SOME ASPECTS OF COVID-19 TREATMENT -CURRENT RECOMMENDATIONS AND OUR OBSERVATIONS НЕКОИ АСПЕКТИ ВО ЛЕКУВАЊЕТО НА КОВИД-19 -АКТУЕЛНИ ПРЕПОРАКИ И НАШИ ПОЗНАВАЊА

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SOME ASPECTS OF COVID-19 TREATMENT – CURRENT RECOMMENDATIONS AND OUR OBSERVATIONS

НЕКОИ АСПЕКТИ ВО ЛЕКУВАЊЕТО НА КОВИД-19 – АКТУЕЛНИ ПРЕПОРАКИ И НАШИ ПОЗНАВАЊА

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Abstract

Treatment of COVID-19 is currently a global challenge. Since the beginning of the infection, owing to a well-planned and organized research, knowledge in its treatment has been gained and recommendations have been made. These recommendations are flexible and subject to changes depending on the results obtained in the latest investigations. There is no officially accepted protocol for treatment of patients with COVID-19 in the Republic of North Macedonia. This has resulted in very diverse therapeutic regimens mainly based on individual experience and intuition and without sufficient consistency with the globally recommended therapeutic principles. By conducting a survey-questionnaire among doctors who are working in COVID-19 centers in our country, the aim of this paper was to verify this statement and to offer a solution for uniform approach to treatment of COVID-19 based on the recommenddations of renowned world health institutions. Each questionnaire distributed among those involved in treatment of COVID-19 contained 10 questions. A total of 194 questionnaires were filled-in anonymously on a voluntary basis, and of 1940 possible answers 851 (44%) were correct. To 6 of the 10 questions, the largest number of surveyed respondents has chosen the correct answer. The incorrect answers among the offered ones were in a range of 0 to 74%. The survey-questionnaire has shown distinct variations in the received answers, which in fact reflects the divergent attitudes to treatment of COVID-19. Therefore, it is indispensable to have a standardized approach to management of patients with COVID-19, supported by an organized and stimulated education of the involved health care workers.

Keywords: treatment, COVID-19, corticosteroid, oxygen

Апстракт

Лекувањето на КОВИД-19 претставува глобален актуелен предизвик. Од неговата појава до денес, благодарение на осмислени и добро организирани иследувања се дојде до доста сознанија за третманот кои се преточени во соодветни препораки. Ваквите препораки се флексибилни и подложни на промени во зависност од резултатите кои се добиваат во најновите иследувања. Во Република Македонија не постои официјално прифатен протокол за лекување на пациентите со КОВИД-19. Резултат на тоа е постоење на најразлични тераписки шеми обично базирани на сопствени искуства и интуиција, честопати без соодветна научна поддржаност и без доволна усогласеност со глобално препорачаните тераписки принципи. Цел на трудот беше преку спроведена анкета - прашалник наменета за лекари кои работат во КОВИД-19 центри во нашата држава да се утврди веродостојноста на ваквото тврдење и да се понуди решение за унифициран пристап во лекување на пациентите, базирано на препораки на авторитетните светски здравствени институции. Меѓу 194 доброволно пополнети анонимни анкетни прашалници од кои секој содржеше по 10 прашања, од вкупно можни 1940 одговори точни беа 851 (44%). Кај 6 од десете поставени прашања најголемиот број на анкетирани го имаа избрано точниот одговор. Застапеноста на избран неточен одговор меѓу понудените беше во интервал од 0 до 74%. Анкетата-прашалник утврди изразена дисперзија на добиените одговори, што всушност ги рефлектира дивергентните ставови околу лекувањето на пациентите со КОВИД-19. Заради тоа е неопходно да се изгради унифициран пристап во менаџирањето на пациентите со КОВИД-19, надополнет со организирана и стимулирана едукација на лекарите.

Клучни зборови: третман, КОВИД-19, кортикостероиди, кислород

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Introduction

More than a year has passed since the beginning of COVID-19 pandemic and the medical science has already reached distinct achievements in fighting the new coronavirus. Rapid identification of virus genome [1], detection of the modes of its transmission [2], determination of the pathogenetic mechanisms [3-5] and consequently defining the stages of the disease [4,6] as well as development of effective vaccines [7] are a constituent part of the success in treatment of COVID-19. Many questions still remain unsolved and there are a lot of unknown issues related to this virus that have to be clarified in the future. The crucial question refers to treatment of patients having in mind that there are no confirmed and approved antiviral drugs [8,9], and on the other hand, the emphasis has been given to agents and procedures that have not yet proved clearly their effect in large randomized controlled studies (RCS), such as convalescent plasma (CP) and specific immunoglobulins [10-12], monoclonal antibodies, cytokine inhibitors, interferons, ivermectin, statins [2,10,11, 13], colchicine [14], numerous nutritional supplements [15], immunoadsoption [16], etc. Today, many universities in the world have prepared their own instructions and strategies (protocols) for treatment. However, they have presented divergent approaches since some institutions accept the attitudes based on the recommend-dations of authoritative world organizations and institutions such as the National Institutes of Health of USA (NIH), Centers for Disease Control and Prevention of USA (CDC), United States Food and Drug Administration (FDA), Infectious Diseases Society of America (IDSA), World Health Organization (WHO), as well as the findings obtained in large RCS or large observational trials leading to systematic reviews and meta-analyses. Recommendations of other institutions, on the other hand, have been based on drugs and procedures that have not still been confirmed and have not passed adequate controls, but are usually inexpensive and promising [5,6].

The first attempt to create an adequate national strategy (protocol) for treatment of patients with COVID-19 in the Republic of North Macedonia was made in October 2020, 8 months after the onset of the first case in the country (conclusion of the Commission for Infectious Diseases at the Ministry of Health from 23.10.2020). Of reasons unknown to the author of this paper, this protocol [17], although prepared, has never been legitimately distributed to the doctors involved in treatment of COVID-19. Thus, in lack of a defined national strategy for treatment of COVID-19, from the very beginning each and every involved doctor has been compelled to manage patients by using different foreign protocols or, to a large extent, using individual experience. This resulted in evident discrepancies and individualism in the therapeutic approach not only among doctors, but among COVID-19 centers in the country; hence confusion and uncertainty have arisen among doctors regarding the treatment, and patients' confidence has also been reduced. Some of these discrepancies are the indications for use of empiric antimicrobial therapy, eventual antimicrobial choice, indications for application of corticosteroids, the choice of the agent and its dosage, indications for application of invasive mechanical ventilation, indications for application of thromboprophylaxis or thrombotherapy, indications for using antiviral and other immunomodulatory agents, etc.

This survey-questionnaire that contained items associated with treatment of COVID-19, based on voluntary will and anonymity, was conducted in order to:

1. recognize the level of essential knowledge among doctors who treat patients with moderate and severe forms of COVID-19 regarding the choice of certain therapeutic decisions;
2. offer well-argued instructions for efficient clarification of the existing dilemmas and to recommend uniform approach in management of this category of patients, predominantly based on the current recommendations given by renowned world health institutions, experts and experiences cited in journals with a high impact factor.

Methodology

This investigation was my personal initiative and the opinions expressed herein reflect my views and do not represent the official position of any institution or organization, nor there has been any financial interest. The author obtained the approval by the Ethics Committee of the Faculty of Medicine in Skopje.

A survey-questionnaire was prepared containing 10 questions with offered multiple answer options. The survey-questionnaire was designed to be anonymous and on a voluntary basis. It was prepared and distributed among doctors who were or were not specialists in some medical specialty. The only criterion for participation in the survey was at least several weeks of clinical experience in the work with patients with moderate and severe form of COVID-19 admitted in the COVID-19 centers in the Republic. The participants in the survey were asked to independently answer the questions and to present their knowledge based on their own experience and learnt by reading and retrieval of medical literature, attendance to webinar presentations or by contacts with medical experts.

Some doctors who are working in different COVID-19 centers in the Republic offered their help in distribution and collection of the filled-in questionnaires and their delivery as a hard copy or via viber to the author of this investigation. After receiving of all filled-in questionnaires, they were analyzed with the Excel program. The answer to the question was assessed as

correct or incorrect. If the question was not answered or if several answers were given, the answer was considered as incorrect. Furthermore, an additional analysis was made regarding the frequency of the selected answer from the offered options. The answers were presented as frequencies and percentages and displayed in figures.

Results

In a two-month period (December 2020-January 2021), a total of 194 filled-in questionnaires were received from 22 institutions from our country where patients with COVID-19 were treated. The survey-questionnaire was not distributed only among specialists from the University Clinic for Infectious Diseases and Febrile Conditions as well as among doctors who worked in the COVID-19 centers within the internal clinics in Skopje.
Of 1940 possible answers, 851 (44%) were correct, 1080 (55.5%) were incorrect, and no answer was given to 9 (0.5%) questions. Herein are the questions and the chosen answers presented in figures along with author's commentary.

Question 1. What is the difference between the severe and moderate form of COVID-19?

    a) presence of clinical or chest x-ray verified pneumonia
    b) comorbidities
    c) age >70 years
    d) saturation <94%
    e) all of the above

Results 1. The choice whether the answer was correct or not (in frequencies and percentages) to question 1 is presented in Figure 1a. The selected answer from the offered options (in percentages) to question 1 is shown in Figure 1b.
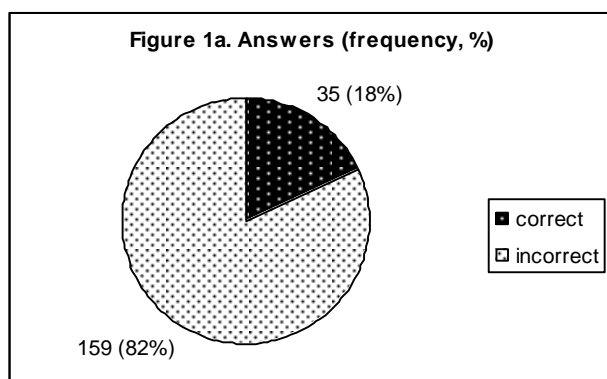
Fig. 1a. Correct/incorrect answer (frequency and %) to question 1
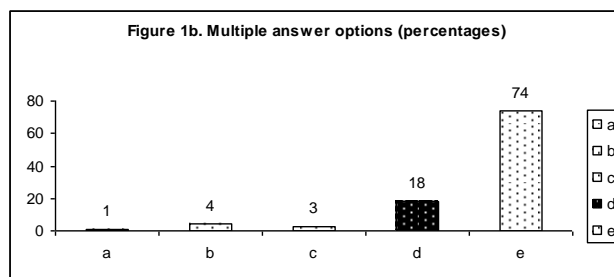
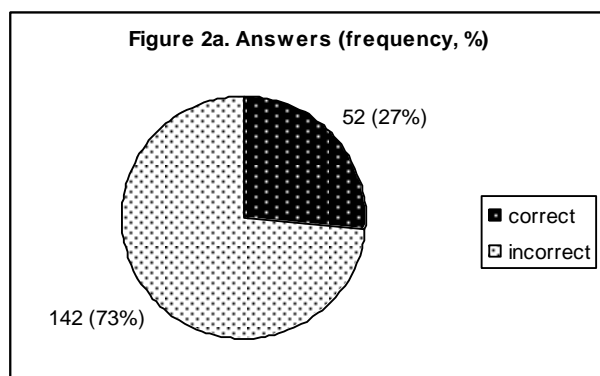**Fig. 1b.** Choice between the offered answer options (in percentages) to question 1

Commentary 1. The correct answer is d). Moderate COVID-19 is present in patients with clinically or chest x-ray confirmed pneumonia in whom oxygen saturation (SpO2) is ≥94%. A severe form of the disease is seen in patients with pneumonia verified with clinical or x-ray examination plus one of the following parameters: (i) respiratory frequency >30/min., (ii) a severe respiratory distress (accessory muscle use, inability to complete full sentences, very severe chest wall indrawing, grunting, central cyanosis) and (iii) SpO2 <94% [10,18,19]. The value of SpO2 <94% in differentiation of a moderate from a severe illness has been presented in many clinical trials [20-23], whereas others have used different modifications of the SpO2 values such as ≤ 94% [11] or <90% [24]. However, it has to be pointed out that these values are arbitrary and should be interpreted cautiously depending on the clinical condition of patients, their previous diseases and eventual progression of the condition [25].
The advanced age and the presence of comorbidities are risk factors for the severity and progression of the disease and are an important indicator for careful monitoring of the patients, but these factors are not included in the definitions of moderate and severe clinical forms of COVID-19. On the other hand, pneumonia offered as one of the answers is characteristic for both forms.
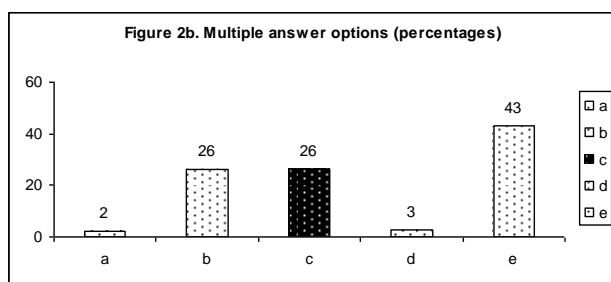
Question 2. The easiest way to clinically verify a severe dyspnea is by observing the following:

    a) persistent irritating cough
    b) saturation <92%
    c) intermittent speech
    d) high levels of ferritin, CRP, DD and IL-6
    e) no improvement in spite of administration of 10 L oxygen

Results 2. The choice whether the answer was correct or not (in frequencies and percentages) to question 2 is presented in Figure 2a. The selected answer from the offered options (in percentages) to question 2 is shown in Figure 2b.

Figure 2a. Answers (frequency, %)

52 (27%)

correct
incorrect

142 (73%)

Fig. 2a. Correct/incorrect answer (frequency and %) to question 2

Figure 2b. Multiple answer options (percentages)

	a	b	c	d	e
	2	26	26	3	43

Fig. 2b. Choice between the offered answer options (in percentages) to question 2

Commentary 2. The correct answer is c). Dyspnea is a subjective feeling and is not always present during hypoxemia [6,26,27] and *vice versa*, there is normal oxygenation even if progressive or severe dyspnea is present [28]. Severe dyspnea is characterized with air hunger while resting, which is an indication for respiratory involvement. Patients cannot complete full sentences [28-30] neither can they perform basic functions for which they use accessory muscles [28]. The patient with COVID-19 has to be asked if his/her breath is so short that he/she cannot say more than a few words, and the assessment has to be made by a direct communication with the patient [31].

Answers listed under b) and e) are indicative of hypoxemia and not dyspnea; coughing is an independent clinical manifestation, and laboratory parameters along with dyspnea are associated with the severity and can serve in assessment of disease evolution, but are not in a direct correlation with dyspnea.

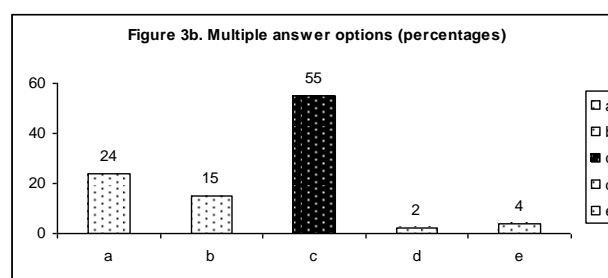**Question 3.** In a severe form of COVID-19, the treatment must consist of:
 a) convalescent plasma
 b) antibiotic
 c) oxygen
 d) Janus kinase inhibitor (baricitinib)
 e) non-specific immunoglobulin

Results 3. The choice whether the answer was correct or not (in frequencies and percentages) to question 3 is presented in Figure 3a. The selected answer from the

offered options (in percentages) to question 3 is shown in Figure 3b.

Figure 3a. Answers (frequency, %)

92 (47%)

102 (53%)
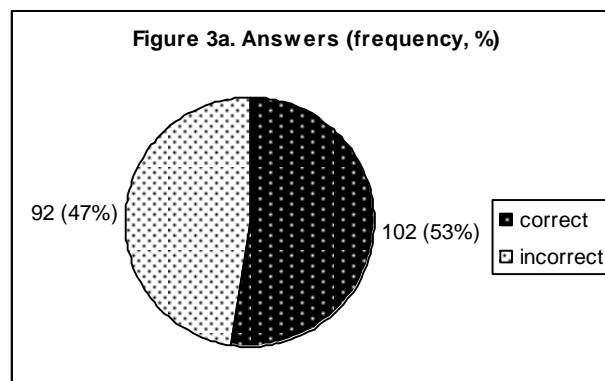
correct
incorrect

Fig. 3a. Correct/incorrect answer (frequency and %) to question 3

Figure 3b. Multiple answer options (percentages)

	a	b	c	d	e
	24	15	55	2	4

Fig. 3b. Choice between the offered answer options (in percentages) to question 3

Commentary 3. The correct answer is c) [10,21,25,30]. Having in mind that in the severe COVID-19 there is hyposaturation, an adequate oxygen substitution is a priority therapeutic procedure and it must be supplemented with a systemic corticosteroid [10,21,23,24]. Contrary to this, in the moderate COVID-19, neither oxygen supplementation nor corticosteroids are recommended [10,21,25,30,32].

The role of convalescent plasma (CP) in COVID-19 treatment including the severe form remains an unsolved puzzle. Certain benefits have been seen in those who received CP (better survival rate when the administration happened within the third day from the onset of symptoms) [12]. However, several randomized studies have found no clear clinical and prognostic benefit [12,19,28]. Currently, some of the institutions approve the use of CP alone in clinical trials [11,19,24], whereas others have no sufficient agruments either for or against the use of CP in the routine treatment [10].

In patients with COVID-19 routine application of empiric antimicrobial therapy is not needed if the suspicion of bacterial infection is small. Thus, the antimicrobial immediate and long-term adverse effects can be eliminated [11,24,33]. At this moment NIH has not enough arguments to recommend the use of a wide-spectrum empiric antimicrobial treatment in patients with severe and critical illness in absence of other indication [10]. Despite administration of antimicrobial thera-

py, clinical non-improvement in patients generally does not alert to bad choice of antibiotics but rather to bad decision for their use. The absence of clinical improvement during antibiotic administration most frequently indicates that there is no bacterial infection and that the cause should be in SARS-CoV-2 virus and the mechanisms it induces. Therefore, it is absolutely unjustified to replace the used antibiotics with others. But, however, antimicrobial therapy can be applied in patients with pneumonia in whom COVID-19 diagnosis has not been confirmed as well as in patients with confirmed COVID-19 when there is clinical suspicion of bacterial pneumonia [24,33,34]. The decision on the empiric antimicrobial treatment has to be made in conjugation with patients' characteristics and in line with the local epidemiological situation. This therapy should be evaluated on daily basis in order to be discontinued as soon as possible [10,24].

Insufficient data show that baricitinib, a Janus kinase inhibitor, gives certain hope in treatment of non-intubated patients with severe COVID-19 who cannot be given corticosteroids. In cases like these baricitinib must be given in combination with remdesivir [10,11]. Using a non-specific SARS-CoV-2 immunoglobulin in treatment of COVID-19 is not recommended, except in clinical trials or when there is another indication for its application [10,19].

Question 4. In which stage of the disease, if indicated, corticosteroids are recommended in COVID-19 patients?

    a) as soon as possible from the onset of symptoms
    b) up to the fifth day from the onset of symptoms at the latest
    c) after the first week from the onset of symptoms
    d) is not related to the onset of symptoms
    e) only in patients with comorbidities independently of the onset of symptoms

Results 4. The choice whether the answer was correct or not (in frequencies and percentages) to question 4 is
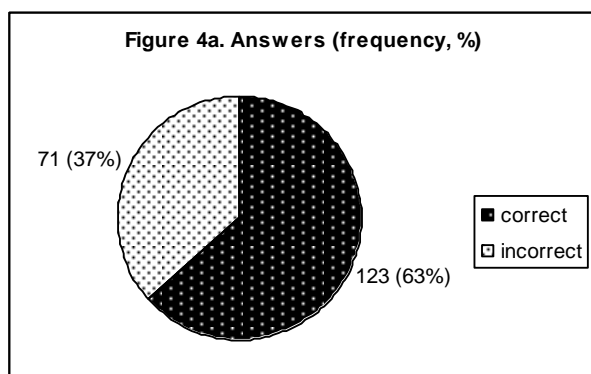
Fig. 4a. Correct/incorrect answer (frequency and %) to question 4

presented in Figure 4a. The selected answer from the offered options (in percentages) to question 4 is shown in Figure 4b.
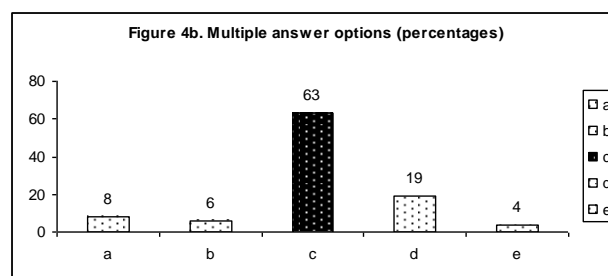
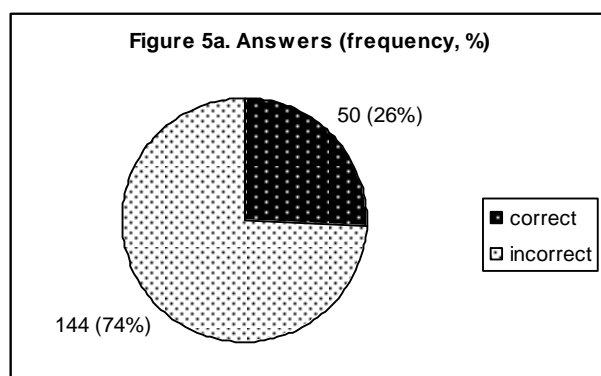**Fig. 4b.** Choice between the offered answer options (in percentages) to question 4

Commentary 4. he correct answer is c) and this recommendation is found in several protocols [2,13,23,35]. The principal role of the corticosteroids in treatment of COVID-19 is to stop or alleviate the harmful systemic hyperinflammatory response. This response can be observed in some of the patients usually by the end of the first and the beginning of the second week. The onset of the systemic inflammatory response coincides with the period when there is an obvious regression of viral replication and of viral load [2,4,6,21]. Hyperinlammatory syndrome leads to respiratory failure and multiorgan dysfunction in some patients [10,11]. Timely administration of systemic corticosteroids can significantly influence on the course of the disease, with evident reduction in mortality [19]. Early administration of corticosteroids within the first week can result in unfavorable effect; it can inhibit the initiation and development of the host immune defense mechanisms and to enable prolonged intensive active viral replication by intensifying immunosuppression and aggravation of the course and outcome of the disease [2,4,32,36]. One study has demonstrated that corticosteroid administered within the second week after the onset of symptoms has improved the favorable outcome in comparison with their administration in the first or third week [37]. Definitely, an absolute precondition to apply corticosteroids in COVID-19 treatment is the existence of a severe or critical form of the disease, which almost always begins within the second week after the onset

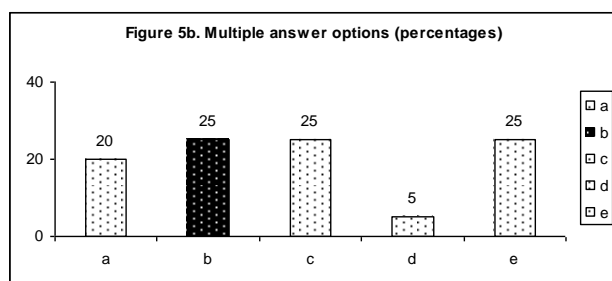**Question 5.** Corticosteroid therapy – recommended choice:

    a) high doses of dexamethasone ($\geq$20 mg/day)
    b) low doses of dexamethasone (6-8 mg/day)
    c) "pulse" doses of methylprednisolone ($\geq$ 240 mg/day)
    d) avoiding dexamethasone and insisting on methylprednisolone
    e) start with "pulse" doses of methylprednisolone and continue with low doses of dexamethasone

of initial symptoms. Systemic corticosteroids are to be given during the first week if hypoxia appears, which is a very rare case [29]. The application of systemic corticosteroids in patients who are not oxygen-dependent can have an opposite effect and can result in higher mortality [10,11,30,32,38].

Results 5. The choice whether the answer was correct or not (in frequencies and percentages) to question 5 is presented in Figure 5a. The selected answer from the offered options (in percentages) to question 5 is shown in Figure 5b.

Figure 5a. Answers (frequency, %)

50 (26%)

144 (74%)

■ correct
□ incorrect

Fig. 5a. Correct/incorrect answer (frequency and %) to question 5

Figure 5b. Multiple answer options (percentages)

	a	b	c	d	e
	20	25	25	5	25

□ a
■ b
□ c
□ d
□ e

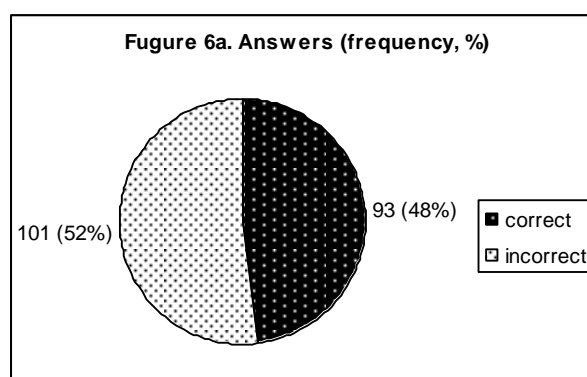**Fig. 5b.** Choice between the offered answer options (in percentages) to question 5

Commentary 5. The correct answer is b). Currently, low doses of dexamethasone (6 mg/day) in duration of 10 days are recommended [10,11,21,38,39]. Low dose and short therapeutic courses with dexamethasone result in minimal adverse effects [19]. It is unknown whether the other corticosteroids show worse, simial or signifycant benefit than dexamethasone since there have been no studies that compared the efficacy of different corticosteroid formulations, but dexamethasone has been associated with the greatest therapeutic benefit compared to other corticosteroids in trials where comparison was between corticosteroid and non-corticosteroid regimens [19]. Still, if dexamethasone is unavailable, then alternative regimes are allowed with other corticosteroids with doses equivalent to 6 mg/day dexamethasone, 40 mg/day prednisone, 32 mg/day methylprednisolone and 160 mg/day hydrocortisone [2,10,11,32].

Contrary to dexamethasone, trials with other corticosteroid formulations have led to inconclusive results and have shown no benefit when compared to treatments with placebo [28,30,39]. There are a few RCS where high doses of dexamethasone have been used [29,30]. Also, there are just few recommendations that favor methylprednisolone as listed under c) and d) [5,6,40]. Higher doses (1-2 mg/kg) of methylprednisolone or other corticosteroids in equvalent doses are recommended in patients with onset of excessive inflammatory response and progressive deterioration of oxygenation, elevation or rising of laboratory markers (CRP>75 mg/L, ferritin>1,000 ng/mL, LDH>300 U/L, and D-dimer>1,000 ng/mL), rapid exacerbation of the x-ray finding and development of ARDS [6,23,32,36]. In situations like these, some suggest methylprednisolone at doses of 250-1000 mg/day as a salvage treatment [5,37,41-43]. The choice of a corticosteroid agent, optimal dose and treatment duration still remain unknown [29,37,44-46]. Also, so far there is no information on the association of high doses of corticosteroids with a greater benefit in comparison with low doses [45,47]. Also, when making decision about the corticosteroid dose and regimen, physicians should always have in mind the possibility of adverse effects, sometimes serious, associated with this category of drugs.

**Question 6.** Thromboprophylaxis in patients with COVID-19 is recommended in:
    a) all subjects (from asymptomatic to critical)
    b) all hospitalized patients
    c) patients with confirmed pulmonary embolism/deep vein thrombosis
    d) all oxygen-dependent patients
    e) patients in whom corticosteroid administration was mandatory indicated

Results 6. The choice whether the answer was correct or not (in frequencies and percentages) to question 6 is presented in Figure 6a. The selected answer from the offered options (in percentages) to question 6 is shown in Figure 6b.

Fugure 6a. Answers (frequency, %)
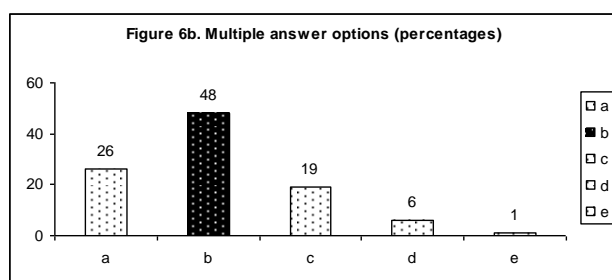
101 (52%)

93 (48%)

■ correct
□ incorrect

Fig. 6a. Correct/incorrect answer (frequency and %) to question 6

Fig. 6b. Choice between the offered answer options (in percentages) to question 6
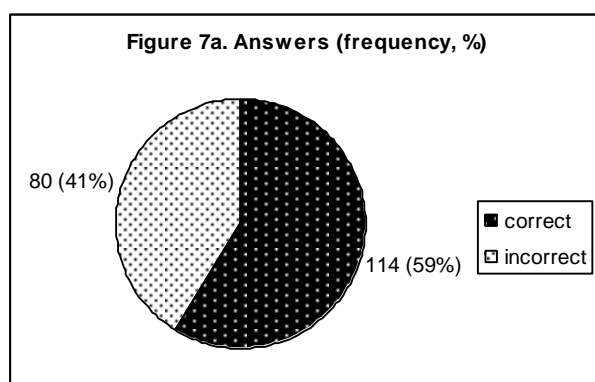

Fig. 7b. Choice between the offered answer options (in percentages) to question 7

Commentary 6. The correct answer is b). Hypercoagulability is an important pathogenetic characteristic of COVID-19. Therefore, all hospitalized adults with COVID-19 should receive anticoagulant prophylaxis if there are no contraindications [2,10,19,24,28]. Anticoagulant or antiaggregation prophylaxis in vein thromboembolism or arterial thrombosis is not recommended in non-hospitalized patients with COVID-19, unless there is another indication [2,10]. In patients with confirmed pulmonary embolism or deep vein thrombosis thrombotherapy is necessary and not prophylaxis.
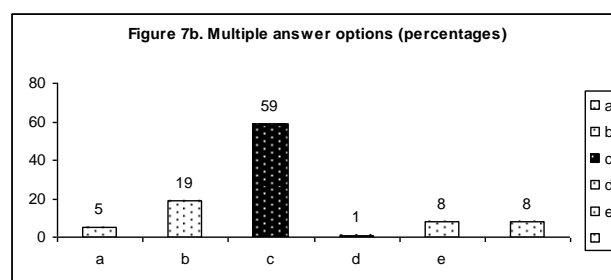
Question 7. In a 74-year-old previously non-hospitalized patient with COVID-19, who was insulin-dependent, with no particular problems over the last year, who was sick for 7 days, with saturation of 86% and parameters indicating bacterial pneumonia, which empiric antimicrobial therapy would you recommend?
  a) piperacillin/tazobactam monotherapy
  b) meropenem monotherapy
  c) ceftriaxone plus azithromycin
  d) piperacillin/tazobactam plus vancomycin
  e) azithromycin plus moxifloxacin
  f) meropenem plus piperacillin/tazobactam plus vancomycin

Results 7. The choice whether the answer was correct or not (in frequencies and percentages) to question 7 is presented in Figure 7a. The selected answer from the offered options (in percentages) to question 7 is shown in Figure 7b.

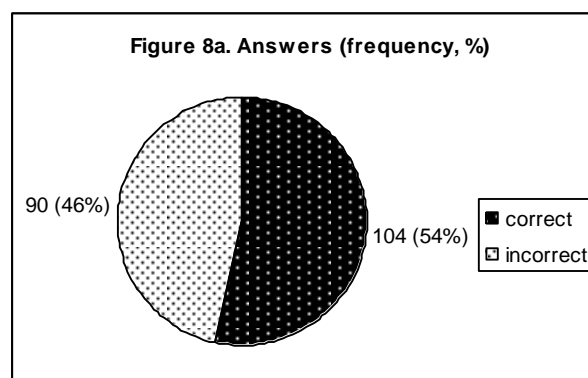**Fig. 7a.** Correct/incorrect answer (frequency and %) to question 7

Commentary 7. This is a case of a community-acquired pneumonia, which should be treated in line with the existing recommendations for treatment of this kind of pneumonia [13,32,35,48]. Consequnetly, the correct answer is c) having in mind that the listed combined therapy can have effect on all possible causes. The offered options a), b), d) should be considered in case of hospital-or ventilatory-acquired pneumonia and when there is a suspicion or proof of highly resistant strains of bacterial causes, whereas the antimicrobial combinations listed under e) and f) are absolutely illogical because of the overlap of the antimicrobial spectrum.

Question 8. If there is an indication of ceftriaxone administration for bacterial pneumonia, the dose should be:
  a) 1 gram twice daily
  b) 2 grams once daily
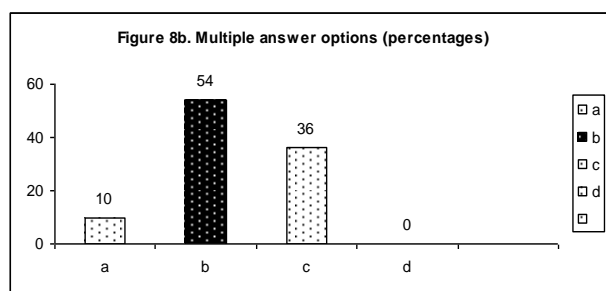 c) 2 grams twice daily
  d) 4 grams once daily

Results 8. The choice whether the answer was correct or not (in frequencies and percentages) to question 8 is presented in Figure 8a. The selected answer from the offered options (in percentages) to question 8 is shown in Figure 8b.

Fig. 8a. Correct/incorrect answer (frequency and %) to question 7

Commentary 8. The correct answer is b). Pharmacological and microbiological specifics of ceftriaxone enable its administration once daily at a dose of 1-2 grams for treatment of bacterial pneumonia [48, 49].

**Figure 8b. Multiple answer options (percentages)**

Fig. 8b. Choice between the offered answer options (in percentages) to question 7

Ceftriaxone is administered twice daily at a maximum dose of 4 grams if the main indication is bacterial neuroinfection [49].

Question 9. In a patient with COVID-19 and pneumonia, which laboratory parameter can in the best way exclude the bacterial etiology of pneumonia?
  a) low ferritin level
  b) low procalcitonin level
  c) high ferritin level
  d) low D-dimers level
  e) high procalcitonin level

Results 9. The choice whether the answer was correct or not (in frequencies and percentages) to question 9 is presented in Figure 9a. The selected answer from the offered options (in percentages) to question 9 is shown in Figure 9b.

Figure 9a. Answers (frequency, %)
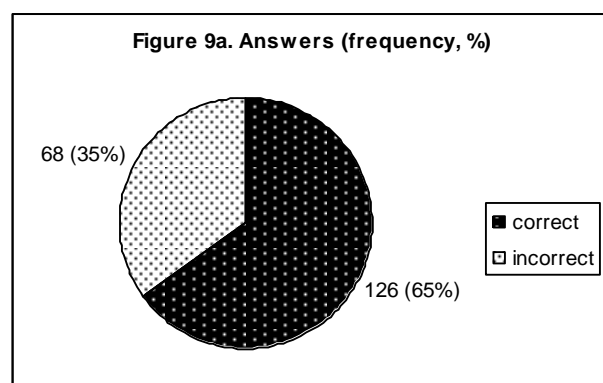
Fig. 9a. Correct/incorrect answer (frequency and %) to question 9

**Figure 9b. Multiple option options (percentages)**
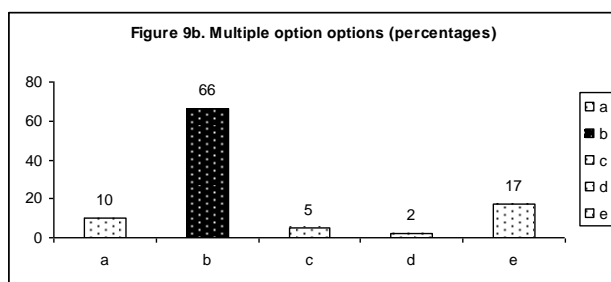
Fig. 9b. Choice between the offered answer options (in percentages) to question 9

Commentary 9. The correct answer is b). There are almost no bacterial coinfections or superinfections in patients with COVID-19 who have a low procalcitonin level and hence, these patients are not to be given antibiotics [35,50]. On the other hand, the increased level of serum procalcitonin in COVID-19 is not a sensitive marker for bacterial superinfection because sometimes it can be found in COVID-19 pneumonia, too [32,35]. D-dimers and ferritin are not sensitive markers for presence or absence of eventual bacterial infection.

Question 10. How long the empricial antimicrobial therapy has to be administered?
  a) 5-7 days
  b) no longer than two weeks
  c) approximately three weeks
  d) until normalization of D-dimers, LDH and CRP
  e) until normal x-ray/CT finding of the lungs is obtained

Results 10. The choice whether the answer was correct or not (in frequencies and percentages) to question 10 is presented in Figure 10a. The selected answer from the offered options (in percentages) to question 10 is shown in Figure 10b.

Figure 10a. Answers (frequency, %)
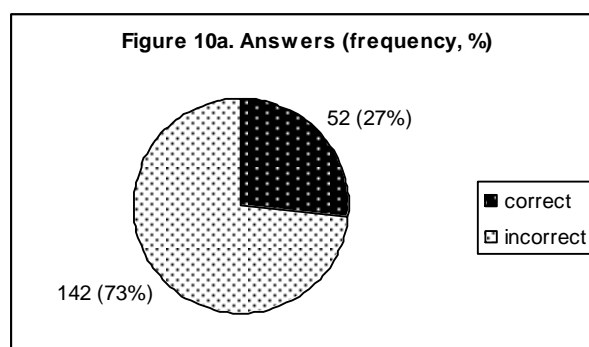
Fig. 10a. Correct/incorrect answer (frequency and %) to question 10

Figure 10b. Multiple answer options (percentages)
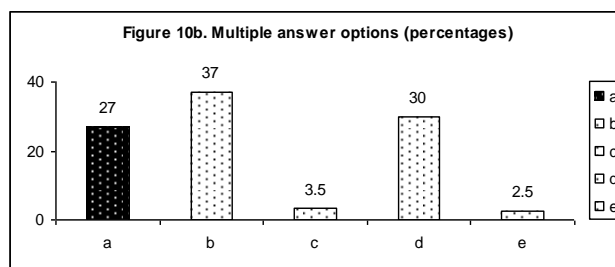
Fig. 10b. Choice between the offered answer options (in percentages) to question 10

Commentary 10. The correct answer is a). The duration of the empirical antimicrobial treatment should last as short as possible, in general 5-7 days [13,24, 35,51]. The duration of antimicrobial therapy should

be based on validated measures of achieved clinical stability-normalization of vital signs and conscience, and antibiotic therapy should be continued until the patient's condition is stabilized [48]. The given options under b) and c) refer to exceptional cases in population at high risk, in clinical instability or when microbiological testing suggest the need of a long-term therapy [51]. It might take longer for normalization of laboratory and radiological parameters after clinical improvement is achieved and they are not a sensitive marker for treatment discontinuation.

Discussion

The results obtained from the survey-questionnaire have shown that there are obvious distinctions in management of patients with a moderate and severe COVID-19 in our country from those of the current world recommendations (presented in Figures 1a-10a). At the same time, these results have demonstrated evident discrepancies among doctors in our country regarding the attitudes in treatment of COVID-19 (presented in Figures 1b-10b). The principal reason for this kind of inconsistency and variations is due to the lack of an uniform strategy for treatment of patients with COVID-19 that would comply with the current recommendations given by renowned world health institutions and consequently protocols given by distinguished universities. The acquired clinical experience, upon which almost without exception therapeutic procedures in the Republic of North Macedonia are based, is not usually grounded on the respected standards for clinical management, but on observation and without a review process. Also, the results obtained have shown insufficient level of information of the doctors included in this survey regarding the basic principles by which COVID-19 patients should be treated at the moment. Possible reasons for this situation might be absence of exchange of staff and experiences amongst health care workers from the neighboring countries and beyond, as well as amongst our doctors who work in COVID-19 centers worldwide, then lack of initiative by our doctors for personal broadening their knowledge by continual search of the available medical literature and participation to different online symposia and groups related to COVID-19 topic, as well as enforcement of non-flexible strategy by appointed coordinators, which differs from the current principles and is based on personal impressions and alleged experience of the coordinator. Overcoming of these discrepancies by education of the doctors and preparation of a uniform approach to management of patients with COVID-19 according to previously given principles might result in adequate benefit for patients' outcome, but at the same time, they can give doctors stimulus, security and motivation in treatment of these patients.

Recommendations (instead of conclusions):

1. Assessment of oxygen saturation is an important step in COVID-19. It enables differentiation of the moderate from severe form of the disease.
2. Treatment of the moderate form of the disease does not require administration of supplementary oxygen or systemic corticosteroid.
3. In patients with a severe form (SpO2 <94%) supplementary oxygen along with systemic low doses of dexamethasone must be administered. Severe form and need for this kind of therapy in general becomes obvious within the second week of the disease.
4. All hospitalized patients with COVID-19 (with moderate and with severe form) must receive tromboprophylaxis.
5. Antibiotics should be given only in rare situations when there is clinical or laboratory suspicion of bacterial coinfection or superinfection or when this infection has been confirmed.

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