Handbook for the care of people with disease-COVI 19

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Introduction

In February 2020, the emergence of the epidemic COVID-19 (Corona Virus Disease 2019) in Italy and especially in Lombardy, with potential fatal outcome in a significant proportion of cases, has resulted in the need to develop tools that are supporting for clinical treatment decisions based on limited data available in the literature.

There is no recorded molecule for the treatment of infections COVI-19. However, there are ongoing trials on the use of certain antivirals that have shown efficacy of COVI-19 both in vitro and in animal models and in anecdotal testing. Above all, you can draw on the expertise resulting from the use of viral agents of viruses belonging to the same family betacoronavirus, specifically the virus responsible for SARS and MERS.

The emergency in which there is the scientific community in addressing the epidemic COVID-19 provides the rationale for the use of antiviral despite scientific evidence is still preliminary.

Lethality and comorbidity COVID-19

The center for the control and prevention of diseases Chinese (China CDC) recently released the most extensive case of COVID-19, updated to 11 February 2020 (1), complementing other more limited reports from the city of Wuhan in China (2, 3). From what is reported in this descriptive analysis, they were 44 672 confirmed cases, of which the majority is included in the age group between 30 and 79 years (87%), while only a minority is placed in the extreme age groups (1% between 1-9 years and 3% ≥80 years). The overall fatality rate was 2.3% (1,023 deaths out of 44,672 confirmed cases). Among the factors determining the risk of death should be noted:

- **The age:** the case fatality rate rises to '8% in patients between 70-79 years and can reach to 14.8% in those aged ≥ 80 years.
- The presence of **comorbidities:** lethality rises to 10.5% in patients with cardiovascular diseases, 7.3% in diabetics, 6.3% of subjects with chronic respiratory diseases, 6% in hypertensives and finally 5.6% in cancer patients.
- The severity of the clinical presentation: 49% mortality in critically ill patients defined.

Even in a descriptive study of the clinical and epidemiological features of 41 patients with COVID-19, the prognostic importance of the presence of associated comorbidities is signaled (3). Of the total of patients (n = 41), 8 (20%) were diabetic, 6 (15%) were hypertensive and 6 (15%) had cardiovascular disease. Among these, 13 patients (32%) have been conducted in ICU for ventilatory support necessity for hypoxemia or respiratory failure.

To date, however, there remain uncertainties about the fatality rate of infection (4).
Overall, the lessons learned from the epidemic of SARS in 2003 have appeared useful to address the epidemic being COVID-19 (5).

Support measures

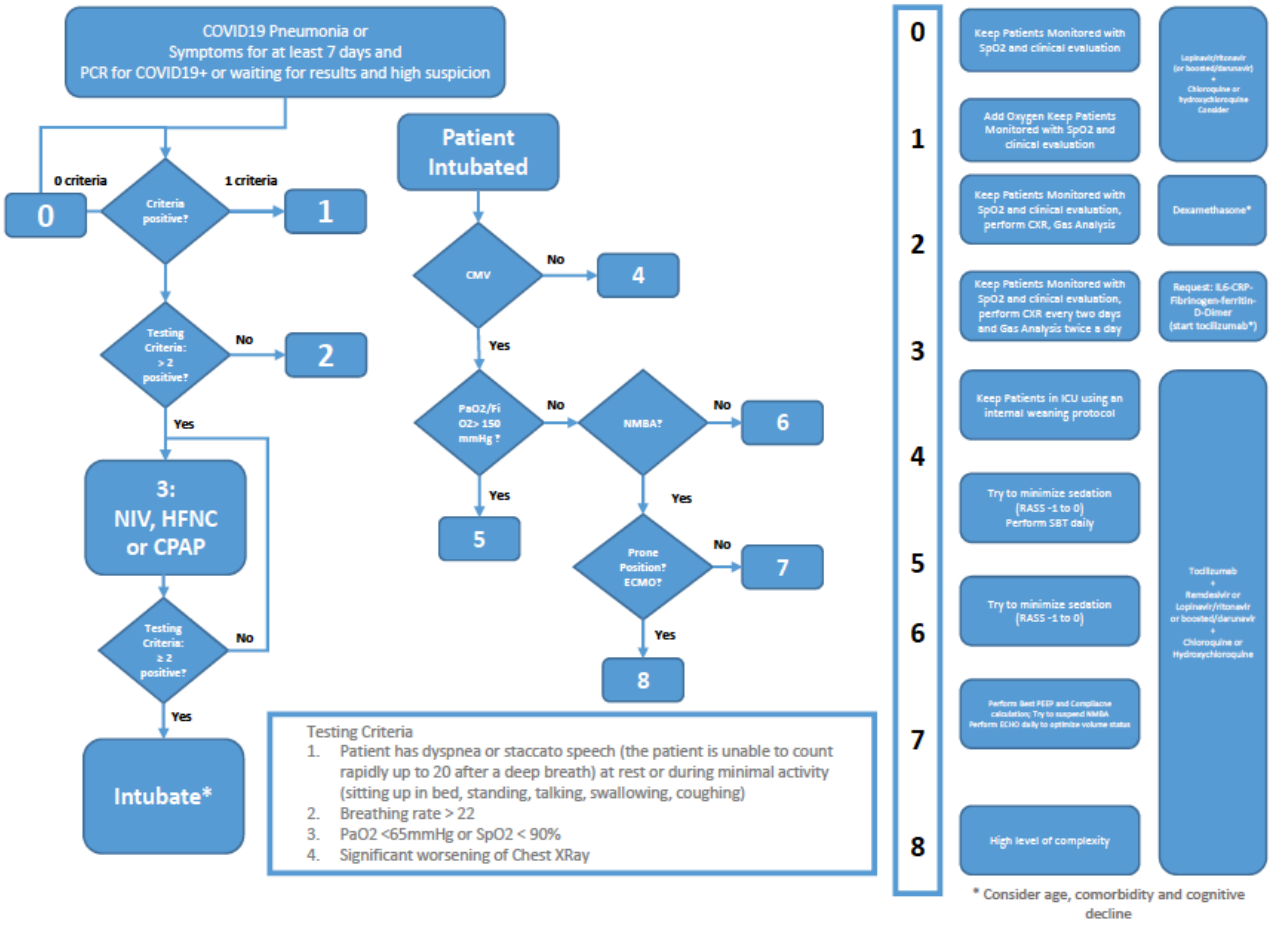
Generally, steroid therapy does not seem to add benefits in terms of clinical outcome in the treatment of COVID-19. Conversely, steroid therapy may slow the clearance of the virus (6).

However, in patients **ARDS confirmed,** but NOT with infections COVI-19, a dexamethasone benefit was quite recently described low dose and for a limited period of time (10 days), the significant reduction in mortality (7). Although this is an indirect evidence, it seems reasonable to consider the use of dexamethasone in patients with ARDS exclusively confirmed or advised intensivistica.

There is strong evidence that the use of NIV in the treatment of pneumonia caused by COVID-19 is associated with a worse outcome. On this basis, the WHO recommends that, where possible, to avoid the use of NIV and instead adopt standards that provide for early intubation. In case of necessity of use of NIV, this must be used within in an intensive care unit (8).

At the expansion of the epidemic light, it has occurred in the last period a growing shortage of beds in intensive therapy that has resulted in the need for certain types of treatment should be able to run outside of these operational units. With regard to this the Working Group advocates the use of non-invasive ventilation even outside the intensive care units. Compared to using the steroid (dexamethasone), the working group is expressed, cautiously, about the possibility of dexamethasone use even outside of intensive care units in patients without ARDS that are oxygen with clinical signs of respiratory failure worsening (score 2) or in patients who require non-invasive ventilation (score 3).

- in which the phase of high viral load can be considered finished (eg. afebrile from> 72h and / or after at least 7 days after the onset of symptoms)
- can be clinically excluded that both act in a bacterial superinfection
- only in the course of worsening of gas exchange and / or significant worsening chest X-ray (increase in compactness and extension of infiltrators). Therefore the working group, in collaboration with resuscitators / intensivists proposes the following criteria for patient stratification. **Brescia-COVID respiratory severity scales (BCRSS)**



Indication in early antiviral treatment

Some studies have shown that the earliest possible start of antiviral therapy (either LPV / r than with remdesivir) reduces serious complications of the disease (especially acute respiratory failure) (6). The treatment is indicated in patients with virological ascertained diagnosis of infection from COVI-19:

- with mild symptoms but with the presence of co-morbidities or increased mortality risk (see above);
- with clinical manifestations of moderate or severe disease.

The working group is in favor of a start as early as possible antiviral therapy. In case of delay reporting of buffer for COVI-19 but with suggestive clinical picture (interstitial pneumonia) it is reasonable to start the antiviral treatment with the maximum earliness even without the report of the buffer (eg. Directly during the patient's waiting in the ER).

Chloroquine Drug treatment

Clinical studies have shown activity in vitro and in animal models of chloroquine phosphate as antiviral against the SARS virus (9, 10) and avian influenza (11). It appears that chloroquine can exert its antiviral efficacy by increasing the pH endosomal fusion required for the virus / host cell; Moreover chloroquine appears to interfere with the glycosylation of VOC SARS cellular receptors 10. Chloroquine has also immunomodulatory activities, which could boost the anti-viral activity in vivo. The drug has a good penetration into the tissue even after oral administration at a dosage of 500 mg.

In February 2020 a panel of experts in China summed up the use of chloroquine results in the acute treatment of COVID-19, suggesting that the use of the drug is associated to the improvement of the clinical success rate, the reduction of ' hospitalization and improving patient outcome. The Panel recommends the use of the drug at a dose of **500 mg BID for 10 days (** 12). Alternatively you can use, if it were not available chloroquine, **hydroxychloroquine 200 mg BID.**

The working group is expressed in against the possible use of chloroquine / hydroxychloroquine in prophylaxis for COVID-19. At present there is no evidence of efficacy of this drug in the prevention of disease COVID-19; Therefore, this strategy is not recommended.

Lopinavir / ritonavir (LPV / R).

Lopinavir is a known antiretroviral second generation which inhibits the viral protease of HIV. In combination with ritonavir (antiviral administered at low dosage for the sole of lopinavir enhancer effect) gave significant results in the reduction of morbidity and mortality in patients with HIV / AIDS. LPV / r is considered a promising treatment option for infections COVI-19, demonstrated against SARS-VOC based on the effectiveness (in combination with ribavirin) (13). The clinical evidence, however, though are rising last month, they remain limited. The clinical efficacy of LPV / r is suggested by anecdotal cases (14). In a similar manner, anecdotal cases suggest how the administration of LPV / r is able to reduce the viral load of COVI-19 very quickly (15).

Darunavir and ritonavir darunavir / cobicistat

Darunavir boosted with ritonavir or cobicistat is a third-generation antiretroviral protease that inhibits viral recommended by the Italian and International Lines Guide for HIV / AIDS treatment.

In fact, in the treatment of this infection it has shown potency in virologic suppression and tolerability greater than lopinavir / riotnavir; however, the evidence that may suggest use in COVID-19 are very limited. Nevertheless, considering that it is a drug with a very similar to that of lopinavir / ritonavir mechanism of action, it is reasonable to assume that it can exert its antiviral efficacy against nCOV-19 analogously.

E 'it was also observed a growing shortage of lopinavir / ritonavir to increase the requirements. Although scientific evidence with less than lopinavir / ritonavir, the working group is expressed positively on reasonable use of darunavir 800 mg 1 cp / day + ritonavir 100 mg 1 cp / day or darunavir / cobicistat 800/150 mg 1 cp / day as an alternative in case of shortage of lopinavir / ritonavir.

Remdesivir (GS-5734).

Remdesivir is a nucleotide analog that is incorporated into the nascent chain of viral RNA resulting in its premature termination. This mechanism is the basis of its possible effectiveness against respiratory coronavirus.

Remdesvir is active, in preclinical studies, of SARS-CoV infection and MERS-CoV coronavirus acting on the viral polymerase (17). In animal models infected with coronavirus MERS, remdesivir seems to be more effective than treatment with lopinavir / ritonavir + interferon beta 1 / b.

Recently a group of North American study demonstrated on an experimental model of MERS infection in mice that the prophylactic use of LPV / RTV-Ifnb reduces *viral load* but it has little impact on disease parameters; Moreover, the therapeutic use while improving pulmonary function did not reduce viral replication or development of severe lung disease (18). In the same study the prophylactic use is that of therapeutic remdesivir proved active both in reducing the viral load, both in improving lung function parameters (18). Another study using a model of infection by MERS-Cov in macaques confirmed the prophylactic and therapeutic activities of RDV (19). In a model *in vitro* of Vero cells infected with the strain nCoV-2019BetaCoV / Wuhan / WIV / 04/2019, both RDV that chloroquine have been shown to be able to block infection at low concentrations (20). In China are currently two ongoing clinical trials of the effectiveness of remdesivir COVID-19:

- to moderate infections COVID19 (NCT04252664 - A Phase 3 Randomized, Double-blind, Placebo-Controlled Multicenter Study to Evaluate the Efficacy and Safety of Remdesivir in Hospitalized Adult Patients with Mild and Moderate-2019 nCoV Respiratory Disease.)
- for severe infections (NCT04257656 - A Phase 3 Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of Remdesivir in Hospitalized Adult Patients with Severe Disease nCoVRespiratory-2019.)

THERAPEUTIC PROTOCOL

Patient positive for COVI-19 ***asymptomatic or mild symptoms: (fever (> 37.5 ° C), cough, cold symptoms without dyspnea), age <70 years with no risk factors (COPD, diabetes and heart disease) and RX normal chest***

Clinical observation, supportive care

Patient positive for COVI-19 ***with mild respiratory symptoms but age> 70 years and / or with risk factors (COPD, diabetes and heart disease) or symptomatic or mild symptoms (fever (> 37.5 ° C), cough, dyspnea on mild to moderate) and chest radiography with pneumonia framework:***

lopinavir / ritonavir 200/50 mg cps, 2 x 2 / day (800 mg darunavir alternatively 1 cp / day + ritonavir 100 mg 1 cp / day or darunavir / cobicistat 1 cp 800/150 mg / day), 500 mg + chloroquine , 1 x 2 / day or hydroxychloroquine cp 200 mg, 1 x 2 / day.

Duration of therapy: 5 to 20 days, with timing to be determined according to clinical evolution.

In case of ***need for oxygen therapy or rapid clinical deterioration (see "supportive measures" and COVID respiratory severity scale)*** Remdesivir request for compassionate use. At the time of its availability suspend LPV / RTV (or DRV / b) and continue with:

Remdesivir vials 150 mg period: 1 day 200 mg IV 30 minutes then 100 mg IV / day for another 9 days in combination with chloroquine 500 mg, 1 x 2 / day or hydroxychloroquine 200 mg, 1 x 2 / day (duration of therapy: from 5 to 20 days, with timing to be determined according to clinical evolution).

If the patient has BCRSS socre ³ Evaluate 2: dexamethasone 20 mg / day for 5 days and then 10 mg / day for 5 days (as indicated by intensivistica) and / or tocilizumab (see specific point p 11)

Positive Patient COVID for-19 with picture of ***severe pneumonia, ARDS or global respiratory insufficiency, hemodynamic failure, need for mechanical ventilation (invasive or not):***

Remdesivir 1 days 200 mg iv as loading dose, then 100 mg / day ev (days 2-10) + chloroquine 500 mg, 1 x 2 / day or hydroxychloroquine 200 mg x 2 via SNG (duration of therapy: from 5 to 20 days , with timing to be determined according to clinical evolution).

Until the time of availability of remdesivir undertake therapy with LPV / RTV 5 mL x 2 / day (or alternatively DRV / r oral suspension or DRV / c shattered and dispersed) via SNG + hydroxychloroquine 200 mg x 2 via SNG.

Patients ARDS: after 24 hours from the diagnosis of ARDS: dexamethasone 20 mg / day for 5 days and then 10 mg / day for 5 days (as indicated by intensivistica) and / or tocilizumab (see specific point p 11)

Drug interactions and drug shortages

The working group recommended that close attention to possible pharmacokinetic interactions, particularly of lopinavir / ritonavir with other classes of drugs. If combined with other drugs, the working group recommended to consult: http://www.covid19-druginte

In case of presence of drugs contraindicated in using lopinavir / ritonavir, the working group expressed reasonably support the use of single chloroquine / hydroxychloroquine.

The working group recommended to use the tablet formulation of lopinavir / ritonavir and possibly in patients who have difficulty in swallowing switch to the formulation in an oral suspension. The tablets of lopinavir / ritonavir can not shatter.

Alternatively, if it were not provided the oral formulation of lopinavir / ritonavir, it is commercially available in a formulation of darunavir oral suspension (200 ml) to associate with ritonavir 100 mg sachet. In case of also a shortage of darunavir in the oral suspension, the working group recalled that the tablets of darunavir and darunavir / cobicistat of can crush, disperse and administered via nose-gastric tube (21).

Supporting anti-infective therapy

The decision to add an antibiotic therapy (empirical or targeted) and / or antiviral (oseltamivir) should be made **only** in the presence of a reasonable evidence of bacterial or viral superinfection.

Access to medicines

To apply for off-label use of registered drugs (lopinavir / ritonavir with chloroquine or hydroxychloroquine) must proceed in accordance with the regulatory requirements relating to the use of off-label drugs.

it is necessary to ask the compassionate use of the drug, through the compilation of a specific form on a personal basis, the company Gilead Sciences Inc. For the use of remdesivir, being the drug is not registered in Italy. and obtaining approval for use by the Ethics Committee.

THERAPEUTIC SIMPLIFIED SCHEME

Patient Type	**clinical Presentation**	**Treatment of support is immunomodulatory**	**antiviral treatment**	**Note**
asymptomatic patient		None - Surveillance	Nobody	
Patient with mild respiratory symptoms	Fever (> 37.5 ° C), cough, cold symptoms without dyspnea	symptomatic treatment	Nobody	
- **Patient with mild respiratory symptoms but age >70 years old and / or presence of comorbidities or risk of increased mortality** - **Patient with mild respiratory symptoms and / or chest x-ray with a picture of pneumonia**	Fever (> 37.5 ° C), cough, dyspnea, mild to moderate	symptomatic treatment - O2 therapy **If the patient score BCRSS ³ 2 Evaluate: dexamethasone 20 mg / day for 5 days, then 10 mg / day for 5 days (on intensivistica indication).** and / or **Tocilizumab (you see specific paragraph pag 11)**	**Lopinavir / ritonavir 200/50 mg BID 2 cp** + **Chloroquine** 500 mg twice daily for 20 days OR **hydroxychloroquine** 200 mg BID regime alternative to Lopinavir / ritonavir: **darunavir 800 mg 1 CPQD + ritonavir 100 mg 1 cp QD or darunavir / cobicistat 800/150 mg QD** (Duration of treatment from 5 to 20 days, with a period to be determined according to clinical evolution)	in case of **need of oxygen therapy** it might be reasonable to require Remdesivir (see patient with severe symptoms)
Patient with severe symptoms	ARDS or Global respiratory insufficiency, hemodynamic decompensation,	Necessary assessment resuscitation is Transfer to intensive care. **ARDS patients: after 24 hours from the diagnosis of ARDS: dexamethasone 20 mg / day for 5 days and then 10 mg / day for 5 days (as indicated by intensivistica)** and / or **Tocilizumab (you see specific paragraph pag 11)**	**Remdesivir** (if available) loading dose on the first day of 200 mg / ev followed by a maintenance dose of 100 mg / ev / day from day 2 to day 10 + **Chloroquine or hydroxychloroquine** (See above) OR **Lopinavir / ritonavir (** see above) + **Chloroquine or hydroxychloroquine** (see above) regime alternative to Lopinavir / ritonavir: **darunavir + ritonavir or darunavir / cobicistat (see above)**	

Using tocilizumab in patients with severe infection COVID-19 Rational

In patients infected with COVI-19 with severe behavior appeared with a picture of pneumonia that can quickly escalate into respiratory failure. The elderly and immunocompromised are at higher risk to progress to a serious picture of ARDS. A recent study showed that patients who require hospitalization in intensive care have a buoyancy perturbation framework cytokine with high levels of IL-6, IL-2, IL-7, IL-10 and TNF-α. Similar changes are observed in the cytokine release syndrome (CRS) associated with the from CAR-T therapy (chimeric antigen receptor (CAR) -T cell therapy) is characterized by fever and multi-organ failure. The cytokines involved in the pathogenesis and clinical manifestations of CRS are IL-6, interferon gamma (IFN-g), tumor necrosis factor alpha (TNF-a) and IL-10 (22).

Although the immuno-inflammatory therapy is not routinely recommended in pneumonia COVID 19, in view of the CRS framework and pathological findings of pulmonary edema and hyaline membrane formation, a therapeutic approach aimed temporally and accompanied from the proper ventilatory support could be beneficial in patients with severe pneumonia who develop ARDS. RoACTEMRA is a drug that blocks the receptor for IL-6. The formulation for intravenous scored the indication for the CRS that manifests itself in the course of therapy with Car-T; given the clinical picture and cytokine in patients with severe pneumonia COVI-19, tocilizumab could have a rational to lock the SIRS caused by the virus in patients with elevated levels of IL-6. In China, the Hospital of Anhui Province,

The dosage used by Xu Xiaoling in a Chinese pilot study (Effective Treatment of Severe COVID-19 Patients with tocilizumab, in press) was 400 mg intravenously as a single dose with a possible second dose if lack of clinical response; The work shows promising results in 21 patients treated with significant reduction of IL-6 and fever with improvement in lung function.

The recommended dosage for the treatment of CRS by intravenous infusion lasting 60 minutes is equal to 8 mg / kg in patients weighing less than 30 kg or 12 mg / kg in patients weighing less than 30 kg. In the absence of clinical improvement of the signs and symptoms of CRS after the first dose, they may be administered up to 3 additional doses of tocilizumab. The interval between consecutive doses should be at least 8 hours.

Patient Selection
The working group recommends a careful selection of patients who may have access to Actemra. Therefore, the working group, in collaboration with resuscitators / intensivists proposes the **Brescia-COVID respiratory severity scales (BCRSS)** as patient stratification criterion (see also "supportive measures" on page 5).

Inclusion criteria

- Term of the initial phase of high viral load COVID-19 (eg. Afebrile from> 72h and / or after at least 7 days after the onset of symptoms)
- Worsening of respiratory exchanges such as to require support non-invasive or invasive ventilation (BCRSS score ≥3)
- Elevated levels of IL-6 (> 40 pg / ml); alternatively high levels of D-dimer and / or PCR and / or ferritin, and / or fibrinogen in progressive increase.

Exclusion criteria

- Age <18 years
- AST / ALT have values greater than 5 times the normal levels.
- Value of neutrophils below 500 cells / mmc.
- PLT value of less than 50,000 cells / mmc.
- Documented sepsis from other pathogens that are not COVID-19.
- Presence of related comorbidities, according to clinical judgment, to a poor outcome
- Complicated diverticulitis or intestinal perforation
- cutaneous infection in act (eg. dermoipodermite not controlled by antibiotic therapy)
- Anti-rejection immunosuppressive therapy

proposed therapeutic Scheme

TO. Maximum 3 infusions at a dose of 8 mg / kg body weight (maximum dose infusion 800 mg)

B. Second infusion of 8-12 hours after the first

C. If partial or incomplete clinical response, POSSIBLE third infusion at 16-24 hours distance from first infusion

After 24 hours from the last administration repeating the plasma assay of IL-6 and / or D-dimer.

The treatment must be accompanied by antiviral treatment (lopinavir / ritonavir or remdesivir + chloroquine / hydroxychloroquine) and / or steorideo (dexamethasone).

Dosages Tocilizumab in COVID-19 for body weight WEIGHT

PATIENT	ACTEMRA DOSAGE	Dose Range mg / Kg
35-45 kg	320 mg (4 fl 80 mg)	9.1 to 7.1
46-55 kg	400 mg (1 vial of 400 mg)	8,7- 7,3
56-65 kg	480 mg (1 fl 400 mg + 1 fl 80 mg)	8.6 to 7.4
66-75 kg	560 mg (1 fl 400 mg + 2 fl 80 mg)	8.5 to 7.5
76-85 kg	600 mg (1 fl 400 mg + 1 fl 200 mg)	7.9 to 7.0
> 86 kg	800 mg (2 fl 400 mg)	9.3

drug availability

Tocilizumab drug is registered in Italy in different directions, so you will have to follow the company's protocol for the use of off-label drugs recorded and signed by the patient (except in case of necessity) informed consent.

Side effects

S refers to the drug data sheet for everything that is not included in these recommendations of use.

Pregnancy

As a monoclonal antibody tocilizumab, it is a teratogenic drug. If you can observe a placental transfer from the 16 weeks of gestation, as all the IgG immunoglobulin. Therefore, the concentration of the fetal circulation at the level of the drug appears to be higher than in the maternal circulation towards the end of pregnancy.

The working group therefore recommended to consider the risks and benefits of treatment, with the understanding that the infant exposed in utero during the third trimester of pregnancy has the ability to be temporarily immunosuppressed waiting for the end clearance of maternal drug.

Therapies supporting anti-infection and reactivation of latent infections

The working group recommended to evaluate well the absence of concomitant systemic infections and possibly set a preventive antibiotic therapy scheme broad-spectrum according to clinical indications, health policies or protocols in use.

The working group, although not mend an increased risk of tuberculosis reactivation in patients with latent tuberculosis infection, and considering the need to begin treatment very quickly, recommended to perform IGRA test for tubecolosi and viral markers for the diagnosis of hepatitis occult HBV .; However, it is not considered necessary to have the results of these tests before starting treatment.

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