Pandémie de coronavirus disease (COVID-19) : Aspects cliniques et thérapeutiques

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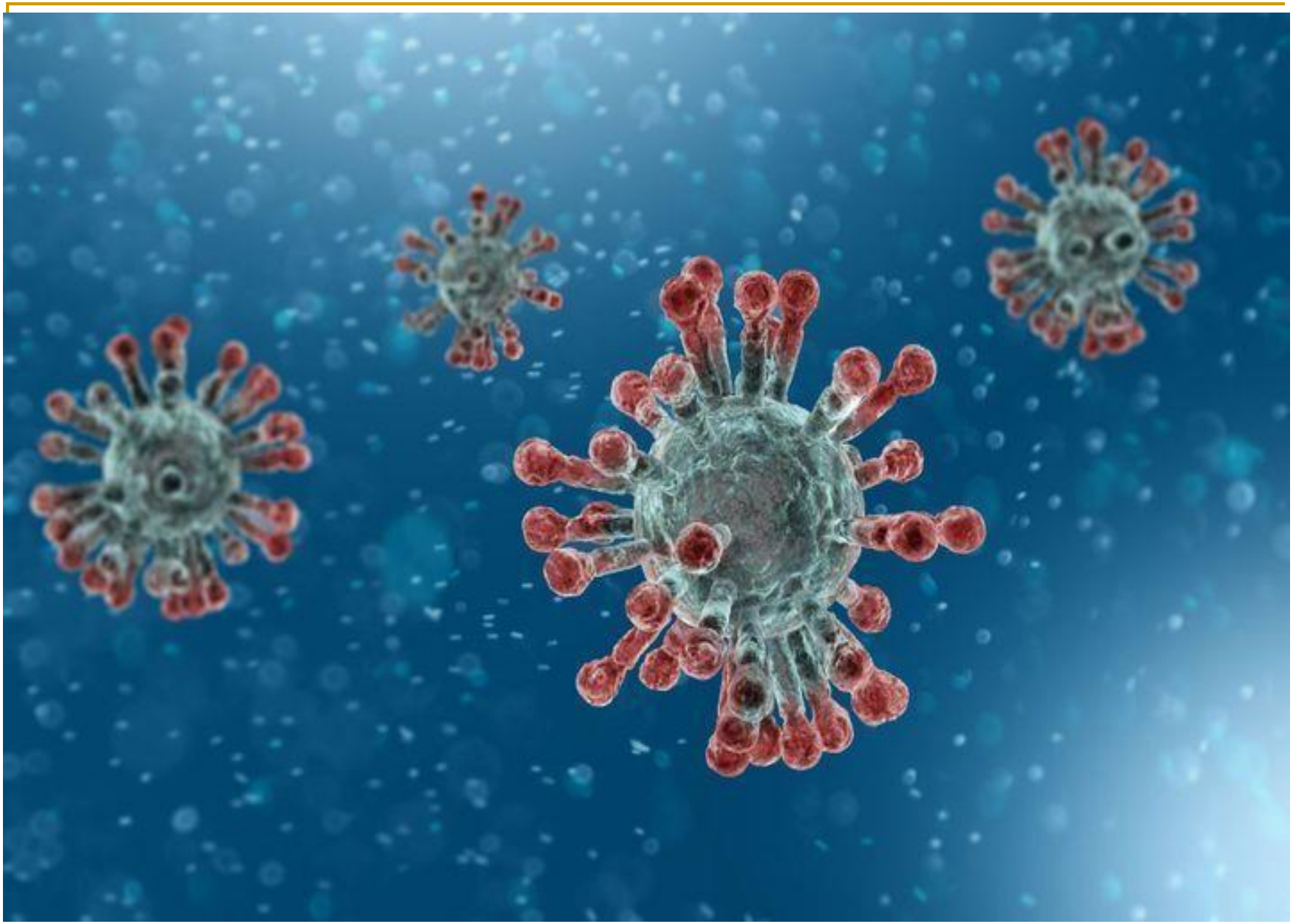

PLAN

I. Introduction

II. Epidémiologie

III. Diagnostic : clinique, virologique, **TDM**

IV. Traitement

V. Prévention

VI. Conclusion

I. INTRODUCTION

❖ Décembre 2019, Wuhan, Hubei - Chine :

- épidémie de pneumonies de cause inconnue

- prélèvements respiratoires : nouveau coronavirus

. 2019-novel coronavirus : **2019-nCoV**

. Severe Acute Respiratory Syndrome coronavirus-2 : **SARS-CoV-2**

I. INTRODUCTION

Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China

Chaolin Huang*, Yeming Wang*, Xingwang Li*, Lili Ren*, Jianping Zhao*, Yi Hu*, Li Zhang, Guohui Fan, Jiuyang Xu, Xiaoying Gu, Zhenshun Cheng, Ting Yu, Jiaan Xia, Yuan Wei, Wenjuan Wu, Xuelei Xie, Wen Yin, Hui Li, Min Liu, Yan Xiao, Hong Gao, Li Guo, Jungang Xie, Guangfa Wang, Rongmeng Jiang, Zhancheng Gao, Qi Jin, Jianwei Wang†, Bin Cao†

Summary

Background A recent cluster of pneumonia cases in Wuhan, China, was caused by a novel betacoronavirus, the 2019 novel coronavirus (2019-nCoV). We report the epidemiological, clinical, laboratory, and radiological characteristics and treatment and clinical outcomes of these patients.

Lancet 2020; 395: 497–506

Published Online
January 24, 2020
https://doi.org/10.1016/

I. INTRODUCTION

❖ Décembre 2019, Wuhan, Hubei - Chine :

- épidémie de pneumonies de cause inconnue

➢ extension rapide vers d'autres pays : **Pandémie**

II. EPIDEMIOLOGIE

Monde (OMS): https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/

- 13 avril 2020 :

  - 1 773 084 cas confirmés

  - 111 652 décès (6,3%)

II. EPIDEMIOLOGIE

Tunisie : Ministère de la Santé

❖ 13 avril 2020 :

- 726 cas confirmés (/11825 analyses, 6,1%)

- 34 décès (/726, 4,7%)

III. DIAGNOSTIC

1. Clinique :

❖ **Formes légères à modérées /** signes non spécifiques :

- généraux : fièvre, céphalées, asthénie, anorexie, arthromyalgies
- respiratoires : toux, dyspnée
- ORL :

. obstruction nasale, odynophagie, otalgie

. anosmie (85%), agueusie (88%) : avant les autres symptômes 11,8%

- digestifs : diarrhée, vomissements, douleur abdominale

….

Lechien JR et al. Eur Arch Otorhinolaryngol. (2020)

III. DIAGNOSTIC - Clinique

European Archives of Oto-Rhino-Laryngology
https://doi.org/10.1007/s00405-020-05965-1

RHINOLOGY

Check for updates

Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study

Jerome R. Lechien[1,2,3,4] · Carlos M. Chiesa-Estomba[1,5] · Daniele R. De Siati[1,6] · Mihaela Horoi[4] · Serge D. Le Bon[4] · Alexandra Rodriguez[4] · Didier Dequanter[4] · Serge Blecic[7] · Fahd El Afia[1,3] · Lea Distinguin[1,3] · Younes Chekkoury-Idrissi[1,3] · Stéphane Hans[3] · Irene Lopez Delgado[1,8] · Christian Calvo-Henriquez[1,9] · Philippe Lavigne[1,10] · Chiara Falanga[1,11] · Maria Rosaria Barillari[1,11] · Giovanni Cammaroto[1,12] · Mohamad Khalife[13] · Pierre Leich[14] · Christel Souchay[14] · Camelia Rossi[15] · Fabrice Journe[2] · Julien Hsieh[1,16] · Myriam Edjlali[17,18] · Robert Carlier[18] · Laurence Ris[19] · Andrea Lovato[20] · Cosimo De Filippis[20] · Frederique Coppee[21] · Nicolas Fakhry[1,22] · Tareck Ayad[1,10] · Sven Saussez[1,2,4,13]

Received: 30 March 2020 / Accepted: 2 April 2020

III. DIAGNOSTIC - Clinique

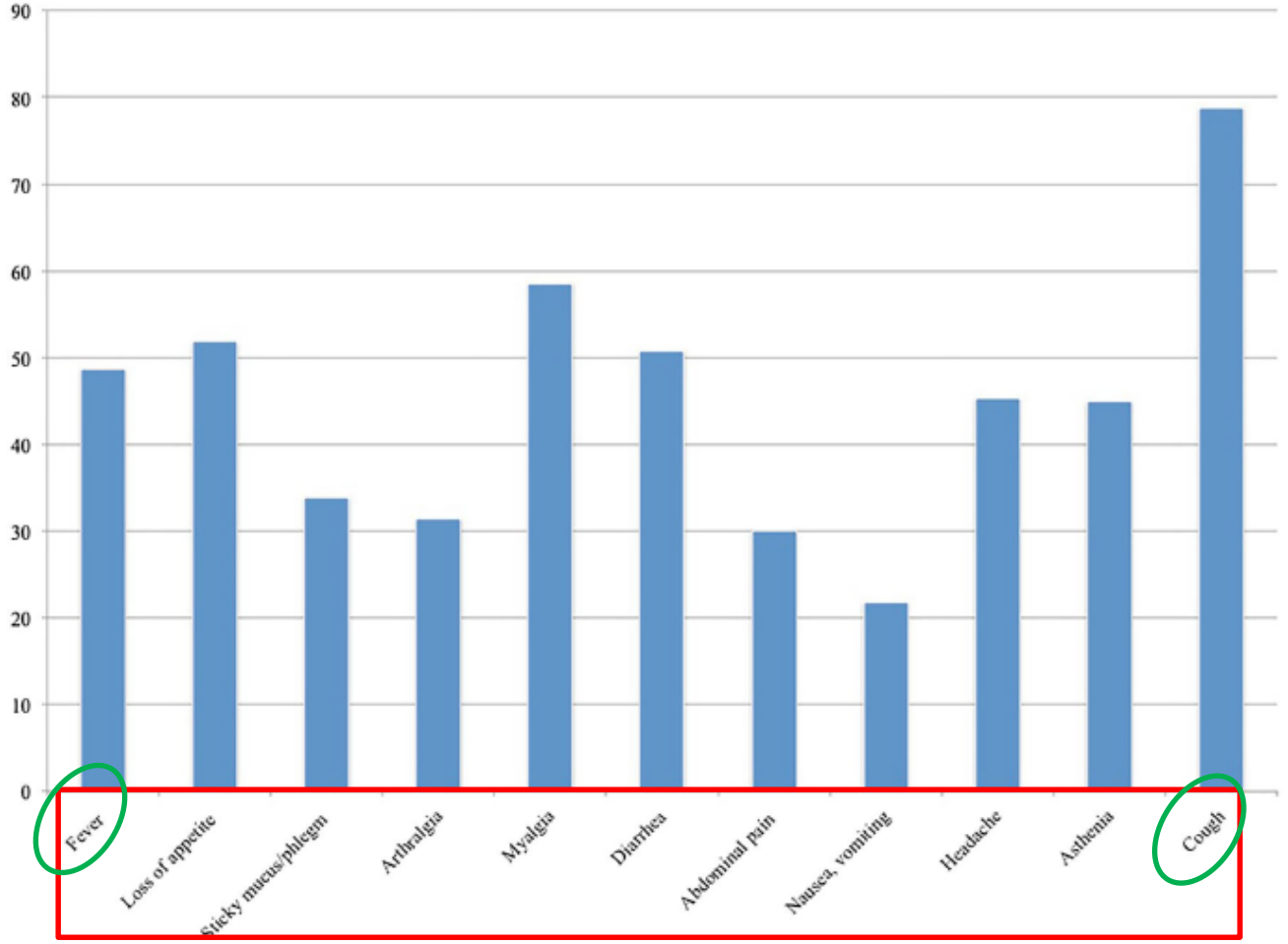

Fig. 2 General symptoms associated with COVID-19 infection. The ordinate axis consists of percentages of patients with such symptoms associated with the infection

Lechien JR et al. Eur Arch Otorhinolaryngol. (2020)

III. DIAGNOSTIC - Clinique

EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original article

Clinical characteristics and outcomes of hospitalised patients with COVID-19 treated in Hubei (epicenter) and outside Hubei (non-epicenter): A Nationwide Analysis of China

Wen-hua Liang, Wei-jie Guan, Cai-chen Li, Yi-min Li, Heng-rui Liang, Yi Zhao, Xiao-qing Liu, Ling Sang, Ru-chong Chen, Chun-li Tang, Tao Wang, Wei Wang, Qi-hua He, Zi-sheng Chen, Sook-San Wong, Mark Zanin, Jun Liu, Xin Xu, Jun Huang, Jian-fu Li, Li-min Ou, Bo Cheng, Shan Xiong, Zhan-hong Xie, Zheng-yi Ni, Yu Hu, Lei Liu, Hong Shan, Chun-liang Lei, Yi-xiang Peng, Li Wei, Yong Liu, Ya-hua Hu, Peng Peng, Jian-ming Wang, Ji-yang Liu, Zhong Chen, Gang Li, Zhi-jian Zheng, Shao-qin Qiu, Jie Luo, Chang-jiang Ye, Shao-yong Zhu, Lin-ling Cheng, Feng Ye, Shi-yue Li, Jin-ping Zheng, Nuo-fu Zhang, Nan-shan Zhong, Jian-xing He

Table 1. Clinical characteristics and outcomes of patients with COVID-19 stratified by Hubei hospitalization and Wuhan-related exposure.

	Total (n=1590)	In Hubei (n=647)	Outside Hubei (n=943)	P Value	No Wuhan-related exposure (n=256)	Wuhan-related exposure (n=1334)	P Value
Characteristics							
Age, years	48.9±16.3	55.1±15.4	44.6±15.5	<0.001	44.9±14.6	49.7±16.5	<0.001
Symptoms							
Any	1517 (95.4%)	621 (96%)	896 (95.0%)	0.395	237 (92.6%)	1280 (96.0%)	0.023
Fever	1351/1536 (88.0%)	552/623 (88.6%)	799/913 (87.5%)	0.576	213/243 (87.7%)	1138/1293 (88.0%)	0.914
Conjunctival congestion	10/1346 (0.7%)	3/554 (0.5%)	7/791 (0.9%)	0.538	3/192 (1.6%)	7/1153 (0.6%)	0.161
Nasal congestion	73/1299 (5.6%)	24/535 (4.5%)	49/764 (6.4%)	0.144	11/185 (5.9%)	62/1114 (5.6%)	0.863
Headache	205/1328 (15.4%)	94/540 (17.4%)	111/788 (14.1%)	0.105	30/191 (15.7%)	175/1137 (15.4%)	0.914
Dry cough	1052/1498 (70.2%)	450/617 (72.9%)	602/881 (68.3%)	0.058	167/233 (71.7%)	885/1265 (70.0%)	0.640
Pharyngalgia	194/1317 (14.7%)	60/530 (11.3%)	134/787 (17.0%)	0.004	31/194 (16.0%)	163/1123 (14.5%)	0.584
Productive cough	513/1424 (36.0%)	234/582 (40.2%)	279/842 (33.1%)	0.007	94/218 (43.1%)	419/1206 (34.7%)	0.021
Fatigue	584/1365 (42.8%)	255/549 (46.4%)	329/816 (40.3%)	0.026	85/209 (40.7%)	499/1156 (43.2%)	0.544
Hemoptysis	16/1315(1.2%)	12/533 (2.3%)	4/782 (0.5%)	0.008	2/189 (1.1%)	14/1126 (1.2%)	1.000
Shortness of breath	331 (20.8%)	235 (36.3%)	96 (10.2%)	<0.001	40 (15.6%)	291 (21.8%)	<0.029
Nausea/vomiting	80/1371 (5.8%)	46/568 (8.1%)	34/803 (4.2%)	0.003	12/200 (6.0%)	68/1171 (5.8%)	0.871
Diarrhea	57/1359 (4.2%)	28/559 (5.0%)	29/800 (3.6%)	0.218	9/195 (4.6%)	48/1164 (4.1%)	0.701
Myalgia/arthralgia	234/1338 (17.5%)	112/551 (20.3%)	122/787 (15.5%)	0.024	32/195 (16.4%)	202/1143 (17.7%)	0.760
Chill	163/1333 (12.2%)	77/547 (14.1%)	86/786 (10.9%)	0.090	35/191 (18.3%)	128/1142 (11.2%)	0.008
Signs							
Throat congestion	21/1288 (1.6%)	7/525 (1.3%)	14/761 (1.8%)	0.655	1/181 (0.6%)	20/1105 (1.8%)	0.343
Tonsil swelling	31/1378 (2.3%)	16/589 (2.7%)	15/787 (1.9%)	0.360	4/184 (2.2%)	27/1192 (2.3%)	1.000
Lymphadenectasis	2/1375 (0.1%)	2/588 (0.3%)	0/787 (0%)	0.183	0/189 (0%)	2/1186(0.2%)	1.000
Rash	3/1378 (0.2%)	2/583 (0.3%)	1/795 (0.1%)	0.577	0/191(0%)	3/1187(0.3%)	1.000
Unconsciousness	20/1421 (1.4%)	16/595 (2.7%)	4/826 (0.5%)	0.001	1/199 (0.5%)	19/1222 (1.6%)	0.342

Liang W-hua et al. Eur Respir J (2020)

III. DIAGNOSTIC

1. Clinique :

❖ **Formes graves /** signes non spécifiques :

- IRA grave / SDRA
- état de choc
- défaillance multiviscérale

❖ Formes asymptomatiques :

- rares (< 5%)
- transmission (risque faible)

Zhou F et al. Lancet (2020)
Liang W-hua et al. Eur Respir J (2020)

III. DIAGNOSTIC

1. Clinique :

- **Formes légères à modérées /** signes non spécifiques
- **Formes graves /** signes non spécifiques

➡ Démarche diagnostique rigoureuse +++

- **Ne pas passer à côté d'une autre maladie (grave) +++**

III. DIAGNOSTIC - Définition des cas

Wang et al. Military Medical Research (2020) 7:17
https://doi.org/10.1186/s40779-020-00245-9

MMR MILITARY MEDICAL RESEARCH

LETTER TO THE EDITOR Open Access

Updating the diagnostic criteria of COVID-19 "suspected case" and "confirmed case" is necessary

Yun-Yun Wang[1], Ying-Hui Jin[1], Xue-Qun Ren[2], Yi-Rong Li[3,4], Xiao-Chun Zhang[4,5], Xian-Tao Zeng[1,5*], Xing-Huan Wang[1,5*] and for the Zhongnan Hospital of Wuhan University Novel Coronavirus Management and Research Team

Abstract

On 6 February 2020, our team had published a rapid advice guideline for diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infection, and this guideline provided our experience and make well reference for fighting against this pandemic worldwide. However, the coronavirus disease 2019 (COVID-19) is a new disease, our awareness and knowledge are gradually increasing based on the ongoing research findings and clinical practice experience; hence, the strategies of diagnosis and treatment are also continually updated. In this letter, we answered one comment on our guideline and provided the newest diagnostic criteria of "suspected case" and "confirmed case" according to the latest Diagnosis and Treatment Guidelines for COVID-19 (seventh version) that issued by the National Health Committee of the People's Republic of China.

Keywords: COVID-19, SARS-CoV-2, 2019-nCoV, Guideline, Prevention, Diagnosis, Treatment, Novel coronavirus

III. DIAGNOSTIC- Définition des cas

cas suspect

1. - Toute personne présentant des signes cliniques d'infection respiratoire aiguë évocatrice (toux ou difficulté respiratoire) avec une fièvre, sans autre étiologie qui explique pleinement le tableau clinique ;

   - ET ayant voyagé ou séjourné dans une zone d'exposition à risque* dans les 14 jours précédant la date de début des signes cliniques

2. Toute personne, sans notion de contact avec un cas confirmé COVID19 ou de voyage ou de séjour dans une zone d'exposition à risque qui présente :

   • Une pneumonie non expliquée par d'autres étiologies possibles, sur la base de critères cliniques, radiologiques et biologiques et dont l'état clinique nécessite une hospitalisation

   • Des signes de détresse respiratoire aiguë pouvant aller jusqu'au SDRA (Syndrome de détresse respiratoire aiguë) sans autre étiologie évidente d'emblée.

3. Au cas par cas des cas groupés d'Infection Respiratoire Aiguë (IRA) et des clusters (chaines de transmission de taille importante) avec ou sans notion de voyage ou de contact avec un cas confirmé de COVID 19 doivent être considérés comme suspects.

cas probable : Toute personne, symptomatique ou non, ayant eu un contact étroit avec un cas confirmé de COVID-19 dans les 14 derniers jours.

cas confirmé : Toute personne, symptomatique ou non, avec un une confirmation d'infection par le SARS-CoV-2 au laboratoire.

Les zones à risque sont définies comme:

• La Tunisie a décrété ses frontières fermées à toutes les destinations du monde depuis le 22 Mars 2020.

• Les régions du pays, déclarées par les autorités sanitaires nationales, comme foyers de transmission locale, La liste de ces régions sera annoncée par le bulletin épidémiologique quotidien et révisée périodiquement selon l'évolution épidémiologique dans le pays.

Bulletin ONMNE 05042020
http://www.onmne.tn/fr/images/COVID-19-dernier-bulletin.pdf

III- DIAGNOSTIC

2. Diagnostic Virologique :

(cf présentation du Pr Ag Salma Mhalla)

- PCR

- tests rapides

III. DIAGNOSTIC

3. Apport de la TDM thoracique :

- tests virologiques : possibilité de faux négatifs

→ intérêt de la TDM thoracique surtout en cas de forte suspicion (épidémiologique et/ou clinique)

III. DIAGNOSTIC - TDM thoracique

Chest CT Findings in Coronavirus Disease-19 (COVID-19): Relationship to Duration of Infection

Abstract

In this retrospective study, chest CTs of 121 symptomatic patients infected with coronavirus disease-19 (COVID-19) from four centers in China from January 18, 2020 to February 2, 2020 were reviewed for common CT findings in relationship to the time between symptom onset and the initial CT scan (i.e. early, 0-2 days (36 patients), intermediate 3-5 days (33 patients), late 6-12 days (25 patients)). The hallmarks of COVID-19 infection on imaging were bilateral and peripheral ground-glass and consolidative pulmonary opacities. Notably, 20/36 (56%) of early patients had a normal CT. With a longer time after the onset of symptoms, CT findings were more frequent, including consolidation, bilateral and peripheral disease, greater total lung involvement, linear opacities, "crazy-paving" pattern and the "reverse halo" sign. Bilateral lung involvement was observed in 10/36 early patients (28%), 25/33 intermediate patients (76%), and 22/25 late patients (88%).

Bernheim A et al. Radiology (2020)

III. DIAGNOSTIC - TDM thoracique

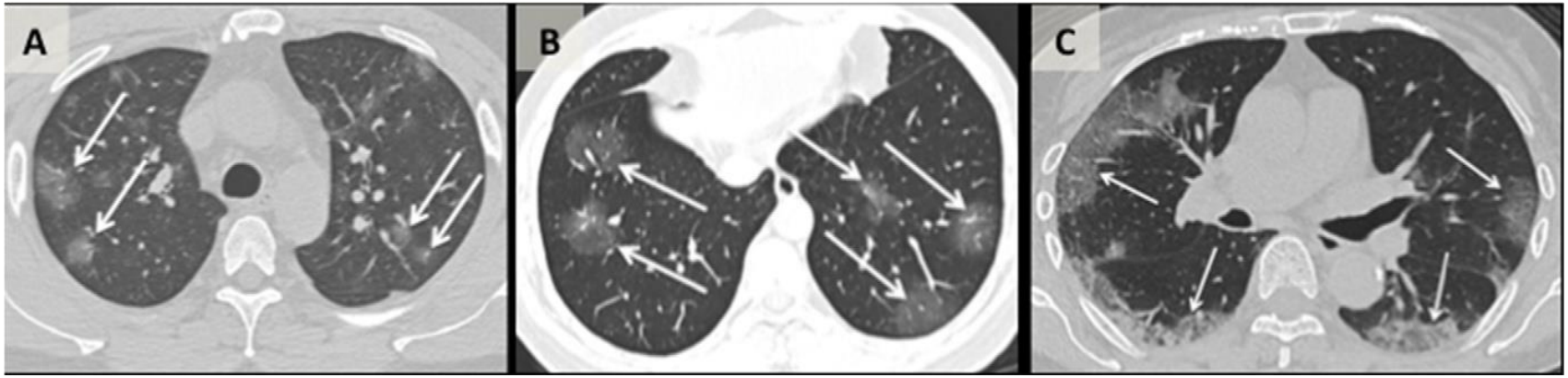

Figure. opacités bilatérales en verre dépoli

Bernheim A et al. Radiology (2020)

III. DIAGNOSTIC - TDM thoracique

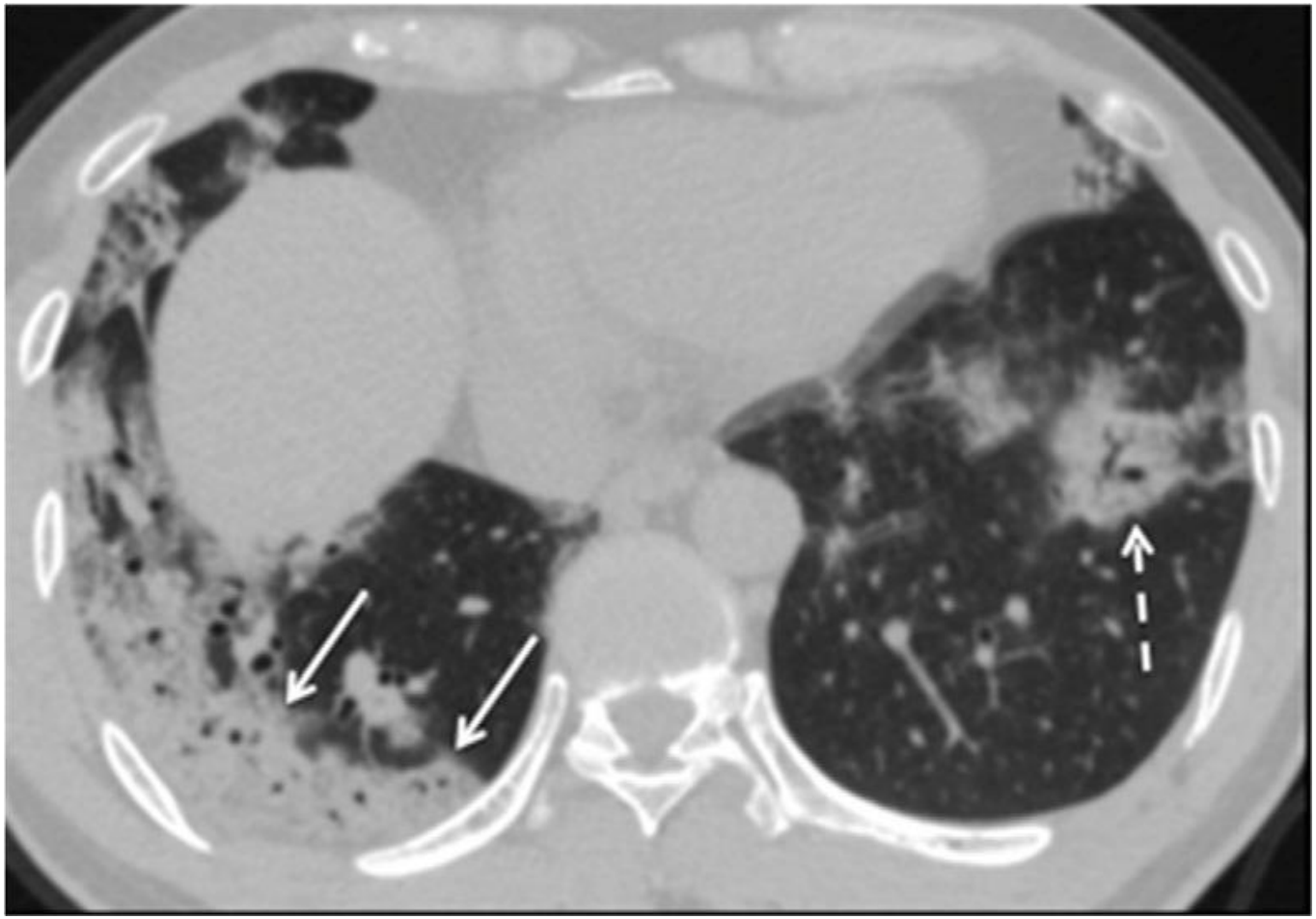

Figure. opacités alvéolaires

Bernheim A et al. Radiology (2020)

III. DIAGNOSTIC

3. Apport de la TDM thoracique :

SYMPTOMS				
Fever	74 (61)	22 (61)	26 (79)	23 (92)
Cough	58 (48)	19 (53)	21 (64)	15 (60)
Sputum Production	20 (17)	7 (19)	5 (15)	6 (24)
RT PCR testing				
Initial RT-PCR Positive	90/102 (88)	33/36 (92)	28/33 (85)	23/25 (92)
Any Positive RT-PCR	121/121 (100)	36/36 (100)	33/33 (100)	25/25 (100)
Mean Day RT PCR was positive after symptom onset	4.5 (range 0-18)	2.3 (range 0-7)	4.7 (range 0-18)	7.2 (range 1-12)

Bernheim A et al. Radiology (2020)

III. DIAGNOSTIC

3. Parfois difficile :

➢ deux risques majeurs **+++ :**

- passer à côté d'un COVID-19
- passer à côté d'une autre maladie

} aggravation / décès

III. DIAGNOSTIC

3. Parfois difficile :

➢ Démarche diagnostique rigoureuse +++ / Arguments :

- épidémiologiques
- cliniques
- TDM
- PCR : si négative avec forte suspicion / gravité → 2ème PCR

➢ **Discussion collégiale +++** (même service / services différents)

IV. TRAITEMENT

1.Traitements non spécifiques :

- oxygénothérapie
- antibiothérapie : ex. amoxicilline-acide clavulanique, céfotaxime

…

IV. TRAITEMENT

1.Traitements non spécifiques

2. Antiviraux :

- chloroquine, hydroxychloroquine
- lopinavir/ritonavir
- remdesivir

IV. TRAITEMENT

1.Traitements non spécifiques

2. Traitement antiviraux

3. Autres (formes graves) :

- corticoïdes
- immunoglobulines IV
- tocilizumab (anti-IL6)
- échanges plasmatiques
- anticoagulation

…

IV. TRAITEMENT - Chloroquine

A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19

Methods: PubMed, EMBASE, and three trial Registries were searched for studies on the use of chloroquine in patients with COVID-19.

Results: We included six articles (one narrative letter, one in-vitro study, one editorial, expert consensus paper, two national guideline documents) and 23 ongoing clinical trials in China. Chloroquine seems to be effective in limiting the replication of SARS-CoV-2 (virus causing COVID-19) in vitro.

Conclusions: There is rationale, pre-clinical evidence of effectiveness and evidence of safety from long-time clinical use for other indications to justify clinical research on chloroquine in patients with COVID-19. However, clinical use should either adhere to the Monitored Emergency Use of Unregistered Interventions (MEURI) framework or be ethically approved as a trial as stated by the World Health Organization. Safety data and data from high-quality clinical trials are urgently needed.

Cortegiani A et al. Journal of Critical Care (2020)

IV. TRAITEMENT - Hydroxychloroquine

Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial

Patients and methods

French Confirmed COVID-19 patients were included in a single arm protocol from early March to March 16th, to receive 600mg of hydroxychloroquine daily and their viral load in nasopharyngeal swabs was tested daily in a hospital setting. Depending on their clinical presentation, azithromycin was added to the treatment. Untreated patients from another center and cases refusing the protocol were included as negative controls. Presence and absence of virus at Day6-post inclusion was considered the end point.

Raoult D et al. Journal Antimicrob Agents (2020)

IV. TRAITEMENT - Hydroxychloroquine

Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial

Results

Six patients were asymptomatic, 22 had upper respiratory tract infection symptoms and eight had lower respiratory tract infection symptoms.

Twenty cases were treated in this study and showed a significant reduction of the viral carriage at D6-post inclusion compared to controls, and much lower average carrying duration than reported of untreated patients in the literature. Azithromycin added to hydroxychloroquine was significantly more efficient for virus elimination.

Raoult D et al. Journal Antimicrob Agents (2020)

IV. TRAITEMENT - Hydroxychloroquine

Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial

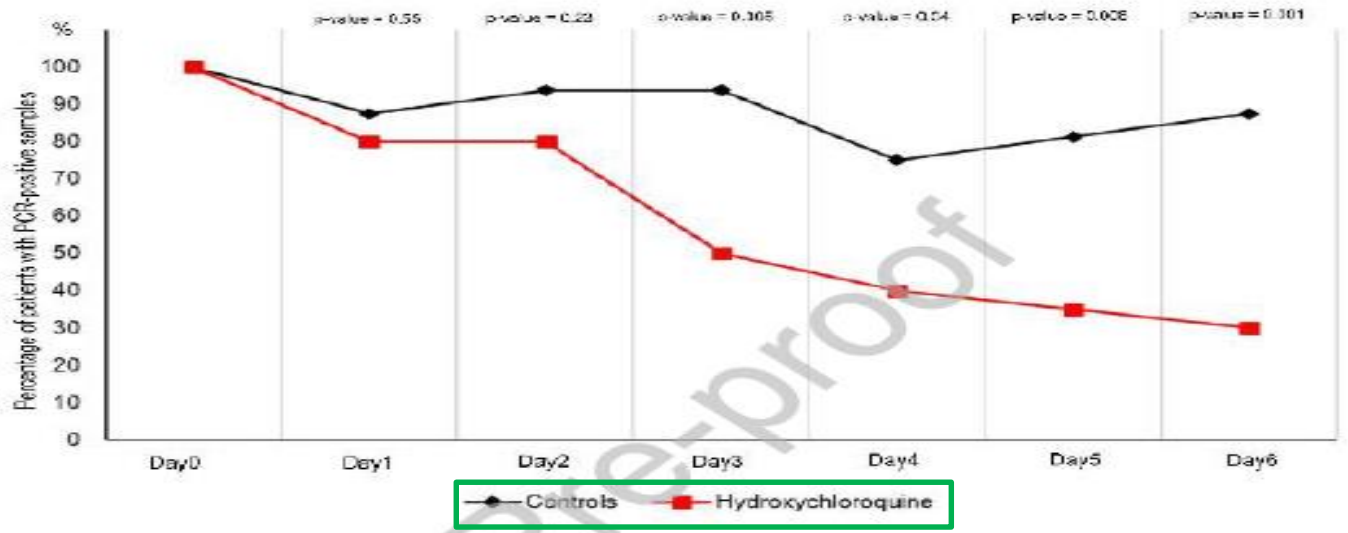

Figure 1. Percentage of patients with PCR-positive nasopharyngeal samples from inclusion to day6 post-inclusion in COVID-19 patients treated with hydroxychloroquine and in COVID-19 control patients.

Raoult D et al. Journal Antimicrob Agents (2020)

IV. TRAITEMENT - Hydroxychloroquine

Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial

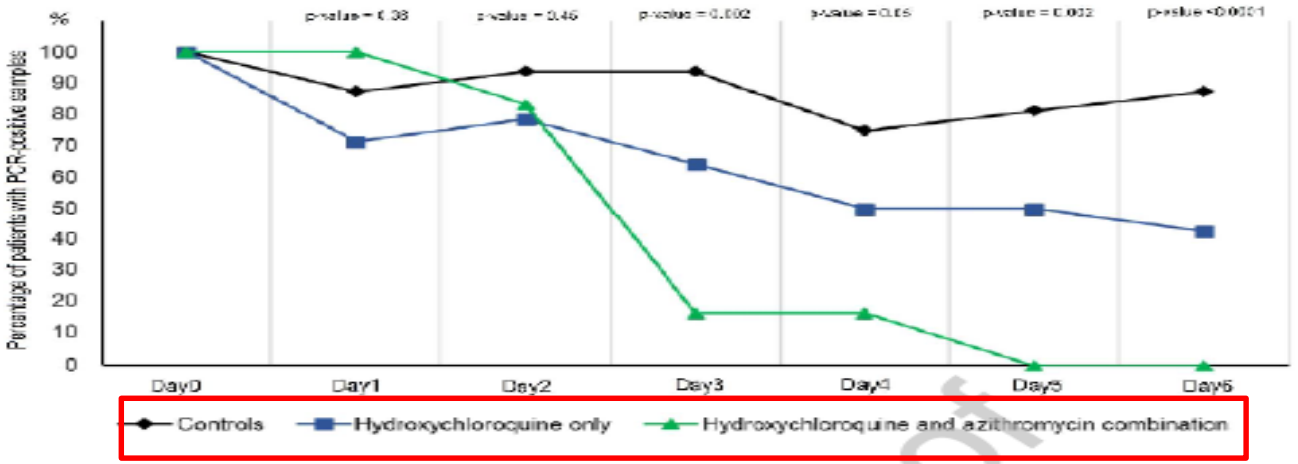

Figure 2. Percentage of patients with PCR-positive nasopharyngeal samples from inclusion t day6 post-inclusion in COVID-19 patients treated with hydroxychloroquine only, in COVID-19 patients treated with hydroxychloroquine and azithomycin combination, and in COVID-1 control patients.

Raoult D et al. Journal Antimicrob Agents (2020)

IV. TRAITEMENT - Hydroxychloroquine

Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial

Conclusion

Despite its small sample size our survey shows that hydroxychloroquine treatment is significantly associated with viral load reduction/disappearance in COVID-19 patients and its effect is reinforced by azithromycin.

Raoult D et al. Journal Antimicrob Agents (2020)

IV. TRAITEMENT - Hydroxychloroquine

Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial

✓ Limites :

- faible nombre de patients : 36 (20 vs 16)

- essai non randomisé, ouvert (pas d'aveugle)

Raoult D et al. Journal Antimicrob Agents (2020)

IV. TRAITEMENT - Lopinavir/r

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19

METHODS

We conducted a randomized, controlled, open-label trial involving hospitalized adult patients with confirmed SARS-CoV-2 infection, which causes the respiratory illness Covid-19, and an oxygen saturation (Sao_2) of 94% or less while they were breathing ambient air or a ratio of the partial pressure of oxygen (Pao_2) to the fraction of inspired oxygen (Fio_2) of less than 300 mm Hg. Patients were randomly assigned in a 1:1 ratio to receive either lopinavir–ritonavir (400 mg and 100 mg, respectively) twice a day for 14 days, in addition to standard care, or standard care alone. The primary end point was the time to clinical improvement, defined as the time from randomization to either an improvement of two points on a seven-category ordinal scale or discharge from the hospital, whichever came first.

Cao B et al. NEJM (2020)

IV. TRAITEMENT - Lopinavir/r

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19

RESULTS

A total of 199 patients with laboratory-confirmed SARS-CoV-2 infection underwent randomization; 99 were assigned to the lopinavir–ritonavir group, and 100 to the standard-care group. Treatment with lopinavir–ritonavir was not associated with a difference from standard care in the time to clinical improvement (hazard ratio for clinical improvement, 1.24; 95% confidence interval [CI], 0.90 to 1.72). Mortality at 28 days was similar in the lopinavir–ritonavir group and the standard-care group (19.2% vs. 25.0%; difference, –5.8 percentage points; 95% CI, –17.3 to 5.7). The percentages of patients with detectable viral RNA at various time points were similar. In a modified intention-to-treat analysis, lopinavir–ritonavir led to a median time to clinical improvement that was shorter by 1 day than that observed with standard care (hazard ratio, 1.39; 95% CI, 1.00 to 1.91). Gastrointestinal adverse events were more common in the lopinavir–ritonavir group, but serious adverse events were more common in the standard-care group. Lopinavir–ritonavir treatment was stopped early in 13 patients (13.8%) because of adverse events.

Cao B et al. NEJM (2020)

IV. TRAITEMENT - Lopinavir/r

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19

CONCLUSIONS

In hospitalized adult patients with severe Covid-19, no benefit was observed with lopinavir–ritonavir treatment beyond standard care. Future trials in patients with severe illness may help to confirm or exclude the possibility of a treatment benefit. (Funded by Major Projects of National Science and Technology on New Drug Creation and Development and others; Chinese Clinical Trial Register number, ChiCTR2000029308.)

Cao B et al. NEJM (2020)

IV. TRAITEMENT - Remdesivir

Cell Research

www.nature.com/cr
www.cell-research.com

LETTER TO THE EDITOR OPEN

Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro

Cell Research (2020) 30:269–271; https://doi.org/10.1038/s41422-020-0282-0

Wang B et al. Cell Res (2020)

IV. TRAITEMENT - Antiviraux

Early antiviral treatment contributes to alleviate the severity and improve the prognosis of patients with novel coronavirus disease (COVID-19)

Wu J et al. J Intern Med(2020)

IV. TRAITEMENT - Antiviraux

Early antiviral treatment contributes to alleviate the severity and improve the prognosis of patients with novel coronavirus disease (COVID-19)

of confirmed 280 cases of novel coronavirus disease (COVID-19) from January 20 to February 20, 2020.

Results. The median age of patients in the mild group was 37.55 years old, while that in the severe group was 63.04 years old. The proportion of patients over 65 years old in the severe group was significantly higher than that of the mild group (59.04% vs. 10.15%, $P < 0.05$). 85.54% of severe patients had diabetes or cardiovascular diseases, which was significantly higher than that of the mild group (51.81% vs 7.11%, $P = 0.025$; 33.73% vs 3.05%, $P = 0.042$). Patients in the mild group experienced earlier initiation of antiviral treatment (1.19 ± 0.45 vs 2.65 ± 1.06 days in the severe group, $P < 0.001$). Our study showed that comorbidity, time from illness onset to antiviral, and age >=65 were three major risk factors for COVID-19 progression, while comorbidity and time from illness onset to antiviral were two major risk factors for COVID-19 recovery.

Conclusions. The elderly and patients with underlying diseases are more likely to experience a severe progression of COVID-19. It is recommended that timely antiviral treatment should be initiated to slow the disease progression and improve the prognosis.

Wu J et al. J Intern Med(2020)

IV. TRAITEMENT - Antiviraux

Early antiviral treatment contributes to alleviate the severity and improve the prognosis of patients with novel coronavirus disease (COVID-19)

Table 3. Logistic regression analysis of risk factors with severity for patients with SARS-CoV-2

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age >=65(y)	16.32(4.59-58.01)	0.001	81.20(1.10-5988.12)	0.045
BMI	1.30(1.09-1.54)	0.003		
Agglomerative epidemic	0.39(0.24-0.65)	0.012		
Comorbidity	47.77(13.68-166.77)	0.002	54.74(1.14-2634.81)	0.043
Time from illness onset to antiviral	11.63(4.51-30.03)	0.001	26.98(1.81-402.93)	0.017
Lymphocyte count	0.09(0.02-0.29)	0.014		
Non-invasive(ie,face mask)	3.97(1.58-9.93)	0.025		
D-dimer	3.20(1.75-5.88)	0.031		
Creatine kinase	1.00(1.00-1.01)	0.083		
Creatine kinase–MB	1.07(1.01-1.14)	0.026		

Wu J et al. J Intern Med(2020)

IV. TRAITEMENT - Antiviraux

Utilisation de l'association hydroxychloroquine ou chloroquine à l'azithromycine chez les patients covid-19 (+) selon la procédure MEURI[1]

- Etude multicentrique nationale :

« Utilisation de l'association hydroxychloroquine ou chloroquine à l'azithromycine chez les patients covid-19 (+) selon la procédure MEURI[1] »

1: Monitored Emergency Use of Unregistered Interventions (utilisation surveillée d'interventions non homologuées et expérimentales en situation d'urgence).

Ministère de la Santé/DSSB. 06 avril 2020

IV. TRAITEMENT - Antiviraux

Utilisation de l'association hydroxychloroquine ou chloroquine à l'azithromycine chez les patients covid-19 (+) selon la procédure MEURI[1]

❖ objectif principal :

- évaluer l'efficacité clinique et virologique et la tolérance de l'hydroxychloroquine ou de la chloroquine en association avec l'azithromycine chez les patients COVID-19 (+).

- traitement prescrit après consentement éclairé et écrit

IV. TRAITEMENT - Antiviraux

Utilisation de l'association hydroxychloroquine ou chloroquine à l'azithromycine chez les patients covid-19 (+) selon la procédure MEURI[1]

objectif principal

schéma thérapeutique :

hydroxychloroquine ou chloroquine (disponibilité) x 10 j

hydroxychloroquine 200 mg x 3/ j à J1 puis 200 mgx2/j de J2 à J10

ou chloroquine 400 mg x 2/jour x 10 jours.

+ azithromycine x 5 jours :

500 mg à J1 puis 250 mg/j de J2 à J5

Ministère de la Santé/DSSB. 06 avril 2020

IV. TRAITEMENT - Autres

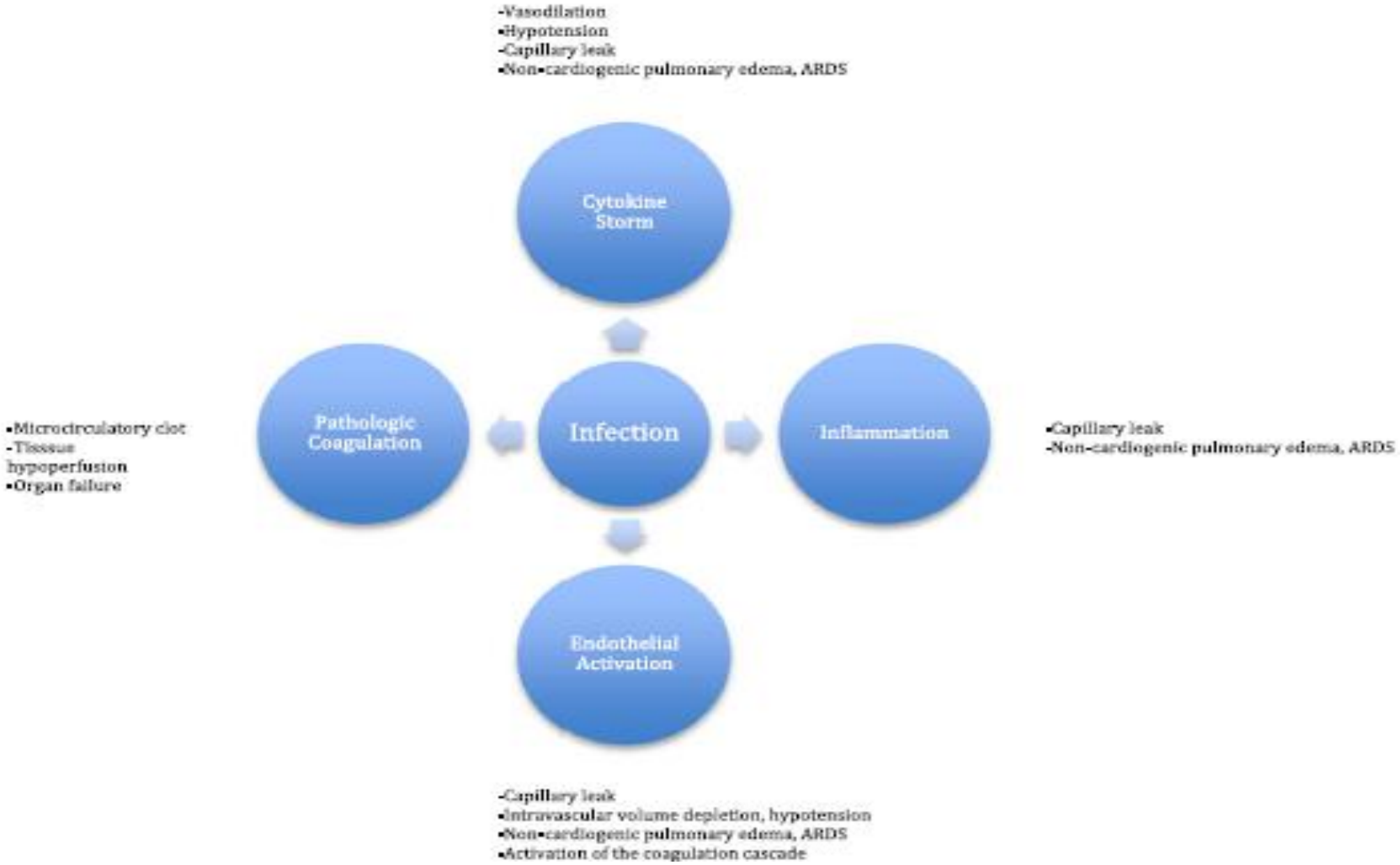

Fig. 1 Physiologic pathway of sepsis which serve as potential targets of therapeutic plasma exchange

Keith P et al. Critical (2020)

IV. TRAITEMENT - Corticoïdes

Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury

The 2019 novel coronavirus (2019-nCoV) outbreak is a major challenge for clinicians. The clinical course of patients remains to be fully characterised, little data are available that describe the disease pathogenesis, and no pharmacological therapies of proven efficacy yet exist.

Corticosteroids were widely used during the outbreaks of severe acute respiratory syndrome (SARS)-CoV[1] and Middle East respiratory syndrome (MERS)-CoV,[2] and are being used in patients with 2019-nCoV in addition to other therapeutics.[3] However, current interim guidance from WHO on clinical management of severe acute respiratory infection when novel coronavirus (2019-nCoV) infection is suspected (released Jan 28, 2020) advises against the use of corticosteroids unless indicated for

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Russel KD et al. Lancet (2020, February 15)

IV. TRAITEMENT - Corticoïdes

Corticosteroid treatment of patients with coronavirus disease 2019 (COVID-19)

Lei Zha[1], Shirong Li[2], Lingling Pan[3], Boris Tefsen[1], Yeshan Li[2], Neil French[4], Liyun Chen[5], Gang Yang[2], Elmer V Villanueva[1]

Zha L et al. Med J Aust. (2020, Marsh 9)

IV. TRAITEMENT - Corticoïdes

Abstract

Objectives: To assess the efficacy of corticosteroid treatment of patients with coronavirus disease 2019 (COVID-19).

Design, setting: Observational study in the two COVID-19-designated hospitals in Wuhu, Anhui province, China, 24 January – 24 February 2020.

Participants: Thirty-one patients infected with the severe acute respiratory coronavirus 2 (SARS-CoV-2) treated at the two designated hospitals.

Main outcome measures: Virus clearance time, length of hospital stay, and duration of symptoms, by treatment type (including or not including corticosteroid therapy).

Results: Eleven of 31 patients with COVID-19 received corticosteroid treatment. Cox proportional hazards regression analysis indicated no association between corticosteroid treatment and virus clearance time (hazard ratio [HR], 1.26; 95% CI, 0.58–2.74), hospital length of stay (HR, 0.77; 95% CI, 0.33–1.78), or duration of symptoms (HR, 0.86; 95% CI, 0.40–1.83). Univariate analysis indicated that virus clearance was slower in two patients with chronic hepatitis B infections (mean difference, 10.6 days; 95% CI, 6.2–15.1 days).

Conclusions: Corticosteroids are widely used when treating patients with COVID-19, but we found no association between therapy and outcomes in patients without acute respiratory distress syndrome. An existing HBV infection may delay SARS-CoV-2 clearance, and this association should be further investigated.

Zha L et al. Med J Aust. (2020, Marsh 9)

IV. TRAITEMENT - Tocilizumab

Effective Treatment of Severe COVID-19 Patients with Tocilizumab

Xiaoling Xu[1,#*], Mingfeng Han[2,#], Tiantian Li[1], Wei Sun[2], Dongsheng Wang[1], Binqing Fu[3,4], Yonggang Zhou[3,4], Xiaohu Zheng[3,4], Yun Yang[5], Xiuyong Li[6], Xiaohua Zhang[2], Aijun Pan[5], Haiming Wei[3,4*]

Abstract:

Background: In December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified in Wuhan, China, which spread rapidly and has become a world-wide public health challenge. We aimed to assess the efficacy of tocilizumab in severe patients with Corona Virus Disease-19 (COVID-19) and seek a new therapeutic strategy.

Methods: The patients diagnosed as severe or critical COVID-19 in The First Affiliated Hospital of University of Science and Technology of China (Anhui Provincial Hospital) and Anhui Fuyang Second People's Hospital were given tocilizumab in addition to routine therapy between February 5 and February 14, 2020. The changes of clinical manifestations, CT scan image, and laboratory examinations were retrospectively analyzed.

Findings: Within a few days, the fever returned to normal and all other symptoms improved remarkably. Fifteen of the 20 patients (75.0%) had lowered their oxygen intake and one patient need no oxygen therapy. CT scans manifested that the lung lesion opacity absorbed in 19 patients (90.5%). The No obvious adverse reactions were observed. Nineteen patients (90.5%) have been discharged on average 13.5 days after the treatment with tocilizumab and the rest are recovering well.

IV. TRAITEMENT - Immunoglobulines IV

Open Forum Infectious Diseases

BRIEF REPORT

High-Dose Intravenous Immunoglobulin as a Therapeutic Option for Deteriorating Patients With Coronavirus Disease 2019

Wei Cao,[1] Xiaosheng Liu,[2] Tao Bai,[3] Hongwei Fan,[1] Ke Hong,[3] Hui Song,[3] Yang Han,[1] Ling Lin,[1] Lianguo Ruan,[3,a] and Taisheng Li[1,a]

[1]Department of Infectious Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China, [2]Tsinghua-Peking Center for Life Sciences, School of Medicine, Tsinghua University, Beijing, China, and [3]Department of Infectious Diseases, Jin Yin-tan Hospital, Wuhan, China

The outbreak of coronavirus disease 2019 (COVID-19) has spread rapidly in China. Until now, no definite effective treatment has been identified. We reported on 3 patients with severe COVID-19 who received high-dose intravenous immunoglobulin (IVIg) with satisfactory recovery. Based on these observations, randomized studies of high-dose IVIg should be considered in deteriorating patients infected with COVID-19.

IV. TRAITEMENT - Immunoglobulines IV

JAMA | Preliminary Communication

Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma

Chenguang Shen, PhD; Zhaoqin Wang, PhD; Fang Zhao, PhD; Yang Yang, MD; Jinxiu Li, MD; Jing Yuan, MD; Fuxiang Wang, MD; Delin Li, PhD; Minghui Yang, PhD; Li Xing, MM; Jinli Wei, MM; Haixia Xiao, PhD; Yan Yang, MM; Jiuxin Qu, MD; Ling Qing, MM; Li Chen, MD; Zhixiang Xu, MM; Ling Peng, MM; Yanjie Li, MM; Haixia Zheng, MM; Feng Chen, MM; Kun Huang, MM; Yujing Jiang, MM; Dongjing Liu, MD; Zheng Zhang, MD; Yingxia Liu, MD; Lei Liu, MD

EXPOSURES Patients received transfusion with convalescent plasma with a SARS-CoV-2–specific antibody (IgG) binding titer greater than 1:1000 (end point dilution titer, by enzyme-linked immunosorbent assay [ELISA]) and a neutralization titer greater than 40 (end point dilution titer) that had been obtained from 5 patients who recovered from COVID-19. Convalescent plasma was administered between 10 and 22 days after admission.

IV. TRAITEMENT - Immunoglobulines IV

JAMA | Preliminary Communication

Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma

Chenguang Shen, PhD; Zhaoqin Wang, PhD; Fang Zhao, PhD; Yang Yang, MD; Jinxiu Li, MD; Jing Yuan, MD; Fuxiang Wang, MD; Delin Li, PhD; Minghui Yang, PhD; Li Xing, MM; Jinli Wei, MM; Haixia Xiao, PhD; Yan Yang, MM; Jiuxin Qu, MD; Ling Qing, MM; Li Chen, MD; Zhixiang Xu, MM; Ling Peng, MM; Yanjie Li, MM; Haixia Zheng, MM; Feng Chen, MM; Kun Huang, MM; Yujing Jiang, MM; Dongjing Liu, MD; Zheng Zhang, MD; Yingxia Liu, MD; Lei Liu, MD

RESULTS All 5 patients (age range, 36-65 years; 2 women) were receiving mechanical ventilation at the time of treatment and all had received antiviral agents and methylprednisolone. Following plasma transfusion, body temperature normalized within 3 days in 4 of 5 patients, the SOFA score decreased, and PaO_2/FiO_2 increased within 12 days (range, 172-276 before and 284-366 after). Viral loads also decreased and became negative within 12 days after the transfusion, and SARS-CoV-2–specific ELISA and neutralizing antibody titers increased following the transfusion (range, 40-60 before and 80-320 on day 7). ARDS resolved in 4 patients at 12 days after transfusion, and 3 patients were weaned from mechanical ventilation within 2 weeks of treatment. Of the 5 patients, 3 have been discharged from the hospital (length of stay: 53, 51, and 55 days), and 2 are in stable condition at 37 days after transfusion.

IV. TRAITEMENT - échanges plasmatiques

Keith *et al. Critical Care* (2020) 24:128
https://doi.org/10.1186/s13054-020-2836-4

Critical Care

EDITORIAL Open Access

A novel treatment approach to the novel coronavirus: an argument for the use of therapeutic plasma exchange for fulminant COVID-19

Philip Keith[1*], Matthew Day[1], Linda Perkins[1], Lou Moyer[1], Kristi Hewitt[1] and Adam Wells[2]

IV. TRAITEMENT - Anticoagulation

Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy

Ning Tang[1], Huan Bai[1], Xing Chen[1], Jiale Gong[1], Dengju Li[2], Ziyong Sun[1]*

Methods: Coagulation results, medications and outcomes of consecutive patients being classified as severe COVID-19 in Tongji hospital were retrospectively analysed. The 28-day mortality between heparin users and nonusers were compared, also in different risk of coagulopaphy which was stratified by the sepsis-induced coagulopathy (SIC) score or D-dimer result.

IV. TRAITEMENT - Anticoagulation

Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy

Ning Tang[1], Huan Bai[1], Xing Chen[1], Jiale Gong[1], Dengju Li[2], Ziyong Sun[1]*

Results: There were 449 patients with severe COVID-19 enrolled into the study, 99 of them received heparin (mainly with low molecular weight heparin, LMWH) for 7 days or longer. The D-dimer, prothrombin time and age were positively, and platelet count was negatively, correlated with 28-day mortality in multivariate analysis. No difference on 28-day mortality was found between heparin users and nonusers (30.3% vs 29.7%, *P*=0.910). But the 28-day mortality of heparin users were lower than nonusers In patients with SIC score ⩾4 (40.0% vs 64.2%, *P*=0.029), or D-dimer > 6 fold of upper limit of normal (32.8% vs 52.4%, *P*=0.017).

Conclusions: Anticoagulant therapy mainly with LMWH appears to be associated with better prognosis in severe COVID-19 patients meeting SIC criteria or with markedly elevated D-dimer.

IV. TRAITEMENT - Anticoagulation

Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy

Ning Tang[1], Huan Bai[1], Xing Chen[1], Jiale Gong[1], Dengju Li[2], Ziyong Sun[1]*

Table 1 ISTH SIC scoring system

Item	Score	Range
Platelet count ($\times 10^9$/L)	1	100-150
	2	<100
PT -INR	1	1.2-1.4
	2	>1.4
SOFA score	1	1
	2	⩾2
Total score for SIC	⩾4	

INR, International Normalized Ratio; SOFA, sequential organ failure assessment.

IV. TRAITEMENT - IDSA Guidelines

Last updated April 13, 2020 at 9:06 AM EDT and posted online at www.idsociety.org/COVID19guidelines.
Please check website for most updated version of these guidelines.

Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19

Authors

Adarsh Bhimraj[1], Rebecca L. Morgan[2], Amy Hirsch Shumaker[3], Valery Lavergne[4], Lindsey Baden[5], Vincent Chi-Chung Cheng[6], Kathryn M. Edwards[7], Rajesh Gandhi[8], William J. Muller[9], John C. O'Horo[10], Shmuel Shoham[11], M. Hassan Murad[12], Reem A. Mustafa[13], Shahnaz Sultan[14], Yngve Falck-Ytter[3]

IV. TRAITEMENT - IDSA Guidelines

Recommendation 1. Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends hydroxychloroquine/chloroquine in the context of a clinical trial. (Knowledge gap)

Recommendation 2. Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends hydroxychloroquine/chloroquine plus azithromycin only in the context of a clinical trial. (Knowledge gap)

Recommendation 3. Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends the combination of lopinavir/ritonavir only in the context of a clinical trial. (Knowledge gap)

IV. TRAITEMENT - IDSA Guidelines

Recommendation 4. Among patients who have been admitted to the hospital with COVID-19 pneumonia, the IDSA guideline panel suggests against the use of corticosteroids. (Conditional recommendation, very low certainty of evidence)

Recommendation 5. Among patients who have been admitted to the hospital with ARDS due to COVID-19, the IDSA guideline panel recommends the use of corticosteroids in the context of a clinical trial. (Knowledge gap)

Recommendation 6. Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends tocilizumab only in the context of a clinical trial. (Knowledge gap)

Recommendation 7. Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends COVID-19 convalescent plasma in the context of a clinical trial. (Knowledge gap)

IV. PREVENTION

1. Mesures d'Hygiène +++ :

- isolement géographique des patients
- lavage des mains
- équipement de protection individuelle

…

IV. PREVENTION

1. Mesures d'Hygiène +++ :

IV. PREVENTION

1. Mesures d'Hygiène +++ :

IV. PREVENTION

1. Mesures d'Hygiène +++ :

EPI / vidéo préparée par Dr Nadia Ben Lasfar + Int Salihou Fall :

https://drive.google.com/drive/folders/1DjOUnpEVQxZ5DjQOVTtZVG6_0gEDDvj0

IV. PREVENTION

1. Mesures d'Hygiène +++ :

2. **Traitement** des **patients infectés** par le SARS-cov2 :

→ diminution de la durée de l'infection / contagiosité

IV. PREVENTION

1- Mesures d'Hygiène +++ :

2- Traitement des patients infectés par le SARS-cov2 :

→ diminution de la durée de l'infection / contagiosité

3. **Vaccination** : études en cours

IV. PREVENTION

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Immunity
Perspective

CellPress

SARS-CoV-2 Vaccines: Status Report

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https://doi.org/10.1016/j.immuni.2020.03.007

IV. PREVENTION

Table 1. Overview of Vaccine Production Platforms and Technologies for SARS-CoV-2

Platform	Target	Existing, Licensed Human Vaccines Using the Same Platform	Advantages	Disadvantages
RNA vaccines	S protein	No	No infectious virus needs to be handled, vaccines are typically immunogenic, rapid production possible.	Safety issues with reactogenicity have been reported.
DNA vaccines	S protein	No	No infectious virus needs to be handled, easy scale up, low production costs, high heat stability, tested in humans for SARS-CoV-1, rapid production possible.	Vaccine needs specific delivery devices to reach good immunogenicity.
Recombinant protein vaccines	S protein	Yes for baculovirus (influenza, HPV) and yeast expression (HBV, HPV)	No infectious virus needs to be handled, adjuvants can be used to increase immunogenicity.	Global production capacity might be limited. Antigen and/or epitope integrity needs to be confirmed. Yields need to be high enough.
Viral vector-based vaccines	S protein	Yes for VSV (Ervebo), but not for other viral vectored vaccines	No infectious virus needs to be handled, excellent preclinical and clinical data for many emerging viruses, including MERS-CoV.	Vector immunity might negatively affect vaccine effectiveness (depending on the vector chosen).
Live attenuated vaccines	Whole virion	Yes	Straightforward process used for several licensed human vaccines, existing infrastructure can be used.	Creating infectious clones for attenuated coronavirus vaccine seeds takes time because of large genome size. Safety testing will need to be extensive.
Inactivated vaccines	Whole virion	Yes	Straightforward process used for several licensed human vaccines, existing infrastructure can be used, has been tested in humans for SARS-CoV-1, adjuvants can be used to increase immunogenicity.	Large amounts of infectious virus need to be handled (could be mitigated by using an attenuated seed virus). Antigen and/or epitope integrity needs to be confirmed.

Amanat F et al. Immunity (2020)

V. CONCLUSION

COVID-19

❖Diagnostic : pas toujours facile

→ Collaboration +++

❖ Pas de Traitement à efficacité prouvée

→ prise en charge Individualisée

❖ Meilleur traitement : Prévention +++

Le doute est un état mental désagréable, mais la certitude est ridicule.

(Voltaire)

QQcitations

Ensemble, on est plus fort