In the name of God

Antibiotic therapy for COVID19

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- At the end of December 2019, an outbreak of a respiratory disease affecting humans in China was reported. A few days after the outbreak was announced, the causal agent of coronavirus disease 2019 (COVID-19) was identified as severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2), a novel betacoronavirus. COVID-19 affects people of all ages, most of whom will develop mild to moderate symptoms.

- Most people with COVID-19 (80%) develop a mild or uncomplicated illness. However, some develop severe disease requiring hospitalization and oxygen support (15%) with 5% requiring admission to an ICU. For COVID-19 patients admitted to ICU, the disease can be complicated by acute respiratory disease syndrome (ARDS), sepsis and septic shock, and multi-organ failure

- For mild COVID-19 cases, patients can be provided with antipyretics for fever. The management of severe COVID-19 cases includes immediate oxygen therapy and monitoring, it may be necessary to proactively prevent complications and secondary infections
- Treatment of co-infections relies on empirical antimicrobial therapy to treat all likely pathogens causing severe acute respiratory infection (SARI) and sepsis

- In the study, published in *Clinical Infectious Diseases,* researchers looked at data on more than 1,705 hospitalized COVID-19 patients treated at 38 Michigan hospitals, found that more than half received early antibiotic therapy, with antibiotic use as high as 84% in some hospitals. But of the 1,705 patients in the study, only 3.5% were found to have a community-onset bacterial co-infection.

- A meta-analysis of 24 cohort studies of 3338 hospitalized patients with COVID-19 found that bacterial co-infection (estimated on presentation) was identified in 3.5% of patients (95% Confidence Interval (CI)0.4 to 6.7%) and secondary bacterial infection (after presentation) was identified in 14.3% of patients (95%CI 9.6 to 18.9%). The overall proportion of COVID-19 patients with bacterial infection was 6.9% (95%CI 4.3 to 9.5%).

- Bacterial infection was more common in critically-ill patients (8.1%, 95%CI 2.3 to 13.8%).
- The majority of patients with COVID-19 received antibiotics (71.9%, 95%CI 56.1 to 87.7%) which tend to be broad-spectrum agents. However, as bacterial co-infection is relatively infrequent in hospitalized patients with COVID-19, the majority of these patients may not require empiric antibiotics, particularly those without critical illness.

antibiotics

- Hydroxychloroquine (HCQ) and chloroquine are 4-aminoquinoline drugs developed in the mid-20th century for the treatment of malaria. Both drugs have been used in the treatment of autoimmune diseases because of their immunomodulatory effects on several cytokines, including IL-1 and IL-6. There is some evidence that these drugs also have antiviral properties against many different viruses, including the coronaviruses

- Interest in combinations of HCQ with azithromycin (AZ) began when investigators in a small, uncontrolled study of HCQ use for COVID-19 noticed a higher frequency of patients achieving virologic response in the six subjects who received AZ to prevent bacterial infection
- Azithromycin, widely utilized as an antibacterial agent, has also been shown to have *in vitro* antiviral activity. While the exact mechanism of antiviral activity is unknown, possibilities include inhibiting endocytosis and limiting viral replication and the induction of interferon. Macrolides have also been shown to have anti-inflammatory activity

- It has been shown that AZM has significant antiviral properties. In contrast with CQ or HCQ, its antiviral activity has been shown in vitro and/or in vivo on a large panel of viruses: Ebola, Zika, respiratory syncytial virus, infuenzae H1N1 virus, enterovirus, and rhinovirus. Its activity against respiratory syncytial virus has been demonstrated in a randomized study in infants. also reported a significant antiviral effect of AZM alone on SARS-CoV-2.

- The mechanisms of the antiviral effect of AZM support a large-spectrum antiviral activity. Azithromycin appears to decrease the virus entry into cells. In addition, it can enhance the immune response against viruses by several actions. Azithromycin up-regulates the production of type I and III interferons (especially interferon-β and interferon-λ), and genes involved in virus recognition such as MDA5 and RIG-I. These mechanisms are universally involved in the innate response against infectious agents, and potentially against SARS-CoV-2

- The immunomodulation properties of AZM are the rationale of its use against inflammatory manifestations leading to interstitial lung disease . SARS-CoV-2 has been shown to exacerbate the inflammatory response of its host. Indeed, AZM regulates and/or decreases the production of IL-1β, IL-6, IL-8, IL-10, IL-12, and IFN-α.
- Another property of AZM is its antibacterial effect, which may be most interesting to prevent or treat co-infection by bacteria and SARS-CoV-2.

- However, the hydroxychloroquine and azithromycin combination has raised major safety concerns, specifically, drug-drug interactions and cardiotoxicity, including fatal arrhythmia, particularly among infected elderly patients with underlying cardiopulmonary chronic illness . The heightened risk of cardiotoxicity among older patients is of particular concern.

- Also, patients with COVID-19 may develop infection-related cardiomyopathy (frequency is unknown) with direct and indirect cardiovascular complications, including acute myocardial injury, fulminant myocarditis (with a mortality rate up to 40 %–70 %), arrhythmias, and venous thromboembolism

- **Antiviral effects of doxycycline :** Doxycycline and other tetracycline derivatives such as minocycline exhibit anti-inflammatory effects along with in vitro antiviral activity against several RNA viruses. Use of these agents have been associated with clinical improvement, even reversal of cytokine storm in some infections caused by RNA viruses, such as dengue fever

- The mechanism of the antiviral effects of tetracycline derivatives may be secondary to transcriptional upregulation of intracellular zinc finger antiviral protein (ZAP), an encoding gene in host cells. ZAP can also bind to specific target viral mRNAs and represses the RNAs translation

- Experimental studies have used tetracycline to induce the overexpression of host ZAP, rats and monkeys cell lines (Vero cells), which contributed to inhibition of RNA viruses such as the Dengue, Ebola, Human Immunodeficiency Virus, Zika, and Influenza A viruses
- Also, in vitro studies have showed that doxycycline can repress Dengue virus infection in Vero cells through the inhibition of dengue serine protease enzymes and of viral entry

- Similarly, doxycycline controls Chikungunya virus (CHIKV) infection through the inhibition of CHIKV cysteine protease of Vero cells and showed significant reduction of CHIKV blood titer of mice
- In addition, tetracycline derivatives such as doxycycline are highly lipophilic antimicrobials that chelate zinc compounds on matrix metalloproteinases (MMPs) of mammalian cells , and an in vitro study showed that murine coronaviruses rely on MMPs for cell fusion and viral replication

- Importantly, doxycycline reduced pro-inflammatory cytokines, including IL-6 and tumor necrosis factor (TNF)-α, in patients with dengue hemorrhagic fever, and the mortality rate was lower in the doxycycline-treated group (11.2 %) than in the untreated group (20.9 %). Moreover, doxycycline was more effective than tetracycline in the reduction of these pro-inflammatory cytokines

- Recent computational methods study identified doxycycline among the drugs that could potentially be used to inhibit SARS-CoV-2 papain-like protease
- The papain-like protease PLpro is an essential coronavirus enzyme that is required for processing viral polyproteins to generate a functional replicase complex and enable viral spread

- **Fluoroquinolones** are broad spectrum synthetic antimicrobial agents, being chemical derivatives of quinoline, the prodrome of chloroquine. Interestingly, fluoroquinolones may exert antiviral actions against CMV, VZV, HSV-1, HSV-2, HCV and HIV.
- A recent study has shown that the fluoroquinolones, ciprofloxacin and moxifloxacin, may inhibit SARS-CoV-2 replication by exhibiting stronger capacity for binding to its main protease than chloroquine and nelfinavir, a protease inhibitor antiretroviral drug.

- Remarkably, fluoroquinolones have shown multiple immunomodulatory actions leading to an attenuation of the inflammatory response through the inhibition of pro-inflammatory cytokines. Noteworthy, respiratory fluoroquinolones, levofloxacin and moxifloxacin, constitute fist line therapeutic agents for the management of severe community-acquired pneumonia.

- They are characterized by advantageous pharmacokinetic properties; higher concentrations in the lungs; and an excellent safety profile comparable to other antibiotics used to treat respiratory infections, such as macrolides and b-lactams

- Based on their potential antiviral activity and immunomodulatory properties, the favorable pharmacokinetics and safety profile, we propose the use of respiratory fluoroquinolones as adjuncts in the treatment of SARS-CoV-2 associated pneumonia.
- Fluoroquinolones are active against gram-negative and gram-positive bacteria, anaerobes, mycobacteria and atypical pathogens.

- fluoroquinolones, ciprofloxacin and moxifloxacin, exert strong capacity for binding to SARS-CoV-2 main protease (Mpro), indicating that fluoroquinolones may inhibit SARS-CoV-2 replication
- Additionally, experimental studies have demonstrated that levofloxacin exerts antioxidative and NO regulatory effects in an animal model of H1N1 influenza virus induced lung injury, and significantly improves survival

- In particular, levofloxacin exhibited scavenging actions against neutrophil-derived hydroxyl radicals and suppressed NO production, leading to decreased markers of oxidative stress and NO metabolites in the lungs of H1N1 influenza virus infected animals.

- Remarkably, fluoroquinolones exhibit multiple immunomodulatory actions leading to attenuation of inflammatory response through the inhibition of pro-inflammatory cytokines such as IL-1 and TNF-a, as shown in experimental and clinical studies

antimicrobial resistance

- Few patients with COVID-19 experience a secondary bacterial infection. A recent systematic review of patients hospitalized with COVID-19 reported only 8% were reported as experiencing bacterial/fungal co-infection during hospital admission
- Based on previous studies on severe coronavirus infections, serological evidence among SARS patients indicated incidences of acute or recent Chlamydophila pneumonia (30%) or Mycoplasma pneumoniae (9%) infection, respectively.

- The potential propagation of antimicrobial resistance may also be exacerbated by increasing rates of antimicrobial prescribing and potential breakdowns in well-established stewardship programmes. For example, despite few reports of bacterial coinfection, 62% of patients with COVID-19 had received antimicrobial therapy in a recent International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) report. These prescriptions tended to be broad spectrum in nature

- the prioritized allocation of isolation rooms to COVID-19 patients, cohorting and/or management in open bays of patients colonized with carbapenemase-producing Enterobacteriaceae (CPE)/VRE /MRSA/Clostridioides difficile and the inevitable higher workload of healthcare workers may potentially lead to a greater number of hospital transmissions.

Clostridioides diffcile Infection

- The administration of antibiotics can be complicated by a number of unintended consequences, among which gastrointestinal side effects are quite common. Gastrointestinal symptoms occur in up to 25% to 50% of patients depending on the specific antimicrobial agent, patient population, and epidemiology.
- While the majority of these side effects are mild, consisting of minor antibiotic-associated diarrhea (AAD) without systemic signs of illness, some patients can develop frank colitis and severe clinical manifestations, including toxic megacolon, intestinal perforation, sepsis, and death

- Infection with *Clostridioides difcile* (formerly *Clostridium difcile*) is thought to be responsible for about 25% of all cases of AAD and is the underlying etiology in nearly all cases of severe disease and pseudomembranous colitis (PMC).

TABLE 243.1 Risks for Development of *Clostridioides difficile* Infection

Any antibiotic versus no antibiotic:
- Number of antibiotics (risk increases with number)
- Days of antibiotics (increased risk with increased days)

Type of antibiotic:
- *Highest risk:* clindamycin, fluoroquinolones, cephalosporins of second generation and higher
- *Moderate risk:* penicillins, macrolides, penicillin β-lactamase inhibitors, carbapenems, vancomycin, metronidazole
- *Lower risk:* aminoglycosides, tetracyclines, trimethoprim, sulfonamides, rifampin

Proton pump inhibitors and histamine type 2 blockers
Patient age (increased risk with increased age of the patient)
Prior hospitalization
Severity of underlying illness
Abdominal surgery
Nasogastric tube
Duration of hospitalization
Long-term care residency

guidelines

- The prevalence of acute co-infections or secondary infections coinciding with COVID-19 has been not adequately described but appears to be low , and will be based on local factors and endemic or other emerging infections. Antibiotic overuse increases the risk of emergence and transmission of multidrug-resistant bacteria. Infections with multidrug resistant bacteria are more difficult to treat, and associated with increased morbidity and mortality.

WHO

- **suspected or confirmed mild COVID-19, against the use of antibiotic therapy or prophylaxis;**
- **suspected or confirmed moderate COVID-19, that antibiotics should not be prescribed unless there is clinical suspicion of a bacterial infection;**
- **suspected or confirmed severe COVID-19, the use of empiric antimicrobials to treat all likely pathogens, based on clinical judgment, patient host factors and local epidemiology, and this should be done as soon as possible (within 1 hour of initial assessment if possible), ideally with blood cultures obtained first.**

NIH

- If bacterial pneumonia or sepsis is suspected, administer empiric antibiotic treatment, re-evaluate the patient daily, and de-escalate or stop antibiotics if there is no evidence of bacterial infection.
- In patients with severe or critical COVID-19, there is insufficient evidence for the Panel to recommend either for or against empiric broad-spectrum antimicrobial therapy in the absence of another indication.
  - If antimicrobials are initiated, the Panel recommends that their use should be reassessed daily to minimize the adverse consequences of unnecessary antimicrobial therapy **(AIII)**.

- For patients with severe disease, early and appropriate empiric antimicrobial therapy can be administered in the emergency unit and/or pre-hospital setting. Empiric antibiotic treatment should be based on the clinical diagnosis (community-acquired pneumonia, health care-associated pneumonia [if infection was acquired in health care setting] or sepsis), local epidemiology and susceptibility data, and national treatment guidelines

- Empiric antibiotic therapy should be de-escalated on the basis of microbiology results and clinical judgment. Regularly review the possibility of switching of intravenous to oral route of administration and provide targeted treatment based on microbiologic results
- Duration of empiric antibiotic treatment should be as short as possible; generally 5–7 days.

- Procalcitonin (PCT) is the precursor of the hormone calcitonin. Recently, several studies reported that elevated PCT levels are positively associated with the severity of COVID-19
- PCT has been assessed for its role in (1) shortening the duration of antibiotic therapy for bacterial infection based on serial measurements of PCT levels, and (2) avoidance of initiation of antibiotic therapy when the PCT level is low.

- In general, trials assessing PCT guided discontinuation of antibiotic therapy report significantly more antibiotic-free days (2–4 days) in the PCT arm, without a negative effect on mortality

- In community practice, primary and secondary care has rapidly shifted towards telemedicine. This is a vital step in protecting both healthcare workers and patients, but currently has limited data to support its potential to reduce or propagate suboptimal antimicrobial prescribing and therefore AMR.

Chronic infections

- It is currently unknown whether immunosuppression caused by chronic co-infections such as human immunodeficiency virus (HIV) puts persons at greater risk for severe COVID-19 disease. However, people living with HIV with advanced disease have an increased risk of opportunistic infections (notably TB) and related complications in general.

- Facility-based HIV testing services should continue and those newly diagnosed should start antiretroviral therapy as soon as possible. For people living with HIV already on treatment, continuity of antiretroviral therapy and prophylaxis for co-infections is essential, with multi-month prescribing.

Thanks for your attention