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# **A comprehensive strategy for the early treatment of COVID-19 with azithromycin/hydroxychloroquine and/or corticosteroids: Results of a retrospective observational study in the French overseas department of Réunion Island**

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61 **Competing interests:** The authors declare that they have no competing interests.

62

63 **Keywords:** COVID-19; SARS-CoV-2; hydroxychloroquine; azithromycin; corticosteroids.

64

65 **Abbreviations**

66 **COVID-19:** coronavirus disease 2019

67 **ICU:** intensive care unit

68

## 69 **Background**

70 Reunion Island (845,000 inhabitants) is a French overseas department located in the Indian  
71 Ocean at a distance of 10,000 km from Paris. On 17 April 2020, 398 cases of COVID-19 had  
72 been reported in Reunion Island (first case detected on 11 March 2020) [1]. More than 70% of  
73 these cases were imported from Europe, which was an epicentre of the epidemic at the time.  
74 The aim of this study was to evaluate the prognosis of COVID-19 patients in Reunion Island,  
75 with a particular focus on the medical management of patients with hypoxemic pneumonia.

## 76 **Methods**

77 The present study was approved by the Ethics Committee of the French Infectious Disease  
78 Society and was declared to the Commission nationale de l'informatique et des libertés  
79 (N°2206739). This retrospective observational study was conducted from 11 March to 17  
80 April 2020 at the only hospital authorized to manage patients with COVID-19 in Reunion  
81 Island. Patients were systematically hospitalized in the following cases : pneumonia ; sepsis  
82 and comorbidities (age over 65 years, diabetes, heart disease, chronic respiratory disease,  
83 cancer, chronic kidney disease...). All patients with hypoxemic pneumonia due to COVID-19  
84 were consecutively evaluated (i.e. pneumonia requiring oxygen to achieve oxyhemoglobin  
85 saturation > 94%).

## 86 **Pharmaceutical interventions**

87 In accordance with our protocol, all patients with hypoxemic pneumonia due to COVID-19  
88 were treated with: (1) a 3<sup>rd</sup> generation cephalosporin; (2) oral hydroxychloroquine for 10 days  
89 (400 mg twice on the first day, followed by 200mg twice a day for the next 9 days) in  
90 combination with azithromycin for 5 days (500 mg on the first day, followed by 250 mg daily  
91 for the next 4 days) in the absence of contraindications and if the symptoms lasted less than  
92 10 days; and/or (3) corticosteroids, if more than 3L/min of oxygen was required 8 days after  
93 the onset of symptoms (1 mg/kg/day the first week, followed by 0.5 mg/kg/day the next 2

94 weeks). Patients were not treated by hydroxychloroquine/azithromycin if they didn't need  
95 oxygen therapy.

96

## 97 **Statistical analysis**

98 Results were expressed as total numbers (percentages) for categorical variables and as  
99 medians [25<sup>th</sup>-75<sup>th</sup> percentiles] for continuous variables. Continuous variables were compared  
100 using the nonparametric Wilcoxon-Mann-Whitney-test. Categorical variables were compared  
101 using the Fisher's exact test. A *P* value < 0.05 was considered significant. Analyses were  
102 conducted using SPSS 15.0 (SPSS Inc©, Chicago, IL, USA).

## 103 **Results**

104 Over the study period, 398 patients were tested positive for COVID-19 in Reunion Island,  
105 with 285 cases (71.6%) imported from Europe. A total of 164 patients were hospitalized, of  
106 whom 36 (22%) developed hypoxemic pneumonia. The median time from onset of symptoms  
107 to diagnosis of hypoxemic pneumonia was 5.5 [3.8-8] days.

108 Hydroxychloroquine/azithromycin treatment was initiated in 23 patients (63.9%) 8 days [6-  
109 9.5] after the onset of symptoms. Hydroxychloroquine/azithromycin treatment was initiated  
110 with a median delay of 2 [1-3] days after the diagnosis of hypoxemic pneumonia. Of these, 17  
111 were treated in a medical ward.

112 Among the 13 hospitalized patients with hypoxemic pneumonia not treated by  
113 hydroxychloroquine/azithromycin : 2 were already treated by lopinavir/ritonavir, 7 had  
114 symptoms that lasted more than 10 days and 4 had contraindications.

115 Hydroxychloroquine/azithromycin treatment was stopped on day 4 in 1 patient due to QT  
116 prolongation.

117 Corticosteroid treatment was initiated in 12 patients (33.3%) 14 days [12-15] after the onset of  
118 symptoms. Of these, 6 were treated in a medical ward and 6 in ICU. A total of 5 patients  
119 received both hydroxychloroquine/azithromycin and corticosteroids.

120 In bivariate analysis, hydroxychloroquine/azithromycin treatment was associated with a lower  
121 rate of intensive care unit (ICU) admission ( $P=0.008$ ) (**Figure 1**). The factors predictive of  
122 ICU admission with  $P<0.05$  are shown in Table 1.

123 Ten of the 36 patients with hypoxemic pneumonia were admitted to ICU. Of these, 4 patients  
124 received high-flow nasal cannula oxygen therapy (50 L/min of oxygen) and 3 received  
125 invasive mechanical ventilation. Among the 10 patients admitted in ICU, hospital lengths of  
126 stay were 25 [15-35] days in the treated patients with hydroxychloroquine/azithromycin and  
127 40 [25-55] days in the untreated patients ( $P=0.3$ ).

128 One patient under mechanical ventilation has been treated by tocilizumab. There were no  
129 deaths at follow-up (minimum 60 days). At the time of writing, 163 out of 164 hospitalized  
130 patients were discharged from hospital.

131

**132 Discussion**

133 The evolution of patients was excellent overall, as not a single death due to COVID-19 was  
134 reported in Reunion Island. It should be noted, however, that the number of COVID-19 and  
135 the number of hypoxemia pneumonia cases were relatively low on the island. Several  
136 hypotheses can be put forward to explain our results. Our results may be due to the care  
137 bundle used for the management of patients with COVID-19 in Reunion Island. The main  
138 intervention was early treatment with hydroxychloroquine/azithromycin. Indeed, following  
139 bivariate analysis, hydroxychloroquine/azithromycin treatment was associated with a lower  
140 rate of ICU admission ( $P=0.008$ ). Some studies suggest that this drug combination is  
141 associated with viral load decrease and improved prognosis when administered early [2,3]. It  
142 should be noted, however, that the hydroxychloroquine/azithromycin treatment was not  
143 associated with better outcome in some retrospective studies [4]. Likewise, the administration  
144 of corticosteroids to patients with no improvement 8 days after the onset of symptoms may  
145 have contributed to the favourable outcome of patients with COVID-19 (none of the 6  
146 patients treated with corticosteroids were hospitalized in ICU). One study has found  
147 corticosteroid treatment to be associated with decreased mortality in patients with hypoxemic  
148 pneumonia due to COVID-19 [5].

149 This study has many limitations. This was a retrospective study with a relatively small  
150 number of patients, which made it impossible to perform multivariate analyses.

151 Despite the risk profile of COVID-19 patients with severe hypoxemic pneumonia, the  
152 mortality rate of the disease in Reunion Island was 0%. This may be due to the care bundle  
153 used in our hospital (early hospitalisation, treatment with hydroxychloroquine/azithromycin  
154 and/or corticosteroids, non-invasive respiratory support, etc.).

155

156 Figure legends

157 Figure 1- Kaplan-Meier survival curves: Intensive care unit (ICU) admission between treated  
158 and untreated patients by hydroxychloroquine (HCQ)/azithromycin (AZT).

159

160

161 **Declarations**

162 **Ethics approval and consent to participate**

163 The present observational study was approved by the Ethics Committee of the French Society  
164 of Pulmonary Medicine and was declared to the Commission nationale de l'informatique et  
165 des libertés (French Data Protection Agency or CNIL MR004). **Written and verbally**  
166 **informed consent was obtained from all the patients.**

167 **Availability of data and material**

168 The dataset used in the current study are available from the corresponding author on  
169 reasonable request.

170 **Competing interest**

171 None declared.

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173 This work was internally funded.

174 **Authors' Contributions**

175 Drs. Arthur Dubernet, Kevin Larsen, Nathalie Coolen-Allou and Nicolas Allou had full access  
176 to all the study data and take responsibility for the completeness of the data and the accuracy  
177 of the analysis.

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213

In-ICU admission (%)

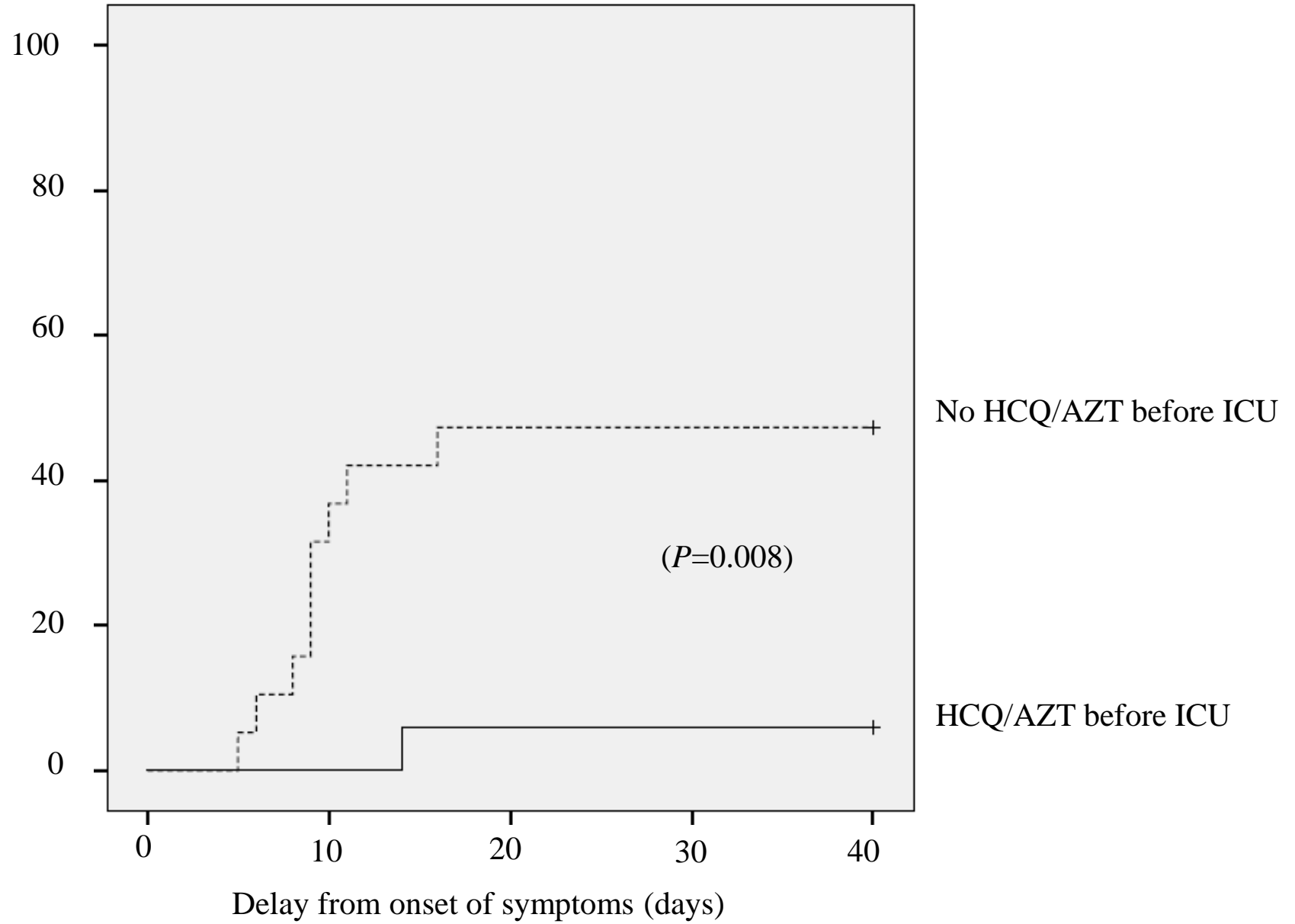


Table 1- Characteristics at hospital admission of the 36 patients with hypoxemic COVID-19 pneumonia

Characteristics	Total (n=36)	ICU admission		P-value
		No (n=26)	Yes (n=10)	
Delay between diagnosis and onset of symptoms	5.5 [2.5-7]	6 [2.5-7]	5 [4-6.8]	0.82
Oxygen therapy (L/min)	3 [1.8-4]	2 [1-3]	6 [8-4.2]	<0.0001
Male sex	25 (69.4)	15 (57.7)	10 (100)	0.02
Age (years old)	66 [56-77]	63 [57-75]	71 [59-74]	0.61
Hypertension	12 (33.3)	6 (23.1)	6 (60)	0.05
Diabetes mellitus	5 (13.9)	2 (7.7)	3 (30)	0.12
Body mass index > 30 kg/m <sup>2</sup>	6 (16.7)	4 (15.4)	2 (20)	0.43
Chronic kidney disease	3 (8.3)	0	3 (30)	0.02
Chronic obstructive pulmonary disease	10 (27.8)	7 (26.9)	3 (30)	0.58
Cardiovascular disease	8 (22.2)	6 (23.1)	2 (20)	0.41
Tobacco smoking (current or former)	11 (30.6)	7 (26.9)	4 (40)	0.69
Renin-Angiotensin System Inhibitor	8 (22.2)	5 (19.2)	3 (30)	0.66
Leucocyte (G/L)	5.6 [4.2-9.8]	5.1 [4-6.9]	9.3 [6.1-13.7]	0.02
Polynuclear neutrophils (G/L)	3.3 [2.3-6.6]	3.2 [2.5-5]	7.9 [4.1-12.3]	0.02
Lymphocytes count (G/L)	1.2 [0.85-1.49]	1.2 [0.9-1.6]	0.9 [0.5-1.2]	0.03
D-dimer level (µg/mL)	0.83 [0.51-1.33]	0.62 [0.51-1.19]	1.16 [0.88-3.92]	0.15
Prothrombin time (%)	79 [68-93]	83 [70-93]	72 [67-81]	0.36
C-reactive protein (mg/dL)	74 [18-113]	97 [17-89]	129 [76-160]	0.02
Cardiac troponin I > 10 ng/L	8 (22.2)	2 (9.1)	6 (60)	0.005
Lactate dehydrogenase (IU/L)	376 [285-429]	334 [259-428]	377 [331-407]	0.57
Glomerular filtration rate (mL/min)	87 [66-95]	88 [71-95]	69 [51-93]	0.21
Pulmonary infiltrates >50% extension on chest Computed tomography scan	11 (30.6)	4 (15.4)	7 (70)	0.003
Lopinavir/ritonavir starting before ICU	2 (5.6)	0	2 (20)	0.07
Corticosteroids starting before ICU	6 (16.7)	6 (23.1)	0	0.16
HCQ/AZT starting before ICU	17 (47.2)	16 (61.5)	1 (10)	0.008

Results are expressed at n (%) or median [25th-75th] as appropriate

Abbreviation: HCQ/AZT: hydroxychloroquine/azithromicine; ICU: intensive care unit.