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ETHICAL DILEMMAS IN THE THERAPEUTIC MANAGEMENT OF PATIENTS WITH SARS-CoV-2 INFECTION

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Abstract

The new coronavirus pandemic has brought into the light-on top of the strain it put on the medical services around the world-a variety of ethical issues in relation to how the treatment is being administered to the patients. Understanding the priority of treating COVID-19 patients, we still ask ourselves how effective these antiviral/immunomodulatory molecules are recommended by national/international protocols and which is the benefit/risk ratio in different categories of patients. To solve these dilemmas, we present the case of a 36-year-old patient, admitted to our clinic in April 2020, with mild symptomatic SARS-CoV-2 infection. Given the suggestive clinical and paraclinical elements, we recommended treatment with lopinavir/ ritonavir according to national protocol, and we explained to patient the benefits of this treatment, as well as the possible side effects. The patient refused this treatment, but later accepted an alternative therapy, hydroxychloroquine. The evolution of clinical and paraclinical parameters allowed the patient to be discharged after 19 days. This apparently simple and solvable medical case becomes complicated when the patient complained about the violation of her rights and of certain articles from deontological code. Beyond the elements of subjectivism, it is necessary an ethical approach of this problem. After 9 months of pandemics, we can say that some anti-COVID -19 therapies have proven a practical effectiveness and others have been partially invalidated by clinical trials and removed from the guidelines, but can we say every information regarding anti - SARS-CoV-2 medication is absolutely clear or that ethical aspects are solved?

Keywords: COVID-19, antiviral medication, off label administration

Introduction

The COVID-19 pandemic is currently a challenge for every important sector of society's life (medical, economic, socio-cultural), requiring rapid adaptations and sustained efforts to combat it. International and national therapeutic protocols have been developed and reconfigured periodically with the main purpose of preventing the evolution of patients diagnosed with SARS-CoV-2 infection to the stage of life-threatening complications. If initially the risks were not fully elucidated, later, during the months of pandemic development, research has revealed defining aspects for this new prototype of infectious disease, whose evolutionary pattern does not overlap in any way with that of existing viral etiology pathologies (Chorin et al, 2020; FDA, 2020a). On the other side, none of the epidemics known to date to be caused by coronaviral strains (SARS- COV1-*Severe Acute Respiratory Syndrome* and MERS-*Middle East Respiratory Syndrome*) have benefited from adequate etiotropic treatments, so it is somehow understandable that patients are skeptical at

the proposal of the new infection management guidelines produced for the new coronavirus (Chorin et al, 2020; Cucinotta & Vanelli, 2020). Among the therapeutic principles outlined since the beginning of the pandemic, antiviral and immunomodulatory medication have had the most intensely debated role, but also the most controversial (Cucinotta & Vanelli, 2020; Bierer et al, 2020; Zou et al, 2020; Bugatti et al, 2020; WHO, 2020). Studies have identified a period of onset of SARS-CoV-2 infection dominated by intense viral replication, during which time the patient may move from the asymptomatic stage to the obvious manifestation of the disease by the presence of symptoms. The use of antiviral molecules aims to reduce the risk of progression to complications (of which the so-called cytokine storm is problematic), as well as reducing the length of hospitalization and related costs (Gilead Sciences, 2020; London & Kimmelman, 2020). People tested positive for SARS-CoV-2 do not receive treatment in the absence of symptoms, because this approach does not reduce the duration of viral excretion (WHO, 2020). However, all therapeutic regimens recommended in treatment of SARS-CoV-2 infection are based on *off label* or *compassionate use* since they are not marketed for this indication. *Off label* use is defined as "*situations where the medicinal product is intentionally used for a medical purpose not in accordance with the authorised product information*" and is used especially for the treatment of infections produced by multiresistant pathogens in critically ill patients (Hunea et al, 2020). *Compassionate use,* being defined by European Agency of Medicines as "*use of an unauthorised medicine outside a clinical study in individual patients under strictly controlled conditions*" is rare situation in our country (Table 1) (Whitfield et al, 2020; Kalil, 2020).

Table 1. Differences between *compassionate use* and *off label use* of medicines (Kalil, 2020)

	Compassionate use (European Agency of Medicines)	**Off-label use**
Purpose	Comparable or satisfactory alternative therapy options not available	Medical judgement - experimental, standard, state-of-the-art treatment
Disease	Immediately life-threatening condition or serious disease	Doses, patient, indications, or routes of administration not mentioned in the approved product labeling
Patients	Cannot be enrolled in clinical trials-	Patient population not mentioned in the approved product labeling (e.g. pediatric patients)
Treatment	Unauthorized	Authorized for other doses, routes of administrations not mentioned in the approved product labeling
Access to the intervention	Compassionate Use Programmes (requires approval from the national authorities)	Medicines available

In the context of the increase in the number of COVID-19 cases in Romania, the increase in the number of moderate and severe forms of the disease, but also due to the accumulation of new clinical data, the therapeutic protocol adopted at national level required a series of revisions, the last one being made on November 27, 2020 (Romanian Ministry of Health 2020a).

Antiviral medication for COVID-19

The first molecules used to treat SARS-CoV-2 infection were protease inhibitors. *Lopinavir* in combination with *ritonavir* has been shown to inhibit coronavirus *in vitro* activity. However, the clinical data published to date on the efficacy of lopinavir are

contradictory. The findings of an observational study indicated an efficacy of lopinavir/ritonavir therapy by accelerating the elimination of the virus from the body under conditions of early administration. According to other literature sources, there were no statistically significant differences between lopinavir/ritonavir, favipiravir and placebo in terms of viral excretion, regression of symptoms and reduced risk of progression to severe disease and even death (Gelinas et al, 2017). *Darunavir/cobicistat*, another protease inhibitor, has been administered to patients with low tolerance to lopinavir / ritonavir as an alternative antiviral medication, but studies have shown no activity *in vitro* on SARS-CoV-2, thereby limiting its use in treatment for COVID-19 (FDA, 2020a). Another molecule, hydroxychloroquine, has proven its *in vitro* activity against SARS-CoV-2 by changing the pH of the cell membrane surface and thus inhibiting viral fusion with target cell membranes. At the same time, it has a role in the process of nucleic acid replication, in the glycosylation of viral proteins, the assembly and release of the virus from the infected cell. Geleris J. and collaborators (2020) demonstrated in a clinical study with 42 patients that the elimination of the virus occurs faster in those receiving hydroxychloroquine. Other studies have shown that there is no significant decrease in the duration of SARS-CoV-2 negation, with an increased incidence of adverse reactions in patients treated with hydroxychloroquine (Chorin et al, 2020; Bierer et al, 2020). Discontinuation of patient enrollment in the UK RECOVERY study due to inefficiency in reducing COVID-19 mortality on 4 June 2020 and suspension of the FDA's provisional authorization of hydroxychloroquine on 15 June 2020 were significant impacts on perception of the efficacy of hydroxychloroquine in the treatment of patients with COVID-19 (FDA, 2020b). *Remdesivir* falls into the category of antivirals potentially useful for the therapy of patients with COVID-19, having a role in inhibiting RNA-dependent RNA polymerase and in premature blocking of RNA transcription (Gelinas et al, 2017). Despite the proven *in vitro* activity on coronaviruses in general and on SARS-CoV-2 in particular, the clinical data obtained during the pandemic were contradictory. Wang Y and collaborators initiated an observational study that included 237 patients and evaluated remdesivir versus placebo comparatively, but the increased incidence of adverse reactions (12% versus 5% in the placebo group) and the insignificant reduction in mortality (8% versus 11, 9%) led to premature discontinuation of research (Edwards, 2013). *Umifenovir* and *Favipiravir* are two antiviral drugs active against influenza viruses, the indication for which has been extended based on laboratory studies that have demonstrated the potential to inhibit viral cell fusion and RNA polymerase, as well as immunomodulatory. It appears that the use of these antivirals in mild and moderate forms of disease has led to regression of lung images and accelerated viral clearance compared to lopinavir / ritonavir and placebo (Edwards, 2013).

Immunomodulatory medication for COVID-19

Regarding the immunomodulatory medication and its overwhelming role in treating patients with COVID-19, it can be said that its usefulness is evident in the case of exacerbation of the immune response and the appearance of the cytokine storm (Table 2) (Geleris et al, 2020). As with antiviral medication, the key to success is to administer it as close as possible to the onset of the inflammatory phase on a benefit / risk basis (depending on the level of proinflammatory molecules, the risk of bacterial infections and other associated side effects).

Table 2. Proposed immunomodulatory medication for the treatment of COVID-19 (Geleris et al, 2020)

Medication	**Dose**	**Standard duration**	**Adverse reactions**
Dexamethasone Methylprednisolone	8-16 mg/day iv	7-10 days	Irritation of the digestive mucosa, large glycemic variations
Tocilizumab	8 mg/bodyweight/day	1-3 doses	Reactivation of chronic infections (chronic viral hepatitis B,

			tuberculosis, herpes infections), liver damage
Anakinra	200 mg/day on day I 100 mg on days II-VII	5-7 days	Liver damage
Convalescent plasma	200-400 mg iv	Single dose	Acute respiratory dysfunction (TRALI), post-transfusion overload, allergic reactions

Unlike antiviral medication, the effectiveness of which has been and will remain debatable in SARS-CoV-2 infection, immunomodulatory therapy has proven to be much more useful in moderate / severe forms of the disease, given that one of the redoubtable complications of the disease is this storm of cytokines, cause of unfavorable evolution in patients with excessive inflammatory response. It is also worth mentioning that, as a rule, the immunocompetent adults, young people, without significant previous diseases, are surprisingly part of the category exposed to the above-mentioned complication. The beneficial effects of immunomodulators may be counterbalanced by intense consecutive immunosuppression, with delayed eradication of SARS-CoV-2 infection and / or probable reactivation of chronic infections (Alijotas-Reig et al, 2020).

Regulatory issues for treatment recommendations

It should be noted that all antiviral and immunomodulatory drugs mentioned in the guidelines approved by the Romanian Ministry of Health during the pandemic were administered outside the indications mentioned in the leaflets and only after adequately informing patients or their legal guardians and obtaining consent (Bierer et al, 2020). The aspects that can be discussed are those related to this *off-label* administration of the already existing treatments on the pharmaceutical market with recommendations for administration in various pathologies except SARS-CoV-2 infection, the situation in which the efficacy has not been fully demonstrated. Controversies start with the use of hydroxychloroquine alone / combination therapy (azithromycin) but can certainly extend to the other categories of drugs mentioned in the therapeutic protocols (lopinavir / ritonavir, darunavir / cobicistat, remdesivir, umifenovir, favipiravir) (Chorin et al, 2020; Geleris et al, 2020). The inclusion of these antiviral agents in the treatment guidelines for COVID-19 is based on the in vitro activity on SARS-CoV-2 and related viruses, but clinical experience is limited. Although the use of hydroxychloroquine in combination with azithromycin has no solid scientific basis, some physicians still recommend it based on previous experience with the treatment of malaria and some personal observations regarding the evolution of patients with COVID-19 under this therapy. The rationale behind the use of antibiotics such as azithromycin or clarithromycin in SARS-CoV-2 infection is unclear. It is known that in general, antibiotic therapy is not effective in treating viral infections, regardless of the location of the non-bacterial infectious process, and such behavior can be classified as irrational and generates redoubtable adverse reactions under conditions of imperceptible benefits (Geleris et al, 2020). Finally, the World Health Organization advocates the cautious administration of any of the above categories, limiting itself to symptomatic therapy and careful monitoring of each patient. Many developed countries such as China, European countries and the United States are also reluctant about the effectiveness of molecules proposed as therapy in SARS-CoV-2 infection, preferring to wait for the results of ongoing clinical trials (Bierer et al, 2020; London & Kimmelman, 2020). On the other hand, some governments have adopted, with the contribution of health policy specialists, the combination of hydroxychloroquine/azithromycin for all COVID – 19 confirmed cases confirmed by COVID-19 (even asymptomatic ones), despite the uncertainty about its effectiveness. In Romania, both hydroxychloroquine and lopinavir/ritonavir were the first recommendations

for treatment of patients infected with the new coronavirus, considering the clinical status, co-medication with interaction potential, and the benefit/risk ratio (Romanian Ministry of Health, 2020b).

Ethical issues -"Sf. Parascheva" Clinical University Infectious Diseases Hospital of Iași experience during COVID-19 pandemic

Since March 2020 when WHO declared the beginning of current pandemic, "Sf. Parascheva" Clinical University Infectious Diseases Hospital of Iași was declared as first line unit COVID-19. During March-November 2020 over 2500 confirmed cases were hospitalized since the beginning of pandemic with a continuous increasing monthly number of patients (Fig. 1).

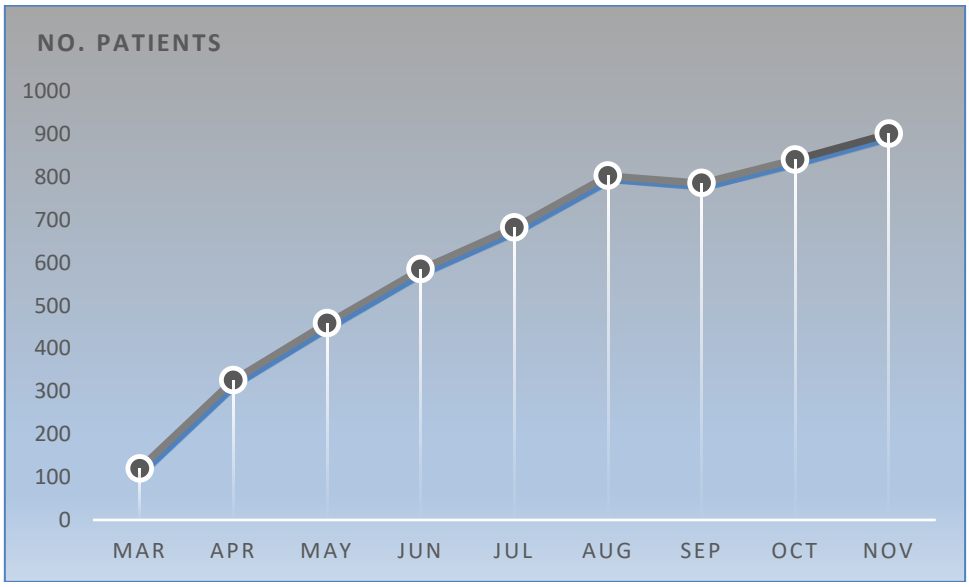

Fig. 1. Hospitalization trends of patients with SARS-CoV-2 infection in the "Sf. Parascheva" Clinical University Infectious Diseases Hospital of Iași during March-November 2020.

During this period, we had a varied experience, in parallel with updating of knowledge on the epidemiology and treatment methods in SARS-CoV2 infection. Our activity had two extremely important goals during the pandemic, namely: ensuring the isolation of people infected and ensuring the medical management of the patients with the clinical form of the disease. It is well known that at the beginning of the pandemic, the methodology applied in Romania required that people with SARS-CoV2 infection confirmed by PCR to be hospitalized / quarantined to prevent the spread of infection. In this regard, otherwise healthy persons were quarantined in hospital for long periods of time, until the results of two successive PCR RNA SARS-CoV2 were negative. We have noted several cases when hospitalization was prolonged up to 3 months. This was the first moment when we had to face ethical concerns regarding the human rights. United Nations (2020) defines human rights as: "*…fundamental to all human beings, regardless of race, sex, nationality, ethnicity, language, religion, or any other status. These rights include the right to life and liberty, freedom from slavery and torture, freedom of opinion and expression, the right to work and education*". On the other side, to address the COVID-19 outbreak, most of the countries imposed limitations and restrictions of local and international movements and physical and social distancing. These measures raised ethical issues, mostly concerning freedom of movement, right to personal liberty and rights to liberty and security (Spadaro, 2020).

During these months, there have been several situations in which hospitalized SARS – CoV2 infected people have expressed (sometimes even in the media) the upset regarding the restriction of their rights to movement. However, it must be highlighted that pandemic is an exceptional situation. In March 2020, European Union Agency for Fundamental Rights (FRA, 2020) noted that "*international human rights law allows for the limitation of certain rights, especially when addressing a major health crisis*" and "*human rights and public health are not an 'either/or' choice*". This stage was somewhat overcome with the update of the epidemiological surveillance methodology, which allowed the isolation or quarantine at home of infected persons. Thus, public health and government measures were rigorously assessed and updated to respect the principle of non-discrimination (Romanian College of Physicians, 2016).

The principal aim of our medical practice was treatment of SARS – CoV2 infection. We have used both *compassionate use* and *off label* drugs in our clinic. The treatments administered followed medical judgment in accordance with national and international guidelines and protocols for the treatment of SARS infection. These have been updated in parallel with deeper understanding of the data on the efficacy, safety of the drugs administered, or other mechanisms associated with the infection. The therapeutic response was variable for each patient, although most of them received lopinavir/ ritonavir (1.967) and hydroxychloroquine (630) (Fig. 2). The experience of using remdesivir in Romania and in the „Sf. Parascheva" Clinical University Infectious Diseases Hospital of Iași, was a positive one, the defining criterion of efficiency being the administration as early as possible after the onset of symptoms, especially in patients with hypoxia who have not yet required mechanical ventilation or extracorporeal oxygenation (ECMO).

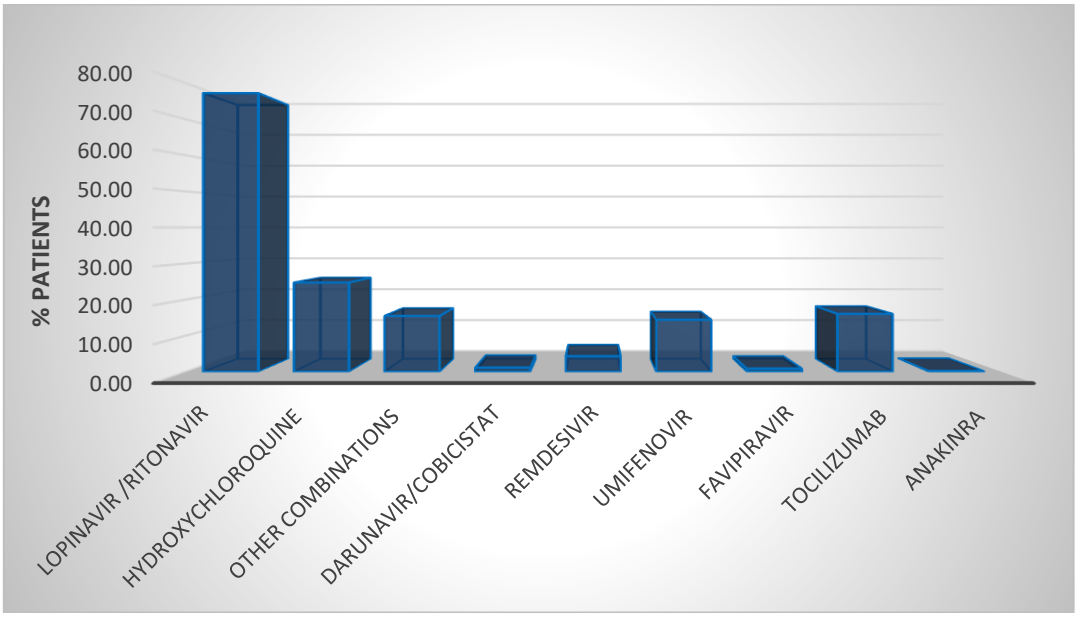

Fig. 2. Antiviral and immunomodulatory medication used for treatment of SARS-CoV-2 infection in the „Sf. Parascheva" Clinical University Infectious Diseases Hospital of Iași during March-November 2020.

To exemplify a situation that raises certain ethical issues related to *off label* therapy, we present the case of one female patient, aged 36, without significant personal pathological history, who was hospitalized in April 2020 in our hospital with mild SARS-CoV-2 infection. The initial treatment recommendation was lopinavir / ritonavir, with concrete mention of the potential benefits and risks, but the patient refused to take it. The refusal was recorded in writing in the informed consent form, which also specified that any type of antiviral and

immunomodulatory medication is administered *off label*. Subsequently, hydroxychloroquine therapy was proposed, an option which was accepted by the patient, so that she received 800 mg / day in two doses on day I and 400 mg / day on days II-VII according to the Therapeutic protocol approved and published in the Official Gazette of Romania on March 24, 2020 (Romanian Ministry of Health, 2020b).

The patient was discharged after 18 days of hospitalization, with two consecutive negative SARS-CoV-2 RNA PCR tests, having a general good condition, afebrile and asymptomatic. Three days after discharge, the patient complains about the violation of her rights and of articles 3 (*Respect of life and human dignity, with no discrimination regarding age, gender, race, etc*.), 5 (*The doctor is obliged to respect the fundamental rights of human rights and ethical principles in the biomedical field*), 11 (*The responsibility for the medical acts belongs to the team leader, within the limits of the administrative coordination attributions*) and 14 (*Professional secrecy is mandatory*) of the Romanian Code of Medical Deontology by the team of doctors who dealt with the management of the case (Romanian College of Physicians, 2016). Although from the point of view of medical aspects, this case is a simple one, the issue of an ethical nature tended to be even more complex and is related to patients' attitude towards *off label* use of medication. To overcome this ethical issue, we have allocated sufficient time to explain to patients the benefits and possible risks associated with their *off label* treatment. In agreement with the Helsinki Declaration, the physicians obtained written informed consent in using *off label* interventions (WMA, 2013; Hunea et al, 2020; Shojaei & Salari, 2020).

Discussions

Since the beginning of the COVID-19 pandemic, based on the legislative authority, the Romanian Government has ordered the compulsory hospitalization of all patients diagnosed with this infectious pathology, to limit the spread of the virus among the population. These decisions generated anxiety, dissatisfaction and even riots of people hospitalized in the „Sf. Parascheva" Clinical University Hospital of Infectious Diseases of Iasi, with direct referral to medical staff in the immediate vicinity. As a result, doctors were put in an ungrateful situation by treating COVID-positive patients with minor symptoms or even asymptomatic, just because the law said so at the time.

On the other hand, if we consider the concept of Rational Use of Medicines (RUM), promoted by the WHO in 1985 and which refers to the objective criteria that a drug therapy must meet to bring more benefits than risks to the people being administered, it seems that anti-COVID-19 medication could not be limited to these universal desiderata. At the core of the notion of RUM is the so-called Evidence-Based Medicine (EBM), which refers to the conscious, explicit and judicious use of scientific resources for the individual benefit of patients. Therefore, after the first months of emergency in pandemic conditions, in many cases the primary pharmacotherapy adopted in SARS-CoV-2 infection seems to be based on clinicians' intuition about the efficacy of one or more drugs rather than solid scientific evidence. A major problem with *off-label* prescriptions would be the unpredictability of risks to the health of the individual beyond the already known indications, especially given that the efficacy in the therapy of a new pathology (COVID-19) has not yet been fully demonstrated (Geleris et al, 2020; Edwards, 2013; Stern & Markel, 2004).

In most of the cases, patients understood the importance of therapy and agreed by signing the approved Informed Consent Form. However, there were isolated cases of refusal, mainly at the beginning of pandemic, when different antivirals (anti – HIV) were recommended in mild to moderate infections. Further protocols were updated, but also the attitude of the patients was significantly changed. Severity of cases hospitalized was increased, and also the patients' trust was considerably improved.

In addition, several ethical issues derived from government measures to limit the spread of infection which included physical and social distancing and quarantine. The European Agency for Human Rights noted in its report from March 2020 that these restrictions "*can affect many fundamental rights, including the rights to liberty and security (Article 6), respect for private and family life (Article 7), […] freedom of expression and information keep together on one line, freedom of assembly and of association (Article 12), […] and freedom of movement and of residence (Article 45)*" (FRA, 2020). However, the priority during this unprecedented crisis was to save lives. The lockdowns and restrictive measures were adopted to protect people (especially vulnerable population, like elderly, people with disabilities, pregnant women, children, etc.) and to support the fight against the pandemic.

Conclusions

The peculiarity of the SARS-CoV2 infection is given by the limitations imposed by the epidemiological restrictions, and the doctor-patient relationship was very affected. The schedule of medical visits was modified, and even the protective equipment used had a psychological impact on patients. Moreover, the abundance of inclusive information regarding off-label treatments has allowed patients to create their own opinions, sometimes contradictory to their medical needs. It was necessary for physicians to adopt a similar attitude in the consent process to that of clinical research, allocating much time to explain to each patient the meaning or benefits and risks of off-label treatments recommended by methodology issued by the government. Our experience confirms previous published information. The ethical component of the epidemiological and therapeutic approach to patient with SARS – CoV2 infection appears to be controversial, with many dilemmas and discussions that may have an answer in the near future.

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