of a diameter more than 5 μm would be droplets [4].

Droplet transmission means infection can be acquired through direct contact of infected secretions, or indirectly through fomites. If SARS-CoV-2 is primarily spread by respiratory droplets, wearing a medical mask, face shield, or keeping 6 ft. distance in between individuals should be adequate to prevent transmission. If, however, SARS-CoV-2 is carried by aerosols, then such methods would not be sufficient, and an N95 respirator would be required.

Investigators have demonstrated that speaking, coughing, and even breathing can produce aerosols [5]. Experimental data have suggested that virus particles of COVID-19 can remain suspended in the air for 3 h [6]. However, the experimental conditions did not replicate a human cough and may not be generalizable to exposures that health-care workers typically encounter. Demonstrating that speaking and coughing can generate aerosols or that it is possible to recover viral RNA from air, however, does not prove aerosol-based transmission as information regarding transmissions in general populations do not match with long-range aerosol-based transmission. The reproduction number for COVID-19 is estimated to be about 2.5, meaning that each person with COVID-19 infected an average of 2–3 other people. This reproduction number is similar to influenza and quite different from that of viruses that are well-known to spread via aerosols such as measles, which has a reproduction number closer to 18 [5].

Evidence suggesting airborne transmission is therefore inconsistent, and thus guidelines also differ in recommendations regarding the type of precautions. However there is a consensus that airborne transmission might occur during aerosol-generating procedures (AGP). AGP are medical procedures that create aerosols *in addition to* those that the patient creates spontaneously [7]. There is poor agreement as to what constitutes an AGP. However, the most consistent association across multiple studies has been identified with tracheal intubation with a pooled odds ratio of 6.6 [8]. Again it must be emphasized that intubation presents a period of prolonged and closed contact with the upper respiratory tract of the patient and that the patients requiring intubation are much sicker indicating a higher viral load. Furthermore these data have been extrapolated from SARS and not SARS-CoV-2.

14.2 Infection Prevention and Control Practices in COVID-19

Apart from usual standard practices involving infection prevention and control (IPC), there are several additional protocols that may be applied in the period of a pandemic to minimize the exposure to COVID-19.

14.2.1 Screening and Triage

Screening for COVID-19 can be performed even before entry to the health-care center with the help of telemedicine. Before scheduling appointments, communication via telephone or video call can be done to assess the symptoms, screen for COVID-19, determine whether the patient requires hospital visit or not, and recommend necessary measures if visit is not required. Many patients with COVID-19 can be managed from home, but they need to be educated about alarming signs and symptoms and told to report urgently if they experience any such manifestations. For those who require additional evaluation, referral to a clinic or health center dedicated to the management of patients with confirmed or presumptive COVID-19 is preferable. In case of unavailability of such facilities, referral to any other center is needed where necessary precautions should be pre-arranged [9].

At the hospital entry, all patients need to be screened for COVID-19 before entering the hospital premises. A high index of suspicion is required. A triage station such as fever clinic can be established, where a compulsory temperature check (infrared thermometers help avoid contact with the patient) and an assessment of symptoms and contact history should be performed. Immediate isolation in a separate area should be performed if there is suspicion of COVID-19. Visitors should be restricted and also screened for exposure and assessed for symptoms and temperature measured [9].

14.2.2 Source Control

Screening cannot identify those who are in their presymptomatic phase of illness or are asymptomatic, which can account for a large proportion of cases (around 40% documented in published literature [10] and may be up to 99% in some places as observed from unpublished sources [11]). Therefore source control becomes a primary modality in prevention of spread of the disease. Hand hygiene is of prime importance, and alcohol-based hand rubs (ABHR) or a sink for hand washing with soap and water should be available at the entry and at places where contact may take place. An ABHR consisting of 60–95% alcohol is preferred over soap and water due to evidence of better compliance. However when hands are visibly soiled, soap and water should be used for at least 20 s [9].

Facemask should be worn by all individuals. The benefit of universal masking has been evidenced in a study done in Mass General Brigham, the largest health-care system in Massachusetts, with more than 75,000 employees. After the universal masking policy was adopted, the proportion of health-care personnel testing positive declined from 14.7 to 11.5% with an average decrease of 0.49% per day [12]. Proper respiratory etiquette should be ensured. A recent systematic review and

meta-analysis reported that transmission of viruses was lower with physical distancing of 1 m or more, compared with a distance of less than 1 m (pooled adjusted odds ratio of 0.18, 95% CI 0.09–0.38), and the protection was increased as distance was lengthened [13]. We support the practice of physical distancing of at least 1 m. Signs that remind people of the precautionary measures should be placed at various areas. Specific seating arrangements and placing markers for those standing in queue are helpful in ensuring physical distancing [9].

14.2.3 Universal Testing

Depending on guidance from health departments, both local and state, testing availability, and how quickly results are available, facilities can consider implementing pre-admission or pre-procedure diagnostic testing [9]. The results can help taking decisions about rescheduling elective procedures or the need for additional transmission-based precautions during patient care. However, false negative results can occur, especially during the incubation period.

14.2.4 Engineering Controls

Engineering controls can be optimized to decrease the potential spread of COVID-19 from infected individuals. Physical barriers and dedicated pathways to guide symptomatic patients through triage areas, remote triage facilities for patient intake areas, outdoor assessment and triage stations for patients with respiratory symptoms, and improving indoor air quality (directionality, filtration, exchange rate, maintenance) in all shared spaces are some of the techniques to help contain infection [9].

14.2.5 Administrative Measures

Policies should be made available whereby the identification of suspected or confirmed COVID-19 is reported within the hospital staffs to promote situational awareness and implementation of necessary precautions. Reporting to necessary public health authorities and designating specific persons responsible for communication is important. COVID-19 patients should be cared for by dedicated healthcare personnel, and thus staffing needs and modifications need to be determined [9]. Prior to designating staffs for the care of COVID-19 patients, adequate training regarding infection prevention techniques, which include donning and doffing methods of PPE, should be provided. An IPC program run by a dedicated team would be ideal to achieve the highest level of effectiveness in controlling the outbreak to achieve the highest level of effectiveness in the response to the outbreak [14].

14.2.6 Patient Placement

Patients with suspected or confirmed SARS-CoV-2 infection should be segregated in a different section of the hospital, away from other patients. Ideally they should be admitted in a single room with a dedicated bathroom. Confirmed patients can be cohorted together if single rooms are not available. Transport and movement of the patient outside of the room should be limited. If necessary, a facemask should be applied to the patient during transport [9].

Airborne infection isolation rooms (AIIRs) should be reserved for patients undergoing aerosol-generating procedures. These rooms are single-patient rooms with anteroom and a dedicated bathroom. To avoid the spread of infected aerosols, a negative pressure is maintained in the room by having the exhaust air flow rate exceed the supply air flow rate [15]. Staff protection inside the AIIR is ensured by air flow patterns within the room. A pressure difference of at least 2.5 Pa and ventilation with at least 6 air changes per hour (ACH) for existing rooms and 12 ACH for new rooms are recommended [16]. However guidelines may vary with some countries suggesting a pressure difference of 30 Pa [17]. In addition to general ventilation, other source control methods such as high-efficiency particulate air (HEPA) filters are required. HEPA filters can capture 99.97% of 0.3 mm particles and are important to remove infectious aerosols before they are dispersed throughout the room or from air that is re-circulated [15]. An anteroom ensures additional protection by creating two door barriers and causing dilution of any aerosols that may escape when AIIR door is opened [15].

14.2.7 Personal Protective Equipment

Apart from standard precautions, all HCP involved in direct care of the patient or handling of their body fluids needs to put on personal protective equipment (PPE). PPE may have to be applied as a universal precaution if there is moderate to substantial community transmission, in which case a facemask and eye protection becomes necessary, with N95 respirator applied for aerosol-generating procedures. Hand hygiene should be performed prior to donning and during doffing of PPE as well as according to the WHO "5 moments of hand hygiene."

- *Respirator or Facemask*: WHO states that a facemask is adequate for general care [14], whereas Centers for Disease Control and Prevention (CDC) guidelines prefer an N95 respirator or equivalent or higher-level respirator but acknowledge a facemask as an acceptable alternative if a respirator is unavailable [9]. For aerosol-generating procedures, a respirator is recommended. Respirators protect against airborne infection, gases, and vapors, whereas facemask only protects against droplets. There is lack of studies comparing the efficacy of respirators versus facemasks in preventing SARS-CoV-2 transmission, but several reports

suggest great reduction in transmission with standard and contact precautions, with respirators being reserved for aerosol-generating procedures. [18, 19]
- Respirators need to be certified by the Centers for Disease Control and Prevention (CDC)/National Institute for Occupational Safety and health (NIOSH) and are classified as filtering facepiece respirators (CDC) or powered air-purifying respirators (PAPRs). FFPs and facemasks are single use and should be discarded appropriately. However during scarcity, N95 respirator can be reused, with a study showing no loss of efficacy up to three times after disinfection [20].
- Prior to use, FFPs need to be fit tested.
- *Eye Protection*: Eye protection device includes either goggles or a face shield. Goggles only cover the eyes, but a face shield covers the eyes as well as the front and sides of the face. Eye protection needs to be compatible with the respirator used as to avoid any interference with positioning [9].
- *Gloves:* Clean, non-sterile gloves are required to be worn upon entry into the care area. The number of layers of gloves to be worn has not been specified by guidelines, and the practice seems to vary among institutions and health-care centers [9].
- *Gowns and Coveralls:* A gown is a protective wear that is worn from the front and thus prevents frontal contamination only with partial neck to knee protection. Coverall is designed to protect the entire body and thus enables 360° of protection from contagion. We prefer a coverall when available as it ensures higher protection; however it is cumbersome to wear and work for longer time periods, and doffing is also more difficult than a gown.

14.2.8 Specific Precautions for Aerosol-Generating Procedures

As discussed earlier, there are certain medical procedures that are considered aerosol generating. The list includes but is not limited to:

- Endotracheal intubation and extubation
- Non-invasive ventilation
- Bag valve mask ventilation
- Cardiopulmonary resuscitation
- Bronchoscopy
- Open suctioning of airways
- Nebulization
- High-flow nasal cannula
- Tracheostomy

Apart from tracheal intubation, there is no robust data to suggest that the procedures mentioned above are aerosol-generating procedures or that there is a higher probability of transmission associated with them. However considering a safety-first approach, it would be reasonable to avoid these procedures if possible and use other alternatives. For example, metered dose inhalers may be used instead of

nebulizers for inhalational therapy of drugs. If performed, however, the following precautions should be mandated. These include wearing an N95 or equivalent or higher-level respirator, eye protection, gloves, and a gown; performing the procedure in an AIIR; restricting the number of health-care personnel in the room to only those essential for patient care; and disinfecting the room surfaces promptly.

14.2.9 Environmental Infection Control

Environmental infection control is a crucial step in mitigating disease transmission, and many hospitals have implemented protocols to disinfect areas where COVID-19 patients have been cared for. Such protocols include the use of dedicated medical equipment or disposable equipment if possible, management of laundry, food service utensils, and medical waste in accordance to routine protocols; and environmental cleaning and disinfection. The importance of environmental disinfection was illustrated in a study from Singapore. Viral RNA was detected on almost all surfaces tested such as handles, light switches, bed, and handrails, when disinfection was not performed; however no viral RNA was detected after cleaning the rooms with sodium dichloroisocyanurate [22].

Prior to disinfection, cleaning of contaminated surfaces is essential to reduce the infective load and remove organic matter that would impede proper disinfection by rapidly inactivating the chemicals. Cleaning should progress from the least soiled (cleanest) to the most soiled (dirtiest) areas, and from the higher to lower levels [19].

Disinfectant solutions must be prepared and used according to the manufacturer's recommendations for volume and contact time as the concentration and contact time are critical for effective surface disinfection, which is considered as >3 $\log^{10}$ reduction of human coronavirus [23]. Hypochlorite-based products are most commonly used in this. They form hypochlorous acid (HOCl) when dissolved in water, which is the primary antimicrobial compound. The recommendation of 0.1% (1000 ppm) will inactivate the vast majority of pathogens that may be present in the health-care setting. However, for blood and body fluids large spills (i.e., more than about 10 mL), a concentration of 0.5% (5000 ppm) is recommended [24]. Ethanol 70–90% and hydrogen peroxide >0.5% can also be used as disinfectants. The routine application of disinfectant by spraying or fogging to environmental spaces, whether indoor or outdoor, is not effective, and is thus not recommended [21]. Personnel performing cleaning and disinfection must don appropriate PPE, including an N95 or equivalent or higher-level respirator, while cleaning AIIR.

Adjunctive disinfection methods, such as ultraviolet (UV) light, have been approved as non-touch techniques. These technologies developed for use in health-care settings are used during terminal cleaning (cleaning a room after a patient has been discharged or transferred), and it must be emphasized that these techniques only supplement but do not replace the manual cleaning techniques. There are also safety concerns, since UV light fixtures can produce sunburn-like skin reactions and eye damage as well as generate ozone if strict safety measures are not utilized in their installation and maintenance [25].

14.2.10 Quarantine

Quarantine is a method of separating persons who may have been exposed to an infectious agent but have not become ill from those who have not been exposed to the agent. It is considered one of the oldest and most effective tools of controlling communicable disease outbreaks [26, 27]. A mathematical model done on the spread of COVID-19 demonstrated that pandemic could not be controlled without strict quarantine [28].

Individuals who may have had prolonged close contact with someone with confirmed COVID-19 patients should undergo quarantine for 14 days after their last contact [29]. A contact has been defined as having face-to-face contact within 1 m for >15 min (CDC extends the perimeter to within 6 ft.), staying in the same close environment as a COVID-19 patient (including sharing a workplace, classroom, or household or being at the same gathering) for any amount of time, or travelling in close proximity with (i.e., within 1 m separation from) a COVID-19 patient in any kind of conveyance [9, 14]. For health-care personnel, providing direct care or performing aerosol-generating procedures without using proper personal protective equipment or having unprotected direct contact with infectious secretions or excretions of the person with confirmed COVID-19 is also considered a close contact [30].

It is difficult to determine the time period from when the patient may have been infectious. The exposure window is considered to start from 2 days before symptom onset up to the time when infection precautions can be discontinued (will be discussed below). For asymptomatic patients, it is even more challenging. Patients with COVID-19 should be considered infectious 2 days after their exposure; when exact time of exposure cannot be determined, it may be reasonable to consider 2 days prior to the positive test result [31].

Testing asymptomatic individuals after an exposure may give false negatives, and therefore it is a better practice to continue precautions for the total time period irrespective of the test result.

14.2.11 Discontinuing Infection Precautions

For patients with COVID-19, the decision to discontinue precautions may be time based (symptom based) or test based [32]. Choosing one strategy over another should be determined on a case-by-case basis, since each strategy has theoretic limitations. Available data indicate that persons with mild to moderate COVID-19 remain infectious no longer than 10 days after symptom onset, but persons with more severe to critical illness or severe immunocompromise likely remain infectious no longer than 20 days after symptom onset [33]. Although recovered persons can continue to shed detectable SARS-CoV-2 RNA in upper respiratory specimens for up to 3 months after illness onset, the concentrations in their secretions are considerably lower than during illness, and thus infectiousness is unlikely [34]. Therefore current guidelines recommend time-based strategy, i.e., infection control precautions may be discontinued when the following criteria are met [31]:

- At least 10 days have passed since symptoms first appeared.
- At least 72 h have passed since recovery (resolution of fever without the use of fever-reducing medications *and* improvement in respiratory symptoms).

In asymptomatic patients, duration of 10 days after the day of exposure is considered.

If a *test-based* strategy is used, patients may discontinue infection control precautions when:

- There is resolution of symptoms (absence of fever without the use of fever-reducing medications *and* improvement in respiratory symptoms)
- There are two negative results of a molecular assay for COVID-19 from respiratory specimens collected ≥24 h apart

For asymptomatic individuals, infection control precautions can be discontinued after obtaining two negative results of a molecular assay for COVID-19.

In immunocompromised patients, a test-based strategy may be preferred as the duration of infectiousness may be prolonged and difficult to ascertain, or if time-based strategy is used, then it may be reasonable to continue precautions for up to 20 days [31].

Some studies have suggested the use of cycle threshold (Ct) to help guide decisions regarding infectivity. Higher Ct values indicate fever RNA copies and a cut-off of 24 can differentiate infective activity [35, 36]. However, as these assays have not been standardized, the results can vary, and as current situation, it cannot be recommended for discontinuation of precautions. Similarly, studies have been investigating the correlation between the development of antibody and disease activity, but data are insufficient to promote the use of antibodies to guide decisions.

14.2.12 Conclusion

Prevention of spread of COVID-19 is a major challenge. Countries worldwide are engaged in developing vaccines, and they remain the principal strategy in the fight against the disease. However the implementation of vaccines is a tardy process that requires rigorous evaluations and trials to determine efficacy as well as safety before they are accepted. Though COVID-19 seems to be less fatal than prior outbreaks caused by the family of coronaviruses, the higher contagiousness has led to far more deaths and a massive burden on health-care resources. Very few management strategies have found success, and so the main strategy against COVID-19 currently remains prevention of transmission. Controlled trials (considered one of the highest levels of evidence) about methods of prevention may be difficult and even unethical; thus much about the disease transmission and prevention has remained poorly understood.

References

1. Worldometers.info. 2020. Coronavirus Update (Live): 15,709,726 cases and 637,582 deaths from COVID-19 virus pandemic - Worldometer [online]. Available from: https://www.worldometers.info/coronavirus/. Accessed 24 July 2020.
2. Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet. 2020;395(10223):514–23. https://doi.org/10.1016/S0140-6736(20)30154-9.
3. Grayson SA, Griffiths PS, Perez MK, Piedimonte G. Detection of airborne respiratory syncytial virus in a pediatric acute care clinic. Pediatr Pulmonol. 2017;52(5):684–8. https://doi.org/10.1002/ppul.23630.
4. Siegel JD, Rhinehart E, Jackson M, Chiarello L. 2007 Guideline for isolation precautions: preventing transmission of infectious agents in health care settings. Am J Infect Control. 2007;35(10 Suppl 2):S65–164.
5. Klompas M, Baker MA, Rhee C. Airborne transmission of SARS-CoV-2: theoretical considerations and available evidence. JAMA. 2020;324(5):441–2. https://doi.org/10.1001/jama.2020.12458.
6. van Doremalen N, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN, et al. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. N Engl J Med. 2020;382(16):1564–7. https://doi.org/10.1056/NEJMc2004973.
7. Judson S, Munster V. Nosocomial transmission of emerging viruses via aerosol-generating medical procedures. Viruses. 2019;11(10):940.
8. 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.
9. United States Centers for Disease Control and Prevention. Interim infection prevention and control recommendations for patients with confirmed 2019 novel coronavirus (2019-ncov) or patients under investigation for 2019-nCoV in healthcare settings [Internet]. 2020. Available from: https://www.cdc.gov/coronavirus/2019-nCoV/hcp/infecion-control.html. Accessed 2 July 2020.
10. Oran DP, Topol EJ. Prevalence of asymptomatic SARS-CoV-2 infection: a narrative review [published online ahead of print, 2020 Jun 3]. Ann Intern Med. 2020:M20–3012. https://doi.org/10.7326/M20-3012.
11. Over 99 per cent COVID-19 patients in Nepal are asymptomatic [Internet]. Gorakha Patra. 2020 [cited 24 July 2020]. Available from: https://risingnepaldaily.com/mustread/over-99-per-cent-covid-19-patients-in-nepal-are-asymptomatic.
12. Wang X, Ferro EG, Zhou G, Hashimoto D, Bhatt DL. Association between universal masking in a health care system and SARS-CoV-2 positivity among health care workers. JAMA. Published online July 14, 2020. https://doi.org/10.1001/jama.2020.12897.
13. Chu DK, Akl EA, Duda S, Solo K, Yaacoub S, Schunemann HJ. COVID-19 Systematic Urgent Review Group Effort (SURGE) study authors et al. Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis. Lancet. 2020;395(10242):1973–87. https://doi.org/10.1016/S0140-6736(20)31142-9.
14. Infection prevention and control during health care when novel coronavirus (nCoV) infection is suspected [Internet]. Who.int. 2020 [cited 24 July 2020]. Available from: https://www.who.int/publications/i/item/10665-331495.
15. Hyttinen M, Rautio A, Pasanen P, Reponen T, Earnest G, Streifel A, et al. Airborne infection isolation rooms – a review of experimental studies. Indoor Built Environ. 2011;20(6):584–94.
16. American Institute of Architects. Guidelines for design and construction of health care facilities. Washington, DC: American Institute of Architects; 2001.

17. Victorian Advisory Committee on Infection Control. Guidelines for the classification and design of isolation rooms in health care facilities. Victoria: Victorian Advisory Committee on Infection Control; 1999.
18. Cheng VCC, Wong SC, Chen JHK, Yip CCY, Chuang VWM, Tsang OTY, et al. Escalating infection control response to the rapidly evolving epidemiology of the coronavirus disease 2019 (COVID-19) due to SARS-CoV-2 in Hong Kong. Infect Control Hosp Epidemiol. 2020;41(5):493–8. https://doi.org/10.1017/ice.2020.58.
19. Wong SCY, Kwong RT, Wu TC, Chan JWM, Chu MY, Lee SY, et al. Risk of nosocomial transmission of coronavirus disease 2019: an experience in a general ward setting in Hong Kong. J Hosp Infect. 2020;105(2):119–27. https://doi.org/10.1016/j.jhin.2020.03.036.
20. Fischer R, Morris D, van Doremalen N, Sarchette S, Matson M, Bushmaker T et al. Effectiveness of N95 respirator decontamination and reuse against SARS-CoV-2 virus. [published online ahead of print, 2020 Jun 3]. Emerg Infect Dis. 2020;26(9). https://doi.org/10.3201/eid2609.201524
21. Cleaning and disinfection of environmental surfaces in the context of COVID-19 [Internet]. Who.int. 2020 [cited 25 July 2020]. Available from: https://www.who.int/publications/i/item/cleaning-and-disinfection-of-environmental-surfaces-inthe-context-of-covid-19.
22. Ong S, Tan Y, Chia P, Lee T, Ng O, Wong M, et al. Air, surface environmental, and personal protective equipment contamination by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from a symptomatic patient. JAMA. 2020;323(16):1610.
23. Kampf G, Todt D, Pfaender S, Steinmann E. Persistence of coronaviruses on inanimate surfaces and their inactivation with biocidal agents. J Hosp Infect. 2020;104:246–51.
24. CDC and ICAN. Best practices for environmental cleaning in healthcare facilities in resource-limited settings. Atlanta: US Department of Health and Human Services, CDC; Cape Town: Infection Control Africa Network; 2019. https://www.cdc.gov/hai/pdfs/resource-limited/environmental-cleaning-RLS-H.pdf. Accessed 6 May 2020.
25. Global Lighting Association. Position statement on germicidal UV-C irradiation. Available from: https://www.globallightingassociation.org/images/files/publications/GLA_UV-C_Safety_Position_Statement.pdf. Accessed 8 June 2020.
26. Pan A, Liu L, Wang C, Guo H, Hao X, Wang Q, et al. Association of public health interventions with the epidemiology of the COVID-19 outbreak in Wuhan, China. JAMA. 2020;323(19):1915–23. https://doi.org/10.1001/jama.2020.6130.
27. Iwasaki A, Grubaugh ND. Why does Japan have so few cases of COVID-19? EMBO Mol Med. 2020;12(5):e12481. https://doi.org/10.15252/emmm.202012481.
28. Sjödin H, Wilder-Smith A, Osman S, Farooq Z, Rocklöv J. Only strict quarantine measures can curb the coronavirus disease (COVID-19) outbreak in Italy, 2020. Euro Surveill. 2020;25(13):2000280. https://doi.org/10.2807/1560-7917.ES.2020.25.13.2000280.
29. Considerations for quarantine of individuals in the context of containment for coronavirus disease (COVID-19) [online] Website u2b41. Accessed 12 April 2020.
30. United States Centers for Disease Control and Prevention. Interim U.S. guidance for risk assessment and work restrictions for healthcare personnel with potential exposure to COVID-19 [Internet]. Centers for Disease Control and Prevention. 2020 [cited 25 July 2020]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/guidance-risk-assesment-hcp.html.
31. United States Centers for Disease Control and Prevention. Duration of isolation and precautions for adults with COVID-19 [Internet]. Centers for Disease Control and Prevention. 2020 [cited 25 July 2020]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/duration-isolation.html.
32. United States Centers for Disease Control and Prevention. Discontinuation of isolation for persons with COVID -19 not in healthcare settings. https://www.cdc.gov/coronavirus/2019-ncov/hcp/disposition-in-home-patients.html. Accessed 24 July 2020.
33. Wölfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Müller MA, et al. Virological assessment of hospitalized patients with COVID-2019. Nature. 2020;581(7809):465–9. https://doi.org/10.1038/s41586-020-2196-x.

34. Li N, Wang X, Lv T. Prolonged SARS-CoV-2 RNA shedding: not a rare phenomenon. J Med Virol. 2020; https://doi.org/10.1002/jmv.25952.
35. Bullard J, Dust K, Funk D, Strong JE, Alexander D, Garnett L, et al. Predicting infectious SARS-CoV-2 from diagnostic samples [published online ahead of print, 2020 May 22]. Clin Infect Dis. 2020:ciaa638. https://doi.org/10.1093/cid/ciaa638.
36. Mermel LA. Disposition of patients with coronavirus disease 2019 (COVID-19) whose respiratory specimens remain positive for severe acute respiratory coronavirus virus 2 (SARS-CoV-2) by polymerase chain reaction assay (PCR) [published online ahead of print, 2020 Jun 10]. Infect Control Hosp Epidemiol. 2020:1–2. https://doi.org/10.1017/ice.2020.286.

Ethical Issues Related to Coronavirus Disease

15

Jaya Wanchoo

The coronavirus disease has emerged as a public health emergency crossing geographical boundaries and overwhelming healthcare systems worldwide. On March 11, 2020, WHO declared COVID-19 as a pandemic. The world was not prepared to deal with a crisis of this magnitude. The health systems were not equipped adequately to provide for their citizens. As the demands exceeded the supply in the health sector, it became evident that ethical planning will be required to overcome this crisis. The earlier goals of putting the patient's needs as a priority had to be changed drastically. Decisions now had to be made keeping public health concerns and physician safety as the first priority. This was difficult for the physicians as it was not their normal way of working. Some of the other ethical dilemmas faced were optimal resource management in terms of critical care beds, ventilators, medicines, and man power, end of life issues, scientific research, data sharing and patient confidentiality, protection of healthcare workers, and their psychological needs. The states have a greater responsibility to contain the spread of infection by declaring a lockdown on all social events, educational institutions, travel, and economic activities but ensuring that essential services are not disrupted. The economic crisis caused by the lockdown compounded the problems. In an emergent situation like this, there are no right or wrong decisions, but doctors are bound by the Hippocratic Oath, and every patient is entitled to basic health care. To overcome these ethical issues, every healthcare institution should lay down certain guiding principles to treat COVID-19 patients, keeping in mind the principles of ethics, namely, justice, autonomy, beneficence, non-maleficence, veracity, and trust [1].This would ensure that there is optimal utilization of limited resources and would maximize the number of lives saved. Ethical decisions should be based on availability and accessibility

J. Wanchoo (✉)
Institute of Critical Care and Anesthesia, Medanta-The Medicity, Gurgaon, India

H. Prabhakar et al. (eds.), *Clinical Synopsis of COVID-19*,
https://doi.org/10.1007/978-981-15-8681-1_15

of resources of the individual healthcare systems. Each hospital should form their own ethics team [2] to ensure ethical delivery of health care in an otherwise difficult situation.

Some of the important ethical issues faced are discussed here:

15.1 Rights and Duties of Personnel

The rapidity of spread, high virulence of infection, uncertain treatment protocols, constantly changing information, and scarcity of resources have all contributed to panic among healthcare workers. The most important ethical question arising in an infectious disease pandemic is "Can the healthcare workers refuse to treat patients, and if they do, can they be charged by the court of law for negligence of duty?". Legal and ethical issues for healthcare professionals during a pandemic are not clearly defined in most of the countries. The American Medical Association states that "physicians should balance the immediate benefits to an individual with ability to care for patients in future." The UK General Medical Council advises that "doctors must not refuse to treat patients because their medical condition may put the doctor to risk." It also lays emphasis on protecting oneself while serving the patients. The Code of Medical Ethics Regulations of the Medical Council of India, 2002 (amended up to 2016), states that "no physician can refuse to treat a patient during an emergency" [3]. The Canadian Medical Association Code of Ethics states that "a physician not only has the responsibility to consider the well-being of the patient but also to maintain their own health." The question then arises—does pandemic pose to be a work place hazard? For a physician the COVID pandemic is an occupational hazard and, like hazards faced by professionals in other fields, should be acceptable; what is unacceptable is when the safety devices are not available or non-functional, in this case proper personal protective equipment [4].

Across the world, healthcare workers are expected to fulfill their duties despite their fears and uncertainties. They are under a lot of stress due to the fact that the disease is highly virulent, with no known or promising treatment options. The greatest fear in their mind is the risk of getting infected and spreading the infection to their family members, especially if they are staying with old parents and children. Another fear is whether they or their family will have access to good medical facilities if they need it. The thought of quarantine and isolation also has serious repercussions [5].

The health services or hospital also has an obligation toward their staff. To allay the fears in the minds of the healthcare workers, the management can take the following steps:

(a) Every healthcare facility dealing with COVID patients should have an ethics committee to formulate their policies and standard operating procedures. The same should be communicated to the frontline workers at regular intervals so that everyone works as a team. There should be good team leaders to motivate the staff members.

(b) There has been an increase in the incidence of mental health issues among healthcare workers like anxiety, depression, and sleep disorders due to overload of work [6]. Social distancing and isolation may add to these woes. To alleviate their stress, hospitals should have regular counselling sessions for their staff. Communication channels should be open for discussing the problems and fears the workers face. Use of other communication options should be encouraged like video chats.
(c) They should be given benefits like adequate remuneration, reduced duty hours, accommodation, and quarantine facilities. Ethical principle of reciprocity, giving priority to those who risk their lives, should be emphasized upon and guaranteed to the healthcare workers. They should be assured of personal protective equipment, medicines, and health care for themselves and their families if the need arises.
(d) Shortage of staff due to quarantine or sickness can cause additional burden on the already overburdened staff. Every effort must be made to deal with it. Some of the methods could be increasing the scope and reach of telemedicine services, deployment of staff from other areas where elective work has been stopped, and recruitment of trainees or retired staff.

Are the other hospital staff like management staff, laundry workers, cleaners, catering staff, and porters bound ethically and legally to work in a pandemic? Is deployment of workers a solution to this issue? They constitute a sizeable number of workforce in any hospital and face an equal risk of getting infected in the pandemic. The reluctance to work among them arises from the fear of getting infected and unavailability of proper personal protective equipment and access to health care if they fall sick [7]. A pandemic should be considered as an occupational hazard, and the principle of proportionality holds good for non-medical staff too. They should be guided and trained on methods to work in a pandemic. Like the healthcare workers, they should also be provided with adequate protective gear, should follow all infection prevention protocols, and should be assured of medical care if they fall sick.

15.2 Allocation of Scarce Resources

As approximately 5–8% of COVID-19 patients present with severe ARDS like symptoms causing acute respiratory failure, the number of people requiring ICU care increased beyond the surge capacity of hospitals around the world [8]. As the disease spread rapidly affecting a large number of people within a short span of time, there was an acute shortage of hospital beds, ventilators, medicine, and personnel. The moral and ethical dilemma on how to use the scarce resources raises a big question mark. Earlier intensivists were working with an aim to provide critical care for all sick patients. Now their dilemma was to provide beneficial care to those who need it the most but in an honest and transparent way. The allocation has to be based on individual resources and preferences of each hospital. Triage protocols and

criteria need to be established in all hospitals by a separate team which can be followed by the doctors to relieve them of moral distress.

A white paper proposed by the University of Massachusetts Medical School on ethical guidelines for the treatment of patients with coronavirus disease lays down principles and values to be followed, some of which are "utilitarianism, justice, autonomy, human dignity, transparency, equity, reasonableness, privacy, proportionality and trust" [9]. Hick et al. apply proportionality to the current crisis in a recent report from the National Academy of Medicine, explaining that the principle demands that "the risks of compromising standards in a given instance should be weighed against the need to do so to optimize benefits to patients, caregivers, and the community" [10]. Another meaningful document is given by the Department of Critical Care Medicine, University of Pittsburgh, "Allocation of Scarce Critical Care Resources During a Public Health Emergency Executive Summary," which lays down guidelines for triaging scarce resources in the event of a pandemic. Admission and prioritization criteria to ICU changed during this pandemic. By definition the utilitarian approach seems to be best suited in these times—the action is judged based on its outcomes and net benefit, in other words patients' chances of survival to hospital discharge. The goal should be to maximize benefit: to save most lives and save most life years [11, 12]. Another principle to be followed for ethical distribution of resources is equity—all patients, regardless of age, sex, gender, ethnicity, or religion should have equal access to medical care. The fundamental argument against this principle is the concept of life years. According to some, priority should be given to younger patients only to give them a chance to live through life stages. The "first-come, first-served" criteria may not be possible to follow in these exceptional circumstances of extreme shortage of resources [13].

A separate allocation should be based on medical criteria, objectively assessed by the SOFA score [14], and patients must be triaged depending upon their needs. Priority should be given to doctors, nurses, respiratory physicians, and maintenance staff if the need arises. Priority should also be given to patients who require critical care beds for non-COVID reasons like congestive heart failure or ARDS due to other reasons [15]. The requirement of critical care beds led to the creation of new ICU facilities, either in the same hospital or at distant locations. Examples of these could be post-operative recovery rooms as elective surgeries are not being carried out or conversion of some hospitals into COVID centers. Ethical issues faced in these new setups included inexperienced workforce or insufficient and inadequate resources.

Once a patient is allotted a critical care bed, reassessment and reallocation [16] plays a very important role in a pandemic for reverse triaging. Reverse triage is a way to create surge capacity and involves discharging patient from critical care units if they are not going to be benefitted. This is done after giving a therapeutic trial to the patient, the duration of which is determined by the disease characteristics. If there is rapid decline in the patient's condition, worsening SOFA scores, and

presence of severe comorbid illnesses, the family should be counselled accordingly. If a patient is not improving with the treatment, he can be shifted to palliative care, and ICU bed can be used for another patient who may benefit. In other words, patients likely to survive are prioritized. A big ethical question arises on the doctor's liability for professional negligence in case the treatment is withdrawn. According to the British Medical Association guidelines, "if there is radically reduced capacity to meet all serious health needs, it is both lawful and ethical for a doctor, following appropriate prioritisation policies, to refuse someone potentially life-saving treatment where someone else has a higher priority for the available treatment" [17]. Having said all this, we cannot have rigid exclusion criteria for access to health care as it is against medical ethics.

Screening and testing of patients are an ethical dilemma too as there is shortage of testing kits worldwide. Testing should be limited to the symptomatic and high-risk population till such time that testing kits are freely available. Universal screening is not advocated [18].

Another ethical consideration is the care of non-COVID patients. As more hospitals are getting converted to COVID hospitals and there is shortage of healthcare workers, the patients with chronic diseases are getting neglected. These patients are not visiting the hospitals for fear of getting infected. Suspension of non-emergency services by some hospitals has made matters worse for patients like those in need of regular hemodialysis or those in need of continuous follow-up and drug modifications.

15.3 Shortage of Personal Protective Equipment

The rapid spread of the COVID infection has created a shortage or unavailability of proper PPE. Centers for Disease Control and Prevention (CDC) identifies three levels of operational status: conventional, contingency, and crisis. The pandemic has put the world in a crisis situation where the supply of personal protective equipment (gown, face mask, gloves, face shield) is falling short of the increasing demand. One of the steps for ensuring supply of PPE is increasing the supply: by increasing manufacture or import from other countries. The demand can also be met by acquiring it from other non-healthcare sources and redirecting them to the health sector [19]. The American College of Physicians (ACP) and Project N95, a national, not-for-profit COVID-19 critical equipment clearing house, have partnered to provide personal protective equipment (PPE) for internal medicine physicians, during the COVID-19 pandemic. Conservation of existing PPE can be achieved by using it beyond the shelf life recommended by the manufacturer. If the masks are not torn or soiled by secretions, they can be re sterilized using ethylene oxide, UV, or gamma irradiation [20]. Another way of reducing the use of PPE is to cancel all non-emergency or elective surgeries.

15.4 End of Life and Palliative Care

It is clear from the experience with COVID pandemic so far that older patients with various comorbidities have a higher rate of mortality despite the best critical care services available. It was realized that good end of life care and palliative services are needed ethically to provide comfort to the patients and their families. Keeping this fact in mind, palliative care should be an integral part of pandemic planning. It is not possible for healthcare workers to provide end of life and palliative care services in a situation where they are already overburdened, resources are scarce, and they themselves may be in need of psychological support. For this reason, there is an increase in the demand for people who can provide end of life care so that people can die in dignity. The European Association for Palliative Care has provided a white paper on core competencies of palliative care which include taking care of the social, psychological, and spiritual needs of the patient and family and developing a strong patient-provider relationship [21]. Additionally, during a pandemic, like we are facing, certain important medical and ethical decisions need to be made.

The University of Washington provided a document for high-quality palliative care during crisis [22]. As there is an increase in demand for workers providing end of life care, every effort should be made to increase the number of people providing palliative care to the dying. This can be achieved by enrolling staff from other areas, training them in palliative care, and expanding the palliative care workforce [23]. Palliative care can also be offered at home or digitally for patients who cannot come to the hospital. Palliative care services should be made available in the emergency area, intensive care unit, and after routine hours to lessen the burden of work on the critical care physician. Some experts have suggested four elements of palliative care—stuff, staff, space, and systems [24–27]. Stuff includes medicines and drug delivery systems without hoarding so that shortage is not felt by others. Staff in the form of psychosocial workers, non-specialist staff, and bereavement counsellors can be trained for this purpose. Systems should be in place, like an advance care plan, which would help the physicians to identify those patients who would not benefit from critical care interventions like invasive ventilation. The pandemic is draining the economic resources of all countries, the low-income and middle-income countries being the most affected. For palliative care to be effective, all countries should increase their opioid reserves and train more people in their use [28].

One very important part of palliative care is communication with patient and family to outline the plan of care and provide them with psychological support [29]. Discussions with the family should include “do not resuscitate” options, benefits and outcomes of treatment, and options of palliative therapy. Anxiety and depression are common among family members of the dying patient too probably due to social isolation, their inability to meet their loved ones, or the fear of losing a family member, which further emphasizes the importance of communication.

It may not always be possible for palliative care workers to be physically present with the family due to strict infection control policies. Is palliative care ethically justified if it is given through digital technology [30, 31]? Will it affect the

relationship between the patient and the healthcare provider which is based on trust and is a core constituent of palliative care (European Association of Palliative Care)? Use of telemedicine for palliative care has not been completely evaluated nor any real benefits appreciated. The reason for this may be the fact that palliative care encompasses interdisciplinary care. The points in favor of remote palliative care are continuity of care, easy accessibility of integrated patient records, and monitoring of warning signs. Some of the limitations may be patient dissatisfaction due to the fact that the doctor spends more time looking at the screen. As a result, there may be less patient interaction. Patients with low literacy levels may be at a disadvantage when it comes to communication through digital methods.

Voluntary-assisted dying and euthanasia are terms being looked into in some countries where it is considered legal. In Netherlands, Australia, and Belgium, these practices are not being changed [32].

15.5 Cardiopulmonary Resuscitation

The COVID pandemic has forced intensivists to relook into the conventional ways of performing CPR. The role and benefits of CPR also need to be redefined in that subset of patients who are critically ill. The traditional ways may have to be modified to ensure safety of the provider. Due to a very high risk of spread of infection and limited availability of resources, the risks and benefits of performing CPR have to be weighed carefully. The ethical questions for the physician are "to do or not to do, and if justified, how much to do?".

The first rule in a pandemic should be to respect the patient's wishes especially in "do not resuscitate" scenarios [33]. Careful planning and communication with the patient and family play a very important role during these times. Having said this, the ethical principles of transparency, equity, and proportionality cannot be forgotten. Several countries have come up with new CPR guidelines during COVID. All of them put physician safety as the first directive.

The European Resuscitation Council has drafted guidelines for CPR during the pandemic, the recommendations of which are subject to change depending on the evolving information. According to these guidelines, the provider should identify which patients would require CPR [34]. In patients with advanced respiratory failure or multiorgan failure, in whom CPR may not be beneficial, it should not be attempted. The International Liaison Committee on Resuscitation (ILCOR) and CDC recommend the use of PPE for all staff involved in performing CPR [35]. CPR guidelines from the Australasian College for Emergency Medicine also emphasize on the fact that balance between appropriateness of CPR and the risk should be evaluated carefully [36]. The question a physician should always ask is "Is the resuscitation appropriate?". The Indian Resuscitation Council has come up with guidelines for the management of cardiac arrest in COVID patients since it presents with a completely new subsets of challenges and problems [37].

Decision to resuscitate depends upon individual countries and regions. If CPR has to be done, the following points should be kept in mind [38]:

(a) PPE is a must for everyone involved in conducting CPR.
(b) The number of people in the room should be the bare minimum required for performing CPR.
(c) The safety of all personnel, self and nursing staff, should be kept in mind by the team leader conducting the CPR.
(d) Chest compression and airway interventions during CPR are aerosol-generating procedures, whereas defibrillation is not. Defibrillation can be performed by first responders provided patients mouth and nose are covered [39].
(e) Avoid chest compressions, bag mask ventilation, and non-invasive ventilation strategies whenever possible, and early insertion of supraglottic devices is recommended.

National Academies of Sciences, Engineering, and Medicine states that "crisis standards of care aim at saving the most lives possible under severe resource constraints, maintaining the core ethical principles of fairness, transparency, accountability, duty to care. The three cardinal points of crisis standard of CPR are-Acknowledge resource limitation, if DNR respect the wishes, forgo CPR if it is not beneficial and ensure safety of personnel" [40].

15.6 Research and Data Sharing

The need for research during the COVID pandemic became imperative as there is no known or proven therapy against this virus. As per the WHO guidelines, research can be carried out during an emergency situation provided ethical standards are followed and it has scientific validity (WHO Working Group on Ethics and Covid, World Health Organization. Guidance for managing ethical issues in infectious disease outbreaks. Geneva: WHO; 2016). Another important consideration should be that research should only be carried out if it does not impede ongoing response efforts. Research should not divert the resources meant for health care. Since COVID-19 is a pandemic, research projects should be coordinated at an international level to avoid duplication and to provide benefit to all. Research methodologies should be ethical and scientific and should keep in mind safety protocols. Individual informed consent is a basic ethical requirement for any research [41]. The same ethical guidelines hold true for development of a vaccine-informed consent and knowledge of the risks involved.

Since the research in a pandemic involves several countries and the timeline is not defined, it is important to develop a core protocol at the beginning of the research. This involves engaging researchers and representatives from the participating countries in forming the primary research questions and main design elements [42]. The Coalition for Epidemic Preparedness Innovations (CEPI), an international non-governmental organization, is coordinating at the international level for rapid development of vaccine against COVID [43]. Results of any research should be shared with the public health officials, the participants, and the affected population. Journals can help in early and widespread dissemination of information.

The International Bioethics Committee (IBC) and Commission on the Ethics of Scientific Knowledge and Technology (COMEST) stress that policies which are not based on sound scientific knowledge and practices are unethical as they work against the effort to build a common response to the pandemic [44].

An example of a drug trial is the Solidarity Trial, launched by WHO on March 18, 2020. On July 4, 2020, it discontinued the hydroxychloroquine and ritonavir/lopinavir arms as they did not produce any significant decrease in the mortality of hospitalized patients when compared to standard care.

What is the ethical standing on compassionate use of drugs like HCQ and remdesivir [45–47]? These are antimalarial and antiviral drugs which are not FDA approved for COVID-19 treatment but have been given a special status of expanded access by the FDA. In low-income countries, it may be ethically justified to use these drugs for life-threatening conditions. In India, the Union Health Ministry has issued a draft notification (June 5, 2020) for compassionate use of any unapproved drug for critically ill patients that is in phase III of clinical trial globally by applying to the central drug regulator.

15.7 Telemedicine

Telemedicine comprises remote diagnosis and treatment of patients by means of electronic communication technology such as video and phone calls or chatting apps. In the present times, telemedicine serves several important purposes—social distancing, early detection of warning signs, and forward triage-sorting of patients before they arrive in the emergency department [48]. Healthcare providers across the world have increased the availability of telemedicine during the pandemic to lessen their burden on home visits. These services are useful for certain set of patients like the geriatric population who cannot travel to the hospital and those living at remote locations who are often unable to travel for follow-up care [49, 50].

Most of the countries have no legal framework or guidelines for medical practitioners to provide remote medical consultations during a pandemic. In India, the Union Ministry of Health and Family Welfare came up with guidelines on telemedicine practices on March 25, 2020. According to these guidelines, only a registered medical practitioner in India is allowed to practice telemedicine after he completes a mandatory online course. Furthermore, doctors using telemedicine shall uphold the same professional and ethical norms and standards as applicable to traditional in-person care, within the intrinsic limitations of telemedicine. It also emphasizes the fact that telemedicine consultation should not be anonymous: both patient and the practitioner need to know each other's identity (Appendix 5 of the Indian Medical Council Professional Conduct, Etiquette and Ethics Regulation, 2002). To meet demand amid the pandemic, US Department of Health and Human Services announced a temporary easing or suspension of various telehealth regulations in mid-March. All physicians who participate in telehealth have an ethical responsibility to uphold fundamental fiduciary obligations by disclosing any financial or other interests the physician has in the telehealth application (Ethical Practice in

Telemedicine-American Medical Association). Also, Medicare is now providing reimbursement for telemedicine visits conducted in both the inpatient and outpatient settings during the COVID-19 pandemic under the 1135 Waiver [51, 52]. The European Data Protection Board has also issued a statement on protecting sensitive personal information and allowed processing of personal data to be used in a public health emergency. These are some of the examples of how the world is trying to use digital data responsibly. Data protection rules and regulations need to be looked into and stricter guidelines implemented as the use of telemedicine will increase in the future. Telemedicine apps with more safety features have to be developed for future use too.

15.8 Ethical Use of Alternative Medicine

India and China are among the few countries who are encouraging the use of traditional and indigenous systems of medicines in this pandemic, either as an immunity booster or as prophylaxis. Monitored Emergency Use of Unregistered and Investigational Interventions (MEURI) is an ethical protocol developed by the World Health Organization to evaluate the potential use of experimental drugs in the event of public health emergencies. The protocol was created by the WHO Ebola Ethics Working Group in 2014 [53]. This is useful in situations when there is no effective treatment available, but can only be used after ethical clearance from the relevant authorities. Patients' informed consent has to be taken and results monitored. This protocol can be used for future pandemics and applies to traditional medicine systems too, provided their safety is proven and documented. In India, there are multiple systems of medicine like homeopathy, Unani, Ayurveda, Siddha, and naturopathy, all of which are grouped under a common name—AYUSH. The National Health Policy of India also emphasizes on the integration of these systems with modern medicine. The people of India have the right to choose and follow any system of medicine. These systems should follow the ethical principles of fairness and transparency [54, 55], though their efficacy still remains unproven.

15.9 Conclusion

As the world unites to fight against a common unknown enemy, the healthcare workers should continue to work keeping ethical principles in mind. "Do no harm" should be the first and foremost dictum. New research is opening up a lot of information on the coronavirus and its treatment. Despite multiple treatment modalities being used the world over, no randomized control trials have proven the efficacy of a drug till date. Development of a vaccine also seems a long way ahead. There are several unanswered questions for the healthcare professionals. Till such time that we are ready with answers, the health workers have to work in difficult circumstances, under a lot of mental stress, keeping all the ethical and legal issues in mind.

Bibliography

1. Simonds AK, Sokol DK. Lives on the line? Ethics and practicalities of duty of care in pandemics and disasters. Eur Respir J. 2009;34(2):303–9.
2. Berlinger N, Wynia M, Powell T, Milliken A, Fabi R, Cohn F, Guidry Grimes LK, et al. Ethical Framework for Health Care Institutions responding to novel coronavirus SARS-CoV-2 (COVID-19),guidelines for institutional ethics services responding to COVID-19 managing uncertainty, safeguarding communities, guiding Practice. The Hastings Center; 16 March 2020.
3. Gopichandran V. Clinical ethics during the Covid-19 pandemic: missing the trees for the forest. Indian J Med Ethics. Online first published April 30, 2020.
4. Davies C, Shaul R. Physicians' legal duty of care and legal right to refuse to work during a pandemic. CMAJ. 2010;182(2):167–70.
5. Tait S, Jonathan R, Mickey T. Addressing sources of anxiety among health care professionals during the COVID-19 pandemic. JAMA. 2020;323(21):2133–4.
6. Menon V, Padhy SK. Ethical dilemmas faced by health care workers during COVID-19 pandemic: issues, implications and suggestions. Asian J Psychiatr. 2020;51:1–2.
7. Draper H, Sorell T, Ives J, Damery S, Greenfield S, Parry J, et al. Non-professional healthcare workers and ethical obligations to work during pandemic influenza. Public Health Ethics. 2010;3(1):23–34.
8. Verano M, Bartolini G, Giannini A, Gristina G, Livigni S, Mistraletti G, et al. Clinical ethics recommendations for the allocation of intensive care treatments in exceptional, resource-limited circumstances: the Italian perspective during the COVID-19 epidemic. Crit Care. 2020;165(24):1–3.
9. De Pergola PA. Ethical guidelines for the treatment of patients with suspected or confirmed novel coronavirus disease (COVID-19). Online J Health Ethics. 2020;16(1):1–59.
10. Hick JL, Hanfling D, Wynia MK, Pavia AT. Duty to plan: health care, crisis standards of care, and novel coronavirus SARS-CoV-2. NAM perspectives discussion paper. National Academy of Medicine; 2020. p. 1–13.
11. White DB, Katz MH, John LJM, Lo B. Who should receive life support during a public health emergency? Using ethical principles to improve allocation decisions. Ann Intern Med. 2009;150(2):132–8.
12. Robert R, Kentish-Barnes N, Boyer A, Laurent A, Azoulay E, Reignier J. Ethical dilemmas due to the Covid-19 pandemic. Ann Intensive Care. 2020;10:84.
13. Singh JA, Moodley K. Critical care triaging in the shadow of COVID-19: ethics considerations. S Afr Med J. 2020;110(5):355–9.
14. Maves R, Downar J, Dichter J, Hick J, Devereaux A, Geiling J, et al. Triage of scarce critical care resources in COVID-19 an implementation guide for regional allocation an expert panel report of the task force for mass critical care and the American College of Chest Physicians. Chest. 2020;158(1):212–25.
15. Emanuel E, Persad G, Upshur R, Thome B, Parker M, Glickman A, et al. Fair allocation of scarce medical resources in the time of Covid-19. N Engl J Med. 2020;382(21):2049–55.
16. White D, Lo B. A framework for rationing ventilators and critical care beds during the COVID-19 pandemic. JAMA. 2020. Viewpoint E1-E2.
17. Hurford J. The BMA COVID-19 ethical guidance: a legal analysis. New Bioeth. 2020;26(2):176–89.
18. Kramer J, Brown D, Kopar P. Ethics in the time of coronavirus: recommendations in the COVID-19 pandemic. J Am Coll Surg. 2020;230(6):1114–8.
19. Livingston E, Desai A, Berkwits M. Sourcing personal protective equipment during the COVID-19 pandemic. JAMA. 2020;323(19):1912–4.
20. Centres for Disease Control and Prevention. Strategies for optimizing the supply of facemasks. 2020. Updated June 28, 2020.

21. White Paper on standards and norms for hospice and palliative care in Europe: part 1 Recommendations from the European Association for Palliative Care. Eur J Palliat Care. 2009;16(6):278–9.
22. Fausto J, Hirano L, Lam D, Mehta A, Mills B, Owens D, et al. Creating a palliative care inpatient response plan for COVID19—The UW medicine experience 2020. J Pain Symptom Manage. 2020;60(1):e21–6.
23. Gamondi C, Larkin P, Payne S. Core competencies in palliative care: an EAPC white paper on palliative care education – part 1. Eur J Palliat Care. 2013;20(2):86–91.
24. Downar J, Seccareccia D. Palliating a pandemic: "all patients must be cared for". J Pain Symptom Manage. 2010;39(2):291–5.
25. Arya A, Buchman S, Bruno Gagnon B, Downar J. Pandemic palliative care: beyond ventilators and saving lives. CMAJ. 2020;early-released 1–5.
26. Etkind S, Bone A, Lovell N, Cripps R, Harding R, Higginson I, et al. The role and response of palliative care and hospice services in epidemics and pandemics: a rapid review to inform practice during the COVID-19 pandemic. J Pain Symptom Manage. 2020;60(1):e31–40.
27. Pattison N. End-of-life decisions and care in the midst of a global coronavirus (COVID-19) pandemic. Intensive Crit Care Nurs. 2020;58:102862.
28. Radbruch L, Knaul F, Lima L, Joncheere C, Bhadelia A. The key role of palliative care in response to the COVID-19 tsunami of suffering. Lancet. 2020;395:1467–9.
29. Fadul N, Elsayem AF, Bruera E. Integration of palliative care into COVID-19 pandemic planning. BMJ Support Palliat Care. 2020;bmjspcare-2020-002364.
30. Payne S, Tanner M, Hughes S. Digitisation and the patient–professional relationship in palliative care. Palliat Med. 2020;34(4):441–3.
31. Hancock S, Preston N, Jones H, Gadoud A. Telehealth in palliative care is being described but not evaluated: a systematic review. BMC Palliat Care. 2019;18:114):1–15.
32. Lapid M, Koopmans R, Sampson E, Block LV, Peisah C. Providing quality end-of-life care to older people in the era of COVID-19: perspectives from five countries. Int Psychogeriatr. 2020:1–8.
33. Joebges S, Biller-Andorno N. Ethics guidelines on COVID-19 triage—an emerging international consensus. Crit Care. 2020;24(201):1–5.
34. Nolan JP, Monsieurs KG, Bossaert L, Bottiger BW, Greif R, Lott C, et al. European Resuscitation Council COVID-19 guidelines executive summary. Resuscitation. 2020;153:45–55.
35. International Liaison Committee on Resuscitation. COVID-19 infection risk to rescuers from patients in cardiac arrest; 30 March 2020.
36. Craig S, Cubitt M, Jaison A, Troupakis S, Hood N, Fong C, et al. Management of adult cardiac arrest in the COVID-19 era. Interim guidelines from the Australasian College for Emergency Medicine. Med J Aust. 2020;213(3):126–33. (published online: 24 April 2020).
37. Singh B, Garg R, Chakra Rao S, Ahmed SM, Divatia JV, Ramakrishnan TV, et al. Indian Resuscitation Council (IRC) suggested guidelines for Comprehensive Cardiopulmonary Life Support (CCLS) for suspected or confirmed coronavirus disease (COVID-19) patient. Indian J Anaesth. 2020;64:S91–6.
38. DeFilippis E, Ranard L, Berg D. Cardiopulmonary resuscitation during the COVID -19 pandemic CPR a view from trainees on the front line. Circulation. 2020;141:1833–5.
39. Ott M, Milazzo A, Liebau S, Jaki C, Schilling T, Krohn A, et al. Exploration of strategies to reduce aerosol-spread during chest compressions: a simulation and cadaver model. Resuscitation. 2020;152:192–8.
40. Kramer D, Lo B, Dickert N. CPR in the Covid-19 Era - an ethical framework. N Engl J Med. 2020;383:e6.
41. Global coalition to accelerate COVID-19 clinical research in resource-limited settings. Lancet. 2020;395:1322–5.
42. Dean N, Gsell P, Brookmeyer R, Crawford F, Donnelly C, Ellenberg S, et al. Creating a framework for conducting randomized clinical trials during disease outbreaks. N Engl J Med. 2020;382(14):1366–9.

43. Lurie N, Saville M, Hatchett R, Halton J. Developing Covid-19 vaccines at pandemic speed. N Engl J Med. 2020;382(21):1969–73.
44. Statement on Covid-19: ethical considerations from a global perspective Statement of the UNESCO International Bioethics Committee (IBC) and the UNESCO World Commission on the Ethics of Scientific Knowledge and Technology (COMEST) at, www.https://en.unesco.org/themes/ethics-science-and-technology/comest (Accessed on 20.09.2020).
45. Tansey S, Cottam B, Dollow S, Lockett A, Miils I, Vranic I. The ethics of conducting clinical trials in the search for treatments and vaccines against COVID-19. Faculty of Pharmaceutical Medicine blog; 21 April 2020.
46. Kalil A. Treating COVID-19—off-label drug use, compassionate use, and randomized clinical trials during pandemics. JAMA. 2020;323(19):1897–8.
47. Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, et al. Compassionate use of remdesivir for patients with severe Covid-19. N Engl J Med. 2020;382:2327–36.
48. Hollander J, Carr B. Virtually Perfect? Telemedicine for Covid-19. N Engl J Med. 2020;382(18):1679–81.
49. Vidal-Alaball J, Acosta-Roja R, Hernandez N, Luque U, Morrison D, Perez S, et al. Telemedicine in the face of the COVID-19 pandemic. Aten Primaria. 2020;52(6):418–22.
50. Hau YS, Kim JK, Hur J, Chang MC. How about actively using telemedicine during the COVID-19 pandemic? J Med Syst. 2020;44:107–8.
51. Ienca M, Vayena E. On the responsible use of digital data to tackle the COVID-19 pandemic. Nat Med. 2020;26:458–64.
52. Calton B, Abedini N, Fratkin M. Telemedicine in the time of coronavirus. J Pain Symptom Manage. 2020;60(1):e12–4.
53. World Health Organization. Notes for the record: consultation on monitored emergency use of unregistered and investigational interventions for Ebola Virus Disease (EVD). Geneva: WHO.
54. Ministry of Health and Family Welfare, National Health Policy 2017. New Delhi: Ministry of Health and Family Welfare, National Health Policy; 27 August 2018.
55. Chaturvedi S, Kumar N, Tillu G, Deshpande S, Patwardhan B. AYUSH, modern medicine and the Covid-19 pandemic. Indian J Med Ethics. Published online on May 13, 2020.

Webliography

16

Vanitha Rajagopalan and Hemanshu Prabhakar

16.1 Society Guidelines

16.1.1 Anesthesiology

1. World Federation of Societies of Anesthesiologists (WFSA): Coronavirus—Guidance for anaesthesia and perioperative care providers
   https://www.wfsahq.org/resources/coronavirus
2. Canadian Anesthesiologists' Society (CAS): COVID-19
   https://www.cas.ca/en/covid-19
3. American Society of Anesthesiologists (ASA): COVID-19 information for healthcare professionals
   https://www.asahq.org/about-asa/governance-and-committees/asa-committees/committee-on-occupational-health/coronavirus
4. American Society of Regional Anesthesia and Pain Medicine (ASRA): COVID-19 resource center
   https://www.asra.com/page/2900/covid-19-resource-center
5. Anesthesia Patient Safety Foundation (APSF): Novel coronavirus (COVID-19) anesthesia resource center
   https://www.apsf.org/novel-coronavirus-covid-19-resource-center/
6. Society for Ambulatory Anesthesia (SAMBA): COVID-19 resources
   https://sambahq.org/covid-19-resources-2/

V. Rajagopalan (✉) H. Prabhakar
Department of Neuroanaesthesiology and Critical Care, All India Institute of Medical Sciences, New Delhi, India

H. Prabhakar et al. (eds.), *Clinical Synopsis of COVID-19*,
https://doi.org/10.1007/978-981-15-8681-1_16

7. Society for Neuroscience in Anesthesiology & Critical Care (SNACC): Consensus statement on anesthetic management of endovascular treatment of acute ischemic stroke during COVID-19 pandemic
   https://www.snacc.org/snacc-home/click-here-for-covid-19-resources/snacc-consensus-statement-on-anesthetic-management-of-endovascular-treatment-of-acute-ischemic-stroke-during-covid-19-pandemic/
8. Society for Obstetric Anesthesia and Perinatology (SOAP): Interim considerations for obstetric anesthesia care related to COVID-19
   https://soap.org/education/provider-education/expert-summaries/interim-considerations-for-obstetric-anesthesia-care-related-to-covid19/
9. Society for Pediatric Anesthesia (SPA): COVID-19 resources
   https://www.pedsanesthesia.org/covid-19-resources/
10. Society of Cardiovascular Anesthesiologists (SCA): COVID-19 resources
    https://www.scahq.org/practice-resources/covid-19-resources/
11. European Society of Anesthesiology (ESA): Coronavirus COVID-19 resource hub
    https://www.esahq.org/coronavirus-covid-19/
12. Association of Anaesthetists: COVID-19 guidance
    https://anaesthetists.org/Home/Resources-publications/COVID-19-guidance
13. The Faculty of Intensive Care Medicine (FICM), Intensive Care Society (ICS), Association of Anaesthetists, and Royal College of Anaesthetists (RCOA): Clinical guidance
    https://icmanaesthesiacovid-19.org/clinical-guidance
14. Australian and New Zealand College of Anaesthetists (ANZCA): Coronavirus/COVID-19 resources—Clinical resources
    https://libguides.anzca.edu.au/covid-19/clinical
    Safe Airway Society (SAS): COVID-19 resources https://www.safeairway-society.org/covid19/

16.1.2 Cardiovascular Medicine

1. World Heart Federation (WHF): COVID-19 resources
   https://www.world-heart-federation.org/covid-19-resources
2. Canadian Cardiovascular Society (CCS): Caring for cardiovascular patients during the COVID-19 pandemic
   http://www.ccs.ca/en/
3. American College of Cardiology (ACC): COVID-19 hub
   https://www.acc.org/latest-in-cardiology/features/accs-coronavirus-disease-2019-covid-19-hub#sort=%40fcommonsortdate90022%20descending
4. American Heart Association (AHA): COVID-19 content—An AHA compendium
   https://professional.heart.org/professional/General/UCM_505868_COVID-19-Professional-Resources.jsp

5. AHA: Interim guidance for basic and advanced life support in adults, children, and neonates with suspected or confirmed COVID-19
   https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.120.047463
6. European Society of Cardiology (ESC): COVID-19 and cardiology
   https://www.escardio.org/Education/COVID-19-and-Cardiology

16.1.3 Emergency Medicine

1. Society of Critical Care Medicine (SCCM): COVID-19 rapid resource center https://www.sccm.org/COVID19RapidResources/Home
2. Canadian Association of Emergency Physicians (CAEP): COVID-19
   https://caep.ca/covid-19/
3. American Academy of Emergency Medicine (AAEM): COVID-19 resources
   https://www.aaem.org/current-news/covid-19-resources
4. American College of Emergency Physicians (ACEP): COVID-19—Clinical assessment & management
   https://www.acep.org/resource/dynamic/79753/78842
5. Eastern Association for the Surgery of Trauma (EAST): COVID-19 resources and information
   https://www.east.org/education/covid-19-resources-and-information
6. Society for Academic Emergency Medicine (SAEM): COVID-19
   https://www.saem.org/resources/emtide/covid-19-provider-resources
7. Royal College of Emergency Medicine (RCEM): COVID-19
   https://www.rcem.ac.uk/RCEM/Quality_Policy/Safety/Covid-19/RCEM/ForProfessionals/Safety/Coronavirus_Covid-19.aspx?Coronavirus

16.1.4 Endocrinology and Diabetes

1. Endocrine Society: Our response to COVID-19 as endocrinologists and diabetologists
   https://academic.oup.com/jcem/article/105/5/1299/5814115
2. International Diabetes Federation (IDF): COVID-19 outbreak—Guidance for people with diabetes
   https://www.idf.org/our-network/regions-members/europe/europe-news/196-information-on-corona-virus-disease-2019-covid-19-outbreak-and-guidance-for-people-with-diabetes.html
3. International Society for Pediatric and Adolescent Diabetes (ISPAD): COVID-19 in children with diabetes resources
   https://www.ispad.org/page/COVID-19inchildrenwithdiabetesResources
4. American Diabetes Association (ADA): Diabetes and coronavirus
   https://www.diabetes.org/coronavirus-covid-19
5. European Association for the Study of Diabetes (EASD): COVID-19 and diabetes

https://easd-elearning.org/covid-19/

6. European Society of Endocrinology (ESE): COVID-19 and endocrine disease—Clinical information and comment from ESE
   https://www.ese-hormones.org/about-us/our-communities/clinicians/covid-19-and-endocrine-disease-clinical-information-and-comment-from-ese/
7. Diabetes UK: Advice for healthcare professionals on coronavirus (Covid-19) and diabetes
   https://www.diabetes.org.uk/professionals/resources/coronavirus-clinical-guidance

16.1.5 Gastroenterology and Hepatology

1. International Liver Cancer Association (ILCA): COVID-19 and liver cancer
   https://ilca-online.org/covid19andlivercancer/
2. International Organization for the Study of Inflammatory Bowel Disease (IOIBD): COVID 19 and IBD webinars and guidelines
   https://ioibd.org/covid-19-and-ibd-webinars-and-guidelines/
3. World Gastroenterology Organisation (WGO): COVID-19—Resources for our global community
   https://www.worldgastroenterology.org/about-wgo/covid-19
4. American Association for the Study of Liver Diseases (AASLD): COVID-19 and the liver
   https://www.aasld.org/about-aasld/covid-19-and-liver
5. American College of Gastroenterology (ACG): COVID-19 and GI
   https://gi.org/media/covid-19-and-gi/
6. American Gastroenterological Association (AGA): Practice updates—Coronavirus (COVID-19)
   https://gastro.org/practice-guidance/practice-updates/covid-19/
7. European Association for the Study of the Liver (EASL): COVID-19 and the liver
   https://easl.eu/covid-19-and-the-liver/
8. European Society of Gastrointestinal Endoscopy (ESGE): ESGE and ESGENA position statement on gastrointestinal endoscopy and the COVID-19 pandemic
   https://www.esge.com/esge-and-esgena-position-statement-on-gastrointestinal-endoscopy-and-the-covid-19-pandemic/
9. British Society of Gastroenterology (BSG): COVID-19 guidance & advice
   https://www.bsg.org.uk/covid-19-advice/

16.1.6 Infectious Diseases

1. American Society of Transplantation (AST): COVID-19 information
   https://www.myast.org/covid-19-information
2. Antimicrobial Stewardship Program (ASP): COVID-19 (SARS-CoV-2)—Current clinical management and drug information

https://www.antimicrobialstewardship.com/covid-19
3. Infectious Diseases Society of America (IDSA): COVID-19 resource center
https://www.idsociety.org/public-health/COVID-19-Resource-Center/
4. British Infection Association (BIA): COVID-19
http://www.britishinfection.org/news/bia-news-updates/covid-19

16.1.7 Nephrology and Hypertension

1. International Society for Peritoneal Dialysis (ISPD): Strategies regarding COVID-19 in PD patients
https://ispd.org/strategies-covid19/
2. International Society of Hypertension (ISH): A statement from the International Society of Hypertension on COVID-19
https://ish-world.com/news/a/A-statement-from-the-International-Society-of-Hypertension-on-COVID-19/
3. International Society of Nephrology (ISN): COVID-19 resources—Global reports and more
https://www.theisn.org/covid-19
4. American Society of Nephrology (ASN): Coronavirus disease 2019 (COVID-19)
https://www.asn-online.org/covid-19/
5. European Society of Hypertension (ESH): Update on COVID-19
https://www.eshonline.org/spotlights/update-on-covid-19/
6. The Renal Association: COVID-19—Information and guidance for renal professionals
https://renal.org/covid-19/

16.1.8 Neurosciences

1. International League Against Epilepsy (ILAE): COVID-19 and epilepsy
https://www.ilae.org/patient-care/covid-19-and-epilepsy
2. American Academy of Neurology (AAN): COVID-19 neurology resource center
https://www.aan.com/tools-and-resources/covid-19-neurology-resource-center/
3. AAN: Preserving stroke care during the COVID-19 pandemic—Potential issues and solutions
https://n.neurology.org/content/95/3/124
4. American Epilepsy Society (AES): COVID-19 resources for epilepsy clinicians
https://www.aesnet.org/about_aes/position_statements/covid-19/for-clinicians
5. American Heart Association (AHA)/American Stroke Association (ASA): COVID-19 content—Stroke community
https://professional.heart.org/professional/General/UCM_505868_COVID-19-Professional-Resources.jsp

6. Child Neurology Society: COVID resource steering group tools
   https://www.childneurologysociety.org/resources/resources-detail-view/covid-resource-steering-group-tools
7. Congress of Neurological Surgeons (CNS): COVID-19 neurosurgical information hub
   https://www.cns.org/covid-19
8. Neurocritical Care Society (NCS): COVID-19 resources
   https://www.neurocriticalcare.org/resources/covid19
9. Society for Neuroscience in Anesthesiology & Critical Care (SNACC): Consensus statement on anesthetic management of endovascular treatment of acute ischemic stroke during COVID-19 pandemic
   https://www.snacc.org/snacc-home/click-here-for-covid-19-resources/snacc-consensus-statement-on-anesthetic-management-of-endovascular-treatment-of-acute-ischemic-stroke-during-covid-19-pandemic/
10. Society for Vascular and Interventional Neurology (SVIN): Coronavirus resource center
    https://www.svin.org/i4a/pages/index.cfm?pageid=3476
11. European Academy of Neurology (EAN): EANcore Covid-19
    https://www.ean.org/ean/eancore-covid-19
12. Association of British Neurologists (ABN): COVID-19 guidance and advice
    https://www.theabn.org/page/COVID-19
13. Neuro Anaesthesia and Critical Care Society (NACCS) - COVID-19 Guides for Clinicians
    https://naccs.org.uk/covid-19-resource-page/covid-19-guides-for-clinicians/
14. World Federation of Neurosurgical Societies (WFNS)- Neuroanesthesia Practice during the COVID-19 Pandemic
    https://www.wfns.org/WFNSData/Uploads/files/Global-Neuroanesthesia-Practice-during-the-COVID-19-Pandemic-21042020.pdf

16.1.9 Obstetrics, Gynecology, and Women's Health

1. International Federation of Gynecology and Obstetrics (FIGO): COVID-19 resources
   https://www.figo.org/resources/covid-19-resources
2. International Society of Ultrasound in Obstetrics and Gynecology (ISUOG): Coronavirus (COVID-19) resources
   https://www.isuog.org/clinical-resources/coronavirus-covid-19-resources.html
3. American College of Obstetricians and Gynecologists (ACOG): COVID-19
   https://www.acog.org/topics/covid-19
4. Royal College of Obstetricians and Gynaecologists (RCOG): COVID-19
   https://elearning.rcog.org.uk/infectious-diseases/viral-infections/covid-19

5. Indian Council of Medical Research (ICMR): Guidance for management of pregnant women in COVID-19 pandemic
https://www.icmr.gov.in/pdf/covid/techdoc/Guidance_for_Management_of_Pregnant_Women_in_COVID19_Pandemic_12042020.pdf

16.1.10 Pediatrics

1. International Pediatric Association (IPA): COVID-19 news & updates
https://ipa-world.org/covid-19-news-and-updates.php
2. American Academy of Child & Adolescent Psychiatry (AACAP): Coronavirus/COVID-19 resource library
https://www.aacap.org/coronavirus
3. American Academy of Pediatric Dentistry (AAPD): COVID-19 resources
https://www.aapd.org/about/about-aapd/news-room/COVID-19-Resources/
4. American Academy of Pediatrics (AAP): Critical updates on COVID-19
https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/
5. American College of Rheumatology (ACR): ACR updates—COVID-19: Clinical guidance for pediatric patients
https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/
6. American Heart Association/AAP: Interim guidance for healthcare providers caring for pediatric patients—CPR & emergency cardiovascular care
https://cpr.heart.org/-/media/cpr-files/resources/covid-19-resources-for-cpr-training/interim-guidance-pediatric-patients-march-27-2020.pdf
7. American Society of Pediatric Hematology/Oncology (ASPHO): COVID–19 resources for pediatric hematologists/oncologists
http://aspho.org/covid-19-resources-for-pediatric-hematologists-oncologists
8. American Society of Pediatric Nephrology (ASPN): COVID-19 information
https://www.aspneph.org/covid-19-information/
9. Child Neurology Society: COVID resource steering group tools
https://www.childneurologysociety.org/resources/resources-detail-view/covid-resource-steering-group-tools

16.1.11 Psychiatry

1. American Psychiatric Association (APA): Coronavirus resources
https://www.psychiatry.org/psychiatrists/covid-19-coronavirus
2. American Psychological Association (APA): APA COVID-19 information and resources
https://www.apa.org/topics/covid-19
3. Royal College of Psychiatrists (RC Psych): Responding to COVID-19

https://www.rcpsych.ac.uk/about-us/responding-to-covid-19/paul-quote-about-covid-19

16.1.12 Pulmonary and Critical Care Medicine

1. Extracorporeal Life Support Organization (ELSO): Guidelines for ECMO in COVID-19
   https://www.elso.org/COVID19.aspx
2. Fleischner Society: A multinational consensus statement on the role of chest imaging in patient management during the COVID-19 pandemic
   https://www.fleischner-covid19.org/
3. Canadian Critical Care Society (CCCS): COVID-19 resources & updates
   https://canadiancriticalcare.org/COVID-19
4. Canadian Thoracic Society (CTS): COVID-19—Information for healthcare professionals and the respiratory community
   https://cts-sct.ca/covid-19/
5. American College of Chest Physicians (CHEST): COVID-19—Guidelines and statements
   https://www.chestnet.org/Guidelines-and-Resources/COVID-19/Guidelines-and-Statements
6. American College of Radiology (ACR): ACR coronavirus (COVID-19) resources
   https://www.acr.org/Coronavirus-Covid-19-Resources
7. American Society of Parenteral and Enteral Nutrition (ASPEN): Resources for clinicians caring for patients with coronavirus
   https://www.nutritioncare.org/Guidelines_and_Clinical_Resources/Resources_for_Clinicians_Caring_for_Patients_with_Coronavirus/
8. American Thoracic Society (ATS): COVID-19 clinician and patient resources
   https://www.thoracic.org/covid/covid19-clinician-resources.php
9. Surviving Sepsis Campaign (SSC): COVID-19 guidelines
   https://www.sccm.org/SurvivingSepsisCampaign/Guidelines/COVID-19
10. European Respiratory Society (ERS): COVID-19 resource center
    https://www.ersnet.org/the-society/news/novel-coronavirus-outbreak%2D%2Dupdate-and-information-for-healthcare-professionals
11. European Society for Clinical Nutrition and Metabolism (ESPEN): Coronavirus, a word from ESPEN
    https://www.espen.org/component/content/article/30-news/283-coronavirus-word-from-the-espen-chairman?Itemid=104
12. European Society of Intensive Care Medicine (ESICM): COVID-19
    https://www.esicm.org/resources/coronavirus-public-health-emergency/
13. British Society of Thoracic Imaging (BSTI): COVID-19 resources
    https://www.bsti.org.uk/covid-19-resources/
14. British Thoracic Society (BTS): COVID-19—Information for the respiratory community

https://www.brit-thoracic.org.uk/about-us/covid-19-information-for-the-respiratory-community/
15. Indian Society of Critical Care Medicine (ISCCM)- Critical Care for COVID-19 Affected Patients: Position Statement
https://isccm.org/pdf/1587101879731_ijccm23395.pdf

16.1.13 Solid Organ Transplantation

1. International Society for Heart and Lung Transplantation (ISHLT): COVID-19—Information for transplant professionals
https://ishlt.org/covid-19-information
2. European Renal Association (ERA)/European Dialysis and Transplant Association (EDTA): COVID-19 news and information
https://www.era-edta.org/en/covid-19-news-and-information/
3. British Transplantation Society (BTS): COVID-19 information
https://bts.org.uk/information-resources/covid-19-information/
4. Liver Transplant Society of India (LTSI): Guidelines for liver transplantation and COVID-19
https://www.icmr.gov.in/pdf/covid/techdoc/Guidelines_for_Liver_Transplantation_and_COVID_13042020.pdf

16.1.14 Surgery

1. American Academy of Ophthalmology (AAO): Coronavirus and eye care
https://www.aao.org/coronavirus
2. American Academy of Otolaryngology—Head and Neck Surgery (AAO-HNS): AAO-HNS COVID-19 resources
https://www.entnet.org/content/covid-19-resource-page
3. American Association for the Surgery of Trauma (AAST): COVID-19 resources
https://www.aast.org/resources-detail/covid-19-resources-links
4. American College of Surgeons (ACS): COVID-19 and surgery—Resources for the surgical community
https://www.facs.org/covid-19
5. Society for Surgical Oncology (SSO): COVID-19 resources
https://www.surgonc.org/resources/covid-19-resources/
6. Society for Vascular Surgery (SVS): COVID-19 resources for members
https://vascular.org/news-advocacy/covid-19-resources
7. Society of American Gastrointestinal and Endoscopic Surgeons (SAGES): COVID-19/coronavirus announcement archives
https://www.sages.org/category/covid-19/
8. Society of Thoracic Surgeons (STS): COVID-19 resources
https://www.sts.org/covid-19/covid-19-resources
9. Royal College of Surgeons (RCS): Coronavirus (COVID-19) information hub
https://www.rcseng.ac.uk/coronavirus/

16.2 International Public Health and Government Guidelines

Centers for Disease Control and Prevention (CDC)
https://www.cdc.gov/coronavirus/2019-ncov/index.html
World Health Organization (WHO)
https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance
Indian Council of Medical Research
https://www.icmr.gov.in/
Government of India Ministry of Health and Family Welfare (MOHFW): Resources
https://www.mohfw.gov.in/

16.3 Journals

1. British Medical Journal (BMJ): https://www.bmj.com/coronavirus
2. Cambridge University Press: https://www.cambridge.org/core/browse-subjects/medicine/coronavirus-free-access-collection
3. Clarivate Analytics: https://clarivate.com/coronavirus-resources/
4. Elsevier: https://www.elsevier.com/connect/coronavirus-information-center
5. JAMA network: https://jamanetwork.com/journals/jama/pages/coronavirus-alert
6. The Lancet: https://www.thelancet.com/coronavirus
7. New England Journal of Medicine (NEJM): https://www.nejm.org/coronavirus
8. Oxford University Press: https://academic.oup.com/journals/pages/coronavirus?cc=us&lang=en&
9. PLOS: https://theplosblog.plos.org/2020/01/novel-coronavirus-2019-ncov-outbreak/
10. SAGE: https://journals.sagepub.com/pb-assets/PDF/SAGE-Publishing_Coronavirus-Related-Articles.pdf
11. Springer Nature: https://www.springernature.com/gp/researchers/campaigns/coronavirus
12. SSRN: https://www.ssrn.com/index.cfm/en/coronavirus/
13. Wiley Online Library: https://novel-coronavirus.onlinelibrary.wiley.com/

16.4 Others

1. Brain Infections Global
   https://braininfectionsglobal.tghn.org/covid-neurology-resource/
2. MSD Manuals COVID-19 Information and Resources
   https://www.msdmanuals.com/professional/resourcespages/covid-19-resources
3. UpToDate
https://www.uptodate.com/home/covid-19-access