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EDITORIAL

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Rescue therapy for refractory ARDS should be offered early: yes

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Clinical vignette A previously healthy 51-year-old woman (height 165 cm, weight 60 kg) was admitted to the ICU with severe community acquired pneumonia. She required intubation and mechanical ventilation 6 h after admission. Her respiratory status declined continuously over the next few hours. Twelve hours after admission, blood gases were as follows: pH = 7.36, $PaCO_2$ = 47 mmHg, PaO_2 = 65 mmHg, HCO_3^- = 26 mmol/L on FiO_2 = 100 %, Vt set at 340 ml, PEEP at 8 cmH_2O, respiratory rate at 28/min, and plateau pressure measured at 28 cmH_2O. She was hemodynamically stable and had a normal renal function.

This patient has severe ARDS according to the Berlin definition [1]. This patient has very low respiratory system compliance (18 ml/cmH_2O) and is ventilated with a high driving pressure (20 cmH_2O). Hypoxemia is extremely severe with a high oxygenation index (43 cmH_2O/mmHg). Recent clinical studies showed that hospital mortality in patients experiencing such severe forms of ARDS ranges from 45 to 60 % [1–6].

What are the first-line options in this situation?

This patient receives only 8 cmH_2O of PEEP. While higher PEEP confers a survival advantage in severe ARDS patients [7], higher levels of PEEP in this patient very likely will further increase the plateau pressure to levels that are certainly associated with an increased risk of ventilator-induced lung injury. Inhaled nitric oxide might have improved arterial oxygenation although this intervention was not shown to improve long-term survival. On the other hand, prone positioning should be rapidly initiated for more than 16 h since a significant increase in survival [8] has been observed in patients with severe ARDS with this maneuver. This patient should also receive continuous infusion of neuromuscular blockade agents [9].

What is the rationale for applying "ultraprotective" MV in this situation?

Lung hyperinflation occurs in approximately 30 % of ARDS patients ventilated using the protective ARDSNet strategy [10]. Moreover, Hager and co-workers retrospectively analyzing data of the "ARDSNet" trial group show a linear relationship between mortality and P_{plat}—a linear relationship in the sense that the lower P_{plat}, the lower the mortality, even for P_{plat} less than 30 cmH_2O [11]. In a proof of concept study, Terragni et al. [12] demonstrated that very low tidal volume ventilation

(3.5–5 ml/kg) and lower P_{plat} (less than 25 cmH_2O) enhance lung protection as indicated by the significant attenuation of the pro-inflammatory signal observed a the pulmonary level.

Because Vt reduction to below 6 ml/kg to achieve P_{plat} less than 25 cmH_2O may induce severe hypercapnia, this "ultraprotective" MV strategy may not be possible without the recourse to extracorporeal carbon dioxide removal ($ECCO_2$-R) which only provides CO_2 removal or venovenous extracorporeal membrane oxygenation (ECMO) which achieves complete extracorporeal blood oxygenation and CO_2 removal.

Why should ECMO be initiated rapidly in this patient?

The patient's lung mechanics and blood gases should be carefully monitored during the prone positioning trial and after turning the patient back to the supine position. In the situation of major improvement of lung compliance and blood oxygenation following this trial, conventional MV should be continued until the patient can be safely extubated. Alternatively, if low respiratory system compliance and severe hypoxemia persist, venovenous ECMO should be instituted as soon as possible for the following reasons.

First, to achieve "ultraprotective" low volume and low pressure MV in this severely hypoxemic patient, ECMO should be preferred over $ECCO_2$-R. Under ECMO, Vt should be dramatically reduced to achieve P_{plat} less than 25 cmH_2O, with PEEP greater than 12 cmH_2O, since these settings were shown to be independently associated with better outcomes [4, 13].

Second, modern ECMO devices are simpler, safer, require less anticoagulation, and are associated with fewer bleeding complications and it is now possible to support patients for weeks [14].

Third, recent series and a randomized trial demonstrated better survival for patients receiving ECMO for severe ARDS [2–4, 15]. The CESAR trial [3] evaluated a strategy of transfer to a single center which had ECMO capability while the patients randomized to the control group received conventional MV. Mortality or severe disability 6 months after randomization was lower for the 90 patients randomized to the ECMO group (37 vs 53 %, $p = 0.03$). Interestingly, more than 60 % of the randomized patients suffered pneumonia and their mean PaO_2/FiO_2 (76 mmHg) was higher than that of the patient described herein. A British collaborative cohort series of pandemic influenza A (H1N1)-induced ARDS patients also showed significantly lower mortality (24 vs 51 %) after propensity matching for 80 patients transferred to ECMO referral centers [2].

Fourth, factors strongly associated with poorer outcomes in series of severe ARDS patients receiving ECMO were older age, a greater number of days of MV before ECMO, a higher number of organ failures, low pre-ECMO respiratory system compliance, absence of paralysis or prone positioning before ECMO, and immunosuppression [15, 16]. Based on these factors, predictive survival models have been developed to help clinicians select appropriate candidates for ECMO. Interestingly, according to the recently developed RESP [15] and PRESERVE [16] scoring systems, hospital mortality after ECMO initiation would be less than 20 % for the patient described above, should ECMO support be initiated within 48 h of tracheal intubation.

Lastly, a high incidence of cognitive impairment and psychiatric symptoms was demonstrated in long-term survivors of acute lung injury in the Fluid and Catheter Treatment Trial [17]. In that study, lower PaO_2 [86 (70–98) vs 71 (67–80) mmHg, $p = 0.02$] was associated with cognitive and psychiatric impairment 12 months following randomization. It can therefore be hypothesized that ECMO might improve long-term quality-of-life and cognitive function by improving blood oxygenation in severely hypoxemic ARDS patients. Indeed, patients randomized to the ECMO arm of the CESAR trial [3] or the 67 long-term survivors of the French multicenter ECMO-treated ARDS cohort [16] exhibited comparable or better of health-related quality-of-life scores than those reported by patients with less severe ARDS treated with conventional management [18].

In conclusion, a strong pathophysiological rationale and data from recent studies of ECMO for severe ARDS argue for the early initiation of ECMO in the patient described above. This strategy might decrease mortality from 45–50 % to less than 20 %, with potentially less cognitive and psychiatric impairment and improved health-related quality-of-life in long-term survivors. The currently ongoing ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial (NCT01470703) [19], an international multicenter randomized controlled trial comparing conventional MV with prone positioning to ECMO in very severe ARDS patients (PaO_2/FiO_2 less than 80 mmHg), might confirm this hypothesis.

Conflicts of interest Dr. Combes is the primary investigator of the EOLIA trial, NCT01470703, a randomized trial of VV-ECMO supported in part by MAQUET. Dr. Combes has received honoraria for lectures from MAQUET. Prof. Ranieri consulted for Hemodec, ALung, Maquet. He also lectured for Novalung. He was the PI of a Maquet supported trial on ECCO2R in patients with COPD.

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EDITORIAL

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Clinical vignette A previously healthy 51-year-old woman was admitted to the ICU with severe community acquired pneumonia. She required intubation and mechanical ventilation 6 h after admission. Her respiratory status declined continuously over the next few hours and her PaO_2/FIO_2 ratio was 65 with a PEEP of 8 cmH_2O at 12 h after admission (plateau pressure was 28 cmH_2O). She was hemodynamically stable and had normal renal function.

Despite the remarkable hypoxemia in this case of severe ARDS, there is no rush to ECMO for several reasons; each related to the fact that aspects of the patient's current ventilator and non-ventilator management should be optimized prior to consideration of ECMO.

First of all, a low-volume, low-pressure ventilation strategy should be undertaken according to the protocols of the ExPress [1] or ARDSNet ARMA [2] trials. We are not given information about the selected tidal volume (VT). However, it should be based on predicted body weight (PBW). As the patient in this case is a woman, it should be mentioned that clinicians tend to use actual body weight instead of PBW for assigning VT and therefore over-ventilate women and people who are of shorter stature [3]. PEEP should be set initially according to the protocol used (standard or high PEEP strategy) [4, 5] and is almost certainly too low in this case. Titration of PEEP may benefit the patient. Bear in mind that after raising PEEP, plateau pressure (Pplat) may increase well above 30 cmH_2O. However, should the lung be recruited by the increase in PEEP, Pplat would then decrease. Furthermore, the assessment of oxygenation response to PEEP also requires only a few minutes [6]. Is there room for Pplat greater than 30 cmH_2O due to impairment of elastic properties of the chest wall? Grasso et al. [7] were able to avoid ECMO in seven severe influenza A(H1N1)-associated ARDS patients with high chest wall elastance that allowed the PEEP to be raised in order to reach a transpulmonary pressure of 25 cmH_2O. Such measurements require the insertion of an esophageal balloon. A more common way of setting PEEP is to use a $PEEP/FIO_2$ table. Suppose FIO_2 is 0.80 in this case, PaO_2 would be 52 mmHg and hence PEEP should range from 14 to 22 cmH_2O depending on the $PEEP/FIO_2$ table [4, 5]. Even though the current concept for setting PEEP is the prevention of the cyclical opening and closing of alveoli during tidal breaths, in a patient like this, the oxygenation response to PEEP is relevant. The post hoc analysis of the trials on PEEP observed that the oxygenation response to PEEP was associated with better outcomes in ARDS patients [8]. Chiumello et al. [9] found that the $PEEP/FIO_2$ table was the only way to set lower PEEP in patients with low potential of recruitment and higher PEEP in patients with high potential of recruitment. In line with the above considerations, a recruitment maneuver should be considered in this patient [10] followed by a higher level of PEEP than prior to the procedure.

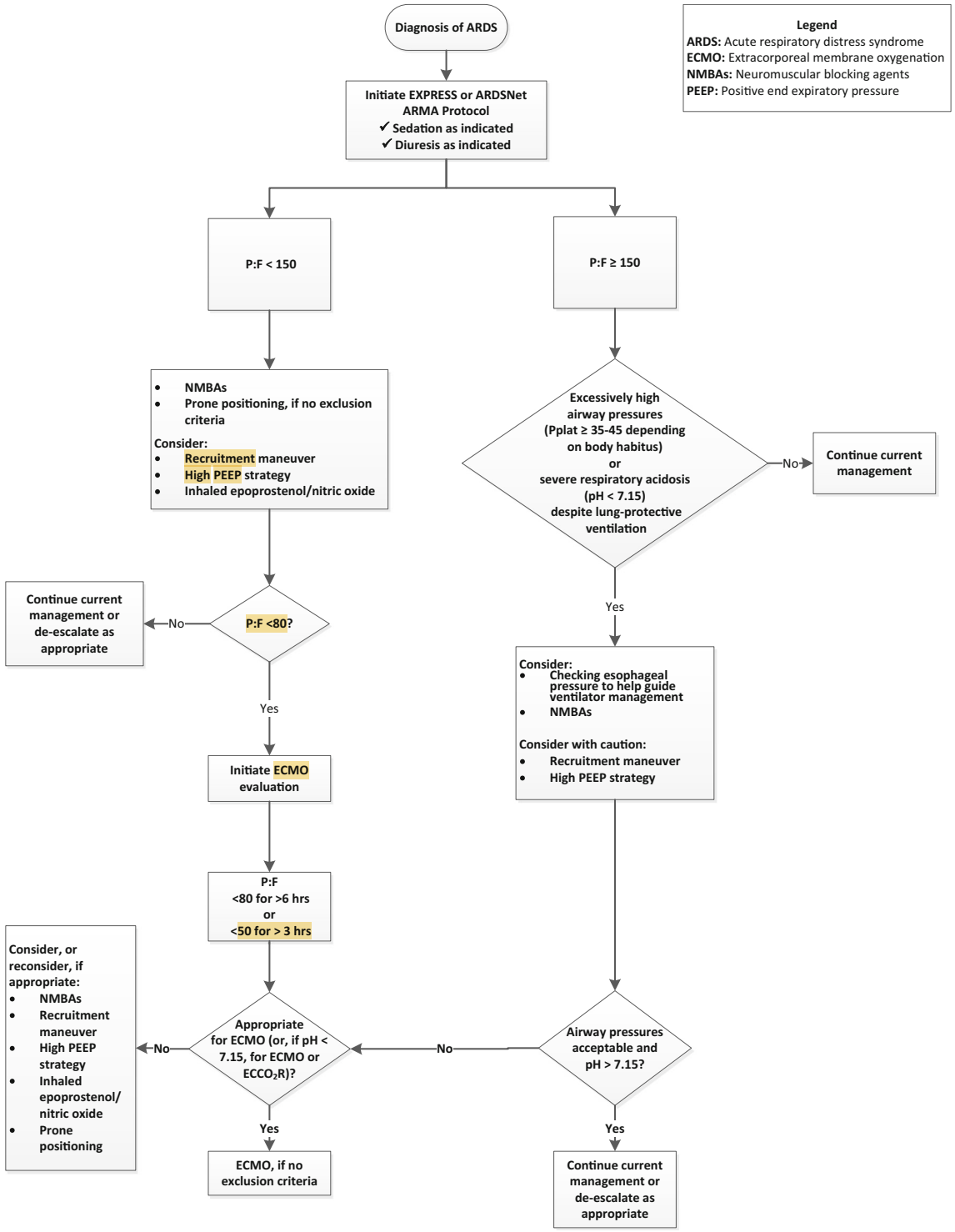

Fig. 1 Management algorithm for patients with ARDS

The second aspect of her care to optimize is sedation and neuromuscular blockade. Deep sedation should be provided to reduce oxygen consumption and improve ventilator synchrony and, once a level of deep sedation is reached, a neuromuscular blocking agent should be promptly started, ideally using cisatracurium for 48 h. With this medication, the oxygenation improves, the rate of pneumothorax is reduced, and the survival is improved [11].

The third item to consider is the fluid balance. With her normal renal function and stable hemodynamics, this patient is a good candidate for receiving early diuretics. Although a large randomized controlled trial failed to show a beneficial effect on mortality [12], a conservative fluid strategy was associated with improvement in the oxygenation index and improvements in ventilator- and ICU-free days. A separate randomized placebo-controlled trial showed that furosemide plus albumin significantly improved oxygenation in hypoproteinemic (plasma protein less than 6 g/dl) ARDS patients [13]. Should this patient be hypoproteinemic, this strategy is quite simple to improve oxygenation, and could be considered.

The fourth opportunity for optimization is in the use of prone positioning. The completion of previous steps should only require a couple of hours and, if the patient is still sufficiently hypoxemic, prone position should be instituted given that there are no known contraindications. Caution should be applied in centers that do not have extensive experience with prone positioning. In patients with ARDS and severity criteria (PaO_2/FIO_2 less than 150 mmHg with PEEP of at least 5 cmH_2O and FIO_2 of at least 0.6) a significant improvement in survival was demonstrated as compared to the supine position in the PROSEVA trial [14]. This benefit was also observed in the lowest quartile of PaO_2/FIO_2 at the time of randomization, which ranged from 45 to 87 mmHg. The current case in question is in this range. Proning should be performed in a complete prone position and for a prolonged session (16 consecutive hours or more as scheduled in PROSEVA).

The fifth item to consider would be inhaled pulmonary vasodilators: inhaled epoprostenol or inhaled nitric oxide. These medications can be used in severe hypoxemia to improve oxygenation by dilating pulmonary vascular beds in those areas of the lungs where ventilation is preserved, thereby decreasing the proportion of blood shunted through areas of poor ventilation. It can be started while the patient is still in the supine position but several studies found an additive effect of prone position and nitric oxide on oxygenation. That said, these medications do not change overall outcomes and, given that the degree of hypoxemia in this case is not immediately life-threatening, delaying the decision for ECMO in order to institute these medications may not be necessary.

Where in the course of treating this patient should we consider ECMO (Fig. 1)? In a patient without life-threatening hypoxemia, we would allow at least 6 h to decide whether or not ECMO should be undertaken. The following criteria for initiating ECMO in ARDS patients have been recently proposed [15]: PaO_2/FIO_2 ratio less than 80 despite high PEEP (15–20 cmH_2O) for at least 6 h in patients with potentially reversible respiratory failure, or hypercapnia with acidemia (pH less than 7.15) or Pplat greater than 35–45 cmH_2O, depending on the patient's body habitus. A similar strategy is being tested in a multicenter randomized controlled trial and final results are expected in the near future.

Conflicts of interest Dr. Brodie previously received research support and provided research consulting for Maquet Cardiovascular. He is on the medical advisory board of ALung Technologies and Kadence (Johnson & Johnson). All compensation for his consulting goes to Columbia University.

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EDITORIAL

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Clinical vignette A previously healthy 51-year-old woman was admitted to the intensive care unit (ICU) with severe community-acquired pneumonia. She required intubation and mechanical ventilation 6 h after admission. Her respiratory status declined continuously over the next few hours, and her PaO_2/FiO_2 ratio was 65 with a positive end-expiratory pressure (PEEP) at 8–12 h after admission (plateau pressure was 28). She was hemodynamically stable and had normal renal function.

Extracorporeal membrane oxygenation (ECMO) is an old technique which is highly dependent on development of new technologies. The concomitant publication of the CESAR trial [1] and the occurrence of the H1N1 2009–2010 pandemic [2] raised numerous questions about the place of ECMO in the symptomatic treatment of acute respiratory distress syndrome (ARDS). Schematically, ECMO should reach two objectives: to maintain adequate gas exchange when there is dramatic hypoxemia and/or profound acidosis with high degree of hypercapnia, and to preserve the lung from potential volu-, baro-, and biotrauma associated with mechanical ventilation. We should therefore consider that, for the first objective, we can wait to a certain degree to start ECMO, while for the second objective we have to be more proactive regarding ECMO. This is the challenge in 2015 while awaiting future significant technological improvements or new scientific proof of the efficacy of ECMO regarding ARDS outcome.

When considering this clinical vignette, this patient is a potential good candidate for ECMO, presenting single organ failure (the lung) with a short delay since intubation [3, 4]. At this point and regarding PEEP and plateau pressure level, we can assume that there is potential for oxygenation improvement by adjusting ventilator parameters. As this ARDS is severe, we should first paralyze this patient. After a bolus dose of a neuromuscular blocker, we have to institute continuous infusion of this drug. Immediately after, we must reassess ventilator parameters. We can increase PEEP and observe the concomitant rise in plateau pressure (if using a volume-controlled mode). The plateau pressure limit is highly dependent on the patient. If she is obese, plateau pressure of 32 cmH_2O would be within acceptable limits; otherwise, 30 cmH_2O is acceptable. However, as the cause of ARDS is community-acquired pneumonia (CAP), the distribution of lung lesions is probably heterogeneous. There is therefore a substantial risk of inefficacy of high PEEP levels related to huge differences in regional compliances. This is the reason why prone position has to be used early after adjusting PEEP level. Since the studies done by Mancebo [5], the meta-analysis of Gattinoni [6], and the PROSEVA study by Guérin [7], we know that

prone positioning can improve survival when applied early in the course of ARDS, when PaO_2/FiO_2 (P/F) ratio is lower than 150. It is therefore difficult to not consider prone positioning before implementing ECMO. Moreover, use of prone positioning has been shown to significantly reduce the need for ECMO in severe ARDS patients [7]. Just before proning the patient, it is essential to evaluate right ventricular function. The presence of right ventricular dysfunction could justify introduction of inhaled nitric oxide. However, improvement of oxygenation by itself can decrease right ventricular afterload by limiting pulmonary vasoconstriction. After turning the patient prone, PEEP level should be reevaluated [8] as the modification of repartition of lung densities can alter PEEP response. However, if after a few hours of proning, there is persistent severe hypoxemia (P/F <70–80 for centers without ECMO and needing to call a mobile unit; P/F <60–70 for ECMO centers), ECMO should be started promptly. To date, the benefit/risk ratio of ECMO treatment needs further evaluation. Therefore, attention should first be paid in this patient to elimination of any contraindication to heparin, any risk factor for intracerebral bleeding or immunosuppression. In this latter case, the prognosis of patients treated with ECMO has been shown to be poor [3, 4]. ECMO should ideally be provided with femoral–jugular cannulation at a flow of at least 60 % of the predicted cardiac output and a sweep gas flow to obtain a $PaCO_2$ compatible with pH > 7.25. No consensus exists on ventilator settings under ECMO. However, one study suggested better prognosis in patients with lower plateau pressure at day 1 after ECMO initiation [2]. Therefore, plateau pressure of 22–25 cmH_2O should be considered as acceptable, with driving pressure of 8–15 cmH_2O and resulting PEEP of 12–18 cmH_2O in order to rest the lung. As discussed above, as the cause of ARDS is CAP, the distribution of lung lesions is probably heterogeneous, and there is therefore substantial risk of inefficacy of high PEEP levels. However, the reduction of both tidal volume and driving pressure under ECMO may allow for higher PEEP levels than under conventional ventilation. Indeed, the risk of overdistension of anterior lung regions is reduced in this situation. Although the prognostic impact of prone positioning under ECMO has not been evaluated, it has been shown to further improve oxygenation [9]. While prone positioning could be insufficient in this patient to prevent ECMO requirement, it should probably be continued after initiating ECMO if performed by trained teams [9]. Criteria for prone positioning initiation and weaning in ECMO patients remain to be evaluated in future studies.

In some patients, ECMO should be considered urgently for immediate life-threatening condition. In such cases, the benefit/risk ratio is very probably in favor of ECMO although the cost/benefit ratio may be questionable. When regarding the present clinical vignette, it is likely that, in this 51-year-old, previously healthy patient, a P/F ratio of 65 mmHg is safe for a period of time sufficient to discuss the indication for ECMO with an experienced team, ideally located in a reference center and equipped with a mobile team. Indeed, ECMO treatment may be associated with better prognosis when initiated and managed by highly trained personnel [10]. The cutoff for P/F ratio and the duration of hypoxemia before ECMO initiation are still a matter of debate and are currently being explored in ongoing randomized controlled trials (RCTs).

In conclusion, ECMO may be indicated in this patient, but not at this stage, since prone positioning has not been performed, having been shown to reduce the need for ECMO in severe ARDS patients [7]. However, in this patient without contraindication and with single organ failure, use of venovenous ECMO should be considered without delay if the P/F ratio decreases below 55–60 mmHg for at least 3 h, despite a protective ventilation strategy (including use of prone positioning). ECMO should be discussed if the P/F ratio is below 80 mmHg when $FiO_2 = 1$ for more than 6 h, despite a protective ventilation strategy (involving use of prone positioning) or in case of respiratory acidosis with pH < 7.20 for over 6 h despite a protective ventilation strategy [10].

Conflicts of interest A.R. and L.P. do not have any conflicts of interest to declare regarding this manuscript.

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