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Review article

Transnasal endoscopic skull base surgery in the COVID-19 era: Recommendations for increasing the safety of the method

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ABSTRACT

Transnasal endoscopic skull base surgery (eSBS) has been adopted in recent years, in great part to replace the extended procedures required by external approaches. Though sometimes perceived as "minimally invasive", eSBS still necessitates extensive manipulations within the nose/paranasal sinuses. Furthermore, exposure of susceptible cerebral structures to light and heat emanated by the telescope should be considered to comprehensively evaluate the safety of the method. While the number of studies specifically targeting eSBS safety still remains scarce, the problem has recently expanded with the SARS-CoV-2 pandemic, which also has implications for the safety of the surgical personnel.

It must be stressed that eSBS may directly expose the surgeon to potentially high volumes of virus-contaminated aerosol. Thus, the anxiety of both the patient and the surgeon must be taken into account. Consequently, safety requirements must follow the highest standards. This paper summarizes current knowledge on SARS-CoV-2 biology and the peculiarities of human immunology in respect of the host-virus relationship, taking into account the latest information concerning the SARS-CoV-2 worrisome affinity for the nervous system. Based on this information, a workflow proposal is offered for consideration. This could be useful not only for the duration of the pandemic, but also during the unpredictable timeline involving our coexistence with the virus. Recommendations include technical modifications to the operating theatre, personal protective equipment, standards of testing for SARS-CoV-2 infection, prophylactic pretreatment with interferon, anti-IL6 treatment and, last but not least, psychological support for the patient.

1. Introduction

Recent years have brought a variety of innovative options for skull base surgery. Thanks to the significant progress of endoscopic techniques, in a selected group of patients, some traditional, extensive, traumatizing and time-consuming external operations have been replaced by elegant endoscopic interventions. Currently, the median skull base may be reached through the nostrils - the epitome keyhole surgery appears to be right on our doorstep (Fig. 1).

Whereas at the beginning of the century only a few highly specialized centres in the world performed an array of procedures of this kind (with the exception of pituitary surgery), today nearly every major medical

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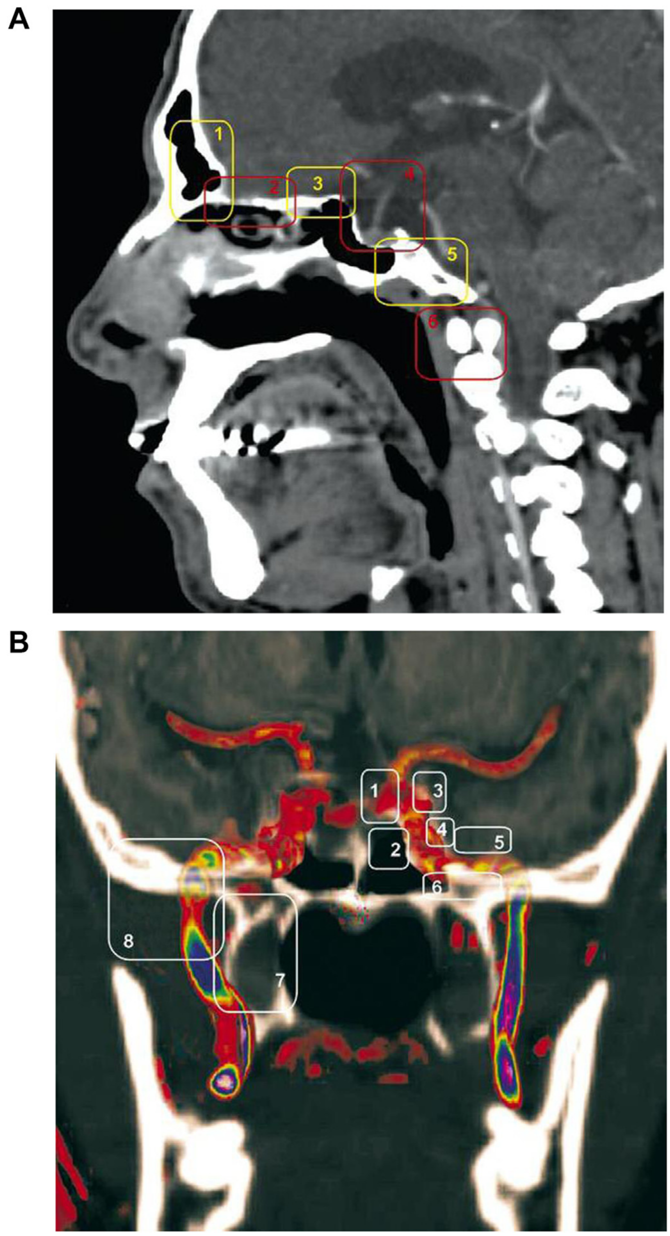

Fig. 1. Picture obtained by merging MR and CT images to show locations of extended transnasal endoscopic approaches. (A) Sagittal plane: 1) frontal sinusotomy according to Draf, 2) transcribriform plate approach, 3) transplanum approach, 4) transsellar approach, 5) transclival approach, 6) transodontoid approach. **(B)** Coronal plane – scan through the pterygoid processes: 1) medial cavernous sinus approach, 2) petrous apex approach, 3) lateral cavernous sinus approach, 4) Meckel cave approach, 5) suprapetrous approach, 6) infrapetrous approach, 7) sphenopalatine fossa approach, 8) infratemporal fossa approach [13]. *Reprinted with permission from:* Transnasal endoscopic approaches to the cranial base. Tomasz Lyson, Andrzej Siesekiewicz, Robert Rutkowski, Jan Kochanowicz, Grzegorz Turek, Marek Rogowski, Zenon Mariak. Neurologia i Neurochirurgia Polska 2013; 47, 1: 63–73. https://doi.org/10.5114/ninp.2012.31474. https://journals.viamedica.pl/neurologia_neurochirurgia_polska/article/view/60868. Copyright © 2013 by Polish Neurological Society.

centre possesses a neurosurgical/otolaryngological team dedicated to this kind of surgery. To date, multiple published clinical series discussing hundreds of patients have dealt with extended endoscopic interventions within the skull base [1–6].

Growing enthusiasm for this "minimally invasive" surgery is mirrored by the ever increasing number of publications related to this topic. A review of bibliographic databases (Web of Science) yields more than 4,000 items matching "endoscopic skull base surgery" (eSBS). However, the main bulk of this literature pertains to the results of surgery; highlighting the engagement of surgeons with the surgical technique. Indeed, progress in surgical instrumentation together with an enhanced level of surgical proficiency [7], have made possible the development of new, increasingly demanding surgical approaches and novel types of operations (Fig. 1) [8–13].

In contrast to the surgical technique itself, the safety of these allegedly “minimally invasive” manipulations at the skull base has to date attracted much less attention. Additionally, the COVID-19 pandemic has brought to light a new, important aspect of eSBS safety – one no longer concerning only the patient, but also the health care personnel involved in the procedure. Consequently, a number of circumstances pertaining to the safety of the method must be reconsidered:

1) these operations are by no means “minimally invasive” because they require the removal of extensive osseous structures, having not only structural but also physiological importance;
2) surgical manipulations usually incur into the vicinity of adjacent, extremely vulnerable brain structures, like the hypophysis, optic nerves, hypothalamus, etc.;
3) surgical instruments themselves give rise to intense light and heat which are generated by the endoscope, high speed drill, cauterisation and ultrasound aspirator;
4) When dealing with highly vascularised tumours, systemic arterial blood pressure must, at times, be reduced to obtain a bloodless operative field. This manoeuvre, though referred to as “controlled”, can potentially exert an unpredictable impact on cerebral neurons [14].
5) Many viruses, among them severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), have a natural affinity for nasopharyngeal mucosa. Recent studies have also indicated the possibility of direct infection of the central nervous system (CNS) by SARS CoV-2. A question which needs further evaluation is the theoretical possibility of the risk that a viral load may be directly inserted into the CNS during surgical manipulations.
6) eSBS belongs to a very narrow group of surgical procedures in which the surgeon is particularly exposed to an abundantly generated, potentially virus-contaminated aerosol.

In view of these potential threats associated with eSBS, this review summarizes the limited amount of available data focusing on Endoscopic Endonasal Approach (EEA) safety. In addition, it provides a summary of current knowledge on SARS-CoV-2 biology and the peculiarities of human immunology in respect of the host-virus relationship, including information concerning SARS-CoV-2 affinity for the nervous system.

2. Material and methods

We carried out a literature review on June 23, 2020 using the MEDLINE/PubMed database (United States National Library of Medicine National Institutes of Health), and Science Direct SciVerse. The results were obtained by using three groups of keywords:

1. ("skull"[Title/Abstract] AND "endoscopy"[Title/Abstract])
   OR "endoscopic"[Title/Abstract]) AND "skull"[Title/Abstract])
   AND "base"[Title/Abstract]) AND "surgery"[Title/Abstract])
   AND "safety"[Title/Abstract]
2. ((sars-cov-2[Title/Abstract])) AND (immunology[Title/Abstract])
3. (SARS-CoV-2[Title/Abstract]) AND (central nervous system[Title/Abstract])

In total, 276 articles were identified, from which 3 duplicate articles were removed and the remaining 273 articles were screened for suitability for the review. A further 164 articles were excluded as either we had no access to the full text, the articles were not published in English or the authors discussed diseases and surgical techniques other than those of interest to the present review. Of the 109 remaining publications, we excluded 37 full-text articles whose content did not match the topic under review or in which the study did not concern humans. Finally, 72 publications were selected for analysis for the purposes of the present study. PRISMA flowchart, adapted from Moher et al. [15] and presented in Fig. 2 summarizes the process of selecting the articles for this review.

3. Review

3.1. eSBS and patients' safety

For the purpose of the present review, the category of "endoscopic skull base surgery" was restricted by means of the term "safety", which yielded only about 200 contributions. On closer examination of this literature, it was evident that most of these items pertain to inherent limitations or complications associated with the surgical technique [5, 16–19]. There was a small number of studies focusing specifically on the general hazards to the patient undergoing this form of surgery. However, with the emergence of the SARS-CoV-2 pandemic, concerns regarding this seemingly underestimated problem have gone beyond ensuring the welfare of the patient undergoing the procedure, also extending to the safety of the health care personnel. It must be stressed, that in this respect eSBS represents a unique domain due to the likelihood of prolonged and intense exposure of the surgical team to potentially virus-contaminated aerosol, abundantly generated during particular phases of the surgical procedure, such as drilling. Consequently, safety requirements in this respect must adhere to the highest standards.

Publications focused specifically on eSBS safety are extremely scarce [20–26]. Since 2005 (the introduction of eSBS in our institution), we have carried out several investigations specifically focused on different aspects of the method's safety. These have included the direct measurement of temperature within the operative field and in the adjacent structures of the brain base, using miniature thermal probes inserted within the operative field [27]. Not only was there a steady increase in the average temperature, reaching up to 45 °C, but also unexpectedly high (up to 60 °C at its peak) temperature excursions during bone drilling were observed. Other studies have confirmed the potential for excessively high temperatures arising within the operating field during eSBS [20,28,29].

3.1.1. Surgery, induced hypotension, immune system

It is well known that any wound or tissue damage will induce a spectrum of immunological reactions comprising local or systemic inflammation. This mechanism also includes immune responses to surgery. Apart from inflammation, any tissue damage might be complicated by infection, which may invade nearby tissues. Infection is, in turn, a cause of increased morbidity, mortality and health service costs.

The first line of the human immune system relies on innate immunity. Human innate immunity consists of soluble substances (i.e. complement proteins or some opsonins) and some immune cells. Natural barriers, constituted by an intact skin or mucosa, play a major defensive role.

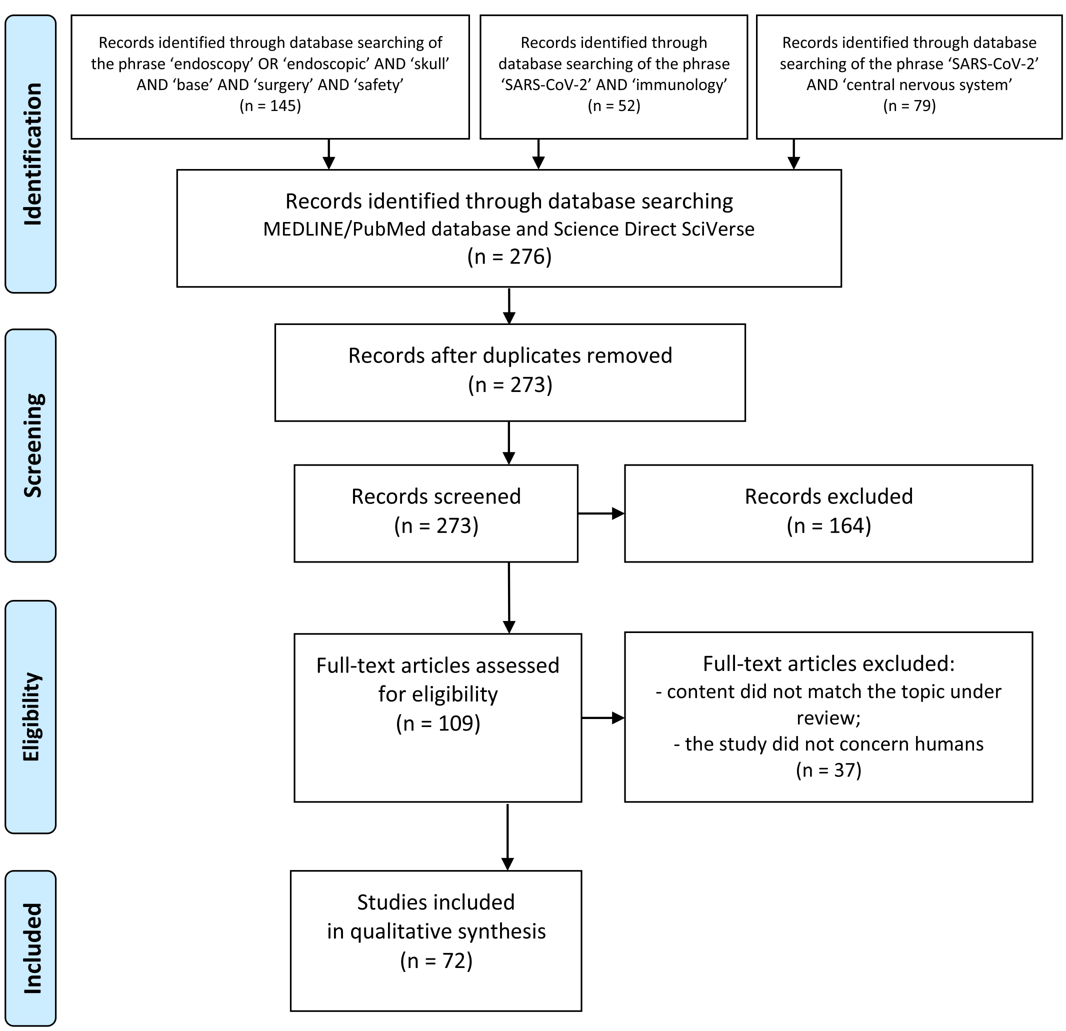

Fig. 2. PRISMA flowchart of study selection process. Adapted from Moher et al. [15].

Every kind of disruption of the mucosa, especially in places where the vast majority of viruses enter the human body – respiratory system, gastrointestinal tract and vaginal mucosa – potentially contribute to infection.

As mentioned previously, endoscopic interventions within the skull base are by no means minimally invasive. As in every other kind of major surgery, extensive tissue damage is associated with significant alterations of the immune response, finally leading to immune depression. Arousal of hypothalamic-pituitary-adrenal (HPA) and sympathoadrenal (SAS) axes releases catecholamines and cortisol. In addition, cytokines, chemokines and inflammatory mediators released at the time of surgery may recruit immune cells to kick-off immunological response. Finally, perioperative injury and subsequent immune system engagement alters the important balance between lymphocytes Th1 and Th2, increases expression of T-helper 2 (Th2) and T regulatory lymphocytes (Tregs), and predisposes the patient to lowered cell mediated immunity [30].

Anaesthetic drugs, irrespective of the route of administration, can influence both innate and adaptive immunity. Anaesthetics can augment the detrimental effect of injury itself, additionally influencing activation of HPA and SAS axes.

Another aspect of safety concerns the adequacy of the cerebral blood supply during the period of seemingly "controlled" arterial hypotension – a manoeuvre used to maintain a bloodless operative field, in certain extended transnasal endoscopic procedures. Using transcranial Doppler we have demonstrated that in around half of our patients, blood flow velocity in the middle cerebral artery drops below the reference range [31]. Our results have been confirmed by subsequent studies leading to the conclusions that the effect may be dangerous, especially in older adult patients [32,33]. Other investigators, using non-invasive infrared oximetry, have noticed the occurrence of excessive desaturation of the cerebral blood during conditions of decreased systemic blood pressure [34]. Based on the above premises we have established that the ultimate criterion for adequacy of cerebral blood supply should be brain oxygenation measured directly in the brain parenchyma. In three out of five patients, the partial pressure of oxygen dropped below 15 mm Hg when blood pressure was reduced to obtain a bloodless operative field. It may be concluded from this result that 15 mm Hg may be considered the threshold for evident material brain ischemia [35].

The hazards of brain ischemia have been confirmed by another study in which we demonstrated an increased concentration of neuron specific enolase (NSE - a known marker of ischemic brain damage) in half of our patients postoperatively [14]. Other investigators have found a significant increase in different biomarkers of neuronal ischemic damage, such as S–100B, glial fibrillary acidic protein (GFAP), microtubule-tubule associated protein tau and neurofilament light (NfL) protein [36,37].

Furthermore, the detrimental effect of "controlled" hypotension on the immune system seems to have been underestimated. Immune cells exhibit high levels of oxygen consumption, as does bone marrow and thymus, their metabolic rate in some situations exceeding 3-fold the rate of surrounding tissues. During induced hypotension, organs with high oxygen consumption, but no autonomic blood flow regulation, will suffer the most. Conversely, hypotension is associated with deterioration of the immunological barriers afforded by mucosa and epithelium. This is also true for organs not equipped with blood flow autoregulation, or in the worst scenario, organs that are a reservoir of blood during centralization of circulation. For this reason, hypotension involves a higher incidence of sepsis, endotoxemia and oxidative stress in blood. In turn, pro-inflammatory cytokines, such as IL-1β, IL-6, and TNFα, sustain and augment hypotension thus creating a self-renewing circle.

3.1.2. eSBS and microbiological threats

The nasal cavity is not a sterile environment; thus, raising another concern as to the patient's (as well as the surgeon's) safety. Currently, the sinonasal corridor cannot be sterilized as required in classical surgery. A biofilm is usually present in the nasal cavity/paranasal sinuses, which normally helps in building host resistance against aggressive microflora. Therefore, according to the current consensus, eSBS in otherwise healthy subjects does not produce any noticeable risk of spreading infection [4]. The incidence of meningitis after eSBS ranges from 0.7% to 3.1% [38–40], which compares well with that for open craniotomy where the range is 0.9% to 2.5% [41–43]. The pathogens involved in most post-surgical infections are Staphylococcus aureus, Streptococcal species, Enterobacteriaceae, and Pseudomonas aeruginosa.

In contrast to intuitive expectations, even if the microflora undergo transformation into a more aggressive form to produce chronic rhinosinusitis, eSBS does not seem to be associated with an increased risk of intracranial infection. One possible factor accounting for this finding is that the marsupialization of the paranasal sinuses facilitates the drainage of mucoid secretions [43]. This effect has been confirmed in patients of differing age, race and gender, and seems valid despite reports of isolated cases of infectious complications. An exception must be made for patients with acute purulent rhinosinusitis or fungal infections, in whom is prudent to stage the surgery [44].

3.2. COVID-19 pathogenesis

3.2.1. SARS-CoV-2 routes of infection

Viruses are part of the microbiological threats potentially complicating eSBS, which is particularly significant in the era of COVID-19, which may affect not only the patient but also the surgical personnel. Problems arising from possible interactions between the host and the virus became even more significant with recent data suggesting that SARS-CoV-2 has a high affinity, not only for the epithelium of the airways, but also for the nervous system.

Coronaviruses (CoV) are widely occurring, single-strand, positive-sense RNA enveloped viruses, which are separated into 4 genera based on phylogeny: alpha-CoV (group 1), beta-CoV (group 2), gamma-CoV (group 3) and delta-CoV (group 4) [2]. CoVs were first isolated from domestic animals in 1937, but the first human coronavirus was obtained from nasal discharge in 1965. The SARS-CoV-2 virus is the seventh known virus from the beta-CoV family that infects humans. It is equipped with RNA composed of 29,903 nucleotides, making it one of the largest RNA viruses. A characteristic virus 'crown' is made of protruding "S" glycoprotein, which can recognize specific receptors on the host cell surface, eventually resulting in cell membrane penetration. In humans, CoVs primarily invade the upper respiratory and gastrointestinal tracts, which explains their abundant presence in the nasopharynx and gastrointestinal mucosa and which is very important from the perspective of invasive procedures in these regions. Nevertheless, some evidence suggest the virus may also be present in the blood, stool and tears [45].

Destruction of the biological barrier (protective biofilm) on the surface of the mucous membranes within the craniofacial area with certainty opens a gate to the spread of the virus. Generally, there are two ways for SARS-CoV-2 to enter the target cell: by endocytosis and by fusion of the viral membrane with a membrane of the target cell, the latter being 100 times more efficient for viral replication than endocytosis. Nevertheless, viral penetration into the cells does not require damage of the mucosa. All it needs is a cell endowed with angiotensin II converting enzyme (ACE2) receptors. Recently, two research groups have demonstrated that successful intracellular entry of SARS-CoV-2 depends on co-expression of type II transmembrane serine protease (TMPRSS2) [46,47]. Cellular ACE2 protein is present abundantly in pneumocytes and enterocytes of the small intestine [48], as well as in the vascular endothelial cells of the heart, kidneys, and other organs, including the brain. SARS-CoV-2 appears to be optimized for binding to the human receptor ACE2 as its inimitable spikes contain protein S (i.e. spike protein), which binds specifically to the receptor. As mentioned previously, penetration of the virus is facilitated by the presence of TMPRSS2, which is upregulated by androgen and highly expressed in epithelial cells at different locations (in descending order: prostate > colon > small intestine > pancreas > kidney > lung > liver) [49]. In the human respiratory and gastro-intestinal system, less than 10% of the epithelial cells co-express ACE2 and

TMPRSS2 [50]. Therefore, it is apparent that the virus can attack different organs, although by common wisdom its main target appears to be the respiratory system, since inhalation is the commonest, and from the virus' perspective, most efficient way of inoculating its potential host.

3.2.2. CNS involvement during SARS-CoV-2 infection

It is commonly known that one of the hallmark manifestations of SARS-CoV-2 is respiratory insufficiency. Apart from the respiratory system, SARS-CoV-2 has been increasingly identified in many other organs, including the CNS. Current evidence suggests, that infected patients commonly present neuromuscular symptoms manifested as acute stroke (6%), impairment of consciousness (15%) and skeletal muscle damage (19%) [51]. Moreover, it is now evident that even patients, who develop severe respiratory symptoms, had often passed through an earlier phase of subtle neurological and neuropsychiatric symptoms, which seem to be common early features of COVID-19 illness, especially in younger patients [52].

Viruses can reach the CNS through haematogenous or neural propagation, especially when blood-brain barrier properties are compromised [53]. As suggested by single studies in humans and confirmed from animal experiments, the neurological manifestations of SARS-CoV-2 are possibly associated with a neural pathway via the olfactory nerve [51]. Anatomically, the olfactory pathway begins with bipolar cells located in the olfactory epithelium that synapse within the olfactory bulb – a structure belonging to the CNS. From the olfactory bulb, the virus can spread to other CNS structures – a finding confirmed by Gu et al. [54], who detected histopathological changes in the cortex and hypothalamus of SARS multiple organ infection victims on autopsy. Dissemination is possible along the nerve axons as well as through the anterograde or retrograde trans-synaptic passage. Spreading of the virus inside neuronal cells is facilitated by microtubules with the aid of two types of proteins: dynein (from + to − end) or kinesin (from − to + end) which may constitute targets for the virus.

Nevertheless, it may be surprising that at least some of the respiratory symptoms are elicited by the presence of the virus in the brainstem and due to general CNS involvement [51]. Breathing is centrally controlled by regulation from a number of neural groups: through the nucleus of the solitary fascicle, the CNS receives information from the chemoreceptors that detect changes in the concentrations of CO2 and O2; alterations in these components lead to an increase or decrease in respiratory effort [55]. Therefore, respiratory distress in patients with COVID-19 occurs not only as a result of pulmonary inflammation, but also due to the damage caused by the virus in the respiratory centres of the brain.

Evidence for potential damage to the nervous system caused by SARS-CoV-2 is still in its nascent phase, despite being supported by an increasing amount of recently published data. In March 2020, Beijing Ditan Hospital published gene sequencing confirming the presence of the virus in the cerebrospinal fluid (CSF) of a patient who presented with a viral encephalitis, but no respiratory symptoms [56]. Zhou et al. [57], detected the presence of the virus genome in the CSF of a 59-year-old patient with COVID-19 pneumonia and the symptoms of viral encephalitis. Poyiadji et al. [58] reported a patient with acute necrotizing COVID-19 encephalopathy, diagnosed by imaging, probably related to a CNS cytokine storm. These findings strengthen the premise that the virus can invade the nervous system directly, and not as was hitherto thought - that damage occurring in the CNS is caused by a cytokine storm generated elsewhere, i.e. in the lungs. Therefore, there is the possible risk that even people who have had no respiratory symptoms of SARS CoV-2 infection, may develop symptoms of CNS involvement. Currently, further assessment of this risk remains unsettled [59].

3.2.3. Immune response during SARS-CoV-2 infection

As with the vast majority of intracellular pathogens, the virus antigen is presented to the host immune system by antigen presenting cells (APCs), which constitute a major line of recognition and initial response against viruses. Thus, following infection, APCs will present SARS-CoV-2 particles on their surface via the major histocompatibility complex (MHC). Therefore, viruses can be recognized as foreign by cytotoxic T lymphocytes (CTLs).

To date, there have been no reports describing in any detail the method by which SARS-CoV-2 MHC presents to the immune system. Therefore, we can only turn to previous data pertaining to the closely related SARS-CoV and MERS-CoV. The SARS-CoV as well as MERS CoV antigen presentation is predominantly MHC class I dependent [60], and only partially MHC class II dependent. On the contrary, it is well known that MHC in the population is highly polymorphic and some of the variants correlate with high susceptibility to SARS-CoV, while others afford lower susceptibility [61,62]. Also, other, less specific defence mechanisms (like for example opsonins), have similar inherent variability thus predisposing an individual to differential effects in immune activation [63]. Therefore, the rules of personalized medicine should also be applied to immunology. Certainly, it might be of great benefit to assess specific types of Human Leukocyte Antigen (HLA) to be used as predictors of clinical outcome. Some calculations predict that HLA-B*15:03 will be the HLA allele with the highest capacity to identify the so-called "highly conserved peptides" associated with SARS-CoV-2. As these peptides are present in many coronaviruses, an individual possessing the HLA-B*15:03 might be better protected from massive viral exposure by cross-protective T-cell based immunity [64].

Presentation of viral particles by antigen presenting cells results in numerous immune reactions, both humoral and cellular. As with many other viruses, SARS-CoV-2 induces production of IgM and IgG over a typical time course. While IgM antibodies are not detectable at the end of 12 weeks after infection, IgG SARS-CoV-2 specific antibodies seem to be long lasting, probably providing long-term immunity. As is known from other types of coronavirus infection (SARS-CoV), the majority of protective IgG are S-specific (spike protein) and N-specific (nucleocapsid) [65]. With regard to cellular immunity, a frequent problem is the insufficient number of T-lymphocytes (both CD4 and CD8), irrespective of their high levels of activation, as shown by the high proportion of double positive HLA-DR (CD4) and CD38 (CD8) [66]. Lymphopenia during COVID 19 is not uncommon and a low lymphocyte count ($<1000/\mu L$) is associated with severe disease – a similar effect was previously demonstrated during SARS-CoV and MERS-CoV infections.

In the majority of cases, the main cause of death associated with SARS-CoV-2 infection is acute respiratory distress syndrome (ARDS) and multiple organ failure. Excessive stimulation of the systemic inflammatory response can evoke a "cytokine storm" of pro-inflammatory cytokines (such as IFNα, IFNγ, IL-1β, IL-6, IL-12, IL-18, IL-33, TNFα, TGFβ) and chemokines (such as CCL2, CCL3, CC5, CXCL8, CXCL10), released from the immune cells.

3.2.4. Immune response during coronavirus infection of the CNS

It is hypothesized that the SARS-CoV-2 virus can damage the CNS not only by "direct" invasion through the olfactory nerves, but can also have a "remote" effect, through distal spreading of the inflammatory response. This notion is supported by the curious finding, that no viral presence was found in patients with evident encephalopathy presenting as part of their initial symptoms. Thus, no evidence was found that the virus had crossed the blood-brain barrier [51]. Moreover, there are data suggesting that the release of huge amounts of various pro-inflammatory cytokines can induce demyelination and even neuronal cell death [67]. Brain surgery (including eSBS) can potentially augment these "distant effects" of the viral infection, because it apparently predisposes weakening of the blood-brain barrier, eventually paving the way for SARS-CoV-2 damage to the CNS.

An additional, possible emerging factor in determining the effect of SARS-CoV-2 on the CNS, is the potential variation in pathogenicity of particular strains of the virus. Publications concerning this issue are scarce, but the theory is supported by an animal model of CNS infection by mouse coronavirus (mouse hepatitis virus, MHV). This type of CNS infection spurs both innate and adaptive immunity with the consequent involvement of numerous cytokines (including α and β, TNFα, interleukins 1α, 1β, IL-12). The most important seems to be IL-6 that, as in many other viral CNS infections, is responsible for the passage of different inflammatory cells across the blood-brain barrier with coexisting up-regulation of adhesion molecules on the surface of brain vascular epithelium. This is likely to contribute to an increased risk of cerebral inflammation and thrombosis. Different strains of mouse coronavirus induce different profiles of immunological response i.e. a strain most lethal to the CNS induces significantly higher inflammatory cytokine production. It is not known whether the same is valid for different strains of human SARS-CoV-2 virus. At present, there are no proven means of preventing all of these negative effects of SARS-CoV-2 on the CNS. Expectations lie with the prophylactic administration of interferon (IFN) type I. SARS-CoV-2 is much more susceptible to IFN-I than SARS-CoV and displays substantial *in vitro* sensitivity and efficacy for IFNα pre-treatment against the virus [68]. There are also published data supporting the effectiveness of IFNα2b sprays in reducing infection rates. Lokugamage et al. [68] propose IFN-I as prophylaxis against SARS-CoV-2. Other authors suggest that IFNβ is likely to be the most effective IFN subtype, and should be administered prophylactically as early as possible [69]. The proposed route of IFN-I administration (sprays) would appear to be an ideal and convenient way of protecting the nasopharynx from SARS-CoV-2 propagation and viral transmission to CNS in the case of eSBS necessity.

These aforementioned findings suggest that IFN-I administration might be a safe and efficient weapon against SARS-CoV-2. Our knowledge from previous animal and human studies on coronaviruses provides us with critical assets in this regard. Intranasal supplementation of recombined IFNβ and IFNα can prevent the transmission and spread of mouse coronavirus into mouse CNS, but does not prevent its clinical manifestation in other organs. This form of pre-treatment appeared to efficiently recruit innate immunity cells in immunodeficient lymphocyte knockout mice, but it was not sufficient to prevent CNS infection. This finding underscores the crucial role of lymphocytes in combating coronavirus infection, although (as stated above) lymphopenia is not uncommon in patients suffering from COVID -19.

It is important to emphasize that treatment with IFN-I should be limited to early phases of the infection [70]. Intensive tissue damage in the course of COVID-19 human pathology presents similar characteristics to interferonopathies, because SARS-CoV-2 probably induces an excessive IFN-I mediated response, whereas IFN itself can increase the possibility of a "cytokine storm". In China, the guidelines for treatment of COVID-19 recommend administration of 5 million units of IFNα by vapour inhalation twice a day, in combination with ribavirin. In light of the above, it seems reasonable to consider IFN-I administration as a prophylactic/therapeutic measure when trying to increase patients' safety before neurosurgical procedures (Fig. 3).

When dealing with advanced phases of COVID-19, anti-inflammatory drugs (such as anti-IL-6 receptor antibodies i.e. tocilizumab, sarilumab) could be considered a therapeutic means of diminishing the overactive immune response. This option is supported by early clinical data showing that the concentration of augmented inflammatory biomarkers is associated with increased mortality [71,72]. Although more studies concerning these issues are required, this approach could be taken into account should the necessity of immediate neurosurgical intervention in a patient with active COVID-19 disease arise.

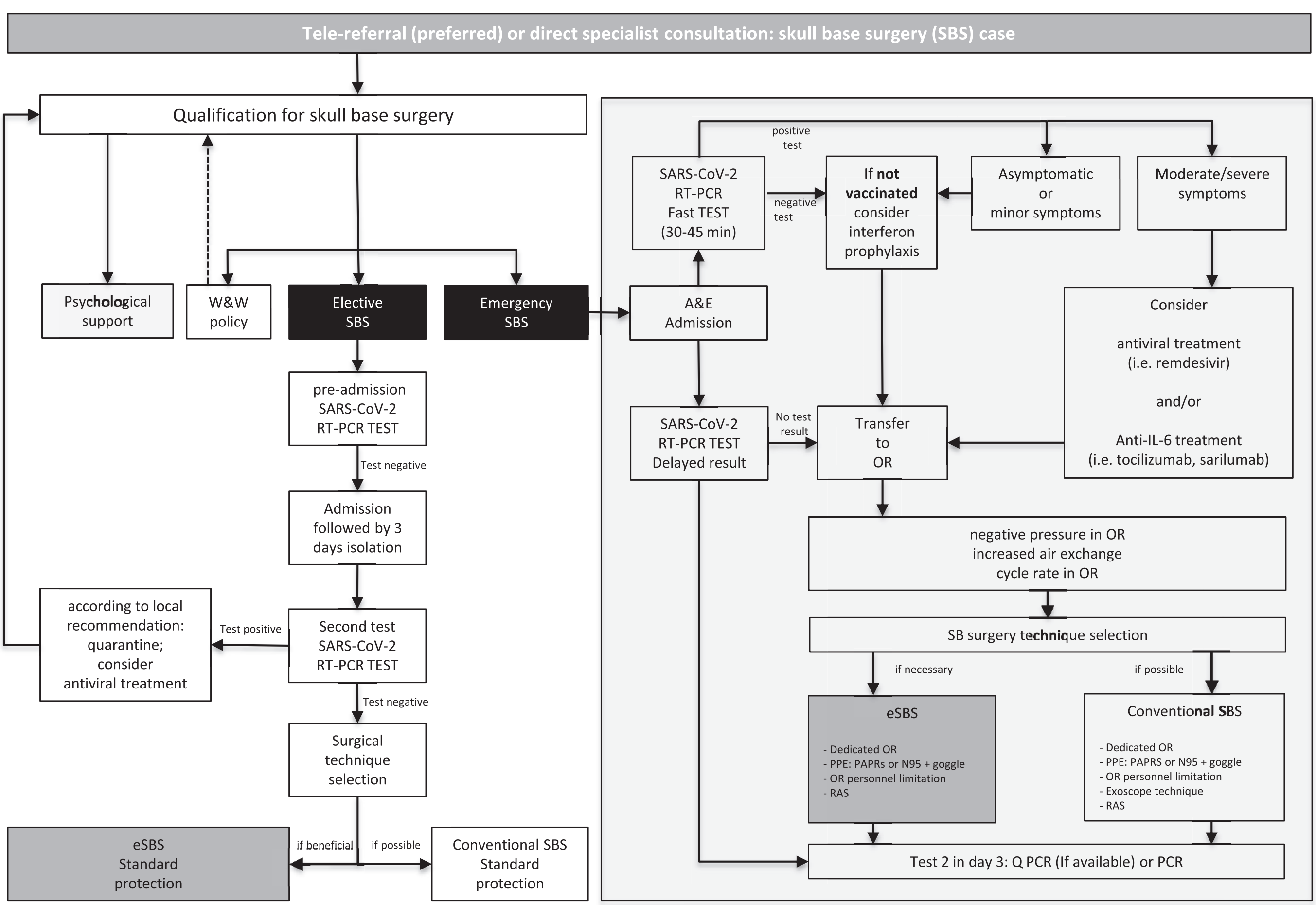

Fig. 3. A flowchart of proposed algorithm for patient qualification and safe performance of endoscopic skull base surgery (eSBS). *Abbreviations*: SB - skull base; eSBS - endoscopic skull base surgery; W&W policy – watch and wait policy; RAS - robot assisted surgery; OR – operating room; PAPR - powered air-purifying respirator; PPE - personal protection equipment.

In summary, SARS-CoV-2 presents as an acute respiratory infection with neurotropic capacities. Though some practical recommendations might be based on the current limited data, more studies are required to unravel all the possible links between COVID-19 and neurological conditions in order to understand the neuroinvasive properties of the virus and to develop more effective precautionary measures.

3.3. Psychological aspects of eSBS during the pandemic - facing two viruses: COVID-19 and rapidly spreading anxiety

In today's world, social media provide a major route for rapid communication allowing memes to "infect" minds in an analogous fashion to the way in which biological viruses affect human brains. As a result, a natural concomitant of the COVID-19 pandemic has been a sharp increase in anxiety levels among people across the world. This is evidenced in the variety of reactions it has elicited, ranging from unrealistic optimism to frank cynicism, as exemplified by politicians' premature claims that the virus is in retreat and presents little more risk than influenza, to reactions of extreme caution, whereby people have stopped presenting to emergency services despite having life-threatening symptoms which are more likely to lead to significant disability and mortality than coronavirus itself [73]. Both reactions are extreme, and therefore, dysfunctional. The former is one of denial, a mental coping strategy that may be employed to restore emotional equilibrium, when a person feels threatened and overwhelmed by the demands of attempting to deal with the perceived threat. The latter is an avoidance strategy, commonly seen in anxiety, which brings temporary relief, but trails many problems in its wake. Neither strategy is a long-term solution, as neither addresses the anxiety-provoking situation directly and this is especially problematic when the perceived threat from the pandemic is likely to be long-term.

A number of conclusions in the current situation may be drawn from the extensive body of literature that exists on stress and anxiety. Whilst the physiological response to a stressor is universal, irrespective of its nature [74], the human stress response is strongly determined by psychological factors. Firstly, how we perceive a given situation is crucial, thereby leaving room for considerable differences among individuals [75], hence the extremes referred to above. Of greatest impact are situations perceived as being uncontrollable or unpredictable [76,77] and there can be little doubt that the COVID-19 pandemic is likely to be appraised as such by the majority of the population with no specialized medical knowledge. Additionally, hospitalization, surgery and life-threatening conditions are among those life events rated highest for eliciting anxiety [78]. There can be little doubt that transnasal eSBS in the context of the current COVID-19 epidemic meets all of the criteria for eliciting profound levels of stress among patients. Indeed, anxiety itself can be like a virus, spreading uncontrollably among the population, exacerbated by false or conflicting information.

The second psychological factor determining the experience of stress results from an appraisal of resources available to the individual to deal with the threat [79]. Emotion-focused coping can be helpful when little of any practical significance can be done, but problem-focused strategies are held to be the most effective. Many in the current predicament feel helpless in the face of the pandemic, as its perceived uncontrollability and unpredictability appear paramount, and there is little that can be done to counteract its threat, except for maintaining hygiene and socially isolating. The latter, however, is a distinct barrier to seeking emotional support as the normal routes to social support have been withdrawn, at least in the short-term. Nonetheless, there is concern that people will be unable to maintain isolation for very long and this is already becoming evident, with many, especially the young, demonstrating a nonchalance towards the pandemic that is clearly unjustified [80].

These considerations suggest an essential role for the psychologist in helping to restore a balanced view of the threat from the pandemic, with which we will have to become bedfellows, albeit reluctantly, for some time still. Lack of a coordinated, evidence-based response to the management of the psychological implications of the pandemic has been identified as a major obstacle to ensuring an appropriate response from health services [59]. Psychological interventions should include a coordinated and timely response with psychologists working as part of the neurosurgical care team, to address the issues raised above. A major role for the psychologist is to help alleviate patients' fears concerning neurosurgical treatment, in particular eSBS, which are exacerbated by their albeit limited knowledge that the surgical approach is transnasal and that inhalation is a major route for viral transmission. This, combined with the perceived unpredictability of the virus, gives rise to an indefinite, "imaginary" enemy, which is likely to be considerably more threatening than the reality of the clinical situation. The expectation of the clinical team (and the patient) is that the psychologist can help to transform this "imaginary" enemy into a more realistic, though nonetheless "actual enemy" with all its real threats and weaknesses. This includes helping patients to modify dysfunctional thinking concerning the threat from coronavirus, providing appropriate education in relation to surgical interventions and aftercare, ensuring they receive appropriate emotional support from care staff and attempting to facilitate contact with family members while they are under hospital care - all of which could be embodied in a cognitive-behavioural approach to management. A summary of the proposed process is presented in Fig. 4.

3.4. Restriction of eSBS applicability and recommendations for increasing the safety of the procedure

In general, every new invention initially appears to provide a solution

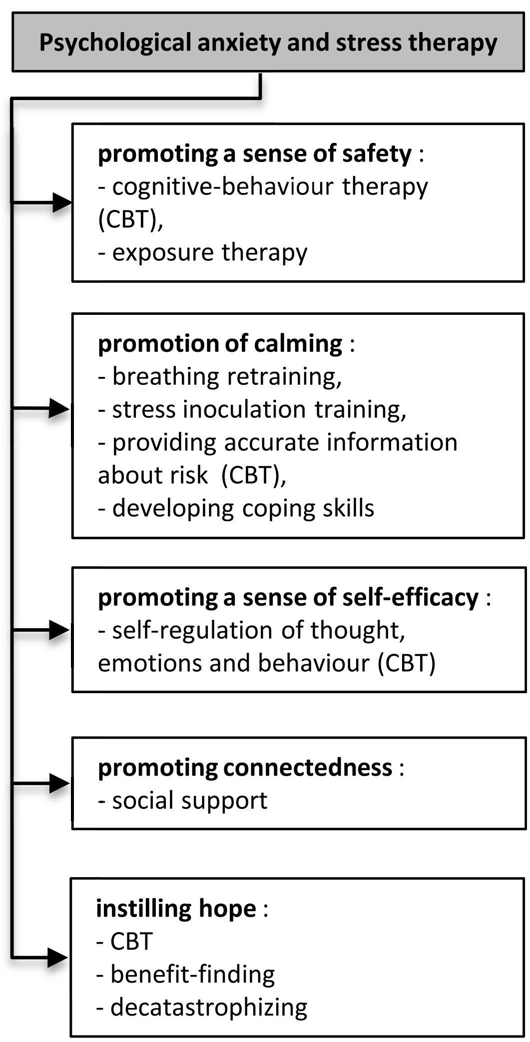

Fig. 4. Psychological support for the patient.

to the problems and restrictions associated with an old technique. However, once the initial euphoria fades, the shortcomings of the new method, together with unpredicted consequences need to be addressed. Today, it may be said that eSBS is undergoing this process. Conclusions from the relatively few studies - referred to above - concerning the safety of the method, lead to the following restrictions with regard to its applicability:

1. The procedure may be safely performed by a highly skilled, interdisciplinary team, working with a constantly updated, and dedicated set of precision instruments. Only with these precautions can the duration of surgery be sufficiently limited to avoid brain ischemia during the phase of "controlled" arterial hypotension and to minimize tissue trauma during creation of a surgical corridor.
2. Bone drilling, cauterization and exposure to the heat generated by light from the endoscope must be considered to minimize adverse thermal effects.
3. The surgery needs a dedicated and experienced anaesthesiology team versed in effective monitoring to assure an optimal trade-off between the need for a bloodless operative field and cerebral blood supply.
4. Finally, eSBS should not be perceived as a "magic wand" for the easy resolution of all problems associated with skull base pathologies. As already pointed out, eSBS is neither minimally invasive nor fully safe and any delayed adverse effects still await more thorough identification. Consequently, it seems reasonable to suggest that eSBS should be used only when it affords a better option with regards to exposure, resection and morbidity. For example, in many cases of anterior skull base pathologies, minimally invasive transcranial approaches may remain a better option.

3.5. eSBS safety in the era of SARS-CoV-2 pandemic

From the above, it is clear that patients' safety must be a priority when dealing with eSBS. Currently, a new factor, in the form of the SARS-CoV-2 pandemic with all its biological, financial, social and psychological implications, has added to these concerns, underscoring the need for ensuring the safety of the operating team. Certainly, a better understanding of this new enemy will help to enhance safety for both patients and medical staff. Important surgical procedures, including eSBS, must be performed even in times of a smouldering pandemic, which is likely to remain with us for the considerable future.

Of all surgical procedures, eSBS is one of the most likely to expose both the patient and the surgeon to viral invasion. A significant number of doctors who became infected and even died during the first phase of the pandemic in the city of Wuhan (China) were anaesthesiologists, ophthalmologists, and otolaryngologists. The alleged reason for their infection was the high level of viral shedding from the nasal and oropharyngeal cavity Thus, protection of the surgical team must be a high priority For this reason, there is an urgent need to design a pattern of workflow which could be useful not only during the current outbreak, but also during the unpredictable timeline of our coexistence with the virus. Speaking illustratively, we must learn ways of "sleeping with the enemy".

Currently, the relevant literature provides only a general recommendation that eSBS should be reserved solely for situations of absolute need [81], whereas for all other instances, a "watch and wait" strategy should be considered. Alternatively, conventional skull base surgery can be used for those locations where a transcranial approach is feasible. While this approach seemed justified at the outbreak of the pandemic, the present time calls for adaptation of a somewhat different approach: one which would secure for the patient the benefits of these modern surgical techniques, and would not hamper further development of the method, while assuring the safety of the medical staff. Such an approach would also help to resolve another problem (considered in a recent meta-analysis), namely, how to deal with all the non-clear-cut cases in which time of intervention may still be crucial [81].

In patients, who are, or who may be infected, aerosol-generating procedures are obviously associated with a higher risk of viral spread. A default solution is using personal protection equipment (PPE). Nevertheless, it must be kept in mind that all "mechanical" means of attempting to ensure the safety of operating room staff are either uncertain, cumbersome, or incompatible with the requirements of this highly demanding type of surgery. When attempted, powered air-purifying respiratory (PAPR) equipment is likely to reduce the risk, but it limits surgeons' comfort and field of vision. Alternatively, an N-95 mask together with tight fitting goggles can be employed. Additionally, a set up ensuring negative pressure in the operating theatre together with an increased air exchange cycle rate are highly recommended to reduce virus dissemination. Robot assisted surgery (RAS) is a potential solution, because it distances the surgeon from the operative field. Nevertheless, in spite of previous successes of RAS in many fields of surgery, its employment in eSBS still remains undeveloped.

Development of vaccinations against COVID-19 and/or new effective therapies are anxiously awaited, despite their recent development and seemingly high effectiveness they may only become available to the general population with some inevitable delay due to production, distribution, and administration limitations.

In summary, eSBS exposes both the patient and the surgical team to a significant risk of viral invasion and spreading. SARS-CoV-2 affinity for the nervous system appears especially disquieting. Unfortunately, all hitherto available surgical recommendations are very general and do not provide any direct propositions for enhancing the safety of the patient and the surgical team. They merely constitute a model and it remains up to particular surgical sub-specialties to create a specific triage system based on the unique characteristics of a given surgical field. Taking the aforementioned factors into consideration, we have tried to work out a more definite scheme for eSBS patients – an algorithm which is likely to be useful also in the chronic SARS-CoV-2 -era (Fig. 3) This proposition, though based on neurosurgical realities, also takes into account up-to-date knowledge of the properties of the virus as well as what has already been worked out by ear-nose-throat (ENT) surgeons with regard to high risk endonasal endoscopic procedures.

3.6. Suggestions for guidelines for eSBS in the COVID-19 era

First of all, patients scheduled for any elective eSBS should be tested for COVID-19 infection, even if asymptomatic and having no history of possible contact with the virus. We propose that SARS-CoV-2 tests should be performed using the real-time (RT)-PCR method of approved manufacturers and commercial laboratories. At the time of writing, 94 kits from different producers have gained FDA emergency use authorization (according to the data available from: https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations#covid19ivd). The test could provide results in the shortest possible time (~1–2 h), with approved sensitivity and specificity. We do not recommend serum immunoglobulin testing, as immunoglobulin response is delayed and time-restricted. Moreover, in some SARS-CoV-2 infected patients limited or no immunoglobulin can be detected.

Nonetheless, PPE should be worn by the entire team even when the patient tests negatively for COVID-19. This precaution is justified because of a certain rate of false-negative results, which have been reported even with genetic tests for COVID-19. For this reason, a subsequent swab with a follow-up RT–PCR test is recommended, the more so since the virus can be latent for several days after infection and thus not detectable in the nasopharyngeal swab (Fig. 3). A 3-day interval between the tests seems to be an optimal trade-off between the viral replication properties and the need for isolation of the patient in hospital, before the procedure is executed; the patient cannot be allowed to stay at home, as self-isolation is too risky and thus not acceptable.

As shown in the relevant block of the chart (Fig. 3), a somewhat modified approach is undertaken when dealing with emergency cases needing eSBS – a situation, which is not likely to be very common. In such patients, an RT-PCR test (either 2-genes or 3-genes) is performed immediately and should receive priority in the lab, with a result obtained within 30–45 min. A patient with a negative result may be given prophylactic interferon inhalation - the same prophylaxis can be applied to an asymptomatic patient with a positive test result. A positive symptomatic patient may be submitted to treatment with antiviral and/or anti-IL-6 preparations (but not to interferon prophylaxis!). In either situation, the highest standards of protection in the operating room are obligatory: both personal and technical, such as the use of negative pressure and intensive forced air exchange. The number of people in the operating room should be reduced to a minimum.

It must not be forgotten, that both the patient and the medical staff usually interpret a situation of this kind as "uncontrollable or unpredictable", thus experiencing considerable levels of stress (see above: chapter "3.3. Psychological aspects of eSBS during the epidemic"). Therefore, psychological support can be of utmost value and in our opinion should be offered both to the patient and to the staff (Fig. 4).

The recent introduction of a program of vaccination against SARS-CoV-2 worldwide provides a certain perspective for the restoration of normality in many areas of life, perhaps most significantly in helping to relieve the psychological stress affecting both patients and health service personnel. Nevertheless, it is not reasonable to expect any "return to the past" of the kind before the pandemic, for which many yearn; much more likely is something of a "return to the future" in which we will have to learn to live with the newly introduced imperatives, such as the wearing of face-masks and frequent hand-washing in order to keep infection rates at bay. The history of harnessing other, once deadly viruses (like HPC, HPV, Polio or rabies), clearly shows that standards of antiseptic procedures did not decrease, but rather imminently increased, despite the introduction of effective vaccines and even following the complete eradication of some pathogens, such as smallpox. Until quite recently, needles and syringes were widely re-sterilized, while today many surgical instruments and even sophisticated and fine devices such as endoscopes are increasingly becoming disposable.

These analogies signal that restraint is called for, at least for the time being, and warn against any major revision of the "policy of extreme caution" outlined in this review. The following arguments speak in favour of this more circumspect attitude:

1. At present, there is no reliable information on the actual efficacy of the different vaccines.
2. The period of immunity gained following vaccination has not been established.
3. The effectiveness of the current vaccines may be less effective against newly emergent mutations of the virus.
4. Even with relatively effective vaccination, testing for the presence of SARS-CoV-2 will still be necessary in all epidemiologically doubtful situations. This uncertainty affects both the patient and the staff involved in the operating room.

4. Conclusions

In conclusion, previous experience with highly infectious pathogens should lead us to expect that for the time being it is only reasonable to maintain our proposition for the management algorithm of patients subjected to eSBS, as eminently valid. In particular, it ought to be applied equally to patients both vaccinated and unvaccinated against SARS-CoV-2.

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