treatment of the acute patient, but also in the weaning of ICU patients, and helps free up beds. The RICU has eliminated any argument for the need to reserve ICU beds "just in case". Refusing a patient access to the ICU in order to assign the place to another patient more likely to survive is justifiable in a pandemic,[11] but even more so when the initial patient can be transferred to a RICU, where IMV can be withdrawn and replaced by NIRT under a level of monitoring and care that is superior to a conventional hospital ward.

The development of joint care protocols with the collaboration of intensive care units, internal medicine, and emergency departments, together with respiratory medicine, is essential to maximize the management of available resources. Pre-selecting patients with easy, intuitive tools, such as the FI, is indispensable for improving decision-making.

Among the many changes that will emerge after the Covid-19 pandemic, we believe that one of the most relevant will surely be the expansion of RICUs and the leadership of respiratory medicine in decision-making on borderline patients, such as the elderly, unifying selection criteria, clarifying the concept of frailty, and integrating its use into our clinical practice.

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Hydroxychloroquine and Potential Drug Interactions in Older Adults

La hidroxicloroquina y las posibles interacciones farmacológicas en ancianos

Dear Editor,

Hydroxychloroquine has in vitro activity against severe acute respiratory syndrome coronavirus (SARS-CoV), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and other coronaviruses. It is currently under investigation in clinical trials for pre-exposure or post-exposure prophylaxis of SARS-CoV-2 infection, and treatment of patients with mild, moderate, and severe coronavirus disease 2019 (COVID-19).[1] There are no currently available data from Randomized Clinical Trials to inform clinical guidance on the use, dosing, interactions, or duration of hydroxychloroquine for prophylaxis or treatment of COVID-19 infection. Recently, Gautret and cols have reported that hydroxychloroquine treatment is significantly associated with viral load reduction/disappearance in COVID-19 patients and its effect is reinforced by azithromycin (drug interaction).[2] Preliminary results have confirmed that viral positivity in respiratory secretions was significantly decreased at day 6 in hydroxychloroquine treated COVID-19 patients versus those with supportive care, supporting the current choice of hydroxychloroquine as first-line treatment.[2,3] Despite of limited studies, nowadays, hydroxychloroquine is recommended for hospitalized patients confirmed COVID-19 patients, with mild-to moderate disease, age >65 years and/or underlying end organ dysfunction (lung, heart, liver, etc.), diabetes, coronaropathy, chronic obstructive pulmonary disease, arterial hypertension or severe disease.

General guiding principles are based on these considerations, however, the therapeutic window is quite narrow (cardiotoxicity/arrhythmia), requiring caution for use at higher cumulative dosages, taking also into account that therapy will be required mostly in older patients and/or in case of severe disease. In addition, the slow elimination and the variable pharmacokinetics of hydroxychloroquine frequently lead to delayed actions and a variable clinical response. It is possible that this variability arises partly from drug-drug interactions (DDIs) and genetic differences in the capacity to metabolize hydroxychloroquine, as has been shown for many other drugs.[4]

Contradictory results of the inhibitory effect of HCQ on cytochrome-P450 isoenzyme 2D6 (CYP2D6) activity in vivo have been published in humans. Generally, all drugs metabolized by CYP2D6 may inhibit each other's metabolism. Because of the great variety of drugs metabolized by CYP2D6 (antiarrhythmics, antihypertensives, β-adrenoceptor antagonists, monoamine oxidase inhibitors, morphine derivatives, antipsychotics and antidepressants), characterization of potential interacting drugs affecting the activity of this enzyme is clinically important and can improve the safety of drug treatment.[4] On the other hand, the P-

Table 1
Main Potential Hydroxychloroquine Drug Interactions in Older Adults.

Drug	ATC	Effects*	Should not Be Coadministered	Potential Interaction: May Require Close Monitoring, Alteration of Drug Dosage or Timing of Administration	Potential Interaction Likely to Be of Weak Intensity. Additional Action/monitoring or Dosage Adjustment Is Unlikely to Be Required	Altered QT/PR	Frequency (%)
Amiodarone	C01BD01	↑	X			X	3.27
Rifampicin	J04AB02	⇓	X				3.4
Phenobarbital	N03AA02	⇓	X				17.4
Phenytoin	N03AB02	⇓	X				1.4
Carbamazepine	N03AF01	⇓	X				1.4
Digoxin	C01AA05	↑		X			1.8
Citalopram	N06AB04	↔		X		X	0.4
Dabigatran	B01AE07	↑		X			5.4
Hydroxyzine	N05BB51	↔		X		X	2.18
Nortriptyline	N06AA10	↑		X		X	0.8
Salmeterol	R03AC12	↔		X		X	0.36
Apixaban	B01AF02	↑			X		2.9

Abbreviations: ATC, Anatomical Therapeutic Chemical code.
↑potencial increased exposure of the comedication.
↓potencialdecreased exposure of the comedication.
⇑potencial increased exposure of coronavirus disease 2019 drug.
⇓potencialdecreased exposure of coronavirus disease 2019 drug.
↔ No significant effect.

glycoprotein (P-gp) transport system is an efflux transporter found most notably in gut luminal and blood-brain barrier endothelial cells. Hydroxychloroquine is an inhibitor of this transporter/pump presenting also as a possible interaction.[5]

Keeping in mind that hydroxychloroquine use is recommended in elderly patients, the number of DDIs should be monitored. Polypharmacy prevalence in elderly people is about 50% and is associated with an increased risk of DDIs, which impact on patient health and effectiveness of drugs including hydroxychloroquine.[6] In addition, combinations of hydroxychloroquine with other QT-prolonging medications can increase the risk of developing a toxic arrhythmia such as ventricular fibrillation.[7–10]

We have developed a retrospective analytical study about most common medical prescription in older adults and potential drug interactions with hydroxychloroquine. We have analyzed chronic medication data about 377 older adults recruited between October 2016 and May 2019 in the North of Spain (Soria) for previous studies.[6] Potential drug interactions with hydroxychloroquine were identified and classified according to information published by Liverpool Drug Interactions Group[11] or Drugbank database. Data were analyzed using relative (percentage) frequencies of the classes of each variable to characterize the sample studied.

We have checked forty-seven drugs and elaborated a table of most common drugs in the aforementioned population and should be monitored in the patients treated with hydroxychloroquine. Of total, we have included information about twelve DDIs (See Table 1). Following recommendations, five drugs should not be coadministered with hydroxychloroquine and seven may require close monitoring. Rifampicin, phenobarbital, phenytoin and carbamazepin could reduce the exposure of hydroxychloroquine. Anticonvulsans, carbamazepine, phenytoin, phenobarbital induce many cytochrome-P450 and glucuronyl transferase enzymes, and can reduce drastically the serum concentration of associated drugs which are substrates of the same enzymes with the attendant risk of related adverse effects.[12,13] We have only found one study about hydroxychloroquine and rifampicin interactions, a case report about a women who due to the drug interaction, suffered from toxicoderma and causing a systemic autoimmune disease due to the drug interaction.[14]

On the other hand, amiodarone coadministered with hydroxychloroquine could increase the effect of the antiarrhythmic medication. Among its adverse effects, pulmonary toxicity causing interstitial pneumonitis is the most dangerous without a causal treatment option.[15] Moreover, Miranda-Aquino reported that the long QT syndrome was present when amiodarone and hydroxychloroquine interacted.[16]

Seven consumed drugs in older adults could cause potential interactions with hydroxychloroquine which may require close monitoring, alteration of drug dosage or timing of administration. Hydroxychloroquine coadministered with digoxin, dabigatran, nortryptiline or apixaban could increase the effect of the comedication, so similar to an overdose. Dabigatran and apixaban are direct oral anticoagulants, substrates of P-gp and inhibitors of this enzyme that may increase bleeding risk. The dose of the oral anticoagulants could be reduced to compensate for the potential interaction.[17] Ido Leden and cols. observed that the digoxin concentration in plasma was reduced in spite of increased administration when hydroxychloroquine was coadministered.[18] In addition, citalopram, hydroxyzine, nortriptyline, salmeterol may require close monitoring, alteration of drug dosage or timing of administration due to their relationship with QT prolongation associated with DDIs in older adults.[19,20]

Despite of limitations, the selection criteria used to classify drugs aimed to be useful in the screening process for potential DDIs during prescribing hydroxychloroquine in older adults. There are numerous hydroxychloroquine drug interactions that are currently known and that are potential, use of these agents with other drug therapy requires consideration for patient safety. Elderly patients are considered to be at increased risk for a more frequent and more severe COVID-19 clinical course, clinicians should be especially cognizant of these potential DDIs.

In conclusion, concomitant administration of hydroxychloroquine increases the bioavailability of several drugs in older adults and could getting worse this situation. Medication errors are known to compromise patient safety. The clinical significance of the interaction of hydroxychloroquine with several drugs and as well as the potential interactions of hydroxychloroquine with other substrates of CYP2D6 would need to be evaluated.

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Repeteability of Circulating Eosinophil Measures and Inhaled Corticosteroids Effect in Bronchiectasis. A Post Hoc Analysis of a Randomized Clinical Trial

Repetibilidad de las mediciones de eosinófilos circulantes y el efecto de los corticosteroides inhalados en las bronquiectasias. Un análisis a posteriori *de un ensayo clínico aleatorizado*

Dear Editor:

Peripheral eosinophils can increase in case of allergic, parasitic, or auto-immune disorders. Absolute and relative counts of peripheral eosinophils have been proposed to prescribe drugs in asthmatic patients and to assess their effectiveness.[1] Their assessment was also suggested in individuals with chronic obstructive pulmonary disease (COPD). Eosinophils counts >300 cells/μL or >3% have been associated with a higher incidence and severity of exacerbations but with a better response to inhaled corticosteroids (ICs).[2] On the other hand, counts <100 eosinophils/μL (<2%) has been associated with poor therapeutic response to ICs and a high incidence of adverse events (e.g., pneumonia).[3]

There is very scarce literature on the role played by peripheral eosinophils in patients with bronchiectasis. It is known that bronchiectasis patients have a higher eosinophil counts in bronchial mucosa in comparison with healthy subjects and, sometimes, an eosinophilic pattern can be the predominant inflammatory cell type in the sputum.[4] Keeping into account the bactericidal activity of eosinophils,[5] the prognostic value of bronchial bacterial infection and its association with eosinophil counts,[6] and the potential immunosuppressive effect of ICs, an interaction between peripheral eosinophils and ICs treatment could be hypothesized also in bronchiectasis. Only one small study conducted by Aliberti et al. found that bronchiectasis patients treated with ICs can show a significant improvement of quality of life only when eosinophilia (at least 150 cells/L or ≥3%) is found.[7]

Usually, baseline counts of circulating eosinophils in patients with clinical stability is used to predict long-term prognosis and therapeutic response, following the demonstration of a correlation between lung tissue and circulating eosinophil counts.[8] However, peripheral eosinophils can fluctuate overtime because of their short half-life and diurnal variation (e.g., peak in the evening).[9] Therefore, before their assessment as a biomarker in large studies in bronchiectasis, it is key to evaluate their time stability, as well as the role played by ICs at different dosages. A randomized controlled trial (RCT) published in 2008 evaluated the effectiveness of ICs in patients with bronchiectasis and performed repeated measures of eosinophils at different time-points.[10]