Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

In the absence of reliable data, premature affirmations from the scientific community about treatment efficacy should be foresworn, as they could lead to avoidable complications.

As an example, chloroquine and hydroxychloroquine have been put in the spotlight as potential game changers in COVID-19 prophylaxis and treatment [3,4]. Without available data from randomized controlled trials evidence sufficient to justify recommendations, off-label use of hydroxychloroquine for COVID-19 patients has been promoted [4].

Such incautious behaviour may entail improper use of drugs, causing harm due to side effects and overdose, and also resulting in drug shortages for patients requiring specific medications for chronic illnesses.

In addition to that, many publishers encourage projects that do not require extensive inquiry and evidence gathering. The growing burden of journals which fail to conduct peer review and have very poor scholarly quality is likely to contribute to the rise of low-quality papers.

Caution by public health professionals, world leaders, and scientific journal editors is called for. Everyone involved in the war against COVID-19 should be made to understand that anecdotal reports with limited *in vitro* data can be detrimental to ongoing research and that only evidence-based, rigorous and high-quality clinical data should be taken into consideration.

In the absence of reputable evidence, our best choice as a scientific community is to adhere to current guidelines, behave sensibly and, if our "expert opinion" may not be of help, exercise our right to uncomfortable silence.

Disclosure of interest

The authors declare that they have no competing interest.

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Mixed mold infection with *Aspergillus fumigatus* and *Rhizopus microsporus* in a severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) patient

Infection mixte à Aspergillus fumigatus et Rhizopus microsporus chez un patient faisant une forme grave de COVID-19

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1. Introduction

In the recent context of the Coronavirus disease 2019 (COVID-19) pandemic, secondary fungal infections, such as invasive pulmonary aspergillosis, have been reported for about 30% of the cases admitted to the ICU, mostly in patients in whom the European organisation for the research and treatment of cancer: Mycoses study group education and research consortium (EORTC/MSGERC) host factors were absent [1–3]. At the university hospital of Besançon (northeastern France), while a similar proportion of putative invasive pulmonary aspergillosis was observed, we also had one case of mixed-mold infection displaying both *Aspergillus fumigatus* and *Rhizopus microsporus* isolated in the respiratory samples of an immunocompromised patient with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). We propose here to report and discuss this rare occurrence.

2. Case

A 55-year-old man was diagnosed in 2017 with follicular lymphoma, which recurred in 2018. After autologous hematopoietic stem cell transplantation (auto-HCT) was planned, the patient tested positive for Influenza B virus (Day –20). Prior to auto-HCT, a SARS-CoV-2 Real-time polymerase chain reaction (RT–PCR) test [4] was performed from a nasopharyngeal sample on Day –7 and was negative. Auto-HCT was performed on Day 0 (D0). Over the following days, the patient became feverish while in aplasia despite antibiotic treatment, and a new SARS-CoV-2 RT–PCR test from a nasopharyngeal swab came back positive with a very high respiratory viral load (D6; cycle threshold (Ct) value = 9.9 and 9.7 for the 2 target genes). The patient was then transferred to the infectious diseases department. His aplasia period ended at D10. A strong inflammatory response was observed with D-Dimer at 3710 ng/mL, fibrinogen at 8.93 g/L and C-reactive protein (CRP) reaching 552 mg/L at D11. At D12, the respiratory status of the patient abruptly worsened and the patient was admitted to an intensive care unit (ICU) to receive mechanical ventilation. On D19 and D21, respiratory samples (tracheal aspirate and bronchoalveolar lavage fluid [BALF]) were positive in culture for both *Aspergillus fumigatus* and *Rhizopus microsporus* (Fig. 1). On D34, a 2nd BALF was positive in culture for *A. fumigatus* (Fig. 1). The parasitology–mycology department of the university hospital of Besançon developed fungal qPCR in-house techniques, targeting *A.*

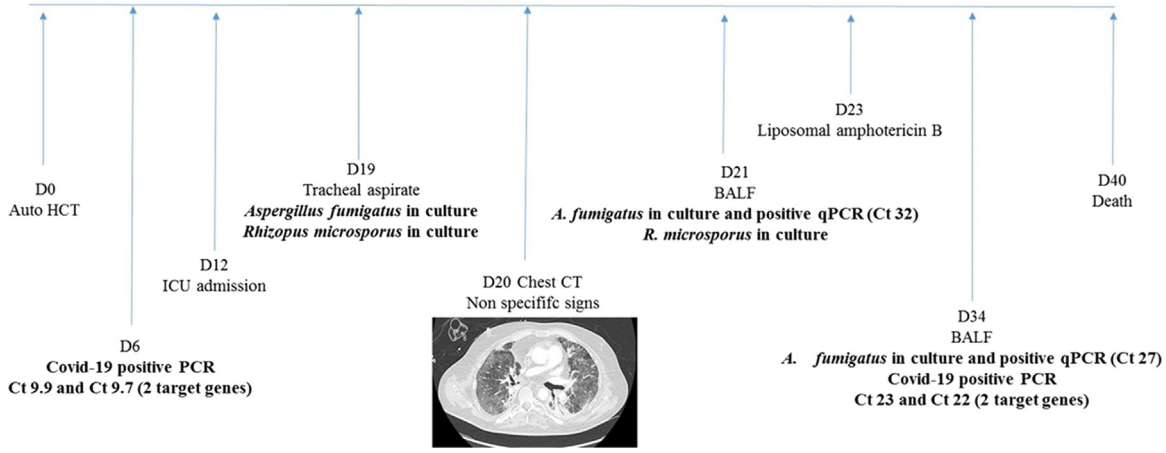

Fig. 1. Chronology of the positivity of culture and qPCRs for the patient.

fumigatus and Mucorales that are routinely used to screen for invasive mold disease (IMD) [5,6]. Fungal qPCR was performed on BALF at D21 and D34 and found positive for *A. fumigatus*, with Ct ranging from 27 to 32 (Fig. 1). Fungal qPCR was performed on serum at D17 and D21 and found negative, as was the galactomannan (GM) antigen in serum (D17 and D21). Due to the patient's positive COVID-19 status, which represented an exposure risk for the technicians, GM measurement in BALF was not performed in our laboratory. Susceptibility testing was carried out by E-test, and both strains were wild types. CT–thorax imagery was performed at D20 and showed non-specific bilateral ground glass opacities, presumably due primarily to the SARS-CoV-2 infection (Fig. 1). Treatment with liposomal amphotericin B began at D23 (5 mg/kg). Despite its administration, pejorative evolution was observed, with development of pulmonary fibrosis. Another secondary infection was sought; the patient was tested negative three times for *Pneumocystis jiroveci*. While no secondary bacterial infection was documented, CMV and HHV6 viremia were observed. SARS-CoV-2 respiratory viral loads remain high on BALF at D13 (Ct = 17.60 and 15.15) and D34 (Ct = 23.07 and 21.93). The patient died at D40.

3. Discussion

While a certain number of invasive pulmonary aspergillosis (IPA) cases in SARS-CoV-2 infected patients have been published [1,2,7], the fungal infection, known as mucormycosis, has seldom been reported. In the context of the COVID-19 epidemic, most IPA cases have occurred in patients without the EORCT/MSGERC host factors, and they necessitated new case definitions to guide a decision to initiate anti-fungal treatment [2,7]. The criteria required to confirm the existence of a "putative" CAPA in the presence of non-specific radiology signs are two or more positives across different test types, or multiple positives within one test type among the following: positive culture from BALF, positive GM in BALF ($\geq$ 1.0), positive GM in serum ($\geq$ 0.5), positive qPCR in BALF or blood, positive beta-D glucan in serum/plasma [7].

In the present case, the patient displayed the EORCT/MSGERC host factors [3] and non-specific radiology signs of IMD. He had two positive cultures and two positive *A. fumigatus* qPCR in BALF (Fig. 1), which meant that the criteria required to confirm the existence of a putative IPA, as defined by White et al., had been fulfilled [7].

The originality of this IMD case consisted in the association of *A. fumigatus* with a Mucorales species. Several cases of mucormycosis in SARS-CoV-2 infected patients have been reported recently, describing varied clinical forms in those without EORCT/MSGERC host factors [8]. The hypothesis put forward to explain these rare occurrences were:

- that the steroids used to treat the SARS-CoV-2 infection may favour the development of molds, providing that the latter were pre-existing and/or colonising the patient and;
- that the SARS-CoV-2 infection itself may induce an immunosuppressive state exposing the patient to IMD [8].

In the present case, from day 6 to day 34, the SARS-CoV-2 viral load in respiratory samples remained high, with a Ct value < Ct 25 [9,10], and it was associated with pronounced elevation of inflammatory markers. The slow decline of SARS-CoV-2 viral load could reflect failed triggering of an effective innate immune response against the virus. A recent study showed that a hematologic malignancy was independently associated with high SARS-CoV-2 viral load (Ct < 25) upon admission [9]; moreover, high SARS-CoV-2 viral load (Ct < 25) has been shown to be independently associated with an outcome of death [9,10].

This patient had two major risk factors: SARS-CoV-2 infection and severe immunosuppression. Even though it was not possible, in our case, to determine which of the two was more damaging, it may have provided some insight into the interactions between molds, such as *A. fumigatus* and Mucorales, and the SARS-CoV-2 infected lung [2].

4. Conclusion

This reported case of secondary fungal infection in an immunocompromised SARS-CoV-2 infected patient is a rare occurrence due to the mixed presence of *A. fumigatus* and a Mucorales species.

Disclosure of interest

The authors declare that they have no competing interest.

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Estimating renal function when adjusting the dosage of antibiotics: Facts and fables

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We read with interest the article entitled “Antibiotics and chronic kidney disease: Dose adjustment update for infectious disease clinical practice”, which was published by Aloy and colleagues in a previous issue of *Médecine et Maladies Infectieuses* [1]. The authors present guidelines for dosage adjustment in patients with Chronic Kidney Disease (CKD). All of their recommendations are based on glomerular filtration rate (GFR), and the authors recommend using the CKD-EPI equation with correction for individual body surface area as a means of estimating GFR in drug dosing. This is questionable, as the use of estimated GFR in the dosing of antibiotics is not supported by pharmacological data.

Table 1
Official information about renal function estimation provided in the summary of product characteristics (SPC) for 55 antibiotics.

	Number (percentages) of SPCs
Renal function index cited	
Creatinine clearance	44 (80%)
Glomerular filtration rate	3 (5.5%)
Serum creatinine	1 (1.8%)
None	7 (12.7%)
Creatinine clearance determination (units)	
Cockcroft–Gault equation (mL/min)	4
No information (mL/min)	31
No information (mL/min/1.73 m^2)	5
No information (no units)	4
Glomerular filtration rate determination (units)	
No information (mL/min)	2
Schwartz equation in children (no units)	1

We examined the summary of product characteristics (SPC) of the antibiotics cited in the article by Aloy et al., our objective being to identify the renal function estimation methods that are officially recommended for drug dosing. The results are summarized in Table 1. The fact of the matter is that the method recommended by Aloy et al. for all antibiotics (CKD-EPI equation in mL/min) is not mentioned in any SPC. Most antibiotics were actually developed before the publication of the CKD-EPI equation, which has consequently never been used in clinical pharmacology studies. For most antibiotics, it seems that Aloy et al. simply duplicated recommendations from SPC or different studies, while substituting “GFR” for “creatinine clearance”. This is not sound, especially when the authors cite supporting references that clearly mention creatinine clearance (CLcr) estimated by the Cockcroft–Gault (CG) equation as the renal function index to be used. One among several examples is ceftolozane/tazobactam [2].

The French health authority (HAS) has clearly stated that the CKD-EPI equation has not been validated for drug dosing, and has recommended the use of creatinine clearance (CLcr) estimated by the Cockcroft–Gault (CG) equation [3]. In point of fact, CLcr is mentioned in most antibiotic SPCs (see Table 1). However, the latter are inadequately informative about the method that should be used to measure or estimate CLcr, and only a few of them clearly cite the CG equation. This is a real issue as concerns safe and effective dosing of drugs. However, given that CLcr is indicated as the renal function index to be used for most agents, a measure or an estimation of CLcr should be used for the dosing of such drugs, rather than a GFR estimate that has not been used in drug development.

Aloy and colleagues call into question the CG equation, criticizing its lack of precision and mentioning the evolution of serum creatinine assays. These limitations indeed exist as regards precise estimation of GFR in nephrology. However, they do not hold true for drug dosing, which has different aims. The goal of renal function estimation for drug dosing is not to precisely estimate GFR, but rather to predict drug exposure and dosage requirements in patients with renal impairment.

The rationale for drug dosing in patients with renal impairment is based on clinical pharmacokinetics (PK). At the steady state, drug exposure depends on drug dosage and total body clearance