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Guideline for the treatment of 2019 novel coronavirus

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Coronaviruses: An Overview of Their Replication and Pathogenesis

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Abstract

Coronaviruses (CoVs), enveloped positive-sense RNA viruses, are characterized by club-like spikes that project from their surface, an unusually large RNA genome, and a unique replication strategy. Coronaviruses cause a variety of diseases in mammals and birds ranging from enteritis in cows and pigs and upper respiratory disease chickens to potentially lethal human respiratory infections. Here we provide a brief introduction to coronaviruses discussing their replication and pathogenicity, and current prevention and treatment strategies. We will also discuss the outbreaks of the highly pathogenic Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and the recently identified Middle Eastern Respiratory Syndrome Coronavirus (MERS-CoV).

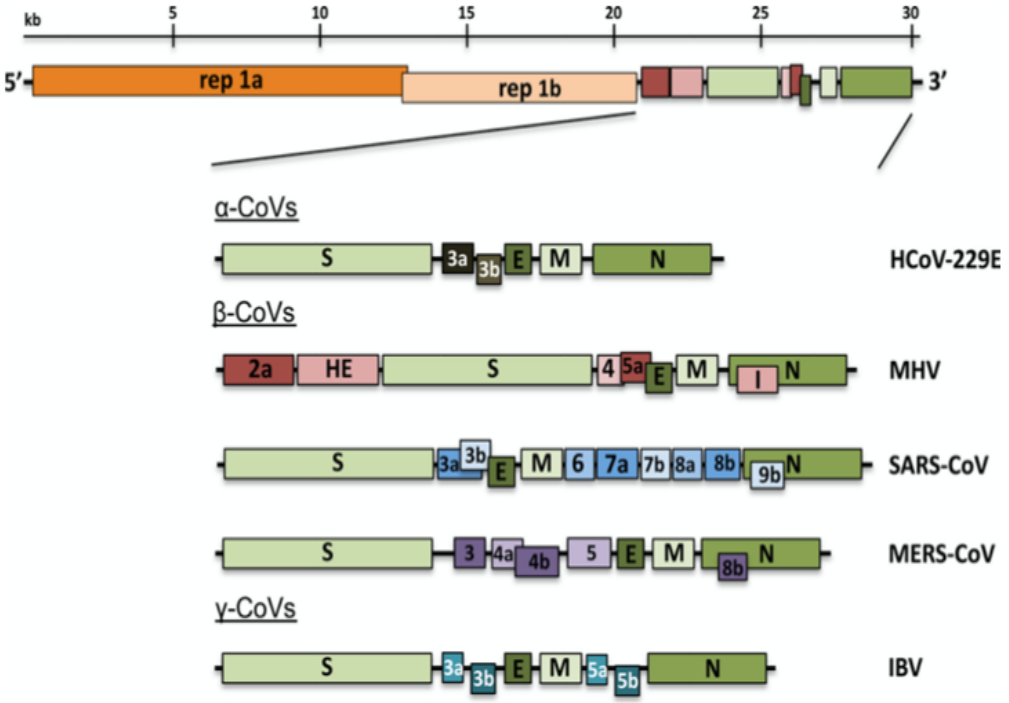
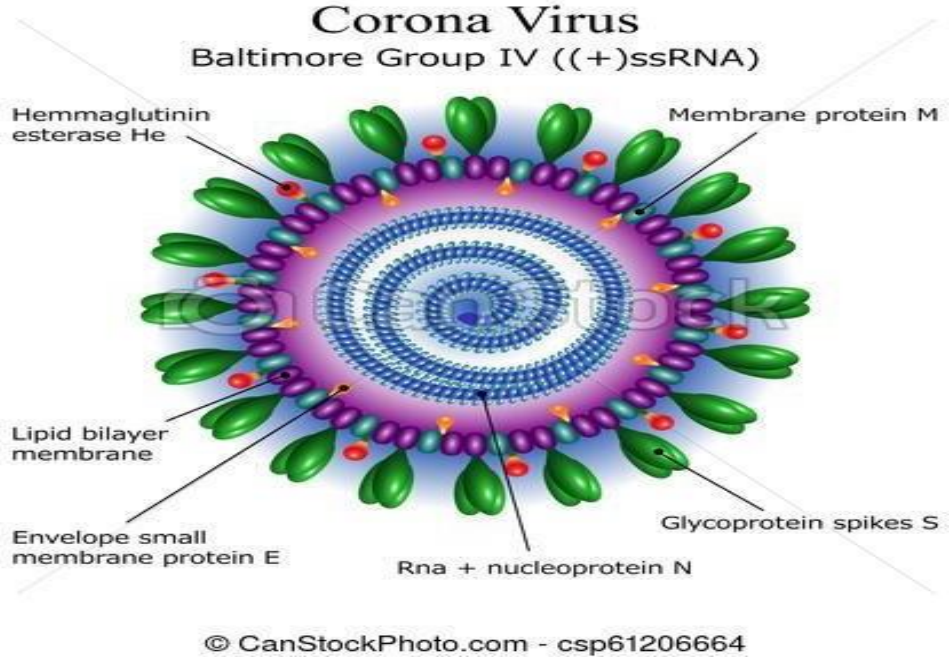


Figure 1. Genomic Orientation of Representative α, β, and γ CoVs
An illustration of the MHV genome is depicted on top. The expanded regions below show the structural and accessory proteins in the 3' regions of the MHV, SARS-CoV, and MERS-CoV. Size of the genome and individual genes are approximated using the legend at the top of the diagram but are not drawn to scale. HCoV-229E, human coronavirus 229E; MHV, mouse hepatitis virus; SARS-CoV, severe acute respiratory syndrome coronavirus; MERS-CoV, Middle East respiratory syndrome coronavirus; IBV, infectious bronchitis virus.



Coronavirus virions are spherical with diameters of approximately **125 nm**
Coronaviruses have helically symmetrical nucleocapsids, which is uncommon among positive-sense RNA viruses, but far more common for negative- sense RNA viruses.

Coronavirus virus particles contain four main structural proteins.
These are the spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins, all of which are encoded within the 3’ end of the viral genome. The S protein (~150 kDa), utilizes an N-terminal signal sequence to gain access to the ER, and is heavily N-linked glycosylated. Homotrimers of the virus encoded S protein make up the distinctive spike structure on the surface of the virus. The trimeric S glycoprotein is a class I fusion protein and mediates attachment to the host receptor

Nasopharyngeal Shedding of Severe Acute Respiratory Syndrome–Associated Coronavirus Is Associated with Genetic Polymorphisms

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Background. A high initial or peak severe acute respiratory syndrome (SARS)–associated coronavirus (SARS-CoV) load in nasopharyngeal specimens was shown to be associated with a high mortality rate. Because all infected individuals were devoid of preexisting protective immunity against SARS-CoV, the biological basis for the variable virus burdens in different patients remains elusive.

Methods. The nationwide SARS database in Taiwan was analyzed, and genotyping of 281 single-nucleotide polymorphisms (SNPs) of 65 genes was performed for 94 patients with SARS, to identify SNPs for which distribution between patients with or without detectable nasopharyngeal shedding of SARS-CoV was biased.

Results. Titers of SARS-CoV shed in nasopharyngeal specimens varied widely, ranging from nondetectable to 10^8 SARS-CoV RNA copies/mL, and they were correlated positively with a high mortality rate ($P < .0001$, by trend test) and with early death (i.e., death occurring within 2 weeks of the onset of illness) ($P = .0015$, by trend test). Virus shedding was found to be higher among male patients ($P = .0014$, by multivariate logistic regression) and among older patients ($P = .015$, by multivariate logistic regression). Detectable nasopharyngeal shedding of SARS-CoV was associated with polymorphic alleles of interleukins 18 ($P = .014$) and 1A ($P = .031$) and a member of NFκB complex (reticuloendotheliosis viral oncogene homolog B [*RelB*]) ($P = .034$), all of which are proinflammatory in nature, as well as the procoagulation molecule fibrinogen-like protein 2 ($P = .008$).

Conclusion. The SARS-CoV load is a determinant of clinical outcomes of SARS, and it is associated with polymorphisms of genes involved in innate immunity, which might be regulated in an age- and sex-dependent manner. The findings of the present study provided leads to genes involved in the host response to SARS-CoV infection; if substantiated with functional studies, these findings may be applicable to other newly emerged respiratory viruses (e.g., the influenza pandemic strain).

Table 1. Genes studied.

Gene symbol[a]	No. of SNPs[b]
ACE2	2/16
ACP5	2/2
ADAR	2/4
AIP	0/3
ANPEP[c]	2/4
B2M	2/3
CAT	2/2
CCL5	1/3
CD209	8/9
CIITA	3/5
CXCL9	1/1
CXCL10	5/5
CYP17A1	1/1
EIF2AK3[c]	4/6
EIF2S1	5/6
EIF4G1	6/8
ESR1	1/2
FGL2[d]	3/4
FN1	2/5
G6PD	1/6
GNB3[c]	6/8
GPX1	2/7
GSS	0/1
HMOX1	2/2
IFNAR1	4/10
IFNAR2	1/1
IFNG	1/1
IFNGR1	2/2
IFNGR2	0/2
IL1A[d]	1/1
IL1B	2/3
IL1RN	1/1
IL4	1/1
IL6	0/1
IL10	5/11
IL10RB	1/3
IL12A	2/5
IL15	1/2
IL18[d]	2/6
IRF1[c]	3/4
IRF3	1/3
IRF7	0/1
MBL2	1/2
MX1	4/9
NFRKB	0/4
OAS1	2/7
PRDX2	0/1
PRKRA	2/2
PTGS2	2/13
RelB[c]	1/2
RFX5	0/6
RNASEL[c]	3/5
SERPINB3[c]	2/2
SH2D1A	1/1
SLAMF1	7/7
SOCS1	0/3
SOCS3	1/2
SOD1	0/1
TBF	1/3
TFRC	0/1
TGFB1	1/2
TLR3	4/11
TLR4	3/19
TRAF6	1/5
WSX1	0/2

NOTE. Detailed information on the SNPs is provided in [23]. SNP, single-nucleotide polymorphism.

[a] HUGO Gene Nomenclature Committee–approved gene symbol [24].

[b] Data are no. of polymorphic loci/total no. of loci studied per gene.

[c] Genes containing SNPs that showed a >10% difference in allele distribution between patients with SARS with or without detectable levels of virus but for which statistical significance could not be determined because of a lack of power (figure 3).

[d] Genes containing SNPs with a statistically significant association ($P < .05$) with virus load.

RESULTS

Nasopharyngeal SARS-CoV load. The virus load in the respiratory tract at the time of admission to the hospital or diagnosis of SARS ranged widely (from undetectable to 10^8 SARS-CoV RNA copies/mL) (figure 1). Although a longitudinal study of patients with SARS indicated that the nasopharyngeal virus load increased between the fifth and the 10th days of illness and decreased by the 15th day of illness [2], the virus loads at the time of admission of all patients with SARS in our data set did not reflect this trend of a rise and fall occurring during the first 2 weeks of the clinical course of SARS. Rather, on any given day within the first week of the clinical course of SARS, the nasopharyngeal virus load in different patients ranged widely. Overall, 111 (41.9%) of 265 patients with SARS had an undetectable level of nasopharyngeal virus shedding, and this lack of detection of virus did not correlate with the time of specimen collection, because successive samples were obtained from these patients, and the test results for these specimens remained negative.

Factors influencing the level of virus shedding. Among patients with SARS, undetectable levels of nasopharyngeal

Table 2. Distribution of 265 patients with severe acute respiratory syndrome (SARS), according to nasopharyngeal (NP) SARS-associated coronavirus (SARS-CoV) load at the time of admission, by demographic and clinical characteristics.

Demographic or clinical characteristic	Patients with undetectable NP SARS-CoV load (N = 111)		Patients with NP SARS-CoV load, RNA copies/mL: $<10^3$ (N = 39)		10^3–10^5 (N = 76)		$>10^5$ (N = 39)		P[b]
	Distribution, %[a]	No.	Distribution, %[a]	No.	Distribution, %[a]	No.	Distribution, %[a]	No.	
Sex									.0015
Male (n = 95)	27.4	26	14.7	14	33.7	32	24.2	23	
Female (n = 170)	50.0	85	14.7	25	25.9	44	9.4	16	
Age,[c] years									.0055
<30 (n = 81)	53.1	43	14.8	12	22.2	18	9.9	8	
30–49 (n = 107)	45.8	49	14.0	15	26.2	28	14.0	15	
50–64 (n = 42)	31.0	13	11.9	5	38.1	16	19.0	8	
≥65 (n = 34)	17.7	6	20.6	7	38.2	13	23.5	8	
Time of swab sampling[d]									.603
≤3 days (n = 86)	43.0	37	12.8	11	29.1	25	15.1	13	
>3 days (n = 179)	41.3	74	15.7	28	28.5	51	14.5	26	
Source of infection									.346
Known (n = 47)	31.9	15	19.2	9	31.9	15	17.0	8	
Unknown (n = 218)	44.0	96	13.8	30	28.0	61	14.2	31	
Underlying disease									.589
Present (n = 219)	46.1	101	13.3	29	26.9	59	13.7	30	
Absent (n = 46)	21.7	10	21.7	10	37.0	17	19.6	9	
Death,[e] by patient age									
≤40 years	4.6	3/65	15.8	3/19	20.0	6/30	26.7	4/15	.0001[f]
>40 years	17.8	8/45	45.0	9/20	53.3	24/45	58.3	14/24	.0004[f]

[a] Percentages were calculated by dividing the no. of patients with an undetectable or detectable NP SARS-CoV load by the no. of patients with a demographic or clinical characteristic.

[b] Multivariate logistic regression model controlled by the date of specimen collection.

[c] Data were missing for 1 patient.

[d] After onset of fever.

[e] Data in the "No." columns are no. of patients who died/no. of patients with the characteristic. P = .0002, multivariate logistic regression model controlled by sex and age.

[f] P value determined using the Cochran-Armitage trend test.

Table 4. Genetic polymorphisms and nasopharyngeal virus loads of 94 patients with severe acute respiratory syndrome (SARS).

Gene (position from start ATG), genotype	Nasopharyngeal SARS-CoV load			Multivariate logistic[a]		All patients with SARS	Reference group[c]	
	Detectable (n = 49)	Not Detectable (n = 45)	P[b]	OR (95% CI)	P	(n = 94)	(n = 94)	P
IL1A (−889)			.024/.028		.008			1.0
CC	37	42		1		79	79	
TC	12	3		10.2 (1.82–56.8)		15	15	
IL18 (−607)			.010/.032		.014			.78
GG	9	18		1		27	25	
GT	27	22		4.47 (1.25–17.4)		49	46	
TT	13	5		10.6 (2.03–55.0)		18	23	
FGL2 (+158)			.070/.041		.031			.61
GG	24	32		1		56	61	
GA	23	11		4.0 (1.39–11.48)		34	30	
AA	2	2		4.57 (0.27–75.2)		4	3	
RelB (+23962)			.043/.033		.034			.16
CC	6	11		1		17	29	
CT	26	26		1.95 (.50–7.52)		52	46	
TT	17	8		7.20 (1.47–35.3)		25	19	

NOTE. Data are no. of patients, unless indicated otherwise. SARS-CoV, SARS-associated coronavirus.

[a] Multivariate logistic model including age and sex.

[b] P values for univariate analysis were determined by exact Mantel-Haenszel/permutation test.

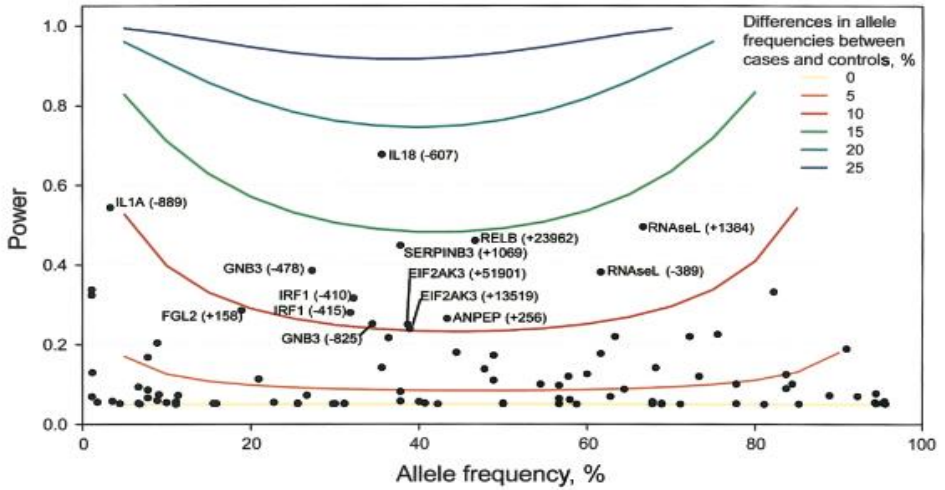

Figure 3. Power plotted against the allele frequency of each single-nucleotide polymorphism. Power is calculated based on the allele frequencies and the sample size of patients with severe acute respiratory syndrome (SARS) with (no. of case patients, 49) or without (no. of control patients, 45) detectable virus shedding. The curved lines denote the zones of differences between the allele frequencies of the case patients and control patients. Each black dot (·) denotes one single-nucleotide polymorphism plotted according to the allele frequency of the control patients with SARS without detectable SARS-associated coronavirus.

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The interferon gamma gene polymorphism +874 A/T is associated with severe acute respiratory syndrome

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Table 2: Allele frequencies and genotype frequencies in SARS patients and controls*

SNP	SARS (n = 476) Number (%)	Control (n = 449) Number (%)	OR (95% CI)	P
Genotype				
IFN-γ +874				<0.001
A/A	332 (69.8)	203 (45.2)	5.19 (2.78 – 9.68)	
A/T	127 (26.7)	189 (42.1)	2.57 (1.35 – 4.88)	
T/T	17 (3.6)	57 (12.7)	Reference	
IL-10 -1082				NS
A/A	439 (92.2)	411 (91.5)	..	
A/G	35 (7.4)	38 (8.5)	..	
G/G	2 (0.4)	0 (0)	..	
IL-10 -592				NS
A/A	244 (51.3)	209 (46.6)	..	
A/C	188 (39.5)	214 (47.7)	..	
C/C	44 (9.2)	26 (5.8)	..	
TNF-α -308				NS
GG	403 (84.7)	377 (83.9)	..	
GA	70 (14.7)	70 (15.6)	..	
AA	3 (0.6)	2 (0.5)	..	
Allele				
IFN-γ +874				<0.001
A	791 (83.1)	595 (66.3)	2.23 (1.75 – 2.83)	
T	161 (16.9)	303 (33.7)		
IL-10 -1082				NS
A	913 (95.9)	860 (95.8)	..	
G	39 (4.1)	38 (4.2)	..	
IL-10 -592				NS
A	676 (71.0)	632 (70.4)	..	
C	276 (29.0)	266 (29.6)	..	
TNF-α -308				NS
G	876 (92.0)	824 (91.8)	..	
A	76 (8.0)	74 (8.2)	..	

NS = not significant.
*P-value and OR (95% CI) were calculated with the use of logistic regression models, adjusted with sex and age.

Table 1: Polymorphisms of the genes genotyped

Genes	SNPs	rs number	References
IFN-γ	*IFN-γ* +874 A/T	rs2430561	[23]
IL-10	*IL-10* -1082 A/G	rs1800896	[23,26-27]
	IL-10 -592 A/C	rs1800872	
TNF-α	*TNF-α* -308G/A	rs1800629	[28]

Table 3: Genotype frequencies among survival and death SARS cases

SNP	Death (n = 57) Number (%)	Survival (n = 415) Number (%)	P
Genotype			
IFN-γ +874			NS
A/A	41 (71.9)	289 (69.6)	
A/T	13 (22.8)	112 (27.0)	
T/T	3 (5.3)	14 (3.4)	
IL-10-1082			NS
A/A	52 (91.2)	383 (92.3)	
A/G	4 (7.0)	31 (7.5)	
G/G	1 (1.8)	1 (0.2)	
IL-10-592			NS
A/A	28 (49.1)	214 (51.6)	
A/C	21 (36.8)	165 (39.8)	
C/C	8 (14.0)	36 (8.7)	
TNF-α-308			NS
GG	46 (80.7)	353 (85.1)	
GA	11 (19.3)	59 (14.2)	
AA	0 (0)	3 (0.7)	

NS = not significant.

Communication

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Discovering drugs to treat coronavirus disease 2019 (COVID-19)

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Table 1. Antivirals included in the Guidelines (version 6) for treatment of COVID-19

Drug	Dosage	Method of administration	Duration of treatment
IFN-α	5 million U or equivalent dose each time, 2 times/day	Vapor inhalation	No more than 10 days
Lopinavir/ritonavir	200 mg/50 mg/capsule, 2 capsules each time, 2 times/day	Oral	No more than 10 days
Ribavirin	500 mg each time, 2 to 3 times/day in combination with IFN-α or lopinavir/ritonavir	Intravenous infusion	No more than 10 days
Chloroquine phosphate	500 mg (300 mg for chloroquine) each time, 2 times/day	Oral	No more than 10 days
Arbidol	200 mg each time, 3 times/day	Oral	No more than 10 days

IFN-α is a broad-spectrum antiviral that is usually used to treat hepatitis, though it is reported to inhibit SARS-CoV reproduction *in vitro*

Lopinavir/ritonavir is a medication for the human immunodeficiency virus (HIV)

Chloroquine is a widely used antimalarial that was found to be a potential broad-spectrum antiviral in 2006 (*7*). Chloroquine was found to block SARS-CoV-2 infection at low- micromolar concentration

Favipiravir is a new type of RNA-dependent RNA polymerase (RdRp) inhibitor

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Reducing mortality from 2019-nCoV: host-directed therapies should be an option

Alimuddin Zumla • David S Hui • Esam I Azhar • Ziad A Memish • Markus Maeurer

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Infection with 2019-nCoV appears to be initially associated with an increased Th2 response, which might reflect a physiological reaction to curb overt inflammatory responses. 2019-nCoV infection is also associated with a cytokine storm, which is characterised by increased plasma concentrations of interleukins 2, 7, and 10, granulo- cyte colony stimulating factor, interferon-γ-inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1 alpha, and tumour necrosis factor α.

Treatment

Several marketed drugs with excellent safety profiles such as **metformin, glitazones, fibrates, sartans, and atorvastin, as well as nutrient supplements** and biologics could reduce immunopathology, boost immune responses, and prevent or curb ARDS.

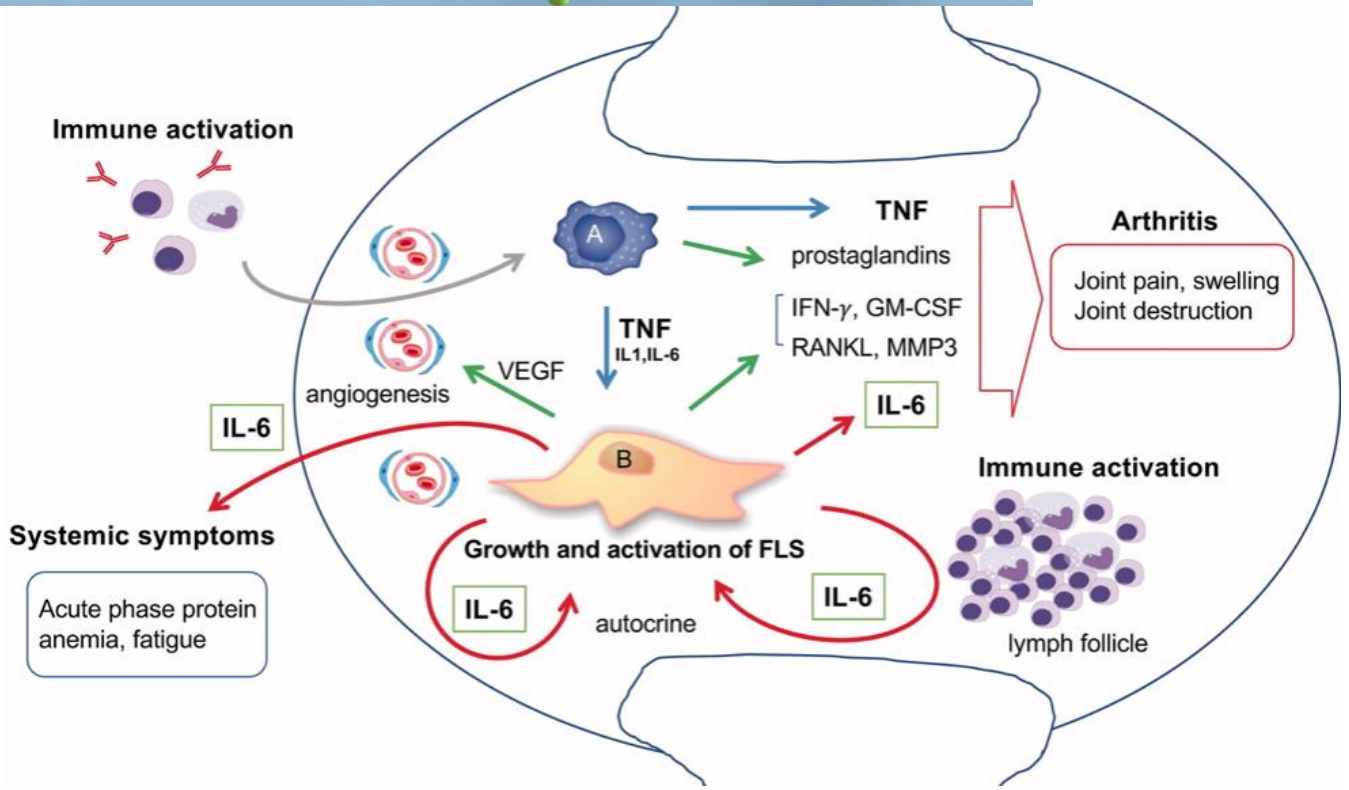
Zinc and other metal- containing formulations appear to have anti-viral activity, are safe, cheap, and readily available.

These formulations could be used as adjuncts to **monotherapy or as combinational therapies with cyclosporine, lopinavir– ritonavir, interferon beta-1b, ribavirin, remdesivir, monoclonal antibodies, and anti-viral peptides targeting 2019-nCoV.**

Tocilizumab, a monoclonal antibody that targets the interleukin 6 receptor, has a good safety profile.

Interleukin 17 blockade might benefit those patients who have a 2019-nCoV infection and increased plasma concentration of interleukin 17.

TOCILIZUMAB



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Tocilizumab

Tocilizumab is a humanized anti-IL-6 receptor antibody that specifically blocks the actions of IL-6, a cytokine that is markedly elevated in active AOSD.

From: Rheumatology (Sixth Edition), 2015

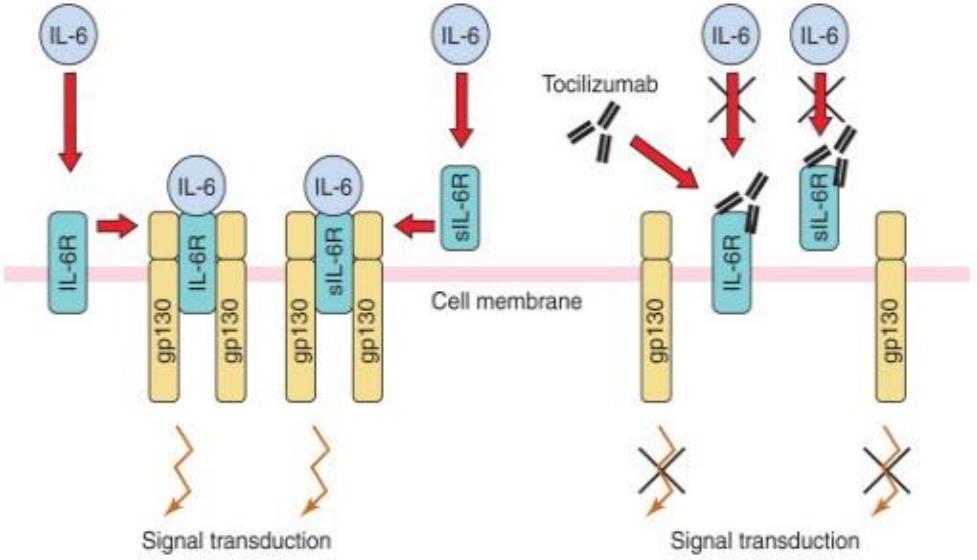

Fig. 62.1. Both the soluble (sIL-6R) and membrane-bound (mIL-6R) forms of the IL-6 receptor are inhibited by tocilizumab. gp130, glycoprotein 130.

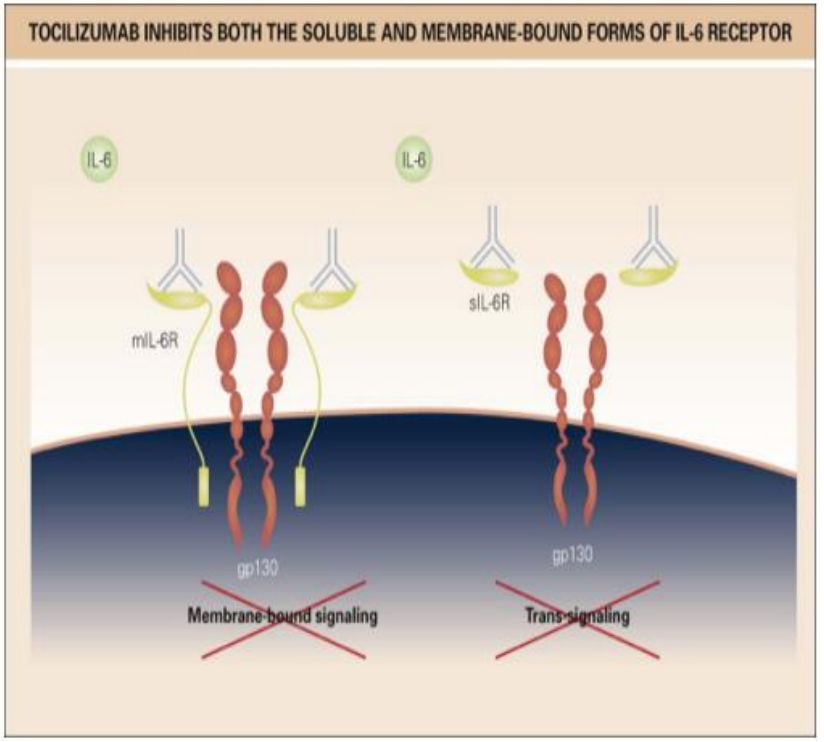

Figure 10J-1. Inhibitory action of tocilizumab in IL-6 signaling. IL-6 signal transduction is mediated by a ligand-binding IL-6R and a non–ligand-binding but signal-transducing chain, gp130, on the cell surface. Soluble IL-6R (sIL-6R) is also capable of signal transduction. Tocilizumab recognizes IL-6 binding sites on both the membranous IL-6R and sIL-6R and inhibits IL-6 signal transduction.

Serum tocilizumab concentrations showed nonlinear pharmacokinetics in the dose range of 2 to 8 mg/kg when intravenously administered by drop infusion for 2 hours

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1,25-dihydroxy Vitamin D3 and Interleukin-6 Blockade Synergistically Regulate Rheumatoid Arthritis by Suppressing Interleukin-17 Production and Osteoclastogenesis

Haneul Kim,[1] Seungye Baek,[2] Seung-Min Hong,[2] Jaeseon Lee,[2] Seung Min Jung,[3] Jennifer Lee,[1,2] Mi-La Cho,[2] Seung-Ki Kwok,[1,2] and Sung-Hwan Park[1,2]

Vit D receptor is expressed on immune cells, and the role of vit D in immunomodulation has been widely investigated. Vit D suppresses the transcription of T-helper (Th) 1 proinflammatory cytokines, such as interferon (IFN)-γ, IL-17, and IL-21. It suppresses IL-17, IL-6, IL-1, and TNF-α production by Th1 cells. Vit D also inhibits Th1 and augments Th2 cell development, as well as decreases IFN-γ and IL-2 production by CD4+ T cells.

Patients with sufficient vit D levels showed better treatment responses 24 and 48 weeks after tocilizumab initiation.

Table 2. Clinical responses to tocilizumab at weeks 24 and 48

Efficacy measure	25(OH)D ≥ 30 ng/mL (n = 34)	25(OH)D < 30 ng/mL (n = 64)	*P* value
At week 24			
DAS28 reduction, %	64.6 ± 15.5	52.7 ± 20.7	0.004
Low DAS28 (DAS28 ≤ 3.2)	31 (91.2)	45 (70.3)	0.018
Remission (DAS28 ≤ 2.6)	28 (82.4)	37 (57.8)	0.014
Clinically significant reduction ≥ 1.2	33 (97.1)	59 (92.2)	0.661
At week 48	(n = 25)	(n = 50)	
DAS28 reduction, %	67.6 ± 13.9	59.8 ± 16.4	0.044
Low DAS28 (DAS28 ≤ 3.2)	24 (96.0)	43 (86.0)	0.256
Remission (DAS28 ≤ 2.6)	23 (92.0)	35 (70.0)	0.032
Clinically significant reduction ≥ 1.2	25 (100.0)	49 (98.0)	1.000

Data are presented as number (%) or mean ± standard deviation.
DAS = disease activity score.

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ORIGINAL ARTICLE

Connective tissue disease-associated interstitial lung disease

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KEYWORDS
Connective tissue disease;
Interstitial lung disease;
Rheumatoid arthritis;
Systemic sclerosis;
Tocilizumab;
Nintedanib

Abstract
Background: Connective tissue diseases (CTD) are frequently associated with interstitial lung disease (ILD), significantly impacting their morbidity and mortality.
Aim: Analyze the experience of an autoimmune specialized unit on treating CTD-ILD and characterize the population based on most frequent diseases, imaging patterns, lung function tests results, serology and treatment. Assess mortality and mortality predictors in these patients.
Methods: Retrospective, descriptive and statistical analysis of the CTD-ILD patients followed up at an autoimmune diseases unit during a 6-year period.
Results: Over the study period, 75 patients with CTD-ILD were treated with a mean follow-up of 49 ± 31 months.

The most frequent CTD were systemic sclerosis and rheumatoid arthritis. ILD was diagnosed prior to CTD in 8% of patients and concomitantly in 35%. Nonspecific interstitial pneumonia was the CT pattern in 60% and 35% had an isolated diminished DLCO on lung function tests. Pulmonary hypertension was present in 12% and it was the single most important mortality predictor (OR 14.41, p = 0.006). Corticosteroids are the mainstay of treatment but biologics were prescribed in 39% of the patients (mostly tocilizumab and rituximab). Two scleroderma patients were recently treated with nintedanib.
Conclusions: ILD is a potential complication of every CTD and can impose a dramatic burden on these patients. The clinical relevance of ILD together with their early expression in the course of the disease underlines the importance of the presence of chest physicians in these units.

Table 1 Description of main characteristics analyzed by disease subgroups and the global cohort.

	SSc (n = 26)	RA (n = 15)	Overlap S. (n = 10)	Mixed CTD (n = 7)	AI Myopathy (n = 5)	ANCA + vasculitis (n = 4)	Total (n = 75)[b]
Demographic characteristics							
Female sex, n (%)	21 (81)	11 (73)	7 (70)	6 (86)	3 (60)	2 (50)	58 (77)
Age at CTD diagnosis, y	54 ± 16	54 ± 18	52 ± 10	51 ± 10	39 ± 25	61 ± 8	52 ± 16
Age at ILD diagnosis, y	58 ± 18	61 ± 14	59 ± 10	55 ± 13	42 ± 23	62 ± 7	56 ± 16
HRCT at time of ILD diagnosis							
NSIP, n (%)	19 (73)	6 (40)	8 (80)	5 (71)	3 (60)[a]	2 (50)	45 (60)
UIP, n (%)	7 (27)	8 (53)	1 (10)	2 (29)	2 (40)	2 (50)	27 (36)
LIP, n (%)	0	0	1 (10)	0	0	0	3 (4)
PFT at time of ILD diagnosis							
Spirometry pattern, n (%)							
Normal	12 (46.2)	5 (33)	5 (50)	2 (29)	2 (40)	2 (50)	35 (46)
Restrictive	13 (50)	8 (53)	4 (40)	5 (71)	3 (60)	2 (50)	35 (46)
Obstructive	1 (3.8)	2 (13)	1 (10)	0	0	0	5 (6)
Mean FVC, % predicted	86.1 ± 31.8	85.3 ± 21.3	107.6 ± 29	71.7 ± 31.9	76.4 ± 20	75.5 ± 12	85 ± 27.3
Mean DLCO, % predicted	50.4 ± 23.7	62.4 ± 36.1	68.7 ± 18.9	49.8 ± 11.8	62.1 ± 14.2	33.7 ± 22.2	52.7 ± 23.3
Treatment							
Corticosteroids, n (%)	22 (85)	15 (100)	8 (10)	5 (71)	5 (100)	4 (100)	65 (87)
MTX, n (%)	6 (23)	8 (53)	4 (40)	4 (57)	0	0	23 (32)
RTX, n (%)	2 (7.7)	1 (6.7)	1 (10)	1 (14)	4 (80)	4 (100)	13 (17.3)
TCZ, n (%)	4 (15.4)	7 (46.7)	1 (10)	0	0	0	13 (17.3)
Mortality rate, n (%)	5 (19.2)	5 (33.3)	3 (30)	0	0	1 (25)	15 (20)

SSc - Systemic sclerosis; RA - Rheumatoid Arthritis; Overlap S. - Overlap syndrome; CTD - connective tissue disorder; AI myopathy - Autoimmune myopathy; ILD - Interstitial lung disease; HRCT - High-resolution computerized tomography; NSIP - Nonspecific interstitial pneumonia; UIP - Usual interstitial pneumoniae; LIP- Limphocytic interstitial pneumonia; PFT - Pulmonary function test; FVC - Forced vital capacity; DLCO - Diffusing capacity for carbon monoxide; MTX - Methotrexate; RTX - Rituximab; TCZ – Tocilizumab.
[a] One patient with anti-synthetase syndrome presented with overlap NSIP/OP.
[b] Total includes subgroups shown plus undifferentiated CTD (n = 4) and Sjögren syndrome (n = 2).

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Tocilizumab attenuates acute lung and kidney injuries and improves survival in a rat model of sepsis via down-regulation of NF-κB/JNK: a possible role of P-glycoprotein.

Ibrahim YF[1], Moussa RA[2], Bayoumi AMA[3], Ahmed AF[4].

⊕ Author information

Abstract

Acute lung injury (ALI) and acute kidney injury (AKI) are major causes of sepsis-induced mortality. The objective of the study is to evaluate the effect of tocilizumab (TCZ), an IL-6 receptor inhibitor, in sepsis-induced ALI and AKI using the cecal ligation and puncture (CLP) rat model of sepsis. Clinical and experimental studies have demonstrated the importance of IL-6 in sepsis; however, the role of TCZ has not been investigated. Rats subjected to CLP developed histological evidence of ALI and AKI at 24 h. We found that TCZ alleviated sepsis-induced ALI and AKI as evidenced by improvements in various pathological changes, a significant reduction in the lung wet/dry weight ratio and total protein content in bronchoalveolar lavage fluid (BALF), and a significant decrease in the elevated serum level of creatinine (CR) and blood urea nitrogen (BUN). TCZ induced an increase in the survival rate of treated rats. Additionally, TCZ markedly inhibited sepsis-induced pulmonary and renal inflammatory responses. Moreover, we found that treatment with TCZ inhibited oxidative stress and apoptosis in lung and kidney tissue. TCZ treatment significantly inhibited NF-κB activation, attenuating JNK signaling pathway and significantly up-regulated P-glycoprotein (P-gp) expression in pulmonary as well as in renal tissues. Our data provide novel evidence that TCZ has a protective effect against sepsis-induced ALI and AKI by blocking IL-6 receptor signaling. This could provide a molecular basis for a new medical treatment for sepsis-induced ALI and AKI.

KEYWORDS: Cecal ligation and puncture; IL-6 receptor inhibitor; Kidney injury; Lung injury; Sepsis; Tocilizumab

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Comment

COVID-19: combining antiviral and anti-inflammatory treatments

The use of corticosteroids for severe is controversial; therefore, systemic use of glucocorticoids needs to be cautious.
Methylprednisolone can be used as appropriate for patients with rapid disease progression or severe illness.

According to the severity of the disease, 40 to 80 mg of methylprednisolone per day can be consid- ered, and the total daily dose should not exceed 2 mg/kg (Weak recommendation).

	Baricitinib	Ruxolitinib	Fedratinib
Daily dose, mg	2–10	25	400
Affinity and efficacy: K_d or IC_{50}, nM*			
AAK1†			
Cell free	17	100	32
Cell	34	700	960
GAK†			
Cell free	136	120	1
Cell	272	840	30
BIKE†			
Cell free	40	210	32
Cell	80	1470	960
JAK1			
Cell free	6	3	20
Cell	12	20	600
JAK2			
Cell free	6	3	3
Cell	11	21	100
JAK3			
Cell free	>400	2	79
Cell	>800	14	2370
TYK2			
Cell free	53	1	20
Cell	106	7	600
Pharmacokinetics			
Plasma protein binding	50%	97%	95%
C_{max} (unbound), nM	103‡	117	170
Safety: tolerated dose	≤10 mg/day	≤20 mg twice daily	≤400 mg/day

See regulatory approval documents for further information on these drugs. K_d=dissociation constant. IC_{50}=half-maximal inhibitory concentration. C_{max}=maximum serum concentration. *All values are IC_{50} except the cell free values for AAK1, GAK, and BIKE; "cell free" values indicate inhibitory activity against purified protein in biochemical assay; "cell" values indicate enzyme-inhibitory activity inside a cell. †In the absence of direct measurements of drug inhibition in cells, the predicted cell affinity and efficacy values are derived from the ratio of each compound for their primary target; for example, for baricitinib, IC_{50} AAK1[cell] = (IC_{50}AK1[cell] / IC_{50}AK1[cell free]) × IC_{50}AAK1[cell free]. ‡At a 10 mg dose.

Table: **Properties of three antiviral and anti-inflammatory candidate drugs**

Trattamento antivirale

- **Interferone-alfa per nebulizzazione** (5 milioni di unità o equivalente per volta per adulto, aggiungere 2 mL di acqua sterile per preparazioni iniettabili, inalazione di aerosol due volte al giorno);
- **lopinavir / ritonavir** (200 mg / 50 mg per capsula, 2 capsule ogni volta, due volte al giorno per gli adulti, il corso del trattamento deve essere ≤10 giorni); **ribavirina** (si consiglia **l'associazione con interferone o lopinavir / ritonav**ir, 500 mg per adulti per volta, iniettare 2-3 volte al giorno per via endovenosa, il ciclo di trattamento deve essere ≤10 giorni).
- **Clorochina fosfato** (adulti dai 18 ai 65 anni di età. Se il peso corporeo è superiore a 50 kg, 500 mg per volta, due volte al giorno per 7 giorni; se il peso corporeo è inferiore a 50 kg, 500 mg per volta, due volte al giorno per il giorno 1 e il giorno 2; 500 mg per volta, una volta al giorno per il giorno 3 al giorno 7)
- **Arbidol** (200 mg per gli adulti, tre volte al giorno, il corso del trattamento dovrebbe essere ≤10 giorni).
- **Immunoterapia**: per i pazienti con lesioni polmonari estese e pazienti gravi e test di laboratorio su livelli elevati di IL-6, può essere provato il trattamento **con tocilizumab**. La prima dose è da 4 a 8 mg / kg, la dose raccomandata è di 400 mg, la soluzione salina allo 0,9% viene diluita a 100 ml e il tempo di infusione è superiore a 1 ora; se dopo la prima dose non si verifica alcun miglioramento clinico dei segni e dei sintomi, può essere applicata la stessa dose di prima ancora dopo 12 ore, il numero cumulativo di somministrazioni è un massimo di 2 volte e la dose singola massima non supera gli 800 mg . Presta attenzione all'ipersensibilità e quelli con infezione attiva come la tubercolosi sono controindicati.

Prestare attenzione agli effetti collaterali, alle controindicazioni (ad esempio, **la clorochina è controindicata nei pazienti con malattie cardiache**) dei suddetti farmaci, nonché all'interazione con altri farmaci e altri problemi. **L'uso simultaneo di tre o più tipi di farmaci antivirali non è raccomandato e il trattamento farmacologico pertinente dovrebbe interrompersi se si verificano effetti collaterali insopportabili.**

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Nutraceuticals have potential for boosting the type 1 interferon response to RNA viruses including influenza and coronavirus

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In light of worldwide concern regarding the recent outbreak of a deadly novel strain of coronavirus in China, it is fortuitous that two recent discoveries point the way to effective nutraceutical measures for potentiating the type 1 interferon response to RNA viruses.

Table 1
Provisional daily dosage suggestions for nutraceuticals that might aid control of RNA viruses including influenza and coronavirus

Ferulic acid	500-1,000 mg
Lipoic acid	1,200-1,800 mg (in place of ferulic acid)
Spirulina	15 g (or 100 mg PCB)
N-Acetylcysteine	1,200–1,800 mg
Selenium	50-100 mcg
Glucosamine	3,000 mg or more
Zinc	30-50 mg
Yeast Beta-Glucan	250-500 mg
Elderberry	600–1,500 mg

Nutraceuticals capable of inhibiting NOX2, promoting clearance of hydrogen peroxide, or aiding restoration of the native structure of Cys98 in TLR7, might be expected to boost the TLR7 mediated induction of type 1 interferon and antiviral antibodies.

Jin et al. Military Medical Research (2020) 7:4
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MMR MILITARY MEDICAL RESEARCH

POSITION ARTICLE AND GUIDELINE Open Access

A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version)

Ying-Hui Jin[1], Lin Cai[2], Zhen-Shun Cheng[3], Hong Cheng[4], Tong Deng[1,5], Yi-Pin Fan[6,7], Cheng Fang[1], Di Huang[1], Lu-Qi Huang[6,7], Qiao Huang[1], Yong Han[2], Bo Hu[8], Fen Hu[8], Bing-Hui Li[1,5], Yi-Rong Li[9], Ke Liang[10], Li-Kai Lin[2], Li-Sha Luo[1], Jing Ma[8], Lin-Lu Ma[1], Zhi-Yong Peng[8], Yun-Bao Pan[9], Zhen-Yu Pan[11], Xue-Qun Ren[5], Hui-Min Sun[12], Ying Wang[13], Yun-Yun Wang[1], Hong Weng[1], Chao-Jie Wei[3], Dong-Fang Wu[4], Jian Xia[14], Yong Xiong[10], Hai-Bo Xu[15], Xiao-Mei Yao[16], Yu-Feng Yuan[2], Tai-Sheng Ye[17], Xiao-Chun Zhang[15], Ying-Wen Zhang[17], Yin-Gao Zhang[2], Hua-Min Zhang[6,7], Yan Zhao[14], Ming-Juan Zhao[1], Hao Zi[1,5], Xian-Tao Zeng[1,18*], Yong-Yan Wang[6,7*], Xing-Huan Wang[1,2*], for the Zhongnan Hospital of Wuhan University Novel Coronavirus Management and Research Team, Evidence-Based Medicine Chapter of China International Exchange and Promotive Association for Medical and Health Care (CPAM)

Nutrition support treatment

In patients are screened for nutrition risk based on the NRS2002 score when they are admitted to the hospital.

The recommended plan for patients with different nutrition risk scores are as follows:

First, if the total score is <3 points, it is recommended to eat protein-rich foods (such as eggs, fish, lean meat, dairy products) and carbohydrate- containing diets. The supposed ideal energy intake is 25–30kcal / (kg·d) and the protein mass are 1.5 g / (kg·d).

Second, if the total score is ≥3 points, the patient should be given nutritional support as early as possible. It is recommended to increase protein intake by oral nutrition supplement, 2–3 times/day (≥ 18 g protein/time).

In order to reach the mount of 18 g protein/time, protein powder can be added on the basis of standard whole protein preparations.

Enteral nutrition tube should to be placed when the patient cannot intake supplemental

Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected

Interim guidance

12 January 2020

WHO/nCoV/Clinical/2020.1

World Health Organization

1. Triage: recognize and sort patients with SARI
2. Immediate implementation of appropriate infection prevention and control (IPC) measures
3. Early supportive therapy and monitoring
4. Collection of specimens for laboratory diagnosis
5. Management of hypoxemic respiratory failure and acute respiratory distress syndrome (ARDS)
6. Management of septic shock
7. Prevention of complications
8. Specific anti-nCoV treatments
9. Special considerations for pregnant patients

Jin et al. Military Medical Research (2020) 7:4
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Abstract

In December 2019, a new type viral pneumonia cases occurred in Wuhan, Hubei Province; and then named "2019 novel coronavirus (2019-nCoV)" by the World Health Organization (WHO) on 12 January 2020. For it is a never been experienced respiratory disease before and with infection ability widely and quickly, it attracted the world's attention but without treatment and control manual. For the request from frontline clinicians and public health professionals of 2019-nCoV infected pneumonia management, an evidence-based guideline urgently needs to be developed. Therefore, we drafted this guideline according to the rapid advice guidelines methodology and general rules of WHO guideline development; we also added the first-hand management data of Zhongnan Hospital of Wuhan University. This guideline includes the guideline methodology, epidemiological characteristics, disease screening and population prevention, diagnosis, treatment and control (including traditional Chinese Medicine), nosocomial infection prevention and control, and disease nursing of the 2019-nCoV. Moreover, we also provide a whole process of a successful treatment case of the severe 2019-nCoV infected pneumonia and experience and lessons of hospital rescue for 2019-nCoV infections. This rapid advice guideline is suitable for the first frontline doctors and nurses, managers of hospitals and healthcare sections, community residents, public health persons, relevant researchers, and all person who are interested in the 2019-nCoV.

Keywords: 2019 novel coronavirus, 2019-nCoV, Respiratory disease, Pneumonia, Infectious diseases, Rapid advice guideline, Clinical practice guideline, Evidence-based medicine

Table 2 Rules for grading the recommendations

Strength of recommendation and quality of evidence	Benefit *vs.* risk and burdens	Methodological quality of supporting evidence[a]	Implications
Strong recommendation, high-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
Strong recommendation, moderate quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
Strong recommendation, low or very low quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Observational studies or case series	Strong recommendation but may change when higher quality evidence becomes available
Weak recommendation, high-quality evidence	Benefits closely balanced with risks and burden	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
Weak recommendation, moderate quality evidence	Benefits closely balanced with risks and burden	RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
Weak recommendation, low or very low quality evidence	Uncertainty in the estimates of benefits, risks and burden; benefits, risk and burden may be in a closely balanced	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable

RCTs randomized controlled trials

[a]The evidence agreed on by more than 70% frontline clinicians in consensus meeting is viewed as high-quality evidence

Table 3 Recommendations for those with close contacts and suspicious exposures

No.	Recommendation items	Recommendation strength
1	Strictly take the observation period of 14 days, and go to the hospital for diagnosis and treatment if symptoms appear (fever, cough, etc.).	Strong
2	If available, inform the designated hospital in advance to send cars to pick up the patients with symptoms to the hospital.	Weak
3	Patients should wear N95 masks (priority strategy).	Strong
4	Using disposable surgical mask (alternative strategy).	Weak
5	Avoid taking public transportation to the hospital, choose an ambulance or private vehicle, and open vehicle windows for ventilation on the way to the hospital (priority strategy).	Strong
6	When walking on the road or waiting in the hospital, try to stay away from other people (at least 1 m away) and wear a mask.	Strong
7	The family members accompanying those for inspection should immediately follow the monitoring recommendations to close contacts, keep the respiratory hygiene and clean their hands properly.	Strong
8	The community or street hospital should be informed before the suspected contacts to the hospital. The vehicle used should be cleaned and disinfected with 500 mg/L chlorine-containing disinfectant, and the window should be opened for ventilation.	Strong

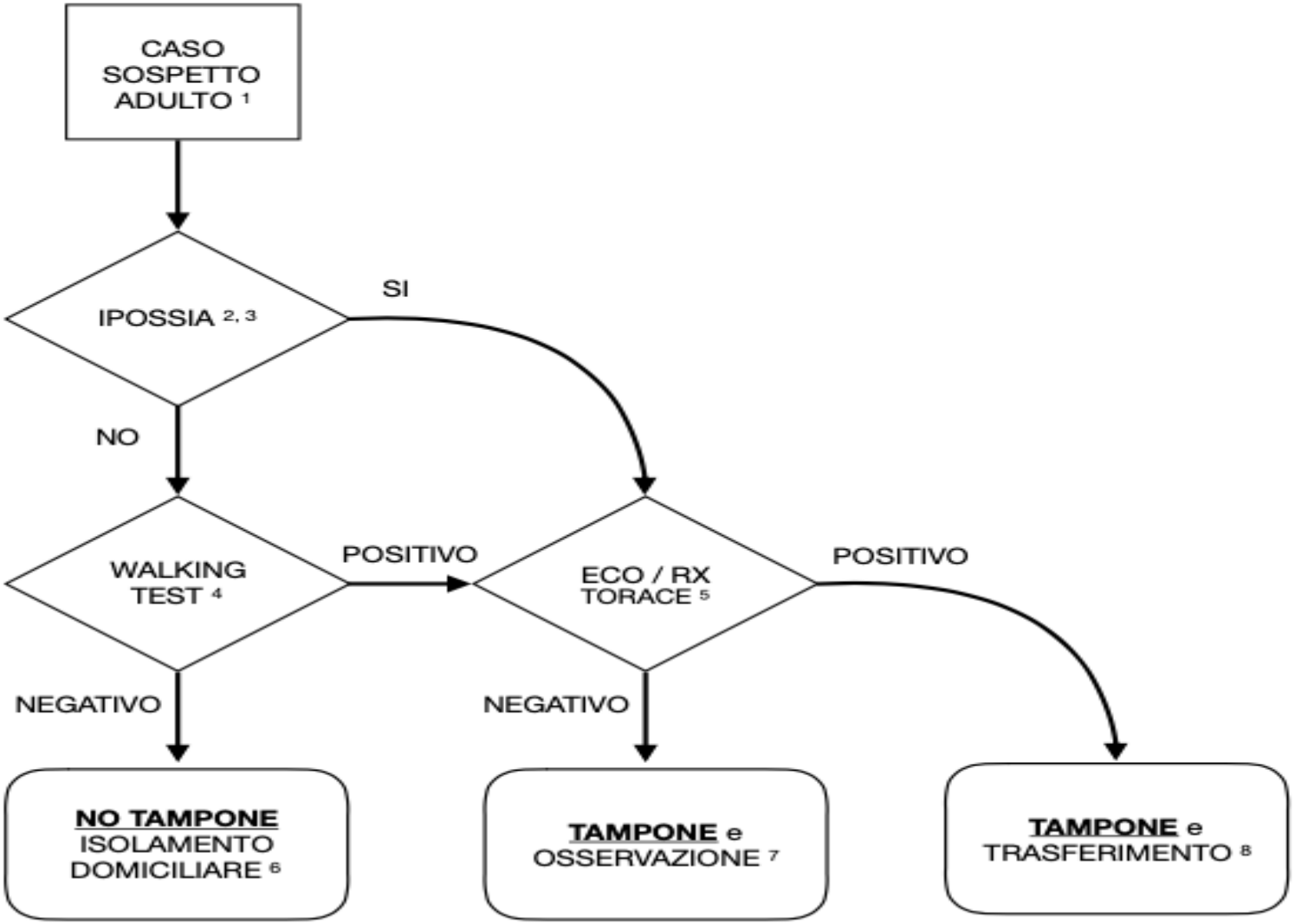
Table 5 Home care and isolation guidelines for suspected patients with mild symptoms

No.	Recommendation items	Recommendation strength
Suspected patients with mild symptoms		
1	Well-ventilated single rooms (preferred strategy).	Strong
2	Maintain a bed distance of at least 1 m from the patient (alternative strategy).	Weak
3	Clean and disinfect household articles using 500 mg/L chlorine-containing disinfectant frequently every day (wide range).	Strong
4	Limit visits by relatives and friends.	Strong
5	The caregiver should be a healthy family member without underlying diseases.	Weak
6	Restrict the patient's activity	Strong
7	Open windows for ventilation in shared areas such as toilets and kitchens.	Strong
8	Avoid sharing toothbrush, towel, tableware, bed sheet and other items with patients. The patient's daily necessities are for single use only and should be placed separately from that of their family members.	Strong
9	When coughing or sneezing, it is necessary to wear a medical mask, or cover with a paper towel and bent elbow, and clean hands immediately after coughing and sneezing.	Strong
10	N95 masks should be worn in the same room with patients (preferred strategy).	Strong
11	Disposable surgical mask (alternative strategy). Use the mask in strict accordance with the instruction manual.	Weak
12	After washing hands with running water, dry them with a paper towel (preferred strategy).	Strong
13	Dry with a towel, and wash and disinfect the towel daily (alternative strategy).	Weak
3	Wear disposable gloves (double layers) when providing oral and respiratory care to patients, handling patient's feces and urine, and cleaning the patient's room, etc. Wash hands before wearing gloves and after removing the gloves.	Strong
4	Wash the patient's clothes, bed sheets, bath towels, towels, etc. with ordinary washing soap and water, or use a washing machine at 60–90 ℃ with ordinary household washing liquid (Strong recommendation), or routinely wash them with washing machine after soaking in low concentration disinfectant (Weak recommendation).	Strong/Weak
5	Put the contaminated bedding into the laundry bag. Do not shake contaminated clothing and avoid direct contact.	Strong
6	The waste generated by the patient should be put into the closed garbage bags and replaced frequently.	Strong

Table 8 Personal protection guidelines checklist *(Strong recommendation)*

Item	Exposure intensity of infection risk[a]	Protective measurement								
		Round hat	N95 mask	Coverall	Eye protector/ Protective panel	Latex gloves	Barrier gown	Protective clothing	Shoe cover/ Bootstrap	Comprehensive respiratory apparatus
Recommendations as per work area										
Pre-examination triage	Low	✓	✓	✓		✓	✓			
General out-patient service	Low	✓	✓	✓		✓				
General ward	Medium	✓	✓	✓	✓	✓	✓			
	High	✓	✓	✓	✓	✓	✓	✓		
Fever clinic	Medium	✓	✓	✓	✓	✓	✓	✓	✓	
	High	✓	✓	✓	✓	✓	✓	✓	✓	✓
Isolation room (Area)	Medium	✓	✓	✓	✓	✓	✓	✓	✓	
	High	✓	✓	✓	✓	✓	✓	✓	✓	✓
Department of infectious diseases	Medium	✓	✓	✓	✓	✓	✓	✓	✓	
	High	✓	✓	✓	✓	✓	✓	✓	✓	✓
Recommendations as per personnel										
Medical staff in the isolation area	High	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Medium	✓	✓	✓	✓	✓	✓	✓	✓	
Staff in pre-examination triage	Medium	✓	✓	✓	✓	✓	✓	✓	✓	
Medical staff in Out-patient Department	Medium	✓	✓	✓	✓	✓	✓	✓	✓	
Medical staff in the observing ward	High	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Medium	✓	✓	✓	✓	✓	✓	✓	✓	
Assisting staff	Medium	✓	✓	✓	✓	✓	✓			
Administrative and supporting staff	Low	✓	✓	✓	✓	✓	✓			

[a]Low risk, general contact with patients or exposure to contaminated environment, such as escorting the patients during diagnosis, triage, palpation, consultation, etc
Medium risk, direct contact with body fluid, mucosa or incomplete skin, such as oral examination, puncture, oral care, surgery, etc
High risk, there is a risk of spatter of secretions or contaminants onto the body and face of medical staff, such as oral diagnosis, endotracheal intubation, etc



[1] Febbre e/o tosse e/o dispnea

[2] Non BPCO: $SpO_2 \leq 94\%$

[3] BPCO: $SpO_2 \leq 90\%$

[4] Positivo se riduzione della SpO_2 di almeno 3 punti percentuali dopo una marcia di 30 metri a passo rapido

[5] Positivo se interstiziopatia bilaterale all'ecografia o RX suggestivo per addensamenti polmonari

[6] Segnalazione al Dipartimento di Prevenzione e isolamento domiciliare del paziente

[7] Ricovero nei reparti ospedalieri dello Spoke di riferimento

[8] Centralizzazione presso centro Hub di riferimento

Canadian experience of SARS

- March 7, 2003, two patients with undiagnosed SARS in two DEAs, a
- Toronto and Vancouver;

- In Vancouver, the patient (with fever and cough) was taken to a reserved waiting room, visited with appropriate PPE, hospitalized in a single room with negative pressure;
- In Vancouver, no autochthonous case of SARS occurred;

- In Toronto, the patient waited in the common waiting room for many hours;
- In Toronto, this episode started an epidemic with 330 cases (77% acquired in a hospital setting) and 44 deaths.

Percorsi ed aree di attesa separate: l'esperienza "improvvisata" della SARS

Figure 1. Due to limited space within the facility, temporary tents used for staff screening were set up at the entrance of the Toronto Western hospital.

ECDC TECHNICAL REPORT

Guidance for wearing and removing personal protective equipment in healthcare settings for the care of patients with suspected or confirmed COVID-19

February 2020

Table 1. Minimal composition of a set of PPE for the management of suspected or confirmed cases of COVID-19

Protection	Suggested PPE
Respiratory protection	FFP2 or FFP3 respirator (valved or non-valved version)*
Eye protection	Goggles (or face shield)
Body protection	Long-sleeved water-resistant gown
Hand protection	Gloves

* In case of shortage of respirators, the use of face masks (surgical or procedural masks) is recommended. When this type of PPE is used, the limitations and risks connected to its use should be assessed on a case-by-case basis.

Figure 1. Suggested minimal PPE set for the management of suspected or confirmed cases of COVID-19: FFP2 or FFP3 respirators, goggles, long-sleeved water-resistant gown and gloves

Wearing (donning) the PPE

Before wearing the PPE for managing a suspected or confirmed COVID-19 case, proper hand hygiene should be performed following international recommendations [7]. This is a critical aspect in this setting and should be performed using an alcohol-based solution in accordance with the manufacturer's instructions (Figure 3).

Figure 3. Hand hygiene performed using alcohol-based solution

Figure 4. Donning of a long-sleeved water-resistant gown

Figure 5. Buttoning up the backside of the gown; performed by an as

Figure 17. Removal of gown: pulling the gown away from the body

Single-use gowns can now be disposed of; reusable gowns have to be placed in a bag or container for disinfection (Figure 18).

Figure 18. Placing the gown in a biohazard container for disinfection

Figure 6. **Wearing of a FFP (class 2 or 3) respirator**

The metal nose clip needs to be adjusted (Figure 7) and the straps have to be tightened to have a firm and comfortable fit. If you cannot achieve a proper fit, position the straps crosswise. However, this minor modification could imply a deviation from the recommendations in the manufacturer's product manual.

Figure 7. **Fitting the respirator's metal nose clip**

If a face mask (surgical mask) is worn as substitution for a respirator (Figure 8), it is important to correctly position it on the face and adjust it with the metal nose clip (Figure 9) in order to achieve a proper fit.

Figure 8. **Wearing of a face mask (surgical mask)**

Figure 21. **Removal of respirator (steps 1 through 4)**

The last PPE items that should be removed are the gloves. Use of alcohol-based solution should be considered before removing the gloves. The gloves should be removed in accordance with the procedure described above. After glove removal, hand hygiene should be performed.

Figure 9. **Fitting the face mask's metal nose clip**

Once the respirator has been properly positioned, put on the goggles for eye protection. Place the goggles over the mask's straps and ensure that the textile elastic strap fits snugly – but not too tightly (Figures 10 and 11).

Figure 10. **Wearing of goggles with textile elastic strap**

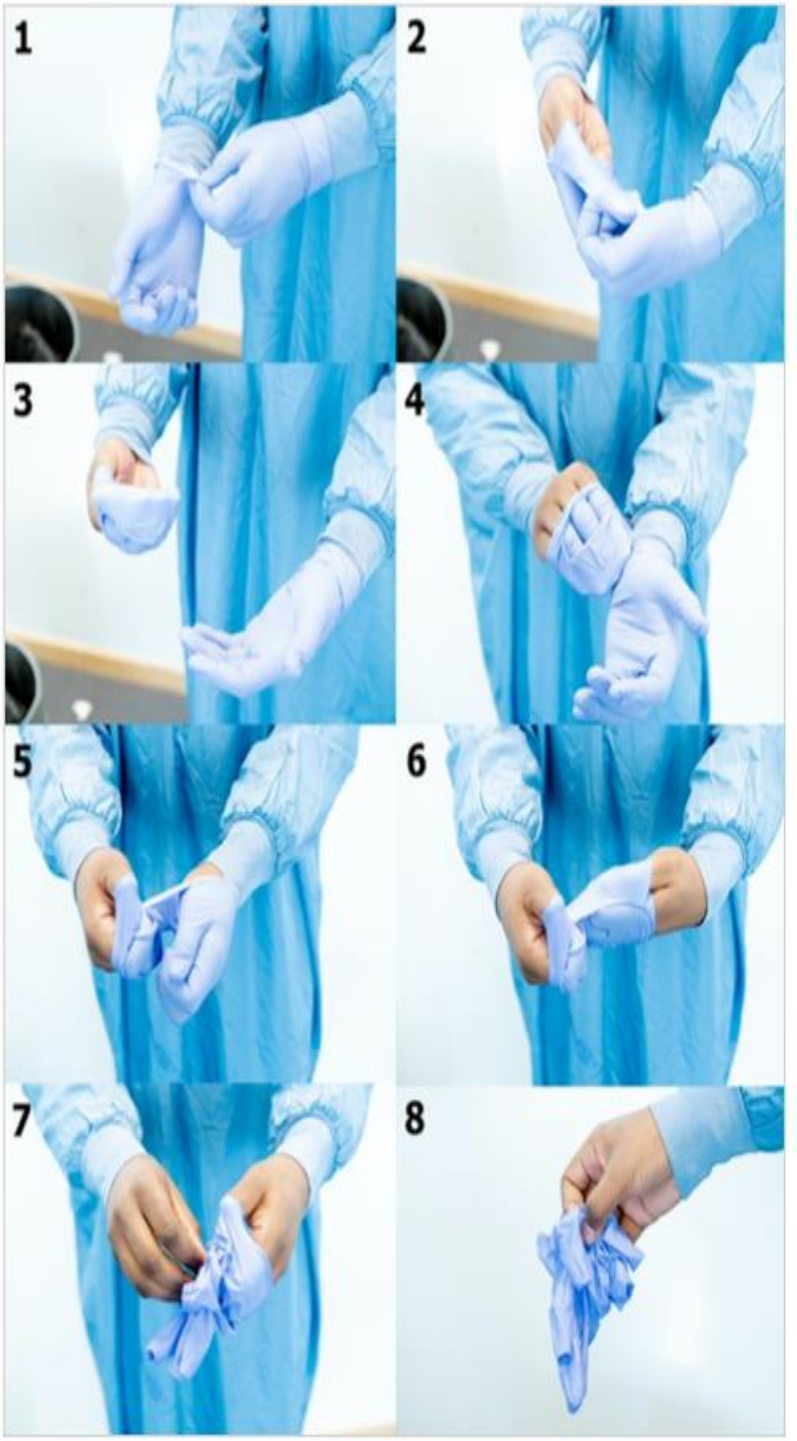
Figure 11. **Side view of goggles with an elastic textile strap**

Figure 19. **Removal of goggles with textile elastic strap (steps 1 to 4)**

Figure 20. **Removal of goggles with temples (steps 1 and 2)**

Figure 13. **Wearing of gloves**

Figure 14. **Removal of gloves (steps 1 to 8)**



After the removal of gloves, hand hygiene should be performed and a new pair of gloves should be worn to further continue the doffing procedure. Using a new pair of gloves will prevent self-contamination.

CONTAMINATION RATES DURING DOFFING PROCEDURE

EBOLA PPE

INFECTED CASES / NUMBER OF SUBJECTS

REMOVE
BOOT OR SHOE COVERS

FOOT
19/29
65.5%

REMOVE
HEADHOOD

HEAD
12/29
41.4%

REMOVE
GOOGLES

FACE
2/29
6.9%

REMOVE
GOWN OR COVERALL

TORSO
9/29
31.0%

REMOVE
RESPIRATOR

HEAD
2/29
6.9%

NECK
21/29
72.4%

TOTAL NUMBER OF CONTAMINATION

HEAD	FACE	NECK	TORSO	FOOT
14	2	21	9	19
48.3%	6.9%	72.4%	31.0%	65.5%

DPI IN DOTAZIONE OPSEDALIERA

Il personale sanitario in contatto con un caso sospetto o confermato di COVID-19 deve indossare DPI adeguati

Numero minimo di set di DPI (Fonte: ECDC)

	Caso sospetto	Caso confermato lieve	Caso confermato grave
Operatori sanitari	Numero di set per caso	Numero di set per giorno per paziente	
Infermieri	1-2	6	6-12
Medici	1	2-3	3-6
Addetti pulizie	1	3	3
Assistenti e altri servizi	0-2	3	3
TOTALE	3-6	14-15	15-24

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Review

Persistence of coronaviruses on inanimate surfaces and their inactivation with biocidal agents

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SUMMARY

Currently, the emergence of a novel human coronavirus, SARS-CoV-2, has become a global health concern causing severe respiratory tract infections in humans. Human-to-human transmissions have been described with incubation times between 2-10 days, facilitating its spread via droplets, contaminated hands or surfaces. We therefore reviewed the literature on all available information about the persistence of human and veterinary coronaviruses on inanimate surfaces as well as inactivation strategies with biocidal agents used for chemical disinfection, e.g. in healthcare facilities. The analysis of 22 studies reveals that human coronaviruses such as Severe Acute Respiratory Syndrome (SARS) coronavirus, Middle East Respiratory Syndrome (MERS) coronavirus or endemic human coronaviruses (HCoV) can persist on inanimate surfaces like metal, glass or plastic for up to 9 days, but can be efficiently inactivated by surface disinfection procedures with 62–71% ethanol, 0.5% hydrogen peroxide or 0.1% sodium hypochlorite within 1 minute. Other biocidal agents such as 0.05–0.2% benzalkonium chloride or 0.02% chlorhexidine digluconate are less effective. As no specific therapies are available for SARS-CoV-2, early containment and prevention of further spread will be crucial to stop the ongoing outbreak and to control this novel infectious thread.

Table I
Persistence of coronaviruses on different types of inanimate surfaces

Type of surface	Virus	Strain / isolate	Inoculum (viral titer)	Temperature	Persistence	Reference
Steel	MERS-CoV	Isolate HCoV-EMC/2012	10^5	20°C	48 h	[21]
				30°C	8—24 h	
	TGEV	Unknown	10^6	4°C	≥ 28 d	[22]
				20°C	3—28 d	
				40°C	4—96 h	
	MHV	Unknown	10^6	4°C	≥ 28 d	[22]
				20°C	4—28 d	
				40°C	4—96 h	
	HCoV	Strain 229E	10^3	21°C	5 d	[23]
Aluminium	HCoV	Strains 229E and OC43	5×10^3	21°C	2—8 h	[24]
Metal	SARS-CoV	Strain P9	10^5	RT	5 d	[25]
Wood	SARS-CoV	Strain P9	10^5	RT	4 d	[25]
Paper	SARS-CoV	Strain P9	10^5	RT	4—5 d	[25]
	SARS-CoV	Strain GVU6109	10^6	RT	24 h	[26]
			10^5		3 h	
			10^4		< 5 min	
Glass	SARS-CoV	Strain P9	10^5	RT	4 d	[25]
	HCoV	Strain 229E	10^3	21°C	5 d	[23]
Plastic	SARS-CoV	Strain HKU39849	10^5	22°-25°C	≤ 5 d	[27]
	MERS-CoV	Isolate HCoV-EMC/2012	10^5	20°C	48 h	[21]
				30°C	8—24 h	
	SARS-CoV	Strain P9	10^5	RT	4 d	[25]
	SARS-CoV	Strain FFM1	10^7	RT	6—9 d	[28]
	HCoV	Strain 229E	10^7	RT	2—6 d	[28]
PVC	HCoV	Strain 229E	10^3	21°C	5 d	[23]
Silicon rubber	HCoV	Strain 229E	10^3	21°C	5 d	[23]
Surgical glove (latex)	HCoV	Strains 229E and OC43	5×10^3	21°C	≤ 8 h	[24]
Disposable gown	SARS-CoV	Strain GVU6109	10^6	RT	2 d	[26]
			10^5		24 h	
			10^4		1 h	
Ceramic	HCoV	Strain 229E	10^3	21°C	5 d	[23]
Teflon	HCoV	Strain 229E	10^3	21°C	5 d	[23]

MERS = Middle East Respiratory Syndrome; HCoV = human coronavirus; TGEV = transmissible gastroenteritis virus; MHV = mouse hepatitis virus; SARS = Severe Acute Respiratory Syndrome; RT = room temperature.

La maggior parte dei dati sono stati descritti con il ceppo endemico di coronavirus umano (HCoV-) 229E.

A temperatura ambiente che HCoV-229E persiste meglio al 50% rispetto al 30% di umidità relativa

Su diversi tipi di materiali può rimanere contagioso **da 2 ore a 9 giorni**.

A una temperatura di 30° C o più la durata della persistenza è più breve.

Table II
Inactivation of coronaviruses by different types of biocidal agents in suspension tests

Biocidal agent	Concentration	Virus	Strain / isolate	Exposure time	Reduction of viral infectivity (log_{10})	Reference
Ethanol	95%	SARS-CoV	Isolate FFM-1	30 s	≥ 5.5	[29]
	85%	SARS-CoV	Isolate FFM-1	30 s	≥ 5.5	[29]
	80%	SARS-CoV	Isolate FFM-1	30 s	≥ 4.3	[29]
	80%	MERS-CoV	Strain EMC	30 s	> 4.0	[14]
	78%	SARS-CoV	Isolate FFM-1	30 s	≥ 5.0	[28]
	70%	MHV	Strains MHV-2 and MHV-N	10 min	> 3.9	[30]
	70%	CCV	Strain I-71	10 min	> 3.3	[30]
2-Propanol	100%	SARS-CoV	Isolate FFM-1	30 s	≥ 3.3	[28]
	75%	SARS-CoV	Isolate FFM-1	30 s	≥ 4.0	[14]
	75%	MERS-CoV	Strain EMC	30 s	≥ 4.0	[14]
	70%	SARS-CoV	Isolate FFM-1	30 s	≥ 3.3	[28]
	50%	MHV	Strains MHV-2 and MHV-N	10 min	> 3.7	[30]
	50%	CCV	Strain I-71	10 min	> 3.7	[30]
2-Propanol and 1-propanol	45% and 30%	SARS-CoV	Isolate FFM-1	30 s	≥ 4.3	[29]
		SARS-CoV	Isolate FFM-1	30 s	≥ 2.8	[28]
Benzalkonium chloride	0.2%	HCoV	ATCC VR-759 (strain OC43)	10 min	0.0	[31]
	0.05%	MHV	Strains MHV-2 and MHV-N	10 min	> 3.7	[30]
	0.05%	CCV	Strain I-71	10 min	> 3.7	[30]
	0.00175%	CCV	Strain S378	3 d	3.0	[32]
Didecyldimethyl ammonium chloride	0.0025%	CCV	Strain S378	3 d	> 4.0	[32]
Chlorhexidine digluconate	0.02%	MHV	Strains MHV-2 and MHV-N	10 min	0.7–0.8	[30]
	0.02%	CCV	Strain I-71	10 min	0.3	[30]
Sodium hypochlorite	0.21%	MHV	Strain MHV-1	30 s	≥ 4.0	[33]
	0.01%	MHV	Strains MHV-2 and MHV-N	10 min	2.3–2.8	[30]
	0.01%	CCV	Strain I-71	10 min	1.1	[30]
	0.001%	MHV	Strains MHV-2 and MHV-N	10 min	0.3–0.6	[30]
	0.001%	CCV	Strain I-71	10 min	0.9	[30]
Hydrogen peroxide	0.5%	HCoV	Strain 229E	1 min	> 4.0	[34]
Formaldehyde	1%	SARS-CoV	Isolate FFM-1	2 min	> 3.0	[28]
	0.7%	SARS-CoV	Isolate FFM-1	2 min	> 3.0	[28]
	0.7%	MHV		10 min	> 3.5	[30]
	0.7%	CCV	Strain I-71	10 min	> 3.7	[30]
	0.009%	CCV		24 h	> 4.0	[35]
Glutardialdehyde	2.5%	SARS-CoV	Hanoi strain	5 min	> 4.0	[36]
	0.5%	SARS-CoV	Isolate FFM-1	2 min	> 4.0	[28]
Povidone iodine	7.5%	MERS-CoV	Isolate HCoV-EMC/2012	15 s	4.6	[37]
	4%	MERS-CoV	Isolate HCoV-EMC/2012	15 s	5.0	[37]
	1%	SARS-CoV	Hanoi strain	1 min	> 4.0	[36]
	1%	MERS-CoV	Isolate HCoV-EMC/2012	15 s	4.3	[37]
	0.47%	SARS-CoV	Hanoi strain	1 min	3.8	[36]
	0.25%	SARS-CoV	Hanoi strain	1 min	> 4.0	[36]
	0.23%	SARS-CoV	Hanoi strain	1 min	> 4.0	[36]
	0.23%	SARS-CoV	Isolate FFM-1	15 s	≥ 4.4	[38]
	0.23%	MERS-CoV	Isolate HCoV-EMC/2012	15 s	≥ 4.4	[38]

SARS = Severe Acute Respiratory Syndrome; MERS = Middle East Respiratory Syndrome; MHV = mouse hepatitis virus; CCV = canine coronavirus; HCoV = human coronavirus.

INATTIVAZIONE DELL'INFETTIVITA' di circa 4 log10 o più con:

- **Etanolo (78 - 95%)**
- **2-propanolo (70e100%)**
- **la combinazione del 45% di 2-propanolo con 30% di 1-propanolo**
- **glutaraldialdeide (0,5 -2,5%),**
- **formaldeide (0,7 e1%)**
- **iodio povidone (0,23- 7 .5%)**

Table III
Inactivation of coronaviruses by different types of biocidal agents in carrier tests

Biocidal agent	Concentration	Virus	Strain / isolate	Volume / material	Organic load	Exposure time	Reduction of viral infectivity (log_{10})	Reference
Ethanol	71%	TGEV	Unknown	50 µl / stainless steel	None	1 min	3.5	[39]
	71%	MHV	Unknown	50 µl / stainless steel	None	1 min	2.0	[39]
	70%	TGEV	Unknown	50 µl / stainless steel	None	1 min	3.2	[39]
	70%	MHV	Unknown	50 µl / stainless steel	None	1 min	3.9	[39]
	70%	HCoV	Strain 229E	20 µl / stainless steel	5% serum	1 min	> 3.0	[40]
	62%	TGEV	Unknown	50 µl / stainless steel	None	1 min	4.0	[39]
	62%	MHV	Unknown	50 µl / stainless steel	None	1 min	2.7	[39]
Benzalkoniumchloride	0.04%	HCoV	Strain 229E	20 µl / stainless steel	5% serum	1 min	< 3.0	[40]
Sodium hypochlorite	0.5%	HCoV	Strain 229E	20 µl / stainless steel	5% serum	1 min	> 3.0	[40]
	0.1%	HCoV	Strain 229E	20 µl / stainless steel	5% serum	1 min	> 3.0	[40]
	0.06%	TGEV	Unknown	50 µl / stainless steel	None	1 min	0.4	[39]
	0.06%	MHV	Unknown	50 µl / stainless steel	None	1 min	0.6	[39]
	0.01%	HCoV	Strain 229E	20 µl / stainless steel	5% serum	1 min	< 3.0	[40]
Glutardialdehyde	2%	HCoV	Strain 229E	20 µl / stainless steel	5% serum	1 min	> 3.0	[40]
Ortho-phtalaldehyde	0.55%	TGEV	Unknown	50 µl / stainless steel	None	1 min	2.3	[39]
	0.55%	MHV	Unknown	50 µl / stainless steel	None	1 min	1.7	[39]
Hydrogen peroxide	Vapor of unknown concentration	TGEV	Purdue strain type 1	20 µl / stainless steel	None	2–3 h	4.9–5.3*	[41]

TGEV = transmissible gastroenteritis virus; MHV = mouse hepatitis virus; HCoV = human coronavirus; *depending on the volume of injected hydrogen peroxide.

L'ipoclorito di sodio agisce a una concentrazione minima di almeno lo **0,21%** per essere efficace.

Il **perossido di idrogeno** si è dimostrato efficace con una concentrazione dello **0,5%** e un tempo di incubazione di 1 minuto.

I dati ottenuti con **cloruro di benzalconio** a tempi di contatto ragionevoli sono contrastanti. Entro 10 minuti una concentrazione dello 0,2% non ha rivelato alcuna efficacia contro il coronavirus mentre una concentrazione **dello 0,05%** è abbastanza efficace.

Lo 0,02% di clorexidina digluconato è sostanzialmente inefficace

PRINCIPI* DELLA GESTIONE DELLE VIE AEREE IN CASO DI

CORONAVIRUS COVID-19

PER CASI SOSPETTI** O CONFERMATI DI COVID-19

PRIMA

PROTEZIONE DELLO STAFF

- Igiene delle mani
- Dispositivi di protezione individuale*** (doppio guanto)
- Riduzione al minimo del personale durante le procedure****
- Camera di isolamento (se disponibile)

PREPARAZIONE

- Preparazione precoce di farmaci e attrezzature
- Meticolosa valutazione delle vie aeree
- Utilizzo di un sistema di aspirazione chiuso
- Monitoraggio standard incluso EtCO2
- Filtro antimicrobico su pallone autoespandibile e circuiti
- Preferenza per video-laringoscopio

DURANTE

DINAMICHE DI TEAM

- Definizione chiara dei ruoli
- Formulazione anticipata del piano di gestione delle vie aeree
- Comunicazione con feedback durante la procedura
- Monitoraggio da parte dei membri del team per possibile contaminazione

ASPETTI TECNICI

- Manovra eseguita dal medico più esperto presente
- Preossigenazione con maschera aderente, con impugnatura a due mani
- Paralisi adeguata per evitare la tosse
- Induzione in sequenza rapida ed evitare la ventilazione con maschera a reservoir quando possibilet
- Dopo la procedura isolamento del laringoscopio nel guanto esterno
- Ventilazione a pressione positiva solo dopo aver gonfiato la cuffia

DOPO

- Evitare disconnessioni inutili del circuito
- Se è necessaria la disconnessione mettere il ventilatore in standby +/- clampare il tubo
- Rispetto rigoroso delle fasi di svestizione dai dispositivi di protezione individuale
- Igiene delle mani
- Debriefing del team

Version 1.0 Feb 2020

*I principi di gestione delle vie aeree di COVID-19 possono applicarsi alla: sala operatoria, terapia intensiva, pronto soccorso e reparto. Principi simili si applicano all'estubazione di pazienti COVID-19
**Esistono variazioni regionali e istituzionali sulla definizione di un caso sospetto / denunciabile. Si prega di fare riferimento ai propri protocolli locali.
***I dispositivi di protezione individuale secondo le vostre raccomandazioni istituzionali, possono includere: Maschera con filtro FFP3, cuffia, protezione degli occhi, tuta impermeabile a maniche lunghe, due paia di guanti.
****Procedure a generazione di aerosol: intubazione tracheale, ventilazione non invasiva, tracheostomia, rianimazione cardiopolmonare, ventilazione manuale prima dell'intubazione, broncoscopia, aspirazione aperta delle vie respiratorie, estubazione.

Riferimenti:
1. World Health Organization. Infection prevention and control during health care when novel coronavirus (nCoV) infection is suspected Interim guidance. January 2020.
2. Center for Disease Control and Prevention. Interim Infection Prevention and Control Recommendations for Patients with Confirmed 2019 Novel Coronavirus (2019-nCoV) or Persons Under Investigation for 2019-nCoV in Healthcare Settings. Februrary 2020.

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