COVID-19 and Adult Acute Leukemia

Subjects: Hematology

Contributor: Franziska Modemann , Susanne Ghandili , Stefan Schmiedel , Katja Weisel , Carsten Bokemeyer , Walter Fiedler

The majority of publications regarding SARS-CoV-2 infections in adult patients with acute leukemia (AL) refer to hematological patients in general and are not focused on acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL). Overall, SARS-CoV-2-associated mortality ranges from 20–52% in patients with adult AL. AML patients have a particularly high COVID-19-related mortality. Of note, most of the available data relate to the pre-vaccination era and to variants before Omicron. The impact of COVID-19 infections on AL treatment is rarely reported. Treatment delay does not appear to be associated with an increased risk of relapse, whereas therapy discontinuation was associated with worse outcomes in AML patients. Therefore, the recommendations suggest delaying systemic AL treatment in SARS-CoV-2-positive patients until SARS-CoV-2 negativity, if immediate AL treatment is not required. It is recommended to offer vaccination to all AL patients; the reported antibody responses are around 80–96%. Seronegative patients should additionally receive prophylactic administration of anti-SARS-CoV-2 monoclonal antibodies. Patients with AL infected with SARS-CoV-2 should be treated early with antiviral therapy to prevent disease progression and enable the rapid elimination of the virus.

adult acute leukemia COVID-19 SARS-CoV-2

1. Introduction

In late 2019, the first cases of pneumonia caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were described in Wuhan, China [1]. Since then, the virus has rapidly spread worldwide, causing more than 525 million confirmed cases of SARS-CoV-2 infection with more than 6.2 million deaths [2].

The course of the disease—called corona virus infection disease 2019 (COVID-19) by the World Health Organization (WHO)—is nonspecific and can vary widely. The main route of infection is droplet and/or aerosol transmission [3]. Therefore, spatial distancing, contact restriction, wearing a protective medical mask, and hygiene measures were generally recommended. Most infections in the general population are mild; around 85% in the pre-vaccination era had mild symptoms such as fever, cough, fatigue, and headache; up to 10% had critical courses, and the mortality rate was around 5–7% [4]. The clinical symptoms are not unique and can range from fever, dry cough, and malaise to life-threatening pneumonia with acute respiratory distress syndrome disseminated intravascular coagulopathy, and associated thrombotic events or neurologic dysfunction and cardiomyopathy, multiorgan failure, and death [5][6]. The average incubation period of SARS-CoV-2 is about five days, but can last two weeks until the infected person becomes ill [7]. However, the infected person may be contagious even for several days before the onset of any symptoms [8]. This often makes it difficult to trace contacts to break chains of

infection. At the same time, it is also becoming difficult in hospitals to isolate patients to properly prevent infections. Furthermore, during the pandemic, different SARS-CoV-2 variants were identified to carry the risk of different virulence, dissemination in the organism, alteration of the disease pattern, or increased mortality [9][10].

By the end of 2020, the US Food and Drug Administration (FDA) authorized the first- and second-in-class SARS-CoV-2 messenger ribonucleic acid (mRNA) vaccines BNT162b2 and mRNA1273 for emergency use [11][12]. The European Medicines Agency (EMA) followed shortly after with the additional approval of the first-in-class anti-SARS-CoV-2 vector vaccine AZD1222 [13][14][15]. Until now, over 10 billion vaccine doses have been administered worldwide [2]. However, the different SARS-CoV-2 variants also play a role in vaccine-induced immunity, with some subtypes in which the reduced effectiveness of protective vaccinations could be observed [16][17].

In general, the risk of pneumonia from respiratory viruses is higher in cancer patients, which also applies to infections with SARS-CoV-2 [18][19][20][21]. A large Chinese pre-vaccination study identified cancer as the highest individual risk factor for severe events during COVID-19 in a logistic regression model (OR: 5.4, p = 0.003) [19]. Moreover, cancer patients had significantly higher rates of severe COVID-19 courses (including admission to the intensive care unit, invasive ventilation, or death) compared with non-cancer patients (p = 0.0003) [19]. Recent meta-analyses reported high COVID-19-associated mortality rates in cancer patients ranging between 17 and 26% [22][23][24]. Patients with hematological malignancies and particularly patients with acute leukemia (AL) during induction chemotherapy are at high risk of developing infection complications due to profound and prolonged neutropenia [25][26]. The knowledge of the disease course and management of patients with AL and COVID-19 is constantly changing. However, only a few comprehensive research provide an overview of the clinical features, prevention, and treatment in this particular population.

Most of the available data on the impact of COVID-19 in hematological patients include various hematologic malignancies and do not focus on acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL). For this reason, the transfer of previous findings in hematological patients to AL patients is restricted. Treating patients with AL and concomitant COVID-19 challenges hematologists worldwide and requires interdisciplinary cooperation between hematologists and infectiologists. On the one hand, newly diagnosed AL requires an urgent need for chemotherapy without long delays. On the other hand, intensive therapy might increase the risk of severe courses of COVID-19. Therefore, the systemic treatment of AL has to be considered carefully.

2. Clinical Courses

Overall, across all COVID-19 waves, the SARS-CoV-2-associated mortality ranged from 20–52% in patients with AL [27][28][29]. However, no comprehensive data are yet available for the Omicron variant.

One of the largest multi-center trials investigating the impact of COVID-19 in adult AML patients was recently published by the European Hematology Association [27]. The EPICOVIDEHA registry included 388 adult AML patients with a COVID-19 diagnosis between February 2020 and October 2021. Severe and critical courses of COVID-19 occurred in 41% and 21%, respectively. Death due to COVID-19 was reported in 20% of patients.

Ongoing or recent AML treatment (defined as less than three months before SARS-CoV-2 infection) was associated with higher mortality rates due to COVID-19, as well as active leukemic disease, older age, and treatment discontinuation. Significantly lower overall survival was observed in patients diagnosed between January 2020 and August 2020 (first wave), compared to those after September 2020 (41% vs. 25%, $p < 0.0001$) [27]. This is the only more extensive data set that allows a comparison between the different SARS-CoV-2 waves. The own experience from the department—treating around 90 newly diagnosed AL patients per year—underlines the results reported by the EPICOVIDEHA trial by observing no cases of severe or critical COVID-19 courses in AL patients since Omicron appeared. Previous results also reported by the EPICOVIDEHA registry trial from the pre-vaccination era regarding patients with hematological malignancies showed a high overall mortality rate of 40% in the subset of adult AML and 26% in adult ALL patients [30]. In the entire cohort of patients with hematological malignancies, AML and high-risk myelodysplastic syndrome (MDS) displayed the highest overall mortality, and AML was the only independent risk factor for mortality in the multivariate analysis [30]. Another two large observational studies reported by the PETHEMA group from the first SARS-CoV-2 wave included 108 and 117 adult AML patients, showing a comparable high mortality rate of 43.5% and 48%, respectively [31][32]. Interestingly, the mortality rates reported from four Latin American countries with limited medical resources did not differ, with a mortality rate of 37% in 83 patients with AL [29]. However, Mitrovic et al. reported a lower mortality rate of 29% in 51 patients with AL from the pre-vaccination era in Serbia, with worse overall survival in patients with newly diagnosed leukemia and those with profound neutropenia [28]. A large proportion of other published data sets include hematological patients in general [33][34][35][36][37]. García-Suárez et al. reported on one of the largest sub-cohorts of AL patients, showing 48% severe courses of COVID-19 and 26% critical courses in 61 patients with AML, leading to an overall mortality rate of 44% [34]. This region- or country-specific high mortality rates are paralleled by an early global data set of the American Society of Hematology (ASH) Research Collaborative COVID-19 Registry for Hematology, which describes a mortality rate of 33% in 80 patients with AL and concomitant SARS-CoV-2 infection [38]. Moreover, two important publications by Italian and Spanish multicenter registries reported the subgroup of adult ALL patients infected with SARS-CoV-2, describing an overall mortality rate between 11% and 33% [39][40].

Most of the further literature explicitly describing the clinical course of COVID-19 in adult AL patients is based on small case series and single case reports [36][41][42][43][44][45].

General risk factors for developing severe and critical courses of COVID-19 are summarized by the European Conference on Infections in Leukemia 9 (ECIL 9) statement: older age, cardiovascular and metabolic comorbidities, and an active or uncontrolled malignancy represent the main risk factors for mortality in AL patients who are infected with SARS-CoV-2 [46].

3. Impact of COVID-19 on AL Treatment

Publications on the impact of COVID-19 on AL treatment and recommendations for treatment modifications in patients with AL are scarce or mostly based on expert opinion. This gap in knowledge makes it difficult to establish the best therapeutic strategies for patients with AL and concomitant SARS-CoV-2 infection. The two main questions arising regarding the therapy of adult AL patients in the setting of COVID-19 are the following:

(1) should AL treatment be delayed or discontinued in the case of SARS-CoV-2 positivity?

(2) can intensive AL treatment schedules still be considered during the COVID-19 pandemic?

In the most recently published cohort of 388 adult AML patients, chemotherapeutic schedules were modified in 45% of patients. Of those, therapy was delayed in 39% and treatment was discontinued in 61% [27]. Interestingly, Marchesi et al. showed that a treatment delay was protective in a multivariate analysis for the clinical course of COVID-19, whereas therapy discontinuation was associated with worse outcomes. These results were also applicable to patients with newly diagnosed AML in whom a treatment delay was possible [27]. The Latin American study investigating 83 patients with AL reported therapy modifications in 49% of patients; the main modification was a delay of treatment, followed by a change in therapy scheme and a dose reduction (no data available about discontinuation). None of the treatment modifications were significantly associated with an increased risk of relapse [29]. At the beginning of the COVID-19 pandemic in 2020, Zeidan et al. recommended to post-pone all AL therapies for 10–14 days in SARS-CoV-2-infected patients, if the immediate treatment of AL was not deemed necessary [47]. This recommendation still applies. If possible, induction treatment should be delayed in the case of SARS-CoV-2 positivity until PCR negativity, according to the current ASH and ECIL 9 recommendations [46][48]. Of note, the time of SARS-CoV-2 clearance might be prolonged in AL patients for up to 82 days [32][41][49]. Furthermore, despite the COVID-19 pandemic, consolidation therapy with high-dose cytarabine should be offered to patients in complete remission. High-dose cytarabine should be reduced to 1.5 g/m^2 and a reduction in the number of consolidation cycles should be considered [47][48][50].

Most reported data sets describing differences in the outcome of AL patients treated with intensive or non-intensive treatment schedules are based on small case series. Remarkably, treatment with demethylating agents before COVID-19 in patients with hematological malignancies displayed the highest mortality rate with 59% in the first published EPICOVIDEHA registry trial [30]. However, these results were not confirmed by the most recent research published by Marchesi et al., who did not observe significant differences between therapeutic approaches of different intensity, and demethylating agents in particular [27]. Nevertheless, these results contrast the observations of Garcia et al. and the Asociación Madrileña de Hematología y Hemoterapia group, reporting a significantly lower mortality rate in 32 patients with AML or MDS receiving hypomethylating agents before COVID-19 [34].

According to the current recommendations of the ASH, the European Society for Blood and Marrow Transplantation (ESBMT), and Zeidan et al., intensive chemotherapy should be offered to AML patients who are considered eligible for intensive chemotherapy [47][48][51]. However, to avoid hospitalization and to reduce transfusion frequency in the case of local outbreaks or a shortage of beds and blood supplies, low-dose therapy with azacytidine in combination with venetoclax may be considered as an alternative, especially in those patients with reduced performance status [34][41][42][48][52][53].

Large data sets are missing for adult ALL patients with COVID-19 due to the low ALL incidence in adults. The ASH recommends delaying systemic ALL treatment. Since the detection of SARS-CoV-2 can be prolonged for up to 91 days in ALL patients, it remains unclear how to proceed with these patients [39]. However, intrathecal therapy

should not be delayed in the case of central nervous system symptoms [54]. Since corticosteroids are essential components of ALL treatment, it is highly recommended by the ESBMT to proceed with a standard dosage of corticosteroids in ALL patients, even if there might be a potential risk for provoking viral rebound [51]. Furthermore, the administration of peg-asparaginase as an essential compound in ALL treatments is challenging due to the increased risk of thrombotic events caused by COVID-19. Nevertheless, peg-asparaginase should be administered under the intensive monitoring of coagulation parameters in SARS-CoV-2-infected ALL patients according to the ESBMT recommendations [51]. For Philadelphia chromosome-positive ALL patients, it is recommended to switch the therapeutic approach to tyrosine-kinase-inhibitor-based treatment in combination with steroids rather than multi-agent chemotherapy [54][55]. This approach has been reported as feasible by the CAMPUS ALL Network [39]. The use of rituximab during consolidation therapy is controversial and no clear recommendations are available [54]. It is recommended to withhold the treatment of patients during maintenance therapy until symptoms are resolved for at least two weeks [54].

Whether profound and prolonged neutropenia is a risk factor for a high mortality rate in AL patients with COVID-19 is still controversial and remains unanswered. In a recent US study, neutropenia seven days before and 28 days after SARS-CoV-2 infection was identified as an independent risk factor for higher mortality [56]. In cancer patients in general, severe neutropenia was also associated with a worse outcome [57]. However, in the large study of 388 adult AML patients by Marchesi et al., neutropenia was not identified in the multivariate analysis as an independent risk factor in COVID-19 [27]. Nevertheless, in the current statement of the ASH and by Zeidan and colleagues, experts recommend strongly considering the use of growth factors to reduce the duration of neutropenia in patients who are not suffering from severe COVID-19 [47][48]. Since there is a rare but potential risk of aggravating COVID-19-related inflammatory pulmonary injury in patients with a severe and critical course of COVID-19 by applying granulocyte stimulating factor, the administration of growth factors is not recommended in this patient cohort [46][47].

4. General Recommendations

In patients with AL it is recommended to:

- continue environmental precautions such as wearing a face mask, social distancing, reducing, e.g., visitor restriction, ventilation of rooms, patient isolation, and following general hygiene measures [28][46][58][59][60]
- before starting treatment, screen for COVID-19 as close to treatment start as possible [47][48][51][54][58][61]
- universally screen of all visitors [58]
- test for COVID-19 if a patient has COVID-19-specific symptoms regardless of the time point of the last negative COVID-19 test [28][48][58]
- use approved disinfectants for regularly decontaminating surfaces in hospitals [58][62][63]

- minimalize hospital stay by discharging early [58]
- shift as many aspects of care into the outpatient setting as possible [46][47][48][50][51][54][58]

5. Vaccination and Treatment of COVID-19

The global impact of the current COVID-19 pandemic has led to the impressively rapid development of multiple SARS-CoV-2-directed vaccines, which are each highly effective in healthy populations. In all AL patients, SARS-CoV-2 vaccination is generally recommended by several hematological societies [46][48][54]. In contrast to most B-cell malignancies after complete vaccination with mRNA vaccines, high serological responses of 80% to 96% were observed in the subsets of AML and ALL patients after complete vaccination with mRNA vaccines [64][65][66][67]. Up to 96% of seroconversion has been observed in elderly AML patients treated with demethylating agents with or without venetoclax [66]. As previously described, the serological vaccination response is impaired in patients who received CD20-directed treatment, which is used in most ALL patients [64].

In addition to vaccination, the intramuscular application of a single dose of the two SARS-CoV-2 neutralizing spike antibodies tixagevimab and cilgavimab should be considered for pre-exposition prophylaxis in AL patients [68]. Therefore, all AL patients should be tested for their antibody levels before AL-specific treatment, irrespectively of their vaccination status. The recently published results of the ongoing phase III PROVENT trial, which included a comparably small subset of 197 immunosuppressed patients, showed an overall risk reduction of 83% for COVID-19-related hospitalization when comparing tixagevimab and cilgavimab to a placebo [69]. Other neutralizing spike antibodies showing promising results regarding the pre-exposition prophylaxis of COVID-19 are casirivimab and imdevimab, and the monoclonal antibody sotrovimab [70]. However, casirivimab, imdevimab, and sotrovimab showed less efficacy in vitro against the currently predominant SARS-CoV-2 variant Omicron and also appeared to be less effective in patients than the other neutralizing spike antibodies in reducing the time to recovery from the SARS-CoV-2 Omicron variant [71][72]. Therefore, the therapeutic impact of anti-spike-protein antibodies for the prevention and treatment of currently circulating SARS-CoV-2 variants (BA.2, BA.4, BA.5) remains unclear. An exception is bebtelovimab, a monoclonal antibody that showed efficacy against the Omicron variant and has now achieved an emergency use authorization by the FDA for the treatment of mild-to-moderate COVID-19 in non-hospitalized patients who are at high risk of progression to severe COVID-19, for whom alternative COVID-19 treatment options are not accessible or clinically appropriate based on the results of the BLAZE-4 trial (NCT04634409). However, up to now it is unknown if patients with acute leukemia were included in the BLAZE-4 trial [73]. In patients with an increased risk of severe courses of COVID-19, several antivirals are now available to prevent severe or critical courses. The orally administered combination of nirmatrelvir/ritonavir demonstrated a reduction in COVID-19-associated hospitalization and mortality compared to the placebo from 7% to 0.8% in non-hospitalized patients with COVID-19 and without additional oxygen requirements, but with at least one risk factor for a severe course of COVID-19, including patients with immunosuppression [74]. Drug interactions, particularly with venetoclax due to its metabolism via CYP3A4 enzymes, must be considered when treating AL patients with antiviral compounds. Moreover, early treatment with molnupiravir therapy also reduced the risk of hospitalization or death in non-hospitalized adults with laboratory-confirmed SARS-CoV-2 infection and at least one risk factor for

severe COVID-19, including cancer patients, from 10% to 7% compared to the placebo [75]. However, both trials reported on the risk reduction in an unvaccinated research population. Moreover, early treatment with remdesivir was associated with a reduction in hospitalization or mortality from 5% to 0.7% among non-hospitalized adults who were at high risk for severe COVID-19, compared to the placebo [76]. Furthermore, an observational trial including 313 patients with hematological malignancies showed a reduced mortality rate in patients treated with remdesivir [77]. The results of reducing severe courses in COVID-19 by administering antivirals cannot generally be transferred to COVID-19 vaccine breakthrough infections since the results are mainly based on cases from the pre-vaccination era. The use of other therapeutic agents with antiviral efficacy such as (hydroxy-) chloroquine, lopinavir/ritonavir and azithromycin have not been studied in clinical trials, and these compounds should not be used. This also applies to ivermectin, arbidol, or favipiravir [46][78][79].

In addition to antivirals, monoclonal anti-SARS-CoV-2 antibodies (SARS-CoV-2-moab) are available for treating SARS-CoV-2-infected patients, such as sotrovimab, casirivimab/imdevimab, bamlanivimab/etesevimab, bebtelovimab or regdanvimab. There is very limited data on the use of these antibodies in patients with AL. The choice of the antibody for treating COVID-19 should be based on national approval, local availability, and the current, local circulating SARS-CoV-2 variants, since not all antibodies could show efficacy against all SARS-CoV-2 variants [46][71][72]. Sotrovimab showed the highest efficacy against the Omicron variant amongst all SARS-CoV-2-moab and reduced the hospitalization and death rates in patients at risk for developing a severe COVID-19 course [80][81]. Unfortunately, there is a lack of information regarding the efficacy in patients with AL. Nevertheless, SARS-CoV-2-moab have low side effects [82][83] and the risk for interactions with AL treatment medication is low. However, judging from the laboratory data, all available monoclonal anti-SARS-CoV-2 antibodies seem to have reduced or no activity against the currently circulating Omicron virus variants [70][71].

Another option to prevent developing severe SARS-CoV-2 courses is the treatment with convalescent plasma. An early administration <72 h after SARS-CoV-2 infection and high-titer convalescent plasma showed a reduced progression rate to severe COVID-19, but in the meta-analysis, higher recovery rates or improved survival were not observed [84][85]. Nevertheless, in patients with hematological malignancies, a statistically significant benefit for clinical recovery and SARS-CoV-2-associated mortality was observed [86]. As SARS-CoV-2-moab, convalescent plasma has low side effects and low risk for drug interactions, but after the approval of the SARS-CoV-2-moabs, this therapy has clearly lost its importance due to the residual risk of infection transmission from the donor.

The main cause of mortality in SARS-CoV-2-infected patients is the development of hyper-inflammation syndrome [87]. There are different therapeutic strategies to treat COVID-19 patients who develop hyper-inflammation. Steroid therapy with dexamethasone 6 mg for 10 days demonstrated a 3% reduction in mortality in the large RECOVERY trial compared to the usage of usual care [88]. Of note, steroids should only be administered in those patients who enter the hyper-inflammatory phase and not in patients in the early viral phase who do not need oxygen therapy, since adverse effects have been shown in these patients [87]. Higher dosages of dexamethasone than 6 mg are not recommended [89]. In addition to steroids, therapy with anti-interleukin-1 (IL-1) and anti-interleukin-6 (IL-6) monoclonal antibodies has also been investigated for patients with hyper-inflammatory syndrome. Anti-IL-6 treatment showed a benefit in clinical recovery and reduced the rate of disease progression and mortality in

patients under oxygen therapy [90][91][92]. For anti-IL-1 treatment, only one study is available, showing the effectiveness of anti-IL-1 administration in patients with high a inflammatory state [93]. Studies on patients with AL are missing.

Treatment recommendations in the case of infection with SARS-CoV-2 in AL patients are dynamically changing. The last recommendations were published by the ECIL in April 2022, suggesting the following approaches for patients with AL based on the available data described above [46]:

- in AL patients with mild COVID-19 disease, SARS-CoV-2-moab, high-titer convalescent plasma for seronegative patients, molnupiravir, nirmatrelvir/ritonavir, and/or remdesivir are recommended. Dexamethasone is not recommended [46]

- in AL patients with moderate or severe COVID-19 disease, remdesivir, dexamethasone, anti-IL-1 antibody, and anti-IL-6 antibody are recommended. If patients are seronegative, SARS-CoV-2-moab or convalescent plasma is additionally suggested. It is not recommended to discontinue or adjust any AL-specific immunosuppressive therapy [46]

- in AL patients with critical COVID-19 disease, dexamethasone and, if necessary, anti-IL-6 antibody treatment is recommended. If patients are seronegative, SARS-CoV-2-moab and/or high titer convalescent plasma are additionally suggested. It is not recommended to discontinue or adjust any AL-specific immunosuppressive therapy [46]

However, the landscape of current virus variants is changing rapidly, and several studies are evaluating the efficacy of the above-mentioned therapeutic options regarding new circulating virus variants. Therefore, the latest recommendations by the ECIL should be individually discussed in every patient. In general, patients with AL should be treated early with antiviral therapy to prevent disease progression. In addition, rapid elimination of the virus should be attempted, otherwise patients with underlying AL may remain positive for a very long time. When hyper-inflammatory syndrome occurs, it should be treated rapidly as well [46].

Another major challenge in AL patients who are infected with SARS-CoV-2 is the prevention of thromb-embolic events, since infection with SARS-CoV-2 is associated with a higher risk for developing thromb-embolic events [94]. The current ASH recommendations conclude that:

- patients without suspected/confirmed thrombosis who are treated in an outpatient setting should not receive anticoagulant thromboprophylaxis [95]

- patients without suspected or confirmed thrombosis who are acutely ill from COVID-19 should be treated with therapeutic-intensity anticoagulation. Acutely ill patients are defined as those who are administered to the hospital due to COVID-19 symptoms but who are not treated at an intensive care unit [95]

- patients without suspected or confirmed thrombosis who are critically ill from COVID-19 should be treated with prophylactic-intensity anticoagulation. Critically ill patients are defined as those who are administered to an intensive care unit due to COVID-19-associated symptoms [95]

Since the majority of AL patients suffer from thrombocytopenia due to the underlying disease or AL therapy, anticoagulation should be adjusted regarding the current thrombocyte count and coagulation status in each patient according to the local hospital standard operating procedures.

References

1. Zhu, N.; Zhang, D.; Wang, W.; Li, X.; Yang, B.; Song, J.; Zhao, X.; Huang, B.; Shi, W.; Lu, R.; et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N. Engl. J. Med. 2020, 382, 727–733.
2. World Health Organization. WHO Corona Virus (COVID-19) Dash Board. Available online: https://covid19.who.int (accessed on 17 June 2022).
3. Salian, V.S.; Wright, J.A.; Vedell, P.T.; Nair, S.; Li, C.; Kandimalla, M.; Tang, X.; Carmona Porquera, E.M.; Kalari, K.R.; Kandimalla, K.K. COVID-19 Transmission, Current Treatment, and Future Therapeutic Strategies. Mol. Pharm. 2021, 18, 754–771.
4. Boban, M. Novel coronavirus disease (COVID-19) update on epidemiology, pathogenicity, clinical course and treatments. Int. J. Clin. Pract. 2021, 75, e13868.
5. Guan, W.J.; Ni, Z.Y.; Hu, Y.; Liang, W.H.; Ou, C.Q.; He, J.X.; Liu, L.; Shan, H.; Lei, C.L.; Hui, D.S.C.; et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N. Engl. J. Med. 2020, 382, 1708–1720.
6. Hu, B.; Guo, H.; Zhou, P.; Shi, Z.L. Characteristics of SARS-CoV-2 and COVID-19. Nat. Rev. Microbiol. 2021, 19, 141–154.
7. Salzberger, B.; Buder, F.; Lampl, B.; Ehrenstein, B.; Hitzenbichler, F.; Holzmann, T.; Schmidt, B.; Hanses, F. Epidemiology of SARS-CoV-2. Infection 2021, 49, 233–239.
8. Johansson, M.A.; Quandelacy, T.M.; Kada, S.; Prasad, P.V.; Steele, M.; Brooks, J.T.; Slayton, R.B.; Biggerstaff, M.; Butler, J.C. SARS-CoV-2 Transmission from People without COVID-19 Symptoms. JAMA Netw. Open 2021, 4, e2035057.
9. Lippi, G.; Mattiuzzi, C.; Henry, B.M. Updated picture of SARS-CoV-2 variants and mutations. Diagnosis 2021, 9, 11–17.
10. Dubey, A.; Choudhary, S.; Kumar, P.; Tomar, S. Emerging SARS-CoV-2 Variants: Genetic Variability and Clinical Implications. Curr. Microbiol. 2021, 79, 20.

11. U.S. Food & Drug. US FDA Moderna COVID-19 Vaccine|FDA: @US_FDA. Available online: https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/spikevax-and-moderna-covid-19-vaccine (accessed on 17 June 2022).
12. U.S. Food & Drug. US FDA Pfizer-BioNTech COVID-19 Vaccine. Available online: https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/comirnaty-and-pfizer-biontech-covid-19-vaccine (accessed on 17 June 2022).
13. European-Medicines-Agency. European-Medicines-Agency Comirnaty. Available online: https://www.ema.europa.eu/en/medicines/human/EPAR/comirnaty (accessed on 17 June 2022).
14. European-Medicines-Agency. European-Medicines-Agency COVID-19 Vaccine Moderna. Available online: https://www.ema.europa.eu/en/medicines/human/EPAR/spikevax (accessed on 17 June 2022).
15. European-Medicines-Agency. European-Medicines-Agency Vaxzevria (Previously COVID-19 Vaccine AstraZeneca). Available online: https://www.ema.europa.eu/en/medicines/human/EPAR/vaxzevria-previously-covid-19-vaccine-astrazeneca (accessed on 17 June 2022).
16. Singh, D.D.; Parveen, A.; Yadav, D.K. SARS-CoV-2: Emergence of New Variants and Effectiveness of Vaccines. Front. Cell Infect. Microbiol. 2021, 11, 777212.
17. Lucas, C.; Vogels, C.B.F.; Yildirim, I.; Rothman, J.E.; Lu, P.; Monteiro, V.; Gehlhausen, J.R.; Campbell, M.; Silva, J.; Tabachnikova, A.; et al. Impact of circulating SARS-CoV-2 variants on mRNA vaccine-induced immunity. Nature 2021, 600, 523–529.
18. von Lilienfeld-Toal, M.; Berger, A.; Christopeit, M.; Hentrich, M.; Heussel, C.P.; Kalkreuth, J.; Klein, M.; Kochanek, M.; Penack, O.; Hauf, E.; et al. Community acquired respiratory virus infections in cancer patients—Guideline on diagnosis and management by the Infectious Diseases Working Party of the German Society for haematology and Medical Oncology. Eur. J. Cancer 2016, 67, 200–212.
19. Liang, W.; Guan, W.; Chen, R.; Wang, W.; Li, J.; Xu, K.; Li, C.; Ai, Q.; Lu, W.; Liang, H.; et al. Cancer patients in SARS-CoV-2 infection: A nationwide analysis in China. Lancet Oncol. 2020, 21, 335–337.
20. Dai, M.; Liu, D.; Liu, M.; Zhou, F.; Li, G.; Chen, Z.; Zhang, Z.; You, H.; Wu, M.; Zheng, Q.; et al. Patients with Cancer Appear More Vulnerable to SARS-CoV-2: A Multicenter Study during the COVID-19 Outbreak. Cancer Discov. 2020, 10, 783–791.
21. Zhang, L.; Zhu, F.; Xie, L.; Wang, C.; Wang, J.; Chen, R.; Jia, P.; Guan, H.Q.; Peng, L.; Chen, Y.; et al. Clinical characteristics of COVID-19-infected cancer patients: A retrospective case study in three hospitals within Wuhan, China. Ann. Oncol. 2020, 31, 894–901.

22. Venkatesulu, B.P.; Chandrasekar, V.T.; Girdhar, P.; Advani, P.; Sharma, A.; Elumalai, T.; Hsieh, C.; Elghazawy, H.I.; Verma, V.; Krishnan, S. A systematic review and meta-analysis of cancer patients affected by a novel coronavirus. medRxiv 2020, 5, pkaa102.
23. Reboot: COVID-Cancer Project. Available online: https://rebootrx.org/covid-cancer (accessed on 17 June 2022).
24. Saini, K.S.; Tagliamento, M.; Lambertini, M.; McNally, R.; Romano, M.; Leone, M.; Curigliano, G.; de Azambuja, E. Mortality in patients with cancer and coronavirus disease 2019: A systematic review and pooled analysis of 52 studies. Eur. J. Cancer 2020, 139, 43–50.
25. Peseski, A.M.; McClean, M.; Green, S.D.; Beeler, C.; Konig, H. Management of fever and neutropenia in the adult patient with acute myeloid leukemia. Expert Rev. Anti-Infect. Ther. 2021, 19, 359–378.
26. Klastersky, J.; de Naurois, J.; Rolston, K.; Rapoport, B.; Maschmeyer, G.; Aapro, M.; Herrstedt, J.; Committee, E.G. Management of febrile neutropaenia: ESMO Clinical Practice Guidelines. Ann. Oncol. 2016, 27, v111–v118.
27. Marchesi, F.; Salmanton-Garcia, J.; Emarah, Z.; Piukovics, K.; Nucci, M.; Lopez-Garcia, A.; Racil, Z.; Farina, F.; Popova, M.; Zompi, S.; et al. COVID-19 in adult acute myeloid leukemia patients: A long-term followup study from the European Hematology Association survey (EPICOVIDEHA). Haematologica 2022.
28. Mitrovic, M.; Pantic, N.; Sabljic, N.; Vucic, M.; Bukumiric, Z.; Virijevic, M.; Pravdic, Z.; Rajic, J.; Todorovic-Balint, M.; Vidovic, A.; et al. Acute leukemia and SARS-CoV-2 infection: Clinical characteristics and risk factors for mortality. Leuk Lymphoma 2021, 62, 3516–3520.
29. Demichelis-Gomez, R.; Alvarado-Ibarra, M.; Vasquez-Chavez, J.; Delgado-Lopez, N.; Gomez-Cortes, C.; Espinosa-Bautista, K.; Cooke-Tapia, A.; Milan-Salvatierra, A.; Gomez-De Leon, A.; Lee-Tsai, Y.L.; et al. Treating Acute Leukemia During the COVID-19 Pandemic in an Environment with Limited Resources: A Multicenter Experience in Four Latin American Countries. JCO Glob. Oncol. 2021, 7, 577–584.
30. Pagano, L.; Salmanton-Garcia, J.; Marchesi, F.; Busca, A.; Corradini, P.; Hoenigl, M.; Klimko, N.; Koehler, P.; Pagliuca, A.; Passamonti, F.; et al. COVID-19 infection in adult patients with hematological malignancies: A European Hematology Association Survey (EPICOVIDEHA). J. Hematol. Oncol. 2021, 14, 168.
31. Palanques-Pastor, T.; Megias-Vericat, J.E.; Martinez, P.; Lopez Lorenzo, J.L.; Cornago Navascues, J.; Rodriguez Macias, G.; Cano, I.; Arnan Sangerman, M.; Vidriales Vicente, M.B.; Algarra Algarra, J.L.; et al. Characteristics, clinical outcomes, and risk factors of SARS-CoV-2 infection in adult acute myeloid leukemia patients: Experience of the PETHEMA group. Leuk Lymphoma 2021, 62, 2928–2938.

32. Martínez, P.; Palanques Pastor, T.; Lopez Lorenzo, J.L.; Cornago Navascués, J.; Rodriguez-Macías, G.; Cano, I.; Arnan Sangerman, M.; Vidriales, M.-B.; Algarra, J.L.; Foncillas, M.A.; et al. Impact of SARS-CoV-2 Infection in Acute Myeloid Leukemia Patients: Experience of the Pethema Registry. Blood 2020, 136, 7–8.

33. Passamonti, F.; Cattaneo, C.; Arcaini, L.; Bruna, R.; Cavo, M.; Merli, F.; Angelucci, E.; Krampera, M.; Cairoli, R.; Della Porta, M.G.; et al. Clinical characteristics and risk factors associated with COVID-19 severity in patients with haematological malignancies in Italy: A retrospective, multicentre, cohort study. Lancet Haematol. 2020, 7, e737–e745.

34. Garcia-Suarez, J.; de la Cruz, J.; Cedillo, A.; Llamas, P.; Duarte, R.; Jimenez-Yuste, V.; Hernandez-Rivas, J.A.; Gil-Manso, R.; Kwon, M.; Sanchez-Godoy, P.; et al. Impact of hematologic malignancy and type of cancer therapy on COVID-19 severity and mortality: Lessons from a large population-based registry study. J. Hematol. Oncol. 2020, 13, 133.

35. Ruthrich, M.M.; Giessen-Jung, C.; Borgmann, S.; Classen, A.Y.; Dolff, S.; Gruner, B.; Hanses, F.; Isberner, N.; Kohler, P.; Lanznaster, J.; et al. COVID-19 in cancer patients: Clinical characteristics and outcome-an analysis of the LEOSS registry. Ann. Hematol. 2021, 100, 383–393.

36. Nunez-Torron, C.; Garcia-Gutierrez, V.; Tenorio-Nunez, M.C.; Moreno-Jimenez, G.; Lopez-Jimenez, F.J.; Herrera-Puente, P. Poor outcome in patients with acute leukemia on intensive chemotherapy and COVID-19. Bone Marrow Transpl. 2021, 56, 267–269.

37. Yigenoglu, T.N.; Ata, N.; Altuntas, F.; Basci, S.; Dal, M.S.; Korkmaz, S.; Namdaroglu, S.; Basturk, A.; Hacibekiroglu, T.; Dogu, M.H.; et al. The outcome of COVID-19 in patients with hematological malignancy. J. Med. Virol. 2021, 93, 1099–1104.

38. Wood, W.A.; Neuberg, D.S.; Thompson, J.C.; Tallman, M.S.; Sekeres, M.A.; Sehn, L.H.; Anderson, K.C.; Goldberg, A.D.; Pennell, N.A.; Niemeyer, C.M.; et al. Outcomes of patients with hematologic malignancies and COVID-19: A report from the ASH Research Collaborative Data Hub. Blood Adv. 2020, 4, 5966–5975.

39. Chiaretti, S.; Bonifacio, M.; Agrippino, R.; Giglio, F.; Annunziata, M.; Curti, A.; Principe, M.I.D.; Salutari, P.; Sciume, M.; Delia, M.; et al. COVID-19 Infection in acute lymphoblastic leukemia over 15 months of the pandemic. A CAMPUS ALL report. Haematologica 2022.

40. Ribera, J.M.; Morgades, M.; Coll, R.; Barba, P.; Lopez-Lorenzo, J.L.; Montesinos, P.; Foncillas, M.A.; Cabrero, M.; Gomez-Centurion, I.; Morales, M.D.; et al. Frequency, Clinical Characteristics and Outcome of Adults with Acute Lymphoblastic Leukemia and COVID 19 Infection in the First vs. Second Pandemic Wave in Spain. Clin. Lymphoma Myeloma Leuk 2021, 21, e801–e809.

41. Ghandili, S.; Pfefferle, S.; Roedl, K.; Sonnemann, P.; Karagiannis, P.; Boenisch, O.; Kluge, S.; Schmiedel, S.; Ittrich, H.; Rohde, H.; et al. Challenges in treatment of patients with acute leukemia and COVID-19: A series of 12 patients. Blood Adv. 2020, 4, 5936–5941.

42. Taurino, D.; Frigeni, M.; Grassi, A.; Cavallaro, G.; Salmoiraghi, S.; Spinelli, O.; Rambaldi, A.; Lussana, F. Concurrent Diagnosis of Acute Myeloid Leukemia and Symptomatic COVID-19 Infection: A Case Report Successfully Treated with Azacitidine-Venetoclax Combination. Mediterr. J. Hematol. Infect. Dis. 2021, 13, e2021057.
43. Rajasurya, V.; Elliott, K.; Dugan, J.; Moreb, J.S. COVID-19 in patients with acute leukemia: Two cases with different outcomes. Leuk Res. Rep. 2021, 15, 100232.
44. Ferrara, F.; Zappasodi, P.; Roncoroni, E.; Borlenghi, E.; Rossi, G. Impact of COVID-19 on the treatment of acute myeloid leukemia. Leukemia 2020, 34, 2254–2256.
45. Papamichalis, P.; Tsinti, G.; Papapostolou, E.; Hadjichristodoulou, C.; Speletas, M. Newly Diagnosed Acute Myeloid Leukemia in a Patient with Severe SARS-CoV-2 Infection. Cureus 2021, 13, e14480.
46. Cesaro, S.; Ljungman, P.; Mikulska, M.; Hirsch, H.H.; von Lilienfeld-Toal, M.; Cordonnier, C.; Meylan, S.; Mehra, V.; Styczynski, J.; Marchesi, F.; et al. Recommendations for the management of COVID-19 in patients with haematological malignancies or haematopoietic cell transplantation, from the 2021 European Conference on Infections in Leukaemia (ECIL 9). Leukemia 2022, 36, 1467–1480.
47. Zeidan, A.M.; Boddu, P.C.; Patnaik, M.M.; Bewersdorf, J.P.; Stahl, M.; Rampal, R.K.; Shallis, R.; Steensma, D.P.; Savona, M.R.; Sekeres, M.A.; et al. Special considerations in the management of adult patients with acute leukaemias and myeloid neoplasms in the COVID-19 era: Recommendations from a panel of international experts. Lancet Haematol. 2020, 7, e601–e612.
48. American Society of Hematology. COVID-19 and Acute Myeloid Leukemia: Frequently Asked Questions. 2022. Available online: https://www.hematology.org/covid-19/covid-19-and-acute-myeloid-leukemia (accessed on 17 June 2022).
49. Altamirano-Molina, M.; Pacheco-Modesto, I.; Amado-Tineo, J. Prolonged viral shedding of SARS-CoV-2 in patients with acute leukemia. Hematol. Transfus. Cell Ther. 2022, 44, 299–300.
50. NCRI AML Working Party. Recommendations for the Managemant of Patients with AML during the COVID 19 Outbreak: A Statement from the NCRI AML Workung Party. 2020. Available online: https://www.rcpath.org/uploads/assets/d23030b6-7379-4f80-9ed9178c5f864343/Recommendations-for-the-management-of-patients-with-acute-myeloid-leukaemia-AML-during-the-COVID19-outbreak.pdf (accessed on 17 June 2022).
51. Brissot, E.; Labopin, M.; Baron, F.; Bazarbachi, A.; Bug, G.; Ciceri, F.; Esteve, J.; Giebel, S.; Gilleece, M.H.; Gorin, N.C.; et al. Management of patients with acute leukemia during the COVID-19 outbreak: Practical guidelines from the acute leukemia working party of the European Society for Blood and Marrow Transplantation. Bone Marrow Transpl. 2021, 56, 532–535.

52. Cristiano, A.; Palmieri, R.; Fabiani, E.; Ottone, T.; Divona, M.; Savi, A.; Buccisano, F.; Maurillo, L.; Tarella, C.; Arcese, W.; et al. The Venetoclax/Azacitidine Combination Targets the Disease Clone in Acute Myeloid Leukemia, Being Effective and Safe in a Patient with COVID-19. Mediterr. J. Hematol. Infect. Dis. 2022, 14, e2022041.
53. Othman, J.; Amer, M.; Amofa, R.; Anderson, L.; Austin, M.J.; Bashford, A.; Belsham, E.; Boot, J.; Campbell, V.L.; Coats, T.; et al. Venetoclax with Azacitidine or Low Dose Cytarabine As an Alternative to Intensive Chemotherapy in Fit Adults during the COVID-19 Pandemic: Real World Data from the UK National Health Service. Blood 2021, 138, 2321.
54. American Society of Hematology. COVID-19 and Adult ALL: Frequently Asked Questions. 2021. Available online: https://www.hematology.org/covid-19/covid-19-and-all (accessed on 17 June 2022).
55. Foa, R.; Bonifacio, M.; Chiaretti, S.; Curti, A.; Candoni, A.; Fava, C.; Ciccone, M.; Pizzolo, G.; Ferrara, F. Philadelphia-positive acute lymphoblastic leukaemia (ALL) in Italy during the COVID-19 pandemic: A Campus ALL study. Br. J. Haematol. 2020, 190, e3–e5.
56. Stahl, M.; Narendra, V.; Jee, J.; Derkach, A.; Maloy, M.; Geyer, M.B.; Mato, A.R.; Roeker, L.E.; Tallman, M.S.; Shah, G.L.; et al. Neutropenia in adult acute myeloid leukemia patients represents a powerful risk factor for COVID-19 related mortality. Leuk Lymphoma 2021, 62, 1940–1948.
57. Yarza, R.; Bover, M.; Paredes, D.; Lopez-Lopez, F.; Jara-Casas, D.; Castelo-Loureiro, A.; Baena, J.; Mazarico, J.M.; Folgueira, M.D.; Melendez-Carmona, M.A.; et al. SARS-CoV-2 infection in cancer patients undergoing active treatment: Analysis of clinical features and predictive factors for severe respiratory failure and death. Eur. J. Cancer 2020, 135, 242–250.
58. Singh, S.; Singh, J.; Paul, D.; Jain, K. Treatment of Acute Leukemia during COVID-19: Focused Review of Evidence. Clin. Lymphoma Myeloma Leuk 2021, 21, 289–294.
59. Thu, T.P.B.; Ngoc, P.N.H.; Hai, N.M.; Tuan, L.A. Effect of the social distancing measures on the spread of COVID-19 in 10 highly infected countries. Sci. Total Environ. 2020, 742, 140430.
60. Esposito, S.; Principi, N.; Leung, C.C.; Migliori, G.B. Universal use of face masks for success against COVID-19: Evidence and implications for prevention policies. Eur. Respir. J. 2020, 55, 2001260.
61. Infectious Diseases Society of America (IDSA). Infectious Diseases Society of America Guidelines on Infection Prevention for Healthcare Personnel Caring for Patients with Suspected or Known COVID-19. Available online: https://www.idsociety.org/practice-guideline/covid-19-guideline-infection-prevention/ (accessed on 17 June 2022).
62. Wu, S.; Wang, Y.; Jin, X.; Tian, J.; Liu, J.; Mao, Y. Environmental contamination by SARS-CoV-2 in a designated hospital for coronavirus disease 2019. Am. J. Infect. Control 2020, 48, 910–914.

63. Gharpure, R.; Miller, G.F.; Hunter, C.M.; Schnall, A.H.; Kunz, J.; Garcia-Williams, A.G. Safe Use and Storage of Cleaners, Disinfectants, and Hand Sanitizers: Knowledge, Attitudes, and Practices among U.S. Adults during the COVID-19 Pandemic, May 2020. Am. J. Trop Med. Hyg. 2020, 104, 496–501.

64. Greenberger, L.M.; Saltzman, L.A.; Senefeld, J.W.; Johnson, P.W.; DeGennaro, L.J.; Nichols, G.L. Antibody response to SARS-CoV-2 vaccines in patients with hematologic malignancies. Cancer Cell 2021, 39, 1031–1033.

65. Herzog Tzarfati, K.; Gutwein, O.; Apel, A.; Rahimi-Levene, N.; Sadovnik, M.; Harel, L.; Benveniste-Levkovitz, P.; Bar Chaim, A.; Koren-Michowitz, M. BNT162b2 COVID-19 vaccine is significantly less effective in patients with hematologic malignancies. Am. J. Hematol. 2021, 96, 1195–1203.

66. Candoni, A.; Callegari, C.; Zannier, M.E.; Fanin, R. Antibody response to mRNA vaccination for COVID-19 in patients with AML receiving hypomethylating agents alone or with venetoclax. Blood Adv. 2022, 6, 3068–3071.

67. Jain, A.G.; Dong, N.C.; Ball, S.; Tan, E.S.; Whiting, J.; Komrokji, R.S.; Sweet, K.; Chan, O.; Sallman, D.A.; Padron, E.; et al. Responses to SARS-CoV-2 Vaccines in Patients with Myelodysplastic Syndrome and Acute Myeloid Leukemia. Blood 2021, 138, 217.

68. U.S. Food & Drug. US FDA Frequently Asked Questions on the Emergency Use Authorization for Evusheld (tixagevimab co- packaged with cilgavimab) for Pre-exposure Prophylaxis (PrEP) of COVID-19. 2022. Available online: https://www.fda.gov/media/154703/download (accessed on 17 June 2022).

69. Levin, M.J.; Ustianowski, A.; De Wit, S.; Launay, O.; Avila, M.; Templeton, A.; Yuan, Y.; Seegobin, S.; Ellery, A.; Levinson, D.J.; et al. Intramuscular AZD7442 (Tixagevimab-Cilgavimab) for Prevention of COVID-19. N. Engl. J. Med. 2022, 386, 2188–2200.

70. O'Brien, M.P.; Forleo-Neto, E.; Musser, B.J.; Isa, F.; Chan, K.C.; Sarkar, N.; Bar, K.J.; Barnabas, R.V.; Barouch, D.H.; Cohen, M.S.; et al. Subcutaneous REGEN-COV Antibody Combination to Prevent COVID-19. N. Engl. J. Med. 2021, 385, 1184–1195.

71. Mazzaferri, F.; Mirandola, M.; Savoldi, A.; De Nardo, P.; Morra, M.; Tebon, M.; Armellini, M.; De Luca, G.; Calandrino, L.; Sasset, L.; et al. Exploratory data on the clinical efficacy of monoclonal antibodies against SARS-CoV-2 Omicron Variant of Concern. medRxiv 2022, 386, 2188–2200.

72. Cao, Y.; Wang, J.; Jian, F.; Xiao, T.; Song, W.; Yisimayi, A.; Huang, W.; Li, Q.; Wang, P.; An, R.; et al. Omicron escapes the majority of existing SARS-CoV-2 neutralizing antibodies. Nature 2022, 602, 657–663.

73. Lilly's Bebtelovimab Receives Emergency Use Authorization for the Treatment of Mild-to-Moderate COVID-19. Available online: https://investor.lilly.com/node/46666/pdf (accessed on 25

July 2022).

74. Hammond, J.; Leister-Tebbe, H.; Gardner, A.; Abreu, P.; Bao, W.; Wisemandle, W.; Baniecki, M.; Hendrick, V.M.; Damle, B.; Simon-Campos, A.; et al. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with COVID-19. N. Engl. J. Med. 2022, 386, 1397–1408.
75. Jayk Bernal, A.; Gomes da Silva, M.M.; Musungaie, D.B.; Kovalchuk, E.; Gonzalez, A.; Delos Reyes, V.; Martin-Quiros, A.; Caraco, Y.; Williams-Diaz, A.; Brown, M.L.; et al. Molnupiravir for Oral Treatment of COVID-19 in Nonhospitalized Patients. N. Engl. J. Med. 2022, 386, 509–520.
76. Gottlieb, R.L.; Vaca, C.E.; Paredes, R.; Mera, J.; Webb, B.J.; Perez, G.; Oguchi, G.; Ryan, P.; Nielsen, B.U.; Brown, M.; et al. Early Remdesivir to Prevent Progression to Severe COVID-19 in Outpatients. N. Engl. J. Med. 2022, 386, 305–315.
77. Levy, I.; Lavi, A.; Zimran, E.; Grisariu, S.; Aumann, S.; Itchaki, G.; Berger, T.; Raanani, P.; Harel, R.; Aviv, A.; et al. COVID-19 among patients with hematological malignancies: A national Israeli retrospective analysis with special emphasis on treatment and outcome. Leuk Lymphoma 2021, 62, 3384–3393.
78. Siemieniuk, R.A.; Bartoszko, J.J.; Ge, L.; Zeraatkar, D.; Izcovich, A.; Kum, E.; Pardo-Hernandez, H.; Qasim, A.; Martinez, J.P.D.; Rochwerg, B.; et al. Drug treatments for COVID-19: Living systematic review and network meta-analysis. BMJ 2020, 370, m2980.
79. Agarwal, A.; Rochwerg, B.; Lamontagne, F.; Siemieniuk, R.A.; Agoritsas, T.; Askie, L.; Lytvyn, L.; Leo, Y.S.; Macdonald, H.; Zeng, L.; et al. A living WHO guideline on drugs for COVID-19. BMJ 2020, 370, m3379.
80. Bruel, T.; Hadjadj, J.; Maes, P.; Planas, D.; Seve, A.; Staropoli, I.; Guivel-Benhassine, F.; Porrot, F.; Bolland, W.H.; Nguyen, Y.; et al. Serum neutralization of SARS-CoV-2 Omicron sublineages BA.1 and BA.2 in patients receiving monoclonal antibodies. Nat. Med. 2022, 28, 1297–1302.
81. Gupta, A.; Gonzalez-Rojas, Y.; Juarez, E.; Crespo Casal, M.; Moya, J.; Rodrigues Falci, D.; Sarkis, E.; Solis, J.; Zheng, H.; Scott, N.; et al. Effect of Sotrovimab on Hospitalization or Death Among High-risk Patients with Mild to Moderate COVID-19: A Randomized Clinical Trial. JAMA 2022, 327, 1236–1246.
82. Chen, P.; Nirula, A.; Heller, B.; Gottlieb, R.L.; Boscia, J.; Morris, J.; Huhn, G.; Cardona, J.; Mocherla, B.; Stosor, V.; et al. SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with COVID-19. N. Engl. J. Med. 2021, 384, 229–237.
83. Weinreich, D.M.; Sivapalasingam, S.; Norton, T.; Ali, S.; Gao, H.; Bhore, R.; Xiao, J.; Hooper, A.T.; Hamilton, J.D.; Musser, B.J.; et al. REGEN-COV Antibody Combination and Outcomes in Outpatients with COVID-19. N. Engl. J. Med. 2021, 385, e81.
84. Janiaud, P.; Axfors, C.; Schmitt, A.M.; Gloy, V.; Ebrahimi, F.; Hepprich, M.; Smith, E.R.; Haber, N.A.; Khanna, N.; Moher, D.; et al. Association of Convalescent Plasma Treatment with Clinical

Outcomes in Patients with COVID-19: A Systematic Review and Meta-analysis. JAMA 2021, 325, 1185–1195.

85. Libster, R.; Perez Marc, G.; Wappner, D.; Coviello, S.; Bianchi, A.; Braem, V.; Esteban, I.; Caballero, M.T.; Wood, C.; Berrueta, M.; et al. Early High-Titer Plasma Therapy to Prevent Severe COVID-19 in Older Adults. N. Engl. J. Med. 2021, 384, 610–618.
86. Thompson, M.A.; Henderson, J.P.; Shah, P.K.; Rubinstein, S.M.; Joyner, M.J.; Choueiri, T.K.; Flora, D.B.; Griffiths, E.A.; Gulati, A.P.; Hwang, C.; et al. Association of Convalescent Plasma Therapy with Survival in Patients with Hematologic Cancers and COVID-19. JAMA Oncol. 2021, 7, 1167–1175.
87. Siddiqi, H.K.; Mehra, M.R. COVID-19 illness in native and immunosuppressed states: A clinical-therapeutic staging proposal. J. Heart Lung Transpl. 2020, 39, 405–407.
88. Group, R.C.; Horby, P.; Lim, W.S.; Emberson, J.R.; Mafham, M.; Bell, J.L.; Linsell, L.; Staplin, N.; Brightling, C.; Ustianowski, A.; et al. Dexamethasone in Hospitalized Patients with COVID-19. N. Engl. J. Med. 2021, 384, 693–704.
89. Group, C.S.T.; Munch, M.W.; Myatra, S.N.; Vijayaraghavan, B.K.T.; Saseedharan, S.; Benfield, T.; Wahlin, R.R.; Rasmussen, B.S.; Andreasen, A.S.; Poulsen, L.M.; et al. Effect of 12 mg vs 6 mg of Dexamethasone on the Number of Days Alive Without Life Support in Adults with COVID-19 and Severe Hypoxemia: The COVID STEROID 2 Randomized Trial. JAMA 2021, 326, 1807–1817.
90. Salama, C.; Mohan, S.V. Tocilizumab in Patients Hospitalized with COVID-19 Pneumonia. Reply. N. Engl. J. Med. 2021, 384, 1473–1474.
91. Group, R.C. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): A randomised, controlled, open-label, platform trial. Lancet 2021, 397, 1637–1645.
92. Gordon, A.C.; Angus, D.C.; Derde, L.P.G. Interleukin-6 Receptor Antagonists in Critically Ill Patients with COVID-19. Reply. N. Engl. J. Med. 2021, 385, 1147–1149.
93. Kyriazopoulou, E.; Poulakou, G.; Milionis, H.; Metallidis, S.; Adamis, G.; Tsiakos, K.; Fragkou, A.; Rapti, A.; Damoulari, C.; Fantoni, M.; et al. Author Correction: Early treatment of COVID-19 with anakinra guided by soluble urokinase plasminogen receptor plasma levels: A double-blind, randomized controlled phase 3 trial. Nat. Med. 2021, 27, 1850.
94. Gorog, D.A.; Storey, R.F.; Gurbel, P.A.; Tantry, U.S.; Berger, J.S.; Chan, M.Y.; Duerschmied, D.; Smyth, S.S.; Parker, W.A.E.; Ajjan, R.A.; et al. Current and novel biomarkers of thrombotic risk in COVID-19: A Consensus Statement from the International COVID-19 Thrombosis Biomarkers Colloquium. Nat. Rev. Cardiol. 2022, 19, 475–495.
95. U.S. Food & Drug. ASH Guidelines on Use of Anticoagulation in Patients with COVID-19. 2022. Available online: https://www.hematology.org/education/clinicians/guidelines-and-quality-

care/clinical-practice-guidelines/venous-thromboembolism-guidelines/ash-guidelines-on-use-of-anticoagulation-in-patients-with-covid-19 (accessed on 17 June 2022).

Retrieved from https://encyclopedia.pub/entry/history/show/63085