# QUE OPÇÕES TERAPÊUTICAS ?

## Abordagem terapêutica dos doentes em Angola no âmbito da COVID-19

Fernanda Dias
FMUAN

# Sumário

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2. • OPÇÕES TERAPÊUTICAS NO CONTEXTO ANGOLANO
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# 1. Enquadramento

| 30 de Janeiro | 1 de Fevereiro | 17 de Março | 21 de Março |
|---|---|---|---|
| • Criada a Comissão Interministerial.<br><br>• Concluído o Plano Nacional de Contingência.<br><br>• OMS declara estado de Emergência em Saúde Pública. | • Iniciada quarentena institucional dos passageiros provenientes da China.<br><br>• Rastreio de todos os casos suspeitos no aeroporto internacional. | • Quarentena institucional para todos os passageiros provenientes de países com transmissão comunitária declarada. | • Diagnosticado primeiro caso da Covid-19<br>• Encerramento das fronteiras. *<br>• Inicia a investigação dos contactos.<br><br>• Activação das equipas de resposta rápida, busca activa de casos e activação da linha SOS – 111. |

# QUE OPÇÕES TERAPÊUTICAS ?

# 2. Algumas Considerações:

✓ Não existe actualmente tratamento eficaz para a COVID-19,

nem evidências clínicas robustas que apontem para um tratamento específico,

apesar dos inúmeros ensaios clínicos em curso !

✓Com base nas recomendações inicias da OMS, apesar da não comprovada eficácia, Angola, adoptou desde o início o tratamento (*off-label*), com **Cloroquina** e seu análogo **Hidroxicloroquina,**

isolada ou em combinação com a **Azitromicina,** para os casos oligossintomáticos a moderados.

# 2. Algumas Considerações – Casos Graves

## 1. Antibióticos

- Ceftriaxona 2g/dia (ou 1 g de 12/12 h) EV
- ou Amoxicilina/ácido clavulânico 2,2 g 8/8 h EV
- + Azitromicina 500mg/dia EV ou Claritromicina 500mg 12/12 h EV

## 2. Antivirais

- Oseltamivir 75 mg (comprimido), 2 comprimidos (150 mg) 12/12 h, via oral +* Lopipinavir 800 mg (ou 10 mg / kg) /dia + Ritonavir 200 mg (ou 2,5 mg / kg ) / dia ???
- Remdesivir 200 mg EV (dose de carga, dia 1) seguida de Remdesivir 100 mg/dia *EV* (dose de manutenção, dias 2 a 10).

# No início da Pandemia ….

TESTAR

TRATAR

ISOLAR

1. **Hidroxicloroquina (HCQ)**
   400 mg de 12/12h – 1º dia,
   seguido de 200 mg de 12/12h durante 4-5 dias - até 10 dias.

2. Ou associada a Azitromicina 500 mg (1xdia) – 5 a 10 dias

?

Parecer Científico da Sociedade Brasileira de Imunologia sobre a utilização da Cloroquina/Hidroxicloroquina para o

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Commentary

## Of chloroquine and COVID-19

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Recent publications have brought attention to the po chloroquine, a broadly used antimalarial drug, in the t tients infected by the novel emerged coronavirus (SARS et al., 2020; Gao et al., 2020). The scientific community this information in light of previous experiments with the field of antiviral research.

The sulfate and phosphate salts of chloroquine h commercialised as antimalarial drugs. Hydroxychloro been used as an antimalarial, but in addition is now autoimmune diseases such as lupus and rheumatoid ar chloroquine and hydroxychloroquine are considered side-effects are generally mild and transitory. Howev between the therapeutic and toxic dose is narrow a poisoning has been associated with cardiovascular disor life-threatening (Frisk-Holmberg et al., 1983). Chlor droxychloroquine use should therefore be subject to self-treatment is not recommended.

The *in vitro* antiviral activity of chloroquine has since the late 1960's (Inglot, 1969; Miller and Lenard, et al., 1972) and the growth of many different viruses in cell culture by both chloroquine and hydroxychloro the SARS coronavirus (Keyaerts et al., 2004). Some evid in mice has been found for a variety of viruses, includ onavirus OC43 (Keyaerts et al., 2009), enterovirus EV- 2018), Zika virus (Li et al., 2017) and influenza A H5 2013). However, chloroquine did not prevent influenz randomized, double-blind, placebo-controlled clinical tr 2011), and had no effect on dengue-infecteds patient i controlled trial in Vietnam (Tricou et al., 2010). Chlor active *ex vivo* but not *in vivo* in the case of ebolavirus i

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Antivira



Articles

## Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis

Mandeep R Mehra, Sapan S Desai, Frank Ruschitzka, Amit N Patel

### Summary

**Background** Hydroxychloroquine or chloroquine, often in combination with a second-generation m ide, are b widely used for treatment of COVID-19, despite no conclusive evidence of their benefit. Although verall e who used for approved indications such as autoimmune disease or malaria, the safety and ben f th treatment regimens are poorly evaluated in COVID-19.

**Methods** We did a multinational registry analysis of the use of hydroxychloroquine oroquine wi thout a macrolide for treatment of COVID-19. The registry comprised data from 671 hosp s in ontinents. We included patients hospitalised between Dec 20, 2019, and April 14, 2020, with a positive laboratory for SARS-CoV-2. Patients who received one of the treatments of interest within 48 h of diagn included in f four treatment groups (chloroquine alone, chloroquine with a macrolide, hydroxychlor ine alone, or hydroxychloroquine with a macrolide), and patients who received none of these treatments formed control g Patients for whom one of the treatments of interest was initiated more than 48 h after diagnosis o le they w on mechanical ventilation, as well as patients who received remdesivir, were excluded. The main outc of int t were in-hospital mortality and the occurrence of de-novo ventricular arrhythmias ( tained o ed ventricular tachycardia or ventricular fibrillation).

**Findings** 96 032 patients (mean age 53·8 years, 46·3% women) OVID-19 were hospitalised during the study period and met the inclusion criteria. Of the patie were in the treatment groups (1868 received chloroquine, 3783 received chloroquine with macro 3016 ived hydroxychloroquine, and 6221 received hydroxychloroquine with a macrolide) and pati in the control group. 10 698 (11·1%) patients died in hospital. After controlling for multiple ( ou ors (p sex, race or ethnicity, body-mass index, underlying cardiovascular disease and its risk fac diabetes derlying lung disease, smoking, immunosuppressed condition, and baseline disease severity), w mpared wi ortality in the control group (9·3%), hydroxychloroquine (18·0%; hazard ratio 1·335, 95% 1·2 457), hydr ychloroquine with a macrolide (23·8%; 1·447, 1·368–1·531), chloroquine (16·4%; 1·365, 18–1·531), chloroquine with a macrolide (22·2%; 1·368, 1·273–1·469) were each independently associated an increased of in-hospital mortality. Compared with the control group (0·3%), hydroxychloroquine (0 2·36 935–2·906), hydroxychloroquine with a macrolide (8·1%; 5·106, 4·106–5·983), chloroquine (4·3%, 4·596), and chloroquine with a macrolide (6·5%; 4·011, 3·344–4·812) were independently associate an inc ed risk of de-novo ventricular arrhythmia during hospitalisation.

**Interpretat** we unabl nfirm a benefit of hydroxychloroquine or chloroquine, when used alone or with a macro on in pital outcomes for COVID-19. Each of these drug regimens was associated with decreased in-hospit reased frequency of ventricular arrhythmias when used for treatment of COVID-19.

**Funding** William rey Distinguished Chair in Advanced Cardiovascular Medicine at Brigham and Women's Hospital.



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### Introduction

The absence of an effective treatment against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has led clinicians to redirect drugs that are known to be effective for other medical conditions to the treatment of COVID-19. Key among these repurposed therapeutic agents are the antimalarial drug chloroquine and its analogue hydroxychloroquine, which is used for the treatment of autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis.[1] These drugs have been shown in laboratory conditions to have antiviral properties as well as immunomodulatory effects.[2–4] However, the use of this class of drugs for COVID-19 is based on a small number of anecdotal experiences that have shown variable responses in uncontrolled observational analyses, and small, open-label, randomised trials that have largely been inconclusive.[5,6] The combination of hydroxychloroquine with a second-generation macrolide, such as azithromycin (or clarithromycin), has also been advocated,



RETRACTED

Comment

## Retraction—Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis

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After publication of our *Lancet* Article,[1] several concerns were raised with respect to the veracity of the data and analyses conducted by Surgisphere Corporation and its founder and our co-author, Sapan Desai, in our publication. We launched an independent third-party peer review of Surgisphere with the consent of Sapan Desai to evaluate the origination of the database elements, to confirm the completeness of the database, and to replicate the analyses presented in the paper.

Our independent peer reviewers informed us that Surgisphere would not transfer the full dataset, client contracts, and the full ISO audit report to their servers for analysis as such transfer would violate client agreements and confidentiality requirements. As such, our reviewers were not able to conduct an independent and private peer review and therefore notified us of their withdrawal from the peer-review process.

We always aspire to perform our research in accordance with the highest ethical and professional guidelines. We can never forget the responsibility we have as researchers to scrupulously ensure that we rely on data sources that adhere to our high standards. Based on this development, we can no longer vouch for the veracity of the primary data sources. Due to this unfortunate development, the authors request that the paper be retracted.

We all entered this collaboration to contribute in good faith and at a time of great need during the COVID-19 pandemic. We deeply apologise to you, the editors, and the journal readership for any embarrassment or inconvenience that this may have caused.

MRM reports personal fees from Abbott, Medtronic, Janssen, Roivant, Triple Gene, Mesoblast, Baim Institute for Clinical Research, Portola, Bayer, NupulseCV, FineHeart, and Leviticus. FR has been paid for time spent as a committee member for clinical trials, advisory boards, other forms of consulting, and lectures or presentations; these payments were made directly to the University of Zurich and no personal payments were received in relation to these trials or other activities since 2018. Before 2018 FR reports grants and personal fees from SJM/Abbott, grants and personal fees from Servier, personal fees from Zoll, personal fees from Astra Zeneca, personal fees from Sanofi, grants and personal fees from Novartis, personal fees from Amgen, personal fees from BMS, personal fees from Pfizer, personal fees from Fresenius, personal fees from Vifor, personal fees from Roche, grants and personal fees from Bayer, personal fees from Cardiorentis, personal fees from Boehringer Ingelheim, other from Heartware, and grants from Mars. ANP declares no competing interests.

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1 Mehra MR, Desai SS, Ruschitzka F, Patel AN. Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. *Lancet* 2020; published online May 22. https://doi.org/10.1016/S0140-6736(20)31180-6.

Letter

**Breakthrough: efficacy in treat clinical studies**

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SUMMARY The coronavir to discover d treatment of n associated pne to be included of Pneumonia Republic of C

Keywords COVID-19, S

The coronavirus disease 20 emerged in December 201 with cases now confirmed i of February 16, 2020, the v infections and 1,770 deaths in infections in Japan (1). A grea made to find effective drugs aga On February 17, 2020, the Sta a news briefing indicating tha an old drug for treatment of n marked efficacy and accep COVID-19 associated pneumo trials conducted in China (3).

In the early *in vitro* studie to block COVID-19 infect concentration, with a ha concentration ($EC_{90}$) of 1.13 concentration ($CC_{50}$) greater th of subsequent clinical trials ChiCTR2000029935, C ChiCTR2000029898, C ChiCTR2000029837, C ChiCTR2000029803, C ChiCTR2000029761, C ChiCTR2000029740, C ChiCTR2000029559, and Ch been quickly conducted in C and safety of chloroquine or h treatment of COVID-19 assoc

Chloroquine is a cheap and safe drug that has been used

Microbial Pathogenesis



Available online at www.sciencedirect.com

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KeAi CHINESE ROOTS GLOBAL IMPACT

Chronic Diseases and Translational Medicine xxx (xxxx) xxx

Editorial

# Interpretation of the 7th edition of the "diagnos guidelines of coronavirus disease 2019 in Chin challenges

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Available online ■ ■ ■

*Keywords:* SARS-CoV-2; COVID-19; Coronavirus disease; Diagnosis and treatment

Since the first patient infected with the novel coronavirus (SARS-CoV-2) was identified in December 2019, the cumulative number of confirmed cases of coronavirus disease 2019 (COVID-19) has exceeded 2,100,000 and has resulted in more than 140,000 deaths globally, as of April 17, 2020. The progression of the epidemic can be divided into two phases. The first phase, which started in December 2019 and ended in February 2020, primarily involved Chinese mainland, which battled the epidemic. The second phase, from February 2020 until now, involves countries other than China that have become the primary battlefields for the virus, whereas the epidemic in Chinese mainland has been largely contained. A review of past experiences and lessons learned suggests that the 1st Trial Edition of the "Novel Coronavirus Pneumonia (COVID-19) Diagnosis and Treatment Guidelines in China", which was released as early as January 23, 2020, largely owing to the Chinese government's prompt response and assemblage of experienced experts from the National Health Commission, pl diagnoses and treatmen over a month, six more been published, incorp back and research progr the 7th edition.[1,2] Com tions, the 7th edition concepts but mainly fo updates regarding trans festations in children, criteria, exclusion crit most importantly, clinic of severely and critica refinement of follow-up addition to the successi nosis and treatment gu COVID-19 cases, some also issued their own views and addresses s pertaining to COVID-1

**Pathological changes COVID-19**

For the first time, on developments, the 7th

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nucleic acid detection, peripheral blood IgM and IgG tests are highly useful for the diagnosis of COVID-19, especially in evaluating the therapeutic effect of plasma therapy and the status of the patient's autoimmune function.

**Clinical warning signs of severe and critical illness**

The early prediction and evaluation of disease severity are extremely important for patient prognosis. However, because COVID-19 is a novel disease, clinical experience summaries can only be created instep with the treatment process. Clinical predictive markers used to guide treatment can only be promptly established by reviewing successful treatment outcomes and data accumulated from past experiences. Compared with the previous versions, the 7th edition guidelines have information regarding clinical warning signs for severe and critical cases. For adults, these include the following: progressive reduction of peripheral blood lymphocyte levels, progressive increase in peripheral inflammatory cytokine levels, such as interleukin (IL)-6 and C-reactive protein (CRP), progressive increase in lactate levels, and rapid progression of lung lesions in the short term.[2] Previous studies have reported that 80% of patients diagnosed with COVID-19 experience mild-to-moderate symptoms. However, some patients can suddenly deteriorate and rapidly progress to a severe or critical status, which consequently increases the mortality rate.[11–13] In contrast, the establishment of clinical warning signs enables prompt identification of these patients so that their treatment and care can be prioritized and delivered in a timely manner to reduce mortality. However, whether the implementation of these indicators can play a role as an early indication of disease severity requires further clinical verification.

**Glucocorticoid therapy**

The role of corticosteroid treatments remains controversial. Although no changes associated with this topic were made in the 7th edition guidelines, in the "Diagnosis and Treatment Guidelines for Severe and Critical COVID-19 Cases (Trial 2nd Edition)", recommendations regarding glucocorticoid therapy included: "As there is currently no clinical evidence of glucocorticoid therapy improving the prognosis of COVID-19 patients, it is not recommended for routine use. For patients exhibiting progressive deterioration in oxygenation, rapid radiological progression, and high levels of cytokine storms, short-term administration of methylprednisolone at a dose of 40 mg every 12 h for a total of 5 days can be considered. And before administration, contraindications to glucocorticoid therapy should be confirmed".

In addition, the Chinese military and local government units have published consensus statements or instructions that have cautiously recommended short-term administration of a certain dose of glucocorticoids in patients with early-stage COVID-19 whose condition is rapidly deteriorating.[3–5] This is further supported by our data from COVID-19 patients in Beijing, China, who received glucocorticoids, which found that glucocorticoid administration was an independent risk factor associated with the development of acid-base disorder. We believe that, despite having immunosuppressive effects, glucocorticoids can inhibit the "cytokine storm". It can also induce other problems, such as susceptibility to secondary infections, disturbance of homeostasis, and prolonged virus shedding. Therefore, it is essential to individualize the administration of glucocorticoids. Based on these data, we recommend that glucocorticoid therapy can be implemented if the disease is in its early stage (within 10 days of onset), progressing rapidly (rapid disease deterioration within 24 h as well as a substantial increase in exudative pulmonary lesions), accompanied by a severe cytokine storm (IL-6/CRP values > 10 times the normal value), and the patient does not exhibit any obvious cellular immunosuppression (absolute lymphocyte count of $\geq 0.6 \times 10^9$/L). The drug should be administered at an appropriate dosage (medium dose of 40–160 mg/day) for a short-term course (usually 5 days and no more than 7–10 days).

**Treatment of severe and critical cases**

Due to the accumulation of clinical experience, treatment recommendations for severely and critically ill patients have been significantly improved and refined in the 7th edition guidelines, providing supplementary information for all treatment sections. These include emphasizing the importance of lung-protective ventilation, defining indications of extracorporeal membrane oxygenation and continuous renal replacement therapy in detail, as well as close monitoring of hemodynamic data. In terms of new treatment methods, in addition to the provision and refinement of specific indications for convalescent plasma and tocilizumab therapy, the 7th edition guidelines also include relevant recommendations and suggestions regarding the treatment of children and pregnant women.[5]

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Therapies

# xychloroquine, tonavir and chloroquine in diac adverse drug reactions Pharmacovigilance Centers

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cepted 5 May 2020

s an unprecedented challenge for physicians and scientists. Several sed with not much evidence of their efficacy such as hydroxychloro- inavir-ritonavir. Yet, the cardiac safety of these drugs in COVID-19 are known to foster cardiac adverse ADRs, notably QTc interval ecardiogram and its arrhythmogenic consequences.
th, 2020, the French Pharmacovigilance Network directed all cardiac ociated with "off-label" use of hydroxychloroquine, azithromycin COVID-19 to the Nice Regional Center of Pharmacovigilance. Each covigilance first assessed causality of drugs. We performed a specific iverse drug reactions amidst an array of risk factors, reassessed the imated their incidence in coronavirus disease 2019.



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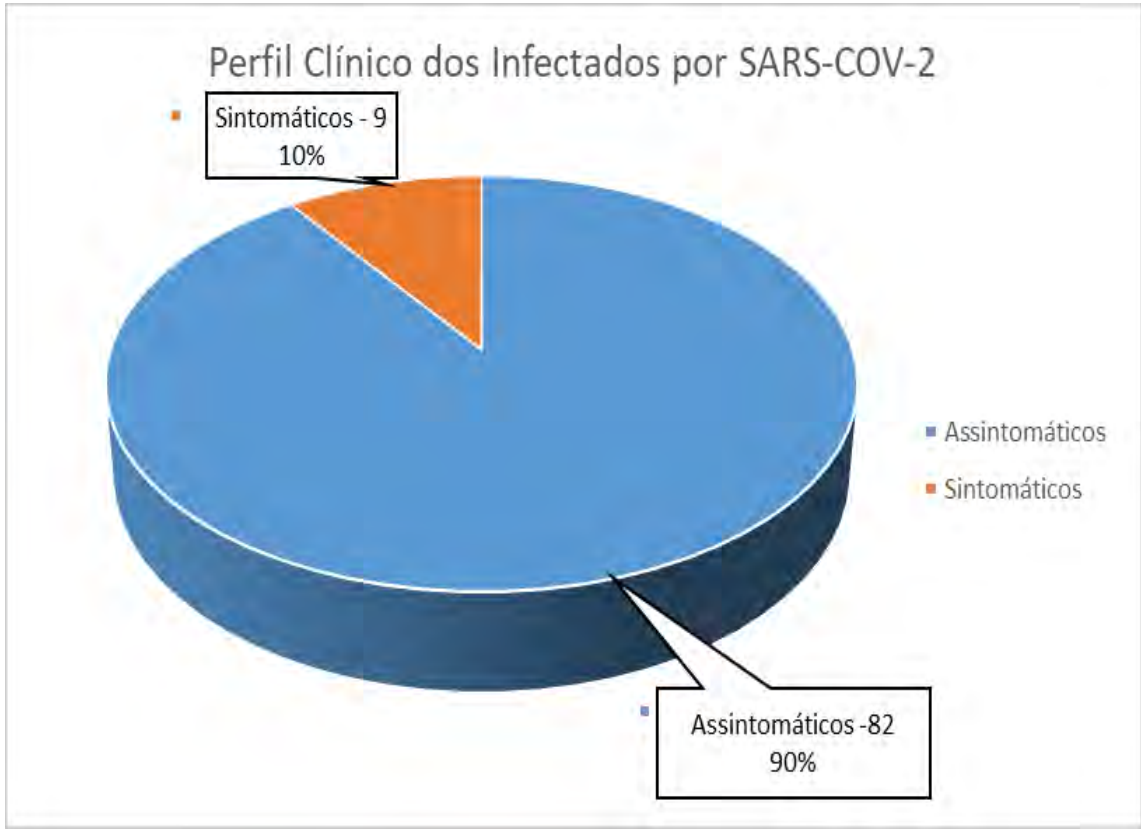
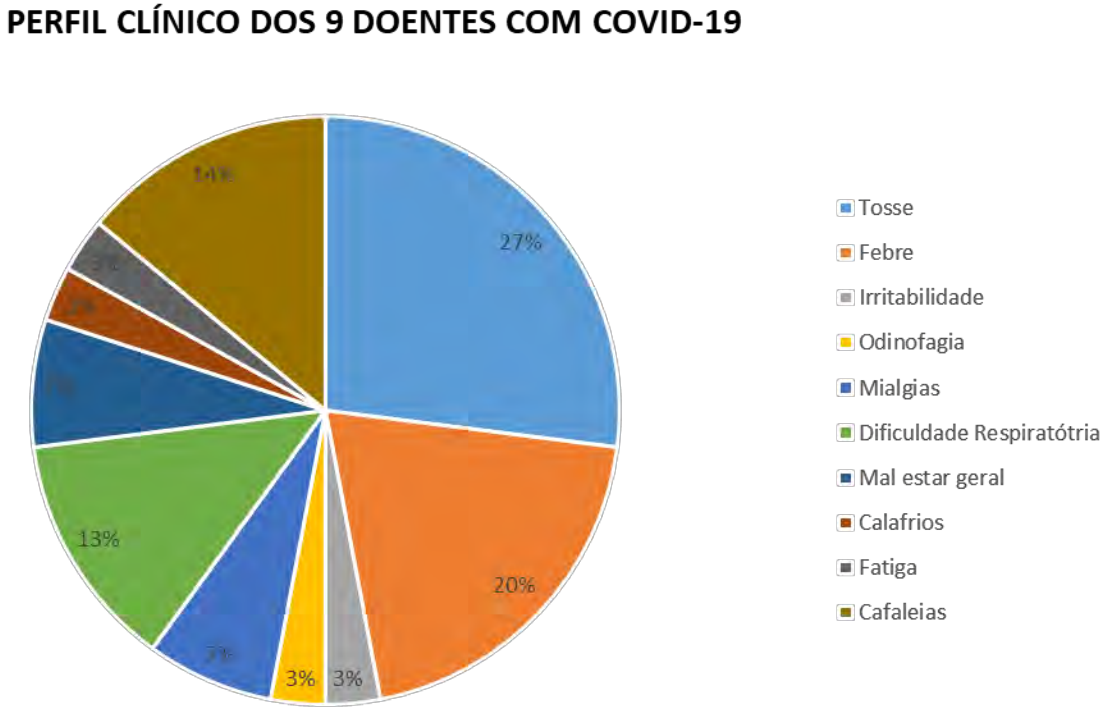
# Actualmente ….




Fonte: Relatório, DNSP de 1-7 Junho,2020

Actualmente.....

# Qual a estratégia terapêutica

**Assintomáticos**

- Comprovada ausência de alterações clínicas, laboratoriais e imagiológicas.
- Vigilância diária, isolamento institucional /domiciliar (MINSA).
- Sem tratamento farmacológico.
- Apoio Psicológico.

**Sintomáticos Leves e Moderados**

- Avaliação diária das alterações clínicas, laboratoriais, imagiológicas e controlo da progressão dos sintomas e sinais de complicações.
- Tratamento sintomático, antibioterapia se sinais de sobreinfecção.
- Avaliar antimaláricos e antivirais no contexto de ensaios clínicos.

**Doentes Graves**

- Internamento em UCI. Não se recomenda o uso de imunomodeladores
- Ceftriaxona 2g/dia (ou 1 g de 12/12 h) EV ou Amoxicilina/ácido clavulânico 2,2 g 8/8 h EV
- + Azitromicina 500mg/dia EV ou Claritromicina 500mg 12/12 h EV.
- Avaliar o uso de antimaláricos e antivirais no contexto de ensaios clínicos.
- Avaliar o uso de corticoides em doentes com critérios de ARDS estádio II/III, em doses baixas a moderadas.

# CONCLUSÕES

As medidas tomadas de prevenção ( não farmacológicas), permitiram:

1. Diminuir o impacto da velocidade de propagação/ transmissão comunitária do vírus.
2. Reduzir o número de casos clínicos graves e óbitos
3. Modelar o comportamento individual e social, no país
4. Melhorar o nível organizacional e educativo das diferentes equipas à nível do sector.

# MUITO OBRIGADA