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1 **Non-influenza respiratory viruses in adult patients admitted with influenza-**
2 **like illness: A three-year prospective multicenter study**

3

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48

49 **ABSTRACT**

50 **Purpose** To describe the burden, and characteristics, of influenza-like illness (ILI) associated
51 with non-influenza respiratory viruses (NIRV).

52 **Methods** We performed a prospective, multicenter, observational study of adults admitted
53 with ILI during 3 influenza seasons (2012-2015). Patients were screened for picornavirus,
54 respiratory syncytial virus (RSV), coronavirus, human metapneumovirus, adenovirus,
55 bocavirus, parainfluenza virus, and influenza, by PCR on nasopharyngeal samples. We
56 excluded patients coinfecting with NIRV and influenza.

57 **Results** Among 1421 patients enrolled, influenza virus was detected in 535 (38%), and NIRV
58 in 215 (15%), mostly picornavirus (n=61), RSV (n=53), coronavirus 229E (n=48), and human
59 metapneumovirus (n=40). In-hospital mortality was 5% (NIRV), 4% (influenza), and 5% (no
60 respiratory virus). As compared to influenza, NIRV were associated with age (median, 73
61 years vs. 68, $P=0.026$), chronic respiratory diseases (53% vs. 45%, $P=0.034$), cancer (14% vs.
62 9%, $P=0.029$), and immunosuppressive drugs (21% vs. 14%, $P=0.028$), and inversely
63 associated with diabetes (18% vs. 25%, $P=0.038$). On multivariable analysis, only chronic
64 respiratory diseases (OR 1.5 [1.1-2.0], $P=0.008$), and diabetes (OR 0.5 [0.4-0.8], $P=0.01$)
65 were associated with NIRV detection.

66 **Conclusions** NIRV are common in adults admitted with ILI during influenza seasons.
67 Outcomes are similar in patients with NIRV, influenza, or no respiratory virus.

68

69 **Keywords** Influenza-like illness; Influenza; picornavirus; respiratory syncytial virus;
70 coronavirus; human metapneumovirus

71 **Introduction**

72 Non-influenza respiratory viruses (NIRV) are responsible for a substantial proportion of
73 influenza-like illness (ILI), and pneumonia [1,2], although epidemiological data on their
74 burden are scarce. The pathogenicity of viruses recently discovered, such as human
75 metapneumovirus in 2001, or bocavirus in 2005 [3,4], remains poorly characterized. Even
76 NIRV discovered earlier (e.g. parainfluenza virus, respiratory syncytial virus (RSV), or
77 adenovirus), have attracted limited clinical interest thus far, as a result of the absence of rapid
78 tests routinely available, and the lack of vaccine or antiviral treatment with proven clinical
79 efficacy [1,2,5,6]. The advent of highly sensitive and specific point-of-care tests for
80 simultaneous detection of the main respiratory viruses is an opportunity to investigate the role
81 of NIRV in common acute respiratory febrile illness, including the risk factors for, and the
82 characteristics of, NIRV-associated ILI. These data may have important implications,
83 including i) screening and early implementation of respiratory isolation for patients with
84 NIRV to prevent nosocomial transmission; ii) identification of the major NIRV that should be
85 targeted for development of antivirals or vaccines. We aimed to determine the characteristics
86 of, and the risk factors for NIRV among adults admitted with ILI during influenza seasons in
87 France.

88

89 **Methods**

90 **Study design and population**

91 We analyzed cases of laboratory-confirmed NIRV infection during three consecutive
92 influenza seasons (2012/2013, 2013/2014, and 2014/2015), in a post-hoc analysis of patients
93 hospitalized with community-acquired ILI, and enrolled in the FLUVAC study. FLUVAC is a
94 prospective observational study of influenza vaccine efficacy conducted in six university

95 hospitals in France (Cochin Hospital, Paris; Bichat Hospital, Paris; Pontchaillou Hospital,
96 Rennes; Dupuytren Hospital, Limoges; Montpellier University Hospital; Edouard Herriot
97 Hospital, Lyon). Patients were invited to participate during periods of influenza circulation
98 (from December to March). We collected data on non-institutionalized adults (>18 years),
99 who were hospitalized for at least 24 h with ILI, with symptoms onset less than 7 days prior
100 to sampling, through an active surveillance system staffed by trained healthcare professionals.
101 ILI was defined as a combination of two criteria: (i) at least one of the following symptoms:
102 fever ($\geq 38^{\circ}\text{C}$), headache, myalgia or malaise, and (ii) at least one of the following respiratory
103 symptoms: cough, sore throat, or shortness of breath (dyspnea) [7]. The characteristics and
104 outcome of patients with influenza [8,9], and RSV [10] in this cohort have been previously
105 reported.

106 **Clinical data**

107 We collected data on demographic, chronic underlying diseases, hospital admission during
108 the previous 12 months, smoking status, hospitalization ward, and main characteristics of
109 current ILI, including date of onset, date of admission, length of hospital stay, and outcome
110 (i.e. complications, and in-hospital mortality). Data were collected on a standardized
111 questionnaire from medical records, and face-to-face interviews with patients.

112 **Virology**

113 Tests for respiratory viruses were performed in nasopharyngeal swabs from all patients by
114 means of multiplex reverse transcription-polymerase chain reaction (mRT-PCR).
115 Bronchoalveolar lavage fluid samples and tracheal aspirates ordered by the physician in
116 charge were also tested. Samples were initially tested in the virology laboratory of each
117 participating hospital by means of real-time influenza A & B PCR. All samples were then sent
118 to the French National Influenza Reference Center (CNR-Lyon) for confirmation. RNA and

119 DNA were extracted with the automated Easymag system from BioMérieux (Marcy l'Etoile,
120 France), and influenza viruses were detected with an in-house real-time RT-PCR protocol
121 [11]. Samples were also screened for a panel of NIRV: adenovirus (52 serotypes), human
122 bocaviruses 1-4, human coronaviruses (229E, NL63, OC43, HKU1), human
123 metapneumoviruses 1-4, parainfluenza viruses 1–4, picornavirus, and RSV, by real-time PCR,
124 using the Respiratory Multiwell System (MWS) r-gene® on an ABI 7300 analyzer.

125 **Ethics**

126 The FLUVAC study (clinicaltrials.gov NCT02027233) respected Good Epidemiological and
127 Clinical Practices in clinical research and the Declaration of Helsinki, and was approved by
128 institutional review board. All study participants provided informed consent for respiratory
129 viruses testing and data collection.

130 **Statistical analysis**

131 We first described the characteristics of all patients hospitalized with ILI who tested positive
132 for at least one NIRV. Results were expressed as mean and standard deviation (SD), or
133 median and interquartile range (IQR) for quantitative variables, and n (%) for qualitative
134 variables. Missing data for each variable were excluded from the denominator. Factors
135 associated with NIRV infection were analyzed by using two different comparison groups: i)
136 patients with negative tests for both NIRV and influenza; ii) patients with documented
137 influenza. The Wilcoxon rank sum test or Fisher's exact test was used, as appropriate, for
138 univariable comparisons. For multivariable analysis, we used a backward stepwise logistic
139 regression model, using NIRV test results (positive/negative) as the dependent variable.
140 Covariables tested in the multivariable model were all variables with a *P*-value <0.2 in the
141 univariable analysis. Results were expressed as odds ratios (OR) and adjusted OR (aOR) with
142 95% confidence intervals (CI). A *P*-value of 0.05 or less was considered statistically

143 significant. All analyses were performed using R software (v3, R Foundation for Statistical
144 Computing, Vienna, Austria) [12].

145

146 **Results**

147 **Characteristics of patients with influenza-like illness, and virus distribution**

148 Overall, 1452 patients hospitalized with ILI were enrolled. Median age was 70 years [IQR,
149 54-82], 780 patients were male (54%), 1155 (80%) had at least one chronic underlying
150 disease (mostly respiratory or heart diseases), 661 (46%) had been hospitalized in the
151 previous 12 months, and 644 (44%) had been vaccinated against influenza. Among the 1452
152 patients tested, 781 (54%) were positive for at least one respiratory virus. We excluded the 31
153 patients (2% of total), who had simultaneous detection of influenza virus, and NIRV. Among
154 the 1421 remaining patients, influenza virus was detected in 535 (38%), and NIRV in 215
155 patients (15%), including 7 with two NIRV. The NIRV detected were picornavirus, n=61
156 (27%), RSV, n=53 (24%), coronavirus 229E, n=48 (22%), human metapneumovirus, n=40
157 (18%), adenovirus, n=12 (5%), and bocavirus, n=8 (4%). No parainfluenza virus was
158 detected. Flow chart is presented in Figure 1. The proportion of positive tests for influenza
159 and for NIRV remained similar during the two first influenza seasons; a significant increase
160 of influenza cases was noted in 2014-2015 winter (Table 1).

161 **Characteristics of patients with non-influenza respiratory viruses (Table 2)**

162 The 215 patients with at least one NIRV detected, had a median age of 73 years [60-83], 116
163 (54%) were male, and 174 (81%) had at least one chronic underlying disease, mostly
164 respiratory (n=114, 53%), or heart diseases (n=90, 42%). Fifty-two patients (24%) were
165 current smokers, 44 (21%) were taking immunosuppressive drugs, and 4 were pregnant (27%

166 of women less than 50-year-old). Mean duration of ILI at the time of admission was 3.0 days
167 [2-4]. Main symptoms were fever (78%), cough (78%), dyspnea (74%), weakness or malaise
168 (26%), headache (22%), and myalgia (21%). Ninety-four patients developed at least one
169 complication during hospital stay, including pneumonia, n=68 (32%), and respiratory failure,
170 n=47 (22%). Median length of stay was 8 days [5-17]. ICU admission was required for 16
171 patients (11%). Eleven patients died during hospitalization (5%).

172 **Comparison of patients who tested positive for non-influenza respiratory viruses, and i)**
173 **patients with influenza; ii) patients with no respiratory virus detected (Table 2)**

174 Patients who tested positive for NIRV were older than patients with influenza (median, 73
175 years versus 68, $P=0.026$), more likely to have chronic respiratory diseases (53% versus 45%,
176 $P=0.034$), solid cancer (14% versus 9%, $P=0.029$), and to be on immunosuppressive drugs
177 (21% versus 14%, $P=0.028$), but less likely to have diabetes (18% versus 25%, $P=0.038$).
178 Fever was less common with NIRV than influenza (79% vs 90%, $P<0.001$). Outcomes were
179 similar, including complications, median length of stay, and in-hospital mortality. On
180 multivariable analysis, only chronic respiratory disease (OR 1.5 [1.1-2.0], $P=0.008$), and
181 diabetes (OR 0.5 [0.4-0.8], $P=0.01$), were significantly associated with NIRV.

182 When compared to patients with no detection of respiratory virus, patients who tested
183 positive for NIRV were more likely to have chronic respiratory diseases (53% versus 44%,
184 $P=0.024$), to be pregnant (27% versus 5%, $P=0.021$), and on immunosuppressive drugs (21%
185 versus 15%, $P=0.041$), but less likely to have diabetes (18% versus 27%, $P=0.011$). Weakness
186 was less common in patients with NIRV than in patients who tested negative for all
187 respiratory viruses (26% vs 33%, $P=0.047$). Regarding outcome, pneumonia was more
188 common in patients who tested positive for NIRV (32% vs 24%, $P=0.019$).

190 **Discussion**

191 In this prospective multicenter study performed during three influenza seasons in France, at
192 least one NIRV was found in 15% of patients admitted with ILI, the major players being
193 picornavirus (27%), RSV (24%), coronavirus 229E (22%), and human metapneumovirus
194 (18%). NIRV were more common in patients with chronic respiratory diseases, and less
195 common in patients with diabetes, whatever the comparison group (patients with influenza, or
196 patients with no respiratory virus), and these associations remained significant in
197 multivariable analysis. Although patients with NIRV were more likely to develop pneumonia
198 than patients with no respiratory virus, mortality was similar in patients with NIRV, in
199 patients with influenza, and in patients with no respiratory virus, at 4-5%.

200 Few studies have evaluated the epidemiology of NIRV in patients with symptoms
201 suggestive of acute respiratory tract infection. Tanner *et al.* performed a prospective study
202 during the 2009-2010 winter season in Central England, both in hospitals, and in general
203 practitioner offices [13]. The two main NIRV were RSV (31%), and picornavirus (24%), as in
204 our study, but the authors did not test for coronavirus, and bocavirus. Ambrosioni *et al.*
205 conducted a two year-prospective study in one referral centre in Switzerland [14], and their
206 findings were in line with ours, with two main differences: i) coronaviruses were more
207 heterogeneous, and included 229E, NL63, OC43, and HKU1 strains; ii) human
208 metapneumovirus was rare, at around 5%, with no significant difference between upper and
209 lower respiratory tract samples, and between adults younger than 65 years, and elderly.

210 Previous studies have identified age >65 years as a risk factor for NIRV, as well as
211 chronic respiratory diseases [1,6,14,15]. For the latter, experimental studies suggested that
212 NIRV may trigger acute exacerbation of chronic obstructive pulmonary diseases (COPD)

213 [16–18]. Interestingly, chronic respiratory diseases remained associated with NIRV in our
214 study, even when the comparison group was patients with influenza, and even in
215 multivariable analysis. This suggests a specific pathogenicity of NIRV in this population, that
216 may be more prone to decompensate during NIRV infection than during influenza. Treatment
217 with immunosuppressive drugs was also associated with NIRV in our study, whatever the
218 comparison group, but the association was no longer significant on multivariable analysis,
219 which suggests that confounding factors are involved. The lower prevalence of diabetes
220 mellitus in patients with NIRV, as compared to patients with influenza, and to patients with
221 no respiratory virus, in our study, was not expected. Diabetes has been associated with a
222 broad range of infectious diseases [19,20], including upper respiratory tract infection in some
223 studies [19], but not all [21]. Although the lower prevalence of diabetes in patients with NIRV
224 as compared to patients with influenza could be related to stronger association between
225 diabetes, and influenza, than between diabetes, and NIRV, we have no explanation for the
226 lower prevalence of diabetes in patients with NIRV as compared to patients with no
227 respiratory virus.

228 Our study has limitations. Firstly, we have no data to support causality between the
229 presence of NIRV in upper respiratory samples, and the ILI that required admission. Other
230 pathogens may be involved (e.g. bacteria), and NIRV may merely be a bystander infectious
231 agent with no role in the symptoms reported. The lack of a control population with no
232 respiratory symptoms is another limitation that precludes any conclusion on the pathogenicity
233 of NIRV. Secondly, we only performed systematic tests for influenza, and a selection of
234 NIRVs, although other pathogens have been associated with acute respiratory infections [22].
235 Thirdly, our study was limited to influenza seasons, in one country, and its findings may not
236 apply to other settings. However, our study has strengths, including its prospective,
237 multicentre design, and the standardization of viral tests for all adult patients admitted with

238 predefined ILI, during three consecutive influenza seasons. These strengths, and the limited
239 number of missing data, reduce the risk of potential biases. Our study adds another brick in
240 the wall by contributing to better characterization of the burden of NIRV in adult patients
241 with suspicion of acute respiratory tract infections. The identification of transmissible, NIRV,
242 in 15% of adult patients admitted with ILI would advocate for more systematic testing of
243 these patients, especially those with chronic respiratory diseases. This would allow early
244 respiratory isolation, as to prevent nosocomial transmission of NIRV, which may have severe
245 consequences on patients with chronic respiratory diseases, and patients on
246 immunosuppressive drugs.

247

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250 producers had no role in the study design, data analysis, decision to publish or preparation of
251 the manuscript

252

253 **Compliance with ethical standards**

254 **Conflict of interest** The authors declare no competing interest related to the study. O Launay
255 is an investigator for clinical trials sponsored by Janssen and other companies and received
256 travel support to attend scientific meetings from pharmaceutical companies.

257

258

259 **Appendix**

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281 **Fig. 1** Flow chart of patients hospitalized with influenza-like illness, and viruses detected in
282 respiratory sample

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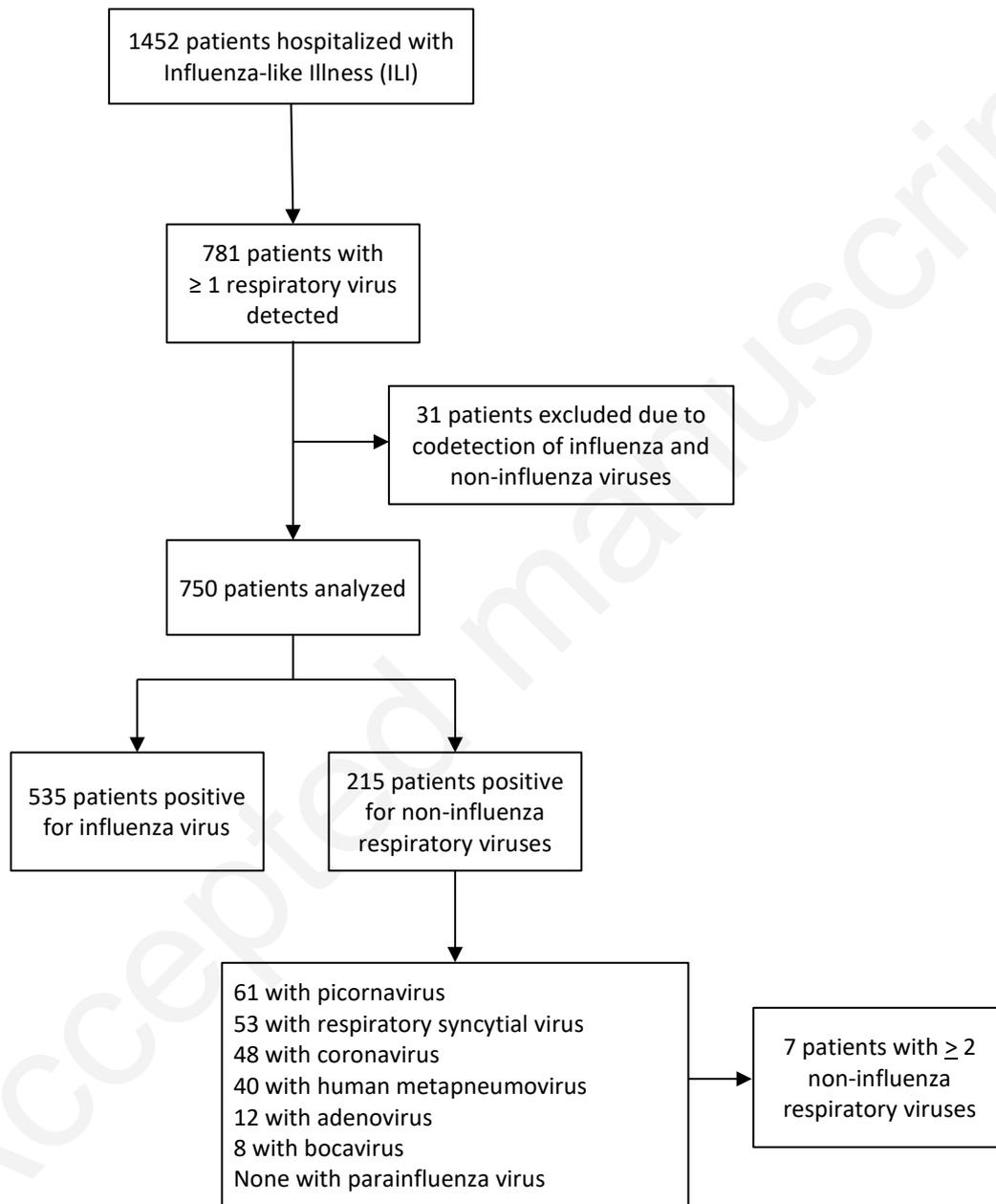
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293 **Table 1** Number and percentage of patients hospitalized with influenza-like illness who tested
 294 positive for non-influenza respiratory viruses, and for influenza, by year.

Influenza season	Non-influenza respiratory virus (NIRV), n (%)	Influenza, n (%)	Co-infection influenza + NIRV, n (%)	No respiratory virus, n (%)	Total
2012/2013	64 (14%) ^{ref}	149 (33%) ^{ref}	13 (3%) ^{ref}	222 (50%) ^{ref}	448
2013/2014	76 (19%) ^{NS}	101 (25%) ^{NS}	11 (3%) ^{NS}	219 (54%) ^{NS}	407
2014/2015	75 (13%) ^{NS}	285 (48%) ^{**}	7 (1%)*	230 (38%) ^{**}	597
Total	215 (15%)	535 (37%)	31 (2%)	671 (46%)	1452

295
 296 Chi square test was done to compare the evolution, with 2012/2013 as the reference season.
 297 ^{Ref}, reference; ^{NS}, non significant; *, $P < 0.05$; **, $P < 0.001$;
 298 NIRV, non-influenza respiratory virus

299
 300

301 **Table 2** Comparison between patients who tested positive for non-influenza respiratory virus
 302 (NIRV), patients with influenza, and patients with no respiratory virus

	NIRV n=215 (15%)	Influenza n=535 (38%)	P-value for comparison between NIRV and influenza	No respiratory virus n=671 (47%)	P-value for comparison between NIRV and no virus
Men	116 (54%)	269 (50%)	0.36	380 (57%)	0.47
Median age, years (IQR)	73 (60-83)	68 (53-81)	0.026	70 (54-83)	0.11
Age >= 65 years	141 (66%)	310 (58%)	0.053	398 (59%)	0.10
Median BMI, kg/m2 (IQR)	24.5 (21-28)	24.9 (22-28)	0.25	24,8 (21-29)	0.32
Chronic diseases	174 (81%)	423 (79%)	0.56	537 (80%)	0.77
Chronic respiratory disease	114 (53%)	237 (45%)	0.034	296 (44%)	0.024
Chronic heart disease	90 (42%)	222 (42%)	0.93	287 (43%)	0.81
Cancer	31 (14%)	48 (9%)	0.029	84 (13%)	0.48
Diabetes	39 (18%)	135 (25%)	0.038	179 (27%)	0.011
Immunosuppressive drugs	44 (21%)	75 (14%)	0.028	98 (15%)	0.041
Pregnancy	4 (27%)	8 (16%)	0.45	3 (5%)	0.021
Current smokers	52 (24%)	121 (23%)	0.38	138 (21%)	0.16
Median time from symptoms onset to admission, days (IQR)	3.0 (2-4)	3.5 (2-4)	0.46	3.0 (2-5)	0.27
Symptoms					
Fever ($\geq 38^{\circ}\text{C}$)	169 (79%)	480 (90%)	<0.001	520 (78%)	0.78
Weakness/Malaise	55 (26%)	165 (31%)	0.14	219 (33%)	0.047
Headache	47 (22%)	134 (25%)	0.33	167 (25%)	0.32
Myalgia	44 (21%)	116 (22%)	0.66	153 (23%)	0.44
Cough	167 (78%)	434 (81%)	0.28	506 (76%)	0.54
Dyspnea	160 (74%)	393 (73%)	0.78	517 (77%)	0.36
Complications	94 (44%)	248 (47%)	0.50	266 (40%)	0.28
Pneumonia	68 (32%)	152 (29%)	0.96	160 (24%)	0.019
Respiratory failure	47 (22%)	125 (23%)	0.69	135 (20%)	0.54
ARDS	20 (9%)	55 (10%)	0.78	50 (7%)	0.38
Heart failure	30 (14%)	78 (15%)	0.85	80 (12%)	0.41
ICU admission	16 (11%)	26 (10%)	1.0	39 (9%)	0.50
Median length of stay, days (IQR)	8 (5-17)	10 (4-23)	0.15	8 (3-16)	0.47
Mortality	11 (5%)	23 (4%)	0.69	32 (5%)	0.85

303 NIRV, non-influenza respiratory virus; BMI, Body mass index; IQR, Interquartile range; SD,
 304 Standard deviation, ARDS; Acute respiratory distress syndrome; ICU, intensive care unit

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