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.

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COVID19 and acute lymphoblastic leukemias of children and adolescents: Updated recommendations (Version 2) of the Leukemia Committee of the French Society for the fight against Cancers and leukemias in children and adolescents (SFCE)

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COVID19 et leucémies lymphoblastiques aiguës de l'enfant et de l'adolescent: recommandations actualisées (Version 2) du Comité « Leucémies » de la Société Française de lutte contre les Cancers et leucémies de l'Enfant et l'adolescent (SFCE)

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Summary

Since the emergence of the SARS-CoV-2 infection, many recommendations have been made. However, the very specific nature of acute lymphoblastic leukemias and their treatment in children and adolescents led the Leukemia Committee of the French Society for the fight against Cancers and leukemias in children and adolescents (SFCE) to propose more specific recommendations. Here is the second version of these recommendations updated according to the evolution of knowledge on COVID19.

Preamble and general recommendations

Preamble

The situation of the current COVID-19 pandemic is continuously evolving. We thus have taken the more recent knowledge into account to update the previous recommendations from the Leukemia committee of the *Société Française de lutte contre les Cancers et leucémies de l'Enfant et de l'adolescent* (SFCE) [1].

Despite an increasing number of publications concerning severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in pediatric oncology and hematology, data in children with cancer are still limited (*table I*). Published recommendations most often relies on an expert-opinion basis [2,3]. While some early studies in adults with cancers suggested that the risk of severe COVID-19 is higher in this population [4,5], more recent data indicate that patients with cancer may not be at greater risk than others when matched for comorbidities [6,7]. However, mortality appears to be higher in adults with haematological malignancies [8,9].

In pediatric oncology, most reports have been limited to cases or small sample populations [10–17] while larger clinical studies have recently been published and/or are still ongoing [18–20]. These reports suggest that COVID-19 is generally asymptomatic, mild or moderate in children receiving anti-cancer therapy. Thus children with cancer appear to have a similar risk of developing severe COVID-19 compare to those in their healthy counterparts. However, some severe cases have been described, mostly in highly immunocompromised children and/or with severe oncologic conditions [14,15,18,21,22].

Since April 2020, a real-time prospective survey has been set up among the 30 SFCE centers. On 17th of December 2020, 127 cases of COVID-19 have been reported, most of them being enrolled in the PEDONCOVID study (NCT04433871). Eight patients required hospitalization in intensive care unit (ICU) and one patient with relapsed acute lymphoblastic leukemia (ALL) died from ARDS with multi-organ failure. Thus, SARS-CoV-2 infection can be severe in some children with cancer and/or HSCT, as suggested by the first reports from the SFCE [21,23] or available through the St-Jude Research Hospital Registry (to which the SFCE is participating) [24].

Fortunately, SARS-CoV-2 infection appears nevertheless to be mild in most children with cancer/ALL [20,23,25,26]. Thus, the main threat to the vast majority of children with ALL still remains the ALL itself. Long-term data including well-matched case-control studies will tell if treatment delays/modifications due to Covid 19 have impacted the outcome if children with ALL.

Beyond the risk of SARS-CoV-2 infection in patients currently treated for a leukemia vigilance must be maintained regarding the danger of delaying the diagnosis of acute leukemia. Such situations have already been reported with tragic consequences [27,28].

General recommendations

There are still insufficient data to support recommendations applicable to all local cases and situations during the care of children and adolescents and young adults (AYA) with ALL. The most experienced practitioners of the hematology-oncology unit must therefore help to decide, on a case-by-case basis, for which patients should the leukemia treatment be initiated or continued, or identify those in whom a delay is possible, depending on clinical symptoms and tumor biology. For patients in the advanced stage of their disease, the real benefit of the treatment in the context of the risk of COVID-19 must be considered and discussed.

Some general recommendations should be reiterated:

- it is recommended to test for SARS-CoV-2 (preferably by PCR or at least by immunological tests, on nasopharyngeal swab) before starting intensive induction chemotherapy or other intensive phase of treatment, for ALL patients, with or without symptoms, especially in the most affected regions. Due to the unpleasant nature of nasopharyngeal swab tests, they may be difficult to repeat in children. Although salivary tests may be an interesting alternative in the general population, their sensitivity is lower than the one of nasopharyngeal tests. Therefore, we recommend testing preferably with nasopharyngeal swabs in pediatric oncology and hematology wards;
- if patients, before induction therapy, are tested positive for SARS-CoV-2, one should delay systemic treatment if possible (e.g. absence of major hyperleukocytosis). During later phases, if positive, tests should be ideally repeated over time

Table I
Selected COVID-19 studies in children with leukemia

Reference	Number of patients	Type of study	Number of patients w ith leukemia	COVID-19 complications	Use of specific COVID-19 treatment	Outcome in patients with leukemia	Commentaries
Millen et al. [20]	54	Multicenter study, national scale	24 ALL 4 AML	2 pts with ALL with moderate to severe presentation of COVID-19	UK	Favorable	
Palomo-colli et al. [67]	38	Monocenter study	21 ALL 3 AML	2 pts requiring invasive ventilation (underlying diagnosis unspecified)	UK	UK	26 pts with delayed oncologic treatment
						No death	21 pts with oxygen need (mask/canula)
Rouger-Gaudichon et al. [23]	37	Multicenter study, national scale	10 ALL	5 pts requiring ICU transfer (including 2 relapsed ALL, and 1 pt with ALL and HSCT)	REM: 1pt	One death (relapsed ALL treated with chemotherapy)	16 pts with oncologic treatment delayed (median time of 14 days)
			1 AML 1 CML		OHQ: 2 pts	Other pts with favourable outcome	
Bisogno et al. [19]	29	Multicenter study, national scale	14 ALL	No complications	OHQ: 9 pts, lopinavir/ ritonavir: 3 pts	Favorable	Prolonged virus shedding in 2 pts (1 AML and 1 ALL)
			2 AML				16 pts with chemotherapy hold (median time of 26 days)
Ferrari et al. [58]	21	Multicenter sudy, regional scale	10 leukemias	No complications in pts with leukemia	UK	Favorable	Modification of oncologic treatment in 10 pts
Gampel et al. [17]	19	Multicenter study, city scale	6 "leukemia or lymphoma"	5 pts in ICU including one patient with B-ALL and hyperleukocytosis	OHQ + AZYTHRO: 3 pts	Favorable	More severity in males in the overall cohort?
De Rojas et al. [11]	15	Multicenter study, city scale	8 ALL	No complications	OHQ: 11 pts, with 3 of them in combination with other drugs (REM, AZITHRO, Toci, steroids)	Favorable	2 pts required oxygen support (no leukemia)
			1 AML				Delayed chemotherapy in 6 pts
Ahmad et al. [59]	10	Monocenter case series	Not specified	No complications	UK	Favorable	One patient with AML with prolonged shedding of SARS-CoV-2 for 4 weeks

Table I **(Continued).**

Reference	Number of patients	Type of study	Number of patients w ith leukemia	COVID-19 complications	Use of specific COVID-19 treatment	Outcome in patients with leukemia	Commentaries
Pérez-Martinez et al. [60]	8	Monocenter case series	2 ALL	Macrophage activation syndrome in a T-ALL pt	OHQ, REM, tocilizumab and dexamethasone	Favorable	
Vicent et al. [15]	8	Multicenter case series	3 ALL 1 AML	1 pt with ALL requiring mechanical ventilation	OHQ, AZITHRO, REM, Toci, lopinavir/ritonavir, siltuximab and anakinra	One death (ALL & alveolar haemorrhage)	
Rossof et al. [61]	6	Monocenter case series	2 ALL 1 AML	One pt with AML required high-flow oxygen	UK	Favorable	One pt with T-ALL with prolonged shedding of SARS-CoV-2 for 5 weeks
Flores et al. [62]	3	Monocenter case series	3 ALL	One pt with recent history of HSCT and under immunosuppressive therapy presented respiratory distress signs, &required mechanical ventilation	UK	One death (patient with history of HSCT) Two pts on consolidation therapy: favorable outcome	
Stokes et al. [14]	2	Monocenter case series	1 AML	ICU hospitalization required	OHQ and REM		High BMI
Phillips et al. [63]	1	Case report	1 ALL	Macrophage activation syndrome Mechanical ventilation required	No specific treatment	Clinical improvement after the beginning of chemotherapy	Concomittant diagnosis of B-ALL and COVID-19
Sieni et al. [13]	1	Case report	1 AML	No complication	OHQ and lopinavir/ritonavir.	Favorable	1-year-old girl with high risk AML
Orf et al. [64]	1	Case report	1 ALL	No complication	Use of REM. Three drugs induction.	Favorable Mild course	Concomitant diagnosis of standard risk B-ALL and SARS-CoV-2 infection
Balashov et al. [41]	1	Case report	1 JMML	Delayed respiratory complications	Toci, methylprednisolone, convalescent plasma	Improvement in 14 days.	Description of the case of a 9-month-old girl with JMML and HSCT history SARS-CoV-2 still

Table I (Continued).

Reference	Number of patients	Type of study	Number of patients w ith leukemia	COVID-19 complications	Use of specific COVID-19 treatment	Outcome in patients with leukemia	Commentaries
							detectable 4 months after initial detection
Velasco-Puyo et al. [65]	1	Case report	1 ALL	Rapid respiratory aggravation with need for high-flow oxygen therapy.	Toci	Clinical improvement after perfusion of Toci.	High-risk KMT2A rearrangement ALL.
Sun et al. [66]	1	Case report	1 ALL	Mechanical ventilation required	UK	Not recovered. Still in ICU at time of publication	Patient under maintenance treatment Co-infection with influenza A virus

ALL: Acute Lymphoblastic Leukemia; AML: Acute Myeloid Leukemia; AZITHRO: azithromycin; BMI: Body Mass Index; HSCT: Hematopoietic Stem Cell Transplantation; ICU: Intensive Care Unit; JMML: Juvenile Myelo-Monocytic Leukemia; OHQ (Hydroxy Chloroquine); pts: patients; REM: remdesivir; Toci: Tocilizumab; UK: Unknown.

until negativity, especially before the beginning of an intensive course;
- if the SARS-CoV-2 test is not available, carefully look for suggestive symptoms (dry cough, high fever, anosmia, rhinorrhoea, digestive signs) and/or any notion of contact with a symptomatic individual and consider a chest CT scan;
- carefully isolate any COVID-negative child or adolescent to allow him to securely advance in the treatment (facial mask, social distancing, barrier measures, no contact with individuals suspect of COVID or COVID + for 3 weeks. . .), in particular for those intended to be allografted;
- visits should be limited to parents and potentially to siblings in hospitalized children, and in the course of hematopoietic stem cell transplantation, with respect of sanitary measures.

Patients with ALL in first line, included in the CAALL-F01 or ESPhALL 2017 protocols or treated according to the FRALLE/EORTC protocols or INTERFANT 06

Are you changing your approach to initial induction?

General considerations

Corticosteroids are a key part of induction therapy and, more generally, of ALL treatments. Initial outcomes of the use of corticosteroids in SARS-CoV-2 infection were controversial. Recent data suggested that dexamethasone is effective in severe COVID-19 in immunocompetent patients [29]. The benefit of using corticosteroids in immunocompromised patients with severe COVID-19 is less clear and has not been proven yet. Still, ALL is life-threatening and very probably more than COVID-19 in most situations. ***Thus, we consider that the risk-benefit ratio calls for regular protocol induction***. However, chemotherapy doses and scheduled administration should be weighted with the clinical status and oxygen saturation of the patient, as well as the results of chest computed tomography scan, which should be performed in all patients during this induction phase. In case of significant desaturation (e.g. < 94% of oxygen), signs of respiratory distress and/or more than a 50% lung parenchyma impairment, we recommend pausing chemotherapy. Chemotherapy doses may also be delayed/reduced. Overall, we recommend a multidisciplinary discussion and/or with the protocol coordinators. After completion of chemotherapy, the use of G-CSF in a SARS-CoV-2-positive patient can be discussed to reduce the duration of neutropenia, in the absence of inflammatory signs attributable to COVID-19. The implementation of all or part of treatment on an outpatient basis must be carefully weighed. Indeed, the comings and goings to the ambulatory clinic and blood samplings at home increase the number of contacts at risk. Conversely, return at home could limit contact with caregivers, also possibly being SARS-CoV-2 carriers. A strict policy for family members is obviously to be established.

Note that the risk of needing an intensive care bed during induction therapy of ALL is low (probably <5%). However, in certain regions and/or time frames, the decrease in the number of pediatric ICU beds (transformed into adult resuscitation beds) implies that the pediatric need is being forcefully re-expressed.

Specific populations

a. Philadelphia chromosome ALL: some adult hematologists (see ASH adult ALL COVID19 recommendations) offer treatment with a tyrosine kinase inhibitor with minimal steroid exposure rather than aggressive induction with multidrug therapy for the initial treatment, in the hope of avoiding prolonged hospitalization during the pandemic [30]. However, the recommendation to keep on, including our patients in the EsPhall 2017 protocol with a regular use of imatinib, still seems appropriate to us.

b. Infants under one year of age: the risk of serious forms of COVID-19 in infants has been reported. The test for SARS-CoV-2, possibly repeated, is absolutely necessary here. Again, the recommendation is to follow the current guidelines i.e. to follow the Interfant 06 protocol.

c. Adolescents and young adults: clinicians may consider adolescents and young adults with a particular attention also taking into account the risk factors observed in adults, such as asthma, obesity and diabetes. To insist on compliance with treatment in general but also on adherence to barrier gestures and general sanitary measures, is of paramount importance.

d. Children with Down syndrome: vigilance is essential in these children susceptible to infections in general, even if this susceptibility rarely concerns viral infections. Some reports suggest that patients with Down syndrome have a greater risk of developing severe COVID-19 [31]. Of note, this group benefits from an induction with "only" 3 drugs in the CAALL-F01 protocol, including dexamethasone.

Are you changing the approach to intensive post-remission therapy (consolidation, delayed intensification)?

In the absence of data, our recommendation is to follow the protocol, including for corticosteroid therapy. As said in the general recommendations paragraph, each intensive course is to be preceded by a test.

For patients with high-risk ALL, an individualized decision regarding transplantation and its timing is necessary, weighing the risks of transplantation in an epidemic context of COVID-19 against the risk linked to ALL.

Are you changing your recommendations for maintenance treatment?

Three problems are mainly to be discussed:

- intensity of maintenance treatment with 6MP/MTX and targets for leukocytosis/neutrophils/lymphocytes: we suggest to follow the usual recommendations of the protocol;
- pulses: monthly pulses (CAALL-F01, B-SR group) or every 10 weeks (CAALL-F01, B-MR group) with vincristine and steroids are to be maintained. In case of symptoms, COVID19 testing the day before, should be performed: if COVID +, then postpone the pulse for about 2 weeks and perform another test before performing the pulse;
- high dose methotrexate cycles in maintenance for T-ALL with high initial leucocyte count ($\geq$ 100 G/L) and/or CNS3 status: any concern could be discussed with the protocol coordinators.

In addition, minimizing hospital visits seems appropriate. Home blood tests are to be preferred and partial use of telemedicine may be considered. However, a physical examination should be performed regularly to avoid any delay in the diagnosis of treatment complications or relapse. Of course, such an attitude is beneficial only if preventive measures are also applied at home.

Patients with second line or more ALL

Patients with relapsed ALL may be at greater risk of severe COVID-19 [23]. Test must be performed before starting a chemotherapy block, and postponing chemotherapy in case of positive test should be discussed in accordance with each specific situation and benefits/risks ratio regarding the leukemia.

- First relapse: we propose to include all eligible patients and/or to follow the INTREALL protocol as much as possible. Patients who reach complete remission n°2 should be considered promptly for allogeneic transplantation, as indicated in the protocol, despite the pandemic.
- Second relapse and refractory relapses:
  - Phase I–II trials: most if not all academic or industrial promoters ask now for SARS-CoV2 testing before inclusion. Any positivity is an at least temporary exclusion criterion.
  - CAR-T cells: The indication for treatment with CAR-T cells must be weighed with the center which would perform the procedure: feasibility of performing apheresis (systematic patient testing, problem of using an operating room for apheresis central line placement for example)? Manufacturing feasibility? Feasibility of administration according to the possible rooms in intensive care unit? [32,33]

What to do if an ALL patient is diagnosed with SARS-CoV-2 infection? What are the interactions between ALL chemotherapy and potential COVID-19 therapy?

General recommendations

1. The diagnosis of SARS-CoV-2 infection during the treatment of ALL should imply to discuss the stopping and/or postponing of all chemotherapies, according to the severity of the ALL, the stage of treatment and the severity of clinical and/or radiological signs. Even if severe forms have been described, most of the experience is currently reassuring [19,20,23].

2. Any "specific" treatment must be discussed with the infectious diseases team.

Potential interactions:

They are described in *table II* aiming to list some of the treatments with antiviral potential and some of those proposed to act against the inflammatory process. Of note, the inflammatory stage of covid19 infection is generally the one of aggravation, and often involves hospitalization in ICU. Chemotherapy, except for steroids, is obviously interrupted at this stage.

Which treatments may be considered in case of severe COVID-19?

As underlined above, any specific anti-COVID-19 treatment should be considered and discussed with the infectious diseases team. Great efforts have been made to evaluate the efficacy of repurposed drugs against SARS-CoV-2 infection (*tables II and III*). Accordingly with the recently published interim analysis of the Solidarity study, there is no clear evidence of efficacy on COVID-19-related mortality of any antiviral agent [34]. Though hydroxychloroquine and lopinavir/ritonavir therapeutic should be abandoned, remdesivir use could eventually be considered. In children, remdesivir may be proposed to positive patients who present potential risk factors of severe COVID-19 and should be given as early as possible in the course of the infection, for 10 days. Above 40 kg of weight, children may receive 200 mg the first day and 100 mg per day the next nine days. Below 40 kg of weight, children may receive 5 mg/kg on the first day and then 2.5 mg/kg once a day until 10 days of treatment [35].

Table II

Current treatments used or tested in clinical trials

Treatments with antiviral potential:
Remdesivir: **at best mild efficacy**
Possible renal adverse events
Not to be initiated or to be stopped if ALAT≥5 N
Low risk of drug interactions (check and update if co-prescription)
Convalescent plasma: **unproven efficacy**
No serious adverse events expected
Monitor according to usual transfusion procedures
Casirivimab and imdevimab monoclonal antibody (Mab) cocktail (REGN-COV2): **unproven efficacy**
No specific interaction expected
Possible hypersensitivity reaction or infusion-related reaction
Monitor as for any mAb infusion
Treatments acting on the consequences of inflammation:
Corticosteroids: **proven efficacy of dexamethasone in immunocompetent adults with a severe form of COVID-19 [29]**
Unproven efficacy in immunocompromised patients
Baricitinib: **potential efficacy in combination with remdesivir**
Potential interaction with methotrexate in theory but no evidence in clinical practice
Tocilizumab: **controversial efficacy**
No obvious interactions with chemotherapy
Anakinra: **unproven efficacy**
No obvious interactions with chemotherapy
Eculizumab: **unproven efficacy**
Randomized protocols in progress in adults

Table III
Treatments no more recommended

Hydroxychloroquine (OHQ): unproven efficacy. Not recommended
Be cautious about the use of OHQ with other agents prolonging the QTc interval such as azoles, macrolides, levofloxacin, tyrosine kinase inhibitors ++ (TKI)
Combination of lopinavir/ritonavir: unproven efficacy. Not recommended
May increase the concentration of methotrexate, monitoring is therefore suggested without empirical dose adjustment
interaction with vincristine. Dose reduction to be considered
Azithromycin: unproven efficacy. Not recommended
Closely monitor ciclosporin and creatinine blood concentrations
Increases QTc

Interestingly, evidence of prolonged viral shedding has been shown in immunosuppressed patients and could lead to discuss a more prolonged administration [36–38].

Among therapies acting on immune system and inflammation, there is no clear evidence that tocilizumab or anakinra are effective. However, dexamethasone use has been proven to be effective [29]. Convalescent plasma use may be safe and beneficial [29,39–41]. Convalescent plasma may especially be useful in immunosuppressed patients [42], but it may not be easily available and, at best, should be considered in a clinical trial setting.

Food and Drug Administration (FDA) has delivered in November 2020 an emergency use authorization for the specific monoclonal antibodies casirivimab and imdevimab against SARS-CoV-2, which may prevent aggravation of COVID-19 in patients who present a high risk of a severe disease [43,44]. An emergency use authorization has also been delivered for a Janus kinase inhibitor, baricitinib, which may be beneficial for patients requiring non-invasive ventilation in association with remdesivir [45]. Interestingly pediatric data are available for baricitinib in the setting of autoinflammatory diseases [46,47]. The french agency (ANSM) has implemented two temporary cohort use authorizations (ATUc) for the casirivimab / imdevimab combination (Roche) and the bamlanivimab / etesevimab combination (Lilly). It is too soon to claim that the monoclonal antibodies and baricitinib are really effective. Their use should ideally be considered in a clinical trial context, which is nevertheless unlikely to occur in the pediatric setting.

What are the recommendations regarding anticoagulation?

SARS-CoV-2 infection is associated with hypercoagulability and an increased risk of thrombosis, which participates to disease morbidity and mortality [48]. In children infected with SARS-CoV-2, hemostasis parameters also suggest a state of hypercoagulability, though the thrombotic risk is not well established in this population [49]. D-dimers and fibrinogen should be dosed and disseminated intravascular coagulation should be sought in the case of proven infection, and such dosages should be repeated during the course of COVID-19 [50]. The combination of the prothrombophilic status of the leukemia, the use of asparaginase and the presence of central venous line potentially increase the COVID-19-related thrombotic risk. Therefore, preventive anticoagulation with low molecular weight heparin should be considered. In case of suggestive symptoms, cerebral thrombophlebitis or any other thrombotic complication should be searched for, even in patients treated with preventive anticoagulation.

Are there biomarkers to predict COVID-19 complications?

There are currently no specific marker to predict COVID-19 complications. However, COVID-19 may be complicated by inflammation dysregulation and macrophage activation syndrome that may require a higher level of care. Thus, one could recommend to monitor ferritin levels, fibrinogen as well as hepatic enzymes and triglyceride levels, especially for patients who may be at a greater risk. Unfavorable outcomes may also be correlated to high SARS-CoV-2 viremia for which monitoring may be beneficial [51]. Tests may also be repeated until virus clearance, since virus shedding seems to be prolonged in the most immunocompromised patients [37]. Although its prognostic value is less clear in children, lymphopenia is associated with severe SARS-CoV-2 infection in both immunocompetent and immunocompromised adults [52–54]. Lymphopenia is common in children treated with chemotherapy, making difficult to clearly associate it with severe COVID-19. However, closely monitoring lymphocyte counts may be interesting in that context.

Who should be vaccinated primarily in the current era?

The recent availability of several vaccines brings a great hope among global population, even if evidence of long-term efficacy and safety are lacking [55–57]. The availability of such vaccines will still be limited in the next months and the priority use will be determined by HTAs (Health Technology Assessments) such as the Haute Autorité de Santé in France. Health care providers aged 50 years or more, or with comorbidities, have been the first professionals in France to receive the vaccine. Those working in our hematology-oncology units should be seen as an example for all health care providers and finally parents and families. Indeed when available, we may recommend to perform the vaccination of parents and siblings of patients who are the most at risk of developing COVID-19 complication (e.g. patients with recent HSCT history, relapsed leukemia under intensive treatment and any patient with significant comorbidity). A recent study suggests that patients with solid tumors may have an effective immune response to SARS-CoV-2, making vaccination in these patients a feasible option [38]. However, the immune response of patients with hematological cancers seems to be impaired, particularly those with B-cell malignancies, which on the one hand may explain their vulnerability and on the other hand argues in favour of vaccination of their relatives [38]. Another issue is the age, since the marketing authorization has been only given according to trial populations age range (lower age limit of 16 and 18 years for the Pfizer and Moderna vaccines respectively). The final issue is that those 2 first vaccines contain polyethylene glycol (PEG), which could be a problem, since children with ALL receive pegylated asparaginase. Vaccination after pegasparagas containg phases or using vaccines without PEG could be reasonable options.

Conclusion

Despite extremely rapid advances obtained in less than one year, our knowledge of SARS-Cov2 and its complications is still incomplete. We presented here an updated version of previous recommendations of the Leukemia committee of the SFCE [1]. We can anticipate that this current version will need an update in the next few months.

Disclosure of interest: the authors declare that they have no competing interest.

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