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# Case Report: Managing a COVID-19 Nursing Home Outbreak a Physician's Perspective

By Dr. Jim Shalom

*Abstract-* I am the medical director and sole physician at a 35-bed nursing home in Western Galilee in Israel. At the end of December 2020, the nursing home experienced a COVID outbreak in which nineteen residents were infected. Four of them were symptomatic, and two died. Ten staff members, including our administrator, likewise caught the disease, and five of them were symptomatic. All recovered. The first part of this paper will examine why, despite all our precautions, the outbreak occurred when it did, and why it spread extensively within the home. The second part will describe how the nursing home functioned after the outbreak, until its residents recovered.

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## I. Introduction

In recent months, numerous published papers by experts in various fields, including economists,[1] geographers,[2] and physicians,[3] have analyzed nursing home outbreaks of COVID-19. To the best of my knowledge, none of these descriptions is based on first-hand experience. This paper will describe and analyze a COVID-19 outbreak in the nursing home where I work.[4] I am the medical director and sole physician at a 35-bed nursing home in Western Galilee, in Israel. Until December 2020, none of our residents had been infected with COVID-19. At the end of December, however, one of our nurses was found to be COVID positive. Despite feeling unwell, she had reported for work, as she is not given to complaining and was well aware of our COVID-related staffing issues. She did not inform the nursing home administration of her illness, but that same day, after completing her shift, she went to her physician, who diagnosed her with strep throat and prescribed antibiotics. Since neither she nor he imagined she had COVID, she was not tested. When she still felt unwell four days later, however, she went for a COVID test and received a positive result that evening. She can recall no possible infectious contact. I should add that she had been careful throughout the entire pandemic, and that now, too, she strove to adhere to COVID protocols and denies having touched any of the residents on the day she felt unwell. However, because of her diagnosis, two residents who had had a fever that day were sent to the E.R. for emergency testing, and one was found to be COVID positive. Because she was the only positive contact, we presume that she was the vector that introduced the virus. Despite our best attempts, COVID-19 had penetrated our nursing home.

All our residents and workers were group-tested the following day, and when the results came back two days later six additional residents were found to be COVID positive. We were in the throes of an outbreak.

Ministry of health policy dictated that all COVID-positive residents were to be transferred out. Those who were significantly symptomatic were referred to hospital for admission to COVID wards, while those who were asymptomatic were referred to one of two other regional nursing homes that were equipped with special facilities and designated for COVID residents.

We pursued a policy of routine testing for all workers and residents every three days, under an arrangement conveniently coordinated with the ministry of health, which sends a team to test all our nursing home staff and residents on-site at one go, regardless of which of the four national health funds they happen to belong to. In addition to each person's receiving their own results, all findings are collectively sent to the medical director or administrator. Unfortunately, because of laboratory backlogs from increased nationwide testing, up to 2 days would pass before results were obtained. All told, 19 residents were infected, 2 of whom died of COVID. Ten out of 30 healthcare workers were likewise infected, of whom 5, including our administrator, were symptomatic. None required hospitalization.

There may well be a presumption that any nursing home that experiences a COVID outbreak must have been guilty of negligence. While it is true that some outbreaks were associated with understaffing, inadequate use of protective gear, and poor implementation of COVID protocols,[5] detailed analysis will show that lax observance of COVID procedures is only one of two possible explanations, and that nursing homes that have strictly followed protective guidelines have also experienced outbreaks.[6]

Let's start with the dos, don'ts, and practical difficulties associated with preventing nursing home outbreaks.

Throughout the pandemic, we strove to take all appropriate precautionary measures. From the outset, we had an available supply of PPE (personal protective equipment), including gloves, masks, gowns, and soaps, and their use was immediately and appropriately implemented. With regard to the CDC guidelines,[7] the

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only step we failed to take was the designation of a specific person responsible for IPC (infection and protection control). In our case, this task was divided and coordinated between the administrator, the head nurse, and me.

- With regard to minimizing outbreaks caused by infected health workers, the literature stresses the importance of identifying staff members who feel ill and ensuring that they stay home from work.[8] However, such a change cannot be effectively instituted without a paradigm shift, as sick leave is typically granted only when the state of an employee's physical health inhibits their performance at work.[9] Taking time off for minor complaints because of the risk of COVID involves a change in thinking on the part of both employer and employee, particularly among disciplined workers with a strong sense of duty. It requires a different and lower threshold for considering missing work, and a new reason for staying away, beyond reduced performance capacity. Then there are the staffing implications: being understaffed has the inadvertent paradoxical consequence of causing staff members to feel obliged to report for work even when slightly unwell. There is no easy solution to this problem. Hiring new help at such a critical time, when peak performance skills are essential from the outset, is not an appealing expedient.
- In addition to adhering to this new absenteeism protocol, we have insisted from the very beginning that health workers take appropriate safety precautions, such as remaining at home as much as possible and being selective about whom they encounter. Sensitivity to the home prevention factor has been part and parcel of our COVID infection control policy.
- In our nursing home, two residents generally share a room. During the pre-pandemic period, this was a practical and effective arrangement. However, during the outbreak, we found that if one resident of a room was COVID positive, the other was often also found to be so when tested 3 days later. This finding is consistent with the literature, in which there is a correlation between increased infection rates and facilities with predominantly double rooms and other space constraints.[10] Moreover, a nursing home structure is not a "musical chairs" situation in which any desired urgent re-arrangement is implementable.

Despite these limitations, we managed to keep the nursing home free of COVID for over 9 months.

The first question I want to address is why the virus penetrated the nursing home *at this particular time*?

Despite the presumption that the higher the level of care and infection control, the smaller the likelihood of viral invasion, growing evidence demonstrates that outbreaks have also occurred in nursing homes with five-star ratings. One report concludes: "COVID-19 cases in nursing homes are related to facility location and size *and not traditional quality metrics such as star rating and prior infection control citations*."[11] Gorges and Konetzka have reached the same conclusion: "The strongest predictor of cases and outbreaks in nursing homes *is per capita cases in the county*."[12]

These findings are consistent with our own experience. During the month of December, the community incidence of COVID-19 was the highest it had ever been, and thus our outbreak coincided directly with elevated COVID-19 rates in the surrounding communities. I should add that during this period there were parallel outbreaks in other nursing homes in Israel, which again correlate with a high COVID-19 community incidence.

The next question is: Once the virus is in the nursing home, why is the spread relentless and usually unpreventable?

The WHO protocols emphasize early detection among health workers and implementation of preventative procedures.[13] While these are important, I believe that there will be situations such as ours in the future, too, in which adherence to these protocols does not prevent internal viral spread.

There are several reasons for this. Let me posit three:

1. In addition to the common contagious mechanism of person-to-person spread through large droplets, there exists a secondary mechanism that, though less contagious, is not negligible, and which, under certain circumstances, may contribute significantly to spread. In their paper "Beyond Six Feet: A Guideline to Limit Indoor Airborne Transmission of COVID-19," Bazant and Bush describe this secondary mechanism of spread,[14] which consists of small aerosol droplets that remain suspended for long periods within closed, well-mixed indoor spaces. In a case study of a nursing home environment in which an infected person is present, they conclude that the six-foot rule will fail after 17 minutes, i.e., that there is a significant likelihood of spread from an infected person to an uninfected person within 17 minutes. Furthermore, the authors assert that infected indoor settings are a setup for inevitable spread throughout the nursing home: "In such well-mixed spaces, one is no safer from airborne pathogens at 60 feet than 6 feet."

This model can well explain how the virus spread from our health worker and how our administrator contracted it despite both having worn appropriate protective gear and neither having come into physical contact with either residents or other health workers: once the virus was present in the nursing home, apart from spreading to the residents' rooms,



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small aerosol droplets also contaminated the nursing station and the administrator's office, which is situated near some of the residents' quarters. While small aerosol droplets disseminate more slowly than large ones, if an individual remains in a contaminated indoor region long enough, this secondary spread mechanism may well come into play. Moreover, while our workers were always masked, the residents were not, further facilitating transmission to both staff members and other residents. To describe the mechanics of spread, I propose an analogy with which most of us are familiar – the use of a portable convector heater: its immediate and most potent effect is to warm the area to which its fans direct the heat. This may be compared to a large droplet that emits short-range contagion. However, if left on long enough, the convected heat will spread throughout the entire room and beyond, and under certain circumstances people some distance away from the heater will feel the warmth it provides. This is analogous to the mechanism of small droplet spread, which, while lower, is not always negligible.

2. A second factor is that some of the spread begins at a pre-symptomatic stage, when no one is aware that the virus is present. There is a difference between (lighter) precautionary behavior protocols that are adopted in order to "stay on the safe side" and the heavier measures taken when viral presence is known. Xi He et al.,[14] in discussing the significance of the pre-symptomatic stage, declared, "Our analysis suggests that viral shedding may begin 5 to 6 days before the appearance of the first symptoms." One frustrating conclusion they reach is the following: "We estimated that *44%* (95% confidence interval, 30-57%) *of secondary cases were infected during the index cases' pre-symptomatic stage*." Furthermore, they have reached the sobering conclusion that "Significant pre-symptomatic transmission would probably *reduce the effectiveness of control measures* that are initiated by symptom onset, such as isolation, contact tracing and enhanced hygiene or use of face masks for symptomatic persons." The stable door may well have been closed only after the horse had bolted. In short, they assert that much of the viral transmission occurs before the administration has any idea that the virus is present; and when that is the case, reactive strict adherence to COVID-19 protective protocols after the fact may not be totally effective.
3. A third explanation that makes sense intuitively, but for which there is only indirect support, relates to viral load. That is, that the greater the viral load, the more the virus will be liable to spread. Little et al.[16] report that experiences with Middle East respiratory syndrome (MERS) – another coronavirus – and with household members who treat COVID-19 patients, together with research on animal models, all suggest that the higher the viral load, the more contagious the virus becomes. It would be reasonable to assume that in an enclosed nursing home containing, at times, six COVID-positive residents, the viral load was substantial.

One should not conclude from this analysis that COVID-19 precautions are ineffective; just that, under certain circumstances, such as a high community viral incidence and an enclosed indoor nursing home environment with shared rooms, even strict precautions will not always be completely effective.

I should like to presume that the precautions we implemented did play a role in somewhat reducing the nursing home's viral load, as most of our cases were mild and deaths were few.

## II. After the Fact

The identification of a COVID-19-positive resident was a dangerous inflection point for the entire nursing home, as it heralded the onset of a crisis of a magnitude never previously faced. Nursing home function subsequently underwent a dramatic transformation.

Under ministry of health policy, all COVID-positive residents had to be transferred out. A ministry of health affiliate removed asymptomatic residents to designated nursing homes equipped with COVID wards and decided who went where. Those who developed symptoms such as fever, cough or decreased oxygen saturation were transferred to hospital. However, this ostensibly straightforward algorithm – symptomatic patients are sent to hospital while asymptomatic residents are dispatched to designated COVID nursing home wards – is not always clear cut in reality. Two examples: If a resident had a high fever yesterday but is fine today, is he/she deemed symptomatic and therefore referred to hospital – or not? Another example: If the ministry has decided to refer a resident to nursing home "A," but the family prefers nursing home "B," should the family be accommodated when possible? Such instances were dealt with on an individual case-by-case basis.

*The Changes Implemented*

Firstly, until they were transferred out, residents who had tested positive needed to be completely separated from those who had not. Unfortunately, the transportation team itself was overwhelmed by parallel outbreaks elsewhere and had become so backlogged that we waited for an unwelcome day and a half before it arrived. Despite all our immediate isolation precautions and ministry support, these two delays, in test results and in transfer, offered the virus further opportunity to incubate and continue spreading within the nursing home.



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Secondly, all nursing home workers were immediately required to don special cumbersome and uncomfortable COVID-19 disposable overalls of the kind worn on COVID wards. These measures were improvisations, as our nursing home is not authorized to deal with COVID-19 patients on a regular basis.

The fact that all six positive residents were largely asymptomatic was encouraging, but we were nonetheless required to transfer them all out.

Thirdly, we went into lockdown protocol. Only essential workers continued to operate within the home; our multidisciplinary team, including myself, was locked out.

Our leadership triumvirate found itself with innumerable tasks at hand. Our administrator was responsible for overseeing the transfer out of COVID-19-positive residents, which took place on a weekend, as it could be postponed no longer. That same day, another designated ministry team arrived to vaccinate our remaining residents and health workers; despite the outbreak, we were determined to Pfizer-vaccinate our residents at the first possible opportunity. Finally, as part of an ongoing process since the outbreak, we had ordered repeat testing to identify possible additional cases among the residents. In sum, three major events converged on a single day that weekend: group testing for COVID, vaccinations, and the transfer out of COVID-positive residents.

Our head nurse began making room changes to separate COVID-positive from COVID-negative residents, leaving many alone in their rooms. While minimizing viral spread, this had the unfortunate effect of isolating them still further. The head nurse also had to ensure that our health workers knew exactly how to wear the awkward new COVID-19 protective gear and that they were following the latest stricter hygienic protocols used in the presence of the virus. At the same time, it was vital that she show understanding and support for the nurses and our health aides as their routine tasks became more burdensome. They were also legitimately fearful that they, too, might become infected with COVID.

As physician and medical director, I had the unenviable task of phoning the families of the COVID-19-positive residents one after another, delivering the bad news and commiserating with them over their angst and the further isolation that they and their loved ones would yet have to endure, together with the danger that lay ahead. I know all these family members well, some of them for several years now, and their trust and grasp of the circumstances facilitated my task. However, I was not misled by their lack of outrage. I fully appreciated that the experience they were undergoing was terrifying for them.

At the same time, we also prepared an announcement to send out to our family WhatsApp group. This had to be formulated in a manner suitable for both categories of families: those related to a resident who had tested COVID-positive and those related to one who had tested negative. It needed to provide enough information to keep the families abreast of what was going on, without breaching confidentiality or being unduly technical. Furthermore, it needed to be sent out quickly, before false rumors could start spreading.

*Maintaining Contact with Families and Recipient Nursing Homes and Hospitals*

Once all that had been done, and the residents had been transferred, the situation in the nursing home itself calmed down. Nonetheless, because they were all *our* residents, we began contacting the various recipient institutions to receive daily professional updates on the status of those who had been transferred. In addition, of course, each family made its own inquiries. Success in communication with these institutions depended in part on the other party's availability and willingness to cooperate. In cases such as hospitals that were unwilling to provide telephone information to the referring physician for reasons of confidentiality, or institutions that did not regularly answer their phones, we worked in cahoots with a family member: if they received an update, they would inform us, and if we managed to get news, we would inform them. Even though I was not physically present in the nursing home during the outbreak, my days, which lasted far beyond nine to five, were spent dealing intensely with outbreak-related tasks, the most poignant being fielding emotion-laden telephone calls from family members who were anxiously tracking the progress of a hospitalized resident in unstable condition. They would ask me about the significance of a finding, what questions they should ask the treatment team, and how they should respond to scenario queries regarding insertion of nasogastric tubes, respiratory support, and intubation. It was inspiring to observe them all, one after another, trying to grasp the situation, take responsibility, and perform effectively under the most challenging conditions.

Regulations for family visits to the different locations varied. No one permitted a "regular" visit. Some allowed relatively close proximity, but only if the visitor were enveloped head to toe in COVID protection gear. Others offered viewing through a window. As anyone who has had a close relative hospitalized for COVID-19 knows only too well, this can be a frustrating and Kafkaesque experience.

For the first few days, we were concerned mainly with whether or not our infected residents would develop dangerous symptoms associated with COVID deterioration. Thankfully, in most instances, this did not happen. An encouraging factor was the understanding that, after several days, the longer these residents remained symptom-free, the less likely they were to develop COVID complications. When eventually deemed



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free of the disease, they would be permitted to return to our nursing home.

As COVID concerns declined, however, everyday nursing issues such as patients' confusion, agitation and constipation surfaced and worsened. In many cases, a stubborn problem that had grudgingly yielded to control in our nursing home reemerged as some of this control was lost in the transfer out. Moreover, the established mechanism that enabled a family member to speak with one of our nursing home workers, who knew their parent well, no longer existed. Nor did the recipient nursing home staff find it easy to deal with unfamiliar patients and family members. Furthermore, as the national crisis worsened, COVID wards in both the hospital and the specially designated nursing homes were on the verge of being overwhelmed.

While far less serious than an imminent COVID death threat, these ostensibly minor issues were nonetheless upsetting. After all, it was often problems such as these that had led the family to institutionalize their loved one in the first place. Worse still, some began as minor issues that later snowballed out of control. In one instance, a resident with a background of psychiatric illness, who was nonetheless medically stable, developed a new nursing problem in one of the recipient nursing homes. When her overall condition then worsened, she was referred to the hospital, where she was found to have non-COVID-related acute kidney failure and cardiac symptoms from which she had never suffered previously. We attributed her deterioration in part simply to her removal from a familiar institution to an unfamiliar one which, because of its preoccupation with containing the COVID crisis, gave less priority to nursing and other medical issues. In another instance, a diabetic patient with a minimal foot skin problem developed a significant distal diabetic ulcer within a matter of days. These disturbing incidents left family members and the rest of us speculating as to what could have / should have been done along the way to prevent them. They also reaffirmed a view I hold: I believe that nursing home residents, even those who are apparently stable medically, appear healthier than they actually are, because an effectively run nursing home provides a large measure of protection for these frail people. When this protective milieu is disrupted, their condition will not infrequently deteriorate.

After our administrator had herself recovered from the virus and was deemed non-contagious, she visited the two recipient nursing homes and met with our residents and the nursing home teams. There is no doubt that her visit improved overall communication with the recipient facilities, while also providing us with a clearer impression of the level of care our residents were receiving. Israel being a small country, we were not surprised to discover that we knew the administrator of one of the nursing homes and the medical director of the other.

Health ministry policy at the time deemed COVID-positive patients non-contagious 10 days after diagnosis, providing they had been asymptomatic for the previous 3 days and subsequently had 2 negative COVID results with at least a 24-hour interval between them. Those who didn't pass this test were released at day 20, provided they had been symptom-free for the last 3 days. Finally, if between day 10 and 17 patients were well and had had two additional negative COVID results, they were returned to us after the second negative result was received. Slowly our residents began to come back. The extra work required to reintegrate them into our nursing home was a small price to pay for our profound sense of relief as we extricated ourselves from the outbreak, began to return to normal and were once more directly involved in their care. It also saved us from having to deal with the obstacles encountered in assessment of our residents while they were hospitalized in other institutions. We did everything we could to expedite their return as soon as possible, and, unsurprisingly, most of the acute nursing issues that had arisen while they were away dissipated within a few days of their return.

*Staff Illness Issues*

Of the five symptomatic infected health workers, only one required hospital assessment. Thankfully, he improved, and was sent to convalesce at home. The administrative team members, including myself, maintained frequent contact with all our homebound workers and followed their progress until recovery, even though all had their own physicians. Our healthcare workers' salaries remained unaffected by COVID-19-related interruptions, as Israel's social security department has a compensation system that reimburses staff for COVID-related absences.

At the same time, scheduling problems caused by their absence needed to be addressed promptly so that we could continue to provide orderly care for our residents. We were fortunate in that all our staff members were imbued with a sense of mission to get through the pre-outbreak and outbreak period as effectively as possible, and our workers displayed great scheduling flexibility. Some went beyond this. As an example, when there was a shortage of health aides, one of our registered nurses volunteered to do a few shifts as an aide.

We extended our shift length. While evidence has shown that there is greater likelihood of viral spread when workers are fatigued, there are also advantages to longer shifts. Indeed, even when there was no staffing shortage, we lengthened shifts to 2 in 24 hours, to reduce comings and goings within the nursing home. The CDC's only stipulated reservation is: "Avoid scheduling staff for more than 12 hours, if possible."[17]



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We took care to express our appreciation for our teams' devotion regularly on WhatsApp, and our administrator, together with some of our locked-out multi-disciplinary team workers, brought along treats for the staff to enjoy during their shift. This "we are all in this morass together" atmosphere helped mitigate the stress our teams were enduring. As soon as the infected workers recovered from their illness and were deemed free of contagion, they returned to work.

*A Community Medical Issue Rather than Just a Patient Medical Issue*

By and large, physicians are trained to follow a particular patient with a particular problem. While this remains true of the situation described here, in this instance we are also dealing with a community-wide issue. I define "community" here as the aggregate of nursing home residents, their families, and the nursing home staff, including the administrative team. Analogous to a patient's having minimal symptoms initially, reaching a peak and then resolving, in this instance we had a nursing home health event (outbreak) in which several members of this community were initially infected, followed by a larger number that rose to a peak before subsiding. Apart from the two patients who died, all the others who had tested COVID-positive overcame the illness and returned to the nursing home and/or to work. Both professionally and emotionally, I found it convenient to treat the outbreak as a somewhat unified phenomenon in which the residents' illnesses were connected, rather than as a cluster of independent medical events.

*Physician Leadership Issues*

At its peak, our situation was particularly distressing: residents were dying, more and more were moved elsewhere, numerous staff members were at home with the virus, our COVID-positive administrator had been ill and was in isolation, and our nursing home was becoming depleted as every few days additional remaining residents were diagnosed as infected. These were undoubtedly difficult times.

Although I was only a salaried worker, and during the lockdown I was not physically present at all, I nonetheless felt an obligation to play a leadership role in guiding our administration, staff, and workers through the crisis. I found myself influential in providing succor for our administration team, the other workers, residents, and family members. I attribute my efficacy to the following factors:

- The physician as father figure: "The image of the father-figure has traditionally been assigned to the doctor and accepted by him."[18] A reassuring message from the symbolic father figure of a physician has the potential to be especially effective. Even if, today, physicians take a less paternalistic approach and place greater emphasis on patient autonomy, I believe that, especially in times of crisis – and regardless of the physician's gender – the parental figure of the physician can unconsciously come into play and assuage fears.
- As terrible as COVID-19 is, in contrast to chronic ailments or irreversible events such as a CVA, for most of those affected it is an acute illness with a start and stop date. Physicians can use this knowledge and their experience of steering acute symptomatic illnesses to their resolution to assure those concerned that there is every reason to believe that things will get better.
- Now, many months into the pandemic, physicians are more familiar with the natural course of COVID. For example, we know that the longer a person remains asymptomatic after disease onset, the less likely he or she is to develop complications later, and that most of those afflicted, including the elderly, will get better. While many members of the public have Google and news access to this information, not everything they read is accurate or easy to interpret. Furthermore, I believe that, in times of crisis, information has greater impact when delivered by a familiar and authoritative figure such as the nursing home physician.
- As part of their training and experience, physicians become familiar with guiding sick people through their illnesses and bolstering them during the downturns. Supporting an individual or a community through a medical crisis requires similar emotional resources; however, the means of doing so has to be modified when dealing with an entire community rather than limiting provision of support to residents and their family members. I adopted a community-oriented approach both because all of us were dealing with the outbreak and I assumed that health workers and administrative staff who were part of the outbreak-affected community were also emotionally stressed and should be provided with appropriately tailored emotional support.
- Physicians are trained and experienced in delivering bad news. During the outbreak, we needed to address three different types of bad news: individual cases, including residents and health workers; parallel cases in which a number of patients simultaneously displayed overlapping symptoms; and disruption of the nursing home's normal functioning. Each category was dealt with slightly differently:

i. Families with an infected resident and health care workers were treated on a one-to-one basis.
ii. We used WhatsApp to convey group announcements and pass on relevant information to all the families simultaneously. The same approach, using the nursing home's WhatsApp worker group, was used to deliver information to staff members.



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iii. Finally, I provided support for our administrative team, which oversees the nursing home as a whole, assuring them that in due course our "stricken nursing home" would recover.

In updating our COVID routine since the outbreak, so far, other than one uninfected resident who has only received one vaccination and 2 COVID positive residents who remain unvaccinated, all health workers and remaining residents have received two Pfizer vaccinations. In accordance with ministry policy, we still do group COVID testing once weekly and will continue to do so for a while yet. Our workers still don masks, gloves, and gowns when necessary, and hand hygiene is still stressed.

These are some of the motifs and aspirations that guided us through this difficult period:

- Provision of good nursing and health aid care for our residents.
- Expressing ongoing appreciation and providing support for our front-line health workers.
- Maintaining continuous contact with families of residents who were transferred out.
- When possible, maintaining constant contact with the treatment teams in the institutions to which our residents had been temporarily transferred.
- Delivering bad news competently, compassionately, and honestly.
- Commiserating with families when a resident's condition deteriorated.
- Being available for families when death was approaching and inevitable.

Until the onset of the COVID pandemic, coping with multiple patients because of a single event was beyond the purview and experience of most physicians, to say the very least. Unless they work in a hospital E.R., by and large community physicians are accustomed to handling individual cases: while they may perhaps deal with several cases at once, they are unused to orchestrating an event in which a dozen or more patients are affected simultaneously. A nursing home outbreak confronted us with a new situation. I believe that, in addition to dealing with each case on its own merits, the physician has a responsibility to the community as a whole and can benefit from viewing such an outbreak not just as a collection of isolated events but rather as a group process that can be handled with much the same tools we use to cope with an individual case.

## III. Summary

As the nursing home physician, I found dealing with a COVID-19 nursing home outbreak a most difficult and challenging experience. It required me, as the physician, to be emotionally exposed and to accompany the suffering of an entire community – residents, their families, and the full complement of our health workers, each of whom had to deal with the innumerable obstacles and complications of his or her own personal predicament. Along the way there were casualties: some residents died; others, together with some health care workers, may suffer from residual COVID-19 complications; and some residents' nursing problems were exacerbated because priority was given to virus-related interventions. Isolation angst was a common motif: residents were cut off from activities and from their families. Metaphorically, the situation was analogous to a war in which here and there battles were lost, but in which, overall, we managed to overcome the menace and return to our previous routine. I feel privileged to have witnessed firsthand so much personal heroism among residents who tolerated difficult conditions; among family members who sought to act in their loved one's best interest while at the same time grasping the complex reality the caregivers had to deal with; among the healthcare workers who overcame their fears and who strove to continue treating our residents with compassion and professionalism; and, finally, among members of our administration team, who oversaw events and assumed total responsibility while rendering an appalling situation more tolerable and pushing the wagon forward until we were able to return to our routine.

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# Correlation of Antibody Level in Covid-19 Recovered Plasma Donors with the Clinical Parameters

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*Abstract-* *Objectives:* To correlate the antibody levels in Covid-19 convalescent plasma donors with the clinical parameters.

*Methods:* 30 Covid-19 recovered and RT-PCR negative plasma donors serum samples were screened for the presence of anti-HIV 1 and 2 antibodies, anti-HCV antibodies and, HBsAg by Chemiluminescence and ID-NAT. Routine hematological investigations were performed and Covid-19 antibody levels were monitored using Elecsys Anti-SARS-CoV-2 kit. Donors with antibody level > 1.0 were considered reactive and fit to donate convalescent plasma.

*Results:* Seventeen cases with the mild disease had Covid-19 antibody levels of 1.1 to 30.0 with the duration of stay in the ward from 0-7 days. The most common symptoms were fever, dry cough, sore throat, lethargy, hyposmia, and shortness of breath of varying severity.

*Keywords:* *antibody level, Covid-19 virus, convalescent, donors, parameters, plasma.*

*GJMR-K Classification:* *NLMC Code: WH 400*




*Strictly as per the compliance and regulations of:*

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# Correlation of Antibody Level in Covid-19 Recovered Plasma Donors with the Clinical Parameters

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*Results:* Seventeen cases with the mild disease had Covid-19 antibody levels of 1.1 to 30.0 with the duration of stay in the ward from 0-7 days. The most common symptoms were fever, dry cough, sore throat, lethargy, hyposmia, and shortness of breath of varying severity. Five cases with the mild disease had Covid-19 antibody levels of 31.0 to 60.0 with a hospital stay of 8-10 days. Eight with the moderate disease had Covid-19 antibody titer more than 60.0 with 11-15 days of hospital stay. Hematologic parameters in all the plasma donors were within normal range with negative indirect coombs test, but 8 donors with the moderate ailment had altered Albumin to Globulin ratio. The prescribed treatment was oral Azithromycin, Ivermectin, Paracetamol, Dexamethasone, and Pantoprazole in different severity of the illness. All the Covid-19 recovered cases had increased antibody levels and convalescent plasma donated by them was transfused to Covid-19 infected, patients.

*Conclusions:* Convalescent Covid plasma is under active investigation as a therapeutic and prophylactic treatment for Covid-19 virus infection and Covid-19 antibody level correlated with the severity of illness and duration of hospital stay.

*Keywords: antibody level, Covid-19 virus, convalescent, donors, parameters, plasma.*

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## I. Introduction

The outbreak of novel coronavirus disease-19 has become a global pandemic. The first case of Covid-19 was reported in Wuhan, China in December 2019, with approximately 62 million infected population till November 2020.[1] Moreover, the threat of SARS CoV-2 is increasing globally and hence declared a pandemic by WHO on March 11, 2020.[1]

Covid-19 is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS CoV-2), an enveloped, nonsegmented, positive-sense RNA virus.[2] It primarily spreads through the respiratory tract by droplets, respiratory secretions, and also by direct contact. Its incubation period varies from 1-14 days and is contagious during the latent phase.[2]

By far, many studies have reported Covid-19 clinical features, epidemiology/ transmission mechanism, and preventive management.[3,4] But the disease may present differently in different locations and manifests differently depending on the age of the person or any underlying co-morbid conditions.[3-5]Mostly, it presents with fever, cough, fatigue, nasal congestion, running nose, and diarrhea.[5-7] Severe cases may rapidly progress to acute respiratory distress syndrome, septic shock, metabolic acidosis, and coagulation dysfunctions.[6,7]

Real-time Reverse Transcriptase polymerase chain reaction (RT-PCR) assays can detect SARS CoV-2 from nasal, and oropharyngeal secretions.[7] Genomic sequencing has been playing an irreplaceable role in identifying various streams of the emerging virus.[8]

After the infection of SARS CoV-2 IgM antibodies are produced within 5-7 days while IgG antibodies show increased levels at 10-15 days, and found in the blood for a prolonged period.[9] IgM mainly detects recent infections.[9-10]

## II. Methods

This study included 30 Covid-19 recovered and real-time Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) negative, plasma donors. Clinical samples of the donors, collected in the Blood and Component Bank, Jawaharlal Nehru Medical College and Hospital, AMU, Aligarh were screened for the presence of anti-HIV 1 and 2 antibodies, anti-HCV



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antibodies, and HBsAg by Chemiluminescence (VITROS 3600 system) and ID-NAT (Porceleix Panther System) with internal quality control performed by using both positive and negative controls supplied by the manufacturers. Hemoglobin, total leukocyte count, and platelet count was performed by 3 part Differential counter (Bene Sphera). Covid-19 antibody titer was determined using Elecsys Anti-SARS-CoV-2 kit. The donor with antibody level > 1.0 was considered reactive and fit to donate convalescent plasma.

For all the enrolled Covid-19 recovered patients, age, clinical symptoms, investigations, treatment provided, and duration of stay in the hospital were obtained from the clinical records. The Institutional Ethical Committee reviewed and approved the study, with the clearance number 22/FM/IEC.

*Inclusion Criteria:* Covid 19-recovered (rRT-PCR) negative donors

*Exclusion Criteria:* Any form of other medical ailment but fit donors.

## III. Results

The study included 30 Covid-19 recovered patients. There were 26 males and 04 females, aged between 18-60 years, with laboratory confirmed SARS-CoV-2 infection, and subsequent recovery with complete resolution of symptoms, and RT-PCR negative report. We evaluated all the patients for different clinicopathological parameters using serum samples collected after 14 days of recovery.

There were 17 cases with mild disease and duration of stay in the isolation ward from 0-7 days. The most common symptoms of these cases were fever, dry cough, lethargy, and hyposmia. The estimated Covid-19 antibody level of these cases ranged from 1.1 to 30.0.

Five cases of mild infection presented with symptoms of fever, sore throat, redness of eye, pain abdomen, hyposmia, and lethargy. They had a prolonged period of stay in the hospital from 8-10 days. The detected Covid-19 antibody level in these cases ranged from 31.0 to 60.0.

Eight cases presented with moderate symptoms of fever, body ache, sore throat, body ache, and shortness of breath, were admitted for 11-15 days in the isolation ward of the hospital. After the recovery, their estimated Covid-19 antibody titer was more than 60.0. Table 1.

*Table 1:* Correlation of Clinical Features with Covid-19 Antibody levels

| Covid-19 Antibody Level | No. of Cases | Severity of Disease | Major Symptoms | Duration of stay (days) |
|---|---|---|---|---|
| 1.1-30.0 | 17 | Mild | Fever, dry cough, lethargy, hyposmia | 0- 7 |
| 31.0-60.0 | 05 | Mild | Fever, redness of eyes, pain abdomen, hyposmia, lethargy, sore throat | 8-10 |
| > 60.0 | 08 | Moderate | Fever, sore throat, bodyache, hyposmia, shortness of breath | 11-15 |

Majority of the cases had hemoglobin, and platelet count within the normal range with negative indirect coombs test. All the Covid-19 recovered cases had increased antibody levels, and their donated convalescent plasma was transfused to Covid-19 infected patients. In our study, the clinical parameters of Covid-19 patients improved with subsidence of symptoms, with high antibody titers. In two of the cases, a serial antibody titer performed after 14 days in repeat donors of Covid-19 convalescent plasma was raised.

In the 17 cases with a mild form of the disease, Covid-19 antibody level was between 1.1-30.0, and hemoglobin ranged from 14.1-16.0 gm%. Total leucocyte count was between 4000-6000 cells/cc, platelet count was 3-4 lakhs/cc with albumin to globulin ratio of 1.5:1-1.7:1.

In the 05 cases with a mild form of the disease, Covid-19 antibody level was between 31.0-60.0, and hemoglobin ranged from 13.1-14.0 gm%. Total leucocyte count was between 6001-11000 cells/cc, platelet count was 2.5-2.9 lakhs/cc with albumin to globulin ratio of 1.3:1-1.5:1. In the 08 cases with moderate disease and Covid-19 antibody level more than 60.0, the hemoglobin ranged from 12.0-13.0 gm%, total leucocyte count was more than 11000 cells/cc, platelet count was 1.5-2.4 lakhs/cc with lowered albumin to globulin ratio of 1.1:1-1.3:1. Table 2.

*Table 2:* Correlation of hematological parameters, A:G ratio with Covid-19 antibody levels

| S. No. | Covid-19 Antibody Level | No. of Cases | Hemoglobin (gm%) | Total Leucocyte count (cells/cc) | Platelet count (lakhs/cc) | Albumin: Globulin Ratio | p value |
|---|---|---|---|---|---|---|---|
| 1 | 1.1-30.0 | 17 | 14.1-16.0 | 4000-6000 | 3.0-4.0 | 1.5:1-1.7:1 | 1:2=0.054 |
| 2 | 31.0-60.0 | 05 | 13.1-14.0 | 6001-11000 | 2.5-2.9 | 1.3:1-1.5:1 | 2:3=0.055 |
| 3 | > 60 | 08 | 12.0-13.0 | > 11000 | 1.5-2.4 | 1.1:1-1.3:1 | 1:3=0.042 |



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In the 17 cases with mild disease and covid-19 antibody level of 1.1 to 30.0, the treatment given was oral Hydroxychloroquine, Paracetamol, Vitamin C, and Doxycycline. Five patients of mild infection, with Covid-19 antibody level of 31.0 to 60.0 were prescribed oral Azithromycin, Ivermectin, Pantoprazole, and Vitamin C. Eight cases presented with moderate symptoms of fever, body ache, sore throat, body ache, and shortness of breath, with Covid-19 antibody titer more than 60.0. Oral medications of Azithromycin, Paracetamol, Dexamethasone, Vitamin C, and Pantoprazole was given to them. All the cases recovered from Covid-19 infection to donate convalescent plasma. Table 3.

*Table 3:* Correlation of Covid-19 antibody titre levels with treatment given and Outcome of Disease

| Covid-19 Antibody Level | No. of Cases | Severity of Disease | Treatment Given | Outcome of Disease |
|---|---|---|---|---|
| 1.1-30.0 | 17 | Mild | Tab Hydroxychloroquine, Tab Paracetamol, Tab Vitamin C, Tab Doxycycline | Recovered |
| 31.0-60.0 | 05 | Mild | Tab Azithromycin, Tab Ivermectin, Tab Pantoprazole, Tab Viatamin C | Recovered |
| > 60 | 08 | Moderate | Tab Azithromycin, Tab Paracetamol, Tab Dexamethasone, Tab VitaminC, Tab Pantoprazole | Recovered |

## IV. Discussion

According to WHO, the management of Covid-19 has mainly focused on infection prevention, case detection, monitoring, and supportive care.[1,9] However, no specific anti-SARS-CoV-2 treatment has been recommended till now. In such cases, Convalescent plasma is considered an experimental therapy and, hence phase 3 randomized controlled trials are recommended. In our study, Covid antibody titer showed increased value after recovery from infection in all the cases, who donated convalescent plasma which were used in active disease patients.

The common clinical manifestations of Covid-19 infections are fever, cough, fatigue, sputum production, shortness of breath, sore throat, and headache.[8-11] Among these fever, and cough are the dominant symptoms.[10] Symptoms were broadly classified as mild, moderate, and severe. Milder cases may represent symptoms of upper respiratory tract infection, with fever, dry cough and, body ache. Moderate cases have shortness of breath, fever with chills, and cough. Severe symptomatic cases present with severe pneumonia, acute respiratory distress syndrome, sepsis, septic shock, respiratory failure, heart failure, and ultimately leading to death. The elderly and those with underlying disorders (i.e. diabetes, hypertension, cardiovascular disease, etc.) present with severe symptoms.[12,13]

In Covid-19 patients, common laboratory abnormalities are lymphopenia, leukopenia, monocytosis, neutrophilia, and eosinopenia.[14,15] Peripheral blood smear findings show single lobed neutrophils, and a greater number of plasmacytoid lymphocytes.[15] In this study, the patients showed varying degrees of symptoms, and abnormal laboratory findings and other hematological findings like lymphocytopenia, neutrophilia, eosinopenia, mild thrombocytopenia, and occasional thrombocytosis during the infective period, which subsequently subsided at discharge. The discharge criteria included normal temperature for more than three days, negative indirect coombs test, normal total protein analysis with no respiratory symptoms, the significant absence of pulmonary lesions by chest CT imaging, and a minimum of two consecutive negative RNA test results, performed at least 24 hours apart.[7,8] In Covid-19 patients, elevated levels of acute-phase reactants like LDH and ferritin have been reported.[16] Haemoglobin, platelet count, procalcitonin, and liver enzymes are usually found to be within the normal range. The ALT/AST, prothrombin time, creatinine, D-dimer, and C-reactive protein are elevated, and high levels are associated with severe disease.[16,17] Radiological investigations like CT scans and chest X-Ray have been recommended to know the severity of the disease.[18,19] Chest X-ray may be normal in early-stage disease and mild cases. X-ray findings are those of atypical pneumonia. Ground-glass opacification is the most common finding of Covid-19 patients, usually multifocal, bilateral, and peripheral.[18] CT scan shows bilateral, subpleural ground-glass opacities that progress to air space consolidation within 1-3 weeks with bronchial thickening and traction bronchiectasis.[19,20]

After the infection of SARS CoV-2, IgM antibodies are produced within 5-7 days, while IgG antibodies show increased levels at 10-15 days, and present in the blood for a prolonged period.[21,22] In Covid recovered cases with Covid RT-PCR negative, the samples are collected within two weeks to evaluate the antibody titer. By monitoring viral shedding and antibody response in patients with severe and mild disease, it has been reported that severity of disease shows a positive correlation with viral shedding and antibody response.[23] Detection of IgM and IgG against SARS-CoV-2 is a fast and simple screening method. As an effective supplement to RNA testing, antibody detection is of



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epidemiological significance and is an important means to understand the occurrence, development, prognosis, and outcome of Covid-19.[23,24]

A study on Covid-19 demonstrated that titers of IgG and IgM in the sera increased in a time-dependent manner at three days after transfusion of convalescent plasma. It was found to maintain a high titer level at seven days after transfusion.[25] The neutralizing antibody titers increased following the transfusion.[25,26] According to WHO, the management of Covid-19 has been mainly focused on infection prevention, case detection and monitoring, and supportive care since there is no specific anti-SARS-CoV-2 treatment recommended.[27] Therefore, it might be useful to test the safety and efficacy of convalescent plasma transfusion in SARS-CoV-2-infected patients. The utility of convalescent plasma therapy is that the antibodies from convalescent plasma might suppress viremia, and it also shows that the effects of this antibody were not only limited to free viral antigenicity, but also it helps in the clearance of infected cell.[26]

Our study indicated that antibody levels were increased since the onset of symptoms and persisted during the recovery phase. These neutralizing antibodies help in infectious disease recovery, and protection against future infection. Antibody levels in asymptomatic or patients with mild symptoms were lower than moderate or severe patients in our study, a finding consistent with previous studies.[28-29] Therefore, antibodies against SARS-CoV-2 increased with the clinical severity of the disease and corresponded to the duration of stay in the hospital.

The outcome of disease mainly focuses on improvements of symptoms, which decreases the length of hospital stay, reduction in oxygen requirement, and decrease ventilator support. Response in published trials is generally measured clinically (PaO2/FiO2 ratio) or radiologically (x-ray, contrast CT-scan, HRCT) according to target organs.[21,30] Since the onset of the outbreak, many treatment protocols followed were effective against Covid-19. However, the treatments including, antiviral drugs, steroids, and intravenous immunoglobulin, affect the plasma antibody levels in covid-19 recovered patients. However, treatment guidelines vary among different areas, but it mainly focuses on the management of symptoms. Chloroquine and hydroxychloroquine are used in the prevention, and treatment of malaria and chronic inflammatory diseases. It appears to block viral entry into cells by inhibiting glycosylation of host receptors, proteolytic processing, and endosomal acidification. These agents also have immunomodulatory effects through mild attenuation of cytokine production and inhibition of autophagy and lysosomal activity in host cells.[31] In this study also, chloroquine showed promising results in mild cases, and the addition of corticosteroids and antimicrobials in moderately ill patients was effective in treating the disease. Vitamin C was also used prophylactically in all the infected patients, as it is known to inhibit the inflammatory cytokines, and IL-6 is known to have a critical role in Covid-19 severity.[32]

While vaccine testing requires a significant time frame and is not considered feasible for emergency conditions, the strategy of convalescent plasma therapy has been reported to have a mild therapeutic effect in Covid-19. It was administered as an alternate therapeutic agent in moderate and severe form of infection. This study also focuses on selecting convalescent plasma donors, after recovery from laboratory confirmed, SARS-CoV-2 infection, with a positive Covid-19 antibody titer and normal hematological parameters. The convalescent plasma was transfused subsequently to other Covid-19 infected patients, so that the polyclonal neutralizing antibodies formed by passive immunization, could reduce viral replication and duration of viremia and be a life-saving treatment.[25]

## V. Conclusions

Convalescent plasma is under active investigation as a therapeutic and prophylactic treatment for Covid-19 infection. The factors to consider in treatment protocols should include the effective schedule of transfusion relative to the onset of illness, the timing of donation relative to the resolution of symptoms, the severity of illness of the donor, pretransfusion serology of the recipients. Limitations of this study are a small sample and lack of sample collection in later stages of the disease for serial antibody titer of donors.

*Author's Contributions:* FT: Collected the patient's details, SW: Performed the relevant investigations, SR: Compiled all the records, KA: Wrote the paper, SHA: Reviewed the manuscript, SAS: Provided the clinical inputs

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# Intensity Prevalence and Hygienic State of the Oral Cavity in Preschool Children Living in the Southern Regions of the Republic of Uzbekstan

By Nodirkhan Sh. Akhrorkhujaev, Saidmurodkhan S. Murtazaev & Foziljon K. Khasanov

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*Abstract-* Early childhood caries was and remains one of the most pressing and acute problems of modern dentistry. The increasing intensity and prevalence of early childhood caries in young children is an increasing medical, social and economic problem [6, 9].

Caries prevention includes a whole range of measures. The use of special therapeutic and prophylactic agents as a necessary element of maintaining rational individual hygiene is a prerequisite in the complex of these measures [11, 12]. This, in turn, contributes to a significant reduction in the incidence of dental caries [4, 10]. Prevention of dental caries includes a whole range of measures aimed at its prevention. A necessary condition in the complex of these measures is a rational individual oral hygiene, which includes the use of special therapeutic and prophylactic agents [10]. Properly organized high-quality oral hygiene can significantly reduce the incidence of dental caries [4, 10].

*Keywords: early childhood caries, caries prevention, therapeutic agents, oral hygiene, prophylactic agents.*

*GJMR-K Classification: NLMC Code: WU 290*




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*Abstract-* Early childhood caries was and remains one of the most pressing and acute problems of modern dentistry. The increasing intensity and prevalence of early childhood caries in young children is an increasing medical, social and economic problem [6, 9].

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## I. Introduction

According to the latest developments of the world's leading dentists, training in rational oral hygiene and teeth cleaning should be carried out in stages, starting from the age of 3. Parents should be involved in this work, since at this age child are too young to understand the need for oral care. It has been established that it is precisely the skills acquired at this age that become especially strong, assimilated for the whole life [1, 2, 5]. In addition, at this age, the foundations of personality formation are laid. The recommended stages of teaching a child to rationalize cleaning of teeth, gums and tongue are explained by the fact that up to 3 years of age, carious cavities are more often formed in places of the enamel that is viciously developed in the antenatal period: on the labial and chewing surfaces of the tooth, and from 4 years old, if the child does not learned to brush his teeth, remove food from the interdental spaces, then carious cavities appear on the lateral surfaces of the teeth, which are poorly formed and poorly hold fillings. Therefore, prevention of caries prevention of this localization should be started before 4 years [7, 8].

*a) Purpose of the research*

The aim of the research is to study the intensity, prevalence and hygienic state of the oral cavity in preschool children living in the southern regions of the Republic of Uzbekistan.

## II. Materials and Methods

For the study, we examined 280 children aged 3 to 6 years. Attending preschool educational institutions of Kashkadarya and Surkhandarya regions. Preschool children from various districts of the Kashkadarya region (240 children, 129 boys and 111 girls were included in the main group; children (40 children; 23 boys and 17 girls) of the Mountain region of the Boysun district of the Surkhandarya region were involved as a control group, this region, according to ecologists is the most ecologically favorable southern region of the republic.

During the examination period, all children were practically healthy and were not registered under observation of related specialists. Children were examined using a standard set of dental instruments in natural light. All data were entered in a special questionnaire card, with the help of preschool educators, parents were questioned to obtain complete information about the child. During the examination, the generally accepted sequence was followed: external examination, assessment of the location of the teeth, dentition, assessment of oral hygiene, study of dental hard tissues.

Hygienic history: when, how many times a day, what and how the child brushes his teeth. As a result of the conducted examinations of children, it was found that all children needed special individual training in hygienic skills and careful, regular quality control of hygienic oral care. The intensity of caries was determined by the average value of the indices CPR + cfc of the teeth of the cavities (T.F. Vinogradova, 1988). To assess the hygienic state of the oral cavity, the hygiene index was determined by the method of Yu.A. Fedorov and V.V. Volodkina. (1972). To assess the severity of gingivitis (and subsequently to register the dynamics of the process), the papillary-marginal-alveolar index (PMA) was used.

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Statistical research methods included methods of variation statistics (determination of the arithmetic mean value - M, and their mean standard error - m, Student's significance criterion - t). The data were processed using the Statistica software package.

*Table 1:* Dental status of preschool children in Kashkadarya and Surkhandarya regions

| Index | Control (n=40) | Maingroup (n=240) | R |
|---|---|---|---|
| CPR + cf (cf) | 2,4+0,3 | 4,84±0,19 | <0,001 |
| PMA | 15,04+1,01 | 19,08±0,67 | <0,001 |
| HI | 1,75+0,1 | 2,29±0,05 | <0,001 |
| Prevalenceofdentalcaries | 85% | 90,6% | |

The prevalence of caries is not significantly different in both areas. However, the intensity index in the main group was 2 times higher than in the control group (R <0.001). In comparative characteristics, it was shown that the hygienic state according to the Fedorov-Volodkina index, the oral cavity of children and the values of the PMA index were also higher in relation to the control group. In children of the main group, the average value of the Hygiene Index (HI) was 2.29, which corresponded to an unsatisfactory state, in children of the control group, the index value was 1.75, which corresponded to satisfactory.

To find out the hygiene habits of preschoolers living in the southern regions, a survey was conducted on the study of dental hygiene, during which the questionnaires were distributed to parents of children of the younger age group and filled out by questioning older children. Based on the questionnaire survey, it was found that the children of the control group did not brush their teeth twice a day, most of them brushed their teeth once a day and 2-3 times a week. Fortunately, there were no children in this group who did not wash at all. In the main group, children who wash twice a day make up 10%, those who wash once - 43%, those who wash 2-3 times a week - 25%, and children who do not wash at all - about 3%.

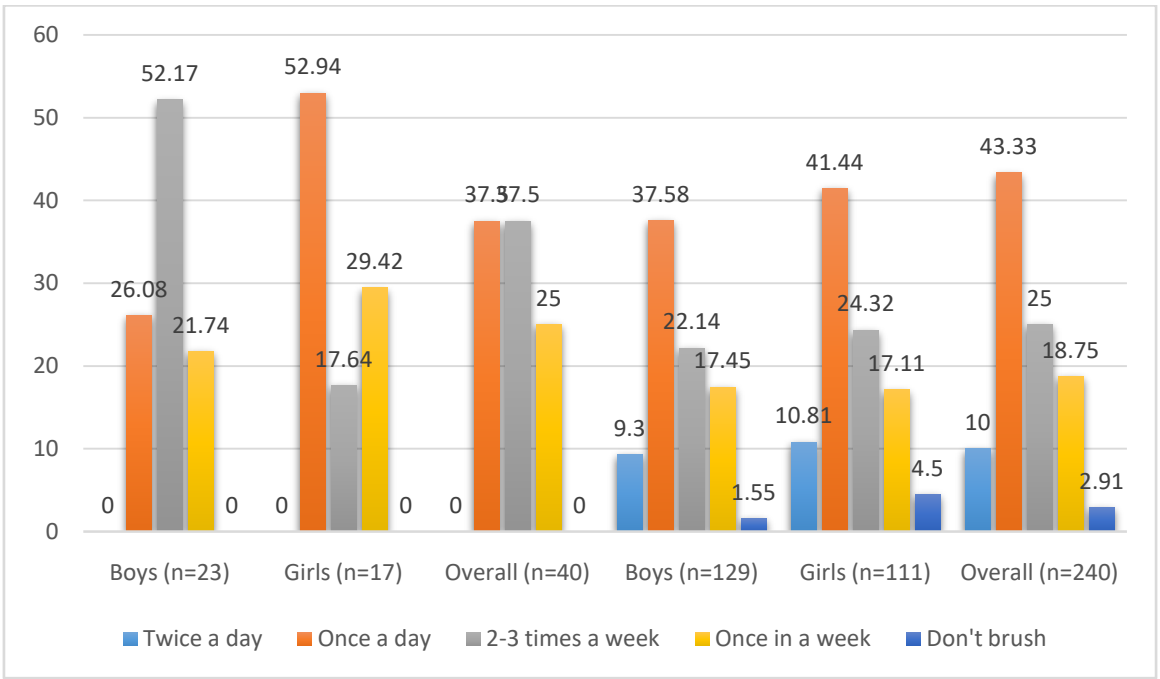



*Figure 1:* Percentage of teeth cleaning of preschoolers living in southern regions (%)

In the research of the situation with changing toothbrushes, all children in the control group have their own toothbrushes, but 85% of children change every 6 months, which shows that they do not have the appropriate skills in this regard. It turned out that 21% of children in the main group change their toothbrushes every 3-4 months and 76% - every 6 months. These cases indicate that children and their parents do not know how often to change their toothbrushes.



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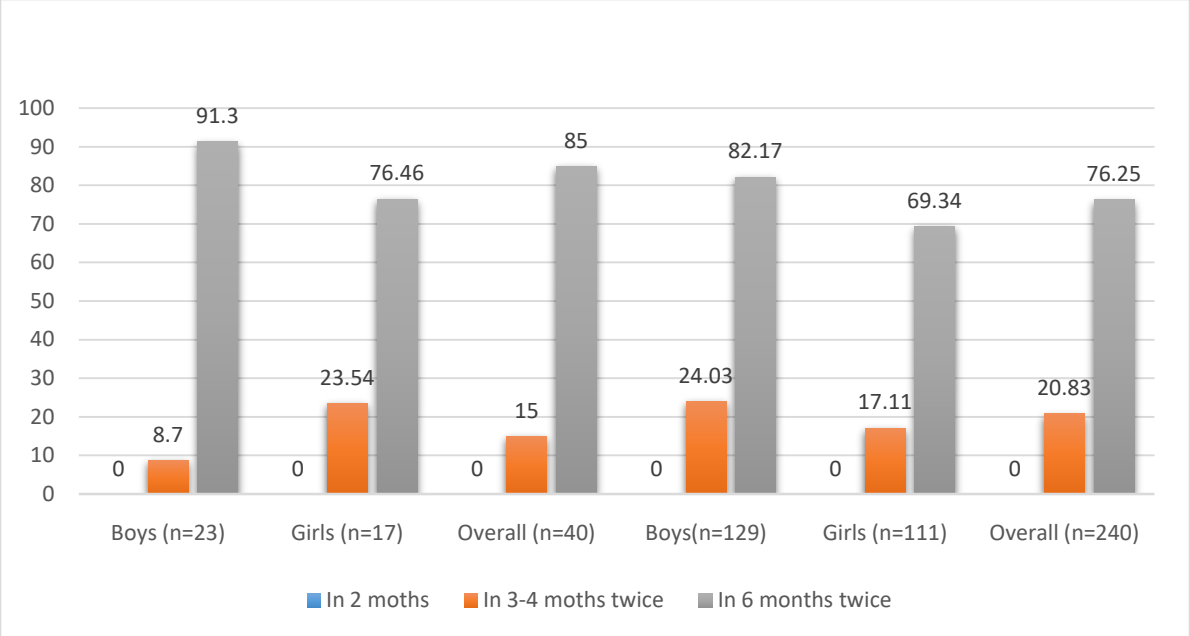



*Figure 2:* Preschool children living in the southern regions toothbrush replacement period (%)

Thus, the results obtained in the mode of the present study test the significant role of hygienic health status based on dental diseases. These data require further in-depth study of causal relationships in the occurrence of major dental diseases in this contingent of children.

## III. Conclusions

1. The prevalence and intensity of dental caries in children of the main group is 2 times (R <0.001) higher than in the comparison group
2. The index of oral hygiene in children of the main group was 2.29 + 0.05 and was significantly higher in relation to the control and corresponded to unsatisfactory.
3. On the basis of questionnaires, they indicate a low level of hygiene skills among children living in the southern regions, only 10% of children regularly brush their teeth and 3% of children do not brush their teeth at all.
4. Comprehensive dental prophylaxis in this contingent of children should be carried out with the inclusion of measures aimed at increasing the hygienic knowledge of parents and improving the hygienic state of the oral cavity in preschool children.

*Conflict of Interests and Contribution of Authors*

The authors declare the absence of obvious and potential conflicts of interest related to the publication of this article and report on the contribution of each author.

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# Communication Skills and Pain Assessment with Case History

By Dr. Mohammed Jamil Hossain

*Introduction-* Communication with the patient must be important skills for a doctor or medical practitioner in practising field. Without good communication with the patient it is difficult to help that patient properly.

In most developed and developing countries in the world health system is changing; political and economic forces are behind the growth of profit driven medicine, managed care and increasingly technological focus.

Good communication skills improve the doctor – patient relationship and decrease the dissatisfaction by the patient and relatives. It offers numerous benefits to the patient.

Communication skills is an interactive process, patient will also need knowledge to take part in decision making and can raised question about the quality of life.

Doctors have a moral and social responsibility towards the community as well as medical responsibility and must preserve their patients' trust.

*GJMR-K Classification: NLMC Code: WL 704*

COMMUNICATIONSKILLSANDPAINASSESSMENTWITHCASEHISTORY

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Communication skills is an interactive process, patient will also need knowledge to take part in decision making and can raised question about the quality of life.

Doctors have a moral and social responsibility towards the community as well as medical responsibility and must preserve their patients' trust.

Communication skills influence the quality of interactions between the doctor and the patients as well as compliance, patient education and health outcomes.

*Improvement of communication skills between doctors and the patient:*

Communication difficulties between doctors and the patients have been looked at by researchers from time to time in several disciplines who have tried to explore why these occur.

In many researches it was shown that doctors talk with the patient in different voice. Sometimes doctors do not want to listen what patient want to say and this is a big barrier for doctors – patient's relationship.

To improve the communication between the doctor and the patients we need also to understand the nature of the decision making that taking place in the consultation. There were studies in United Kingdom found that misunderstanding between doctor and the patient is very common, because of lack of active participation in decision making either by the patient or by the doctor.

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Unvoiced agenda items led to specific problems such as unwanted prescription and non – adherence. That's why it is good to provide enough information to the patient during consultation about the decision making especially for the management plan.

Information exchange helps the doctor understands the patient and ensures that the patient is informed of their treatment options; risks and benefits. It also allows patient to assess whether they feel they can build a relationship of trust with their doctor.

Also, as a doctor we have to explore how much patient knows about his/her illness and the prognosis of the disease as well.

*There are few important criteria need to consider for good communication skills are as follow:*

- Patient centred.
- Active listening.
- Clarify the patient knowledge.
- Identify the goals care.
- Identify patient resources.
- Explore fear and feeling.
- Offer support.
- Help patient with sustain hope.

*For effective counselling to a patient we have to established good communication bond or relationship. For these following things we should always keep in our mind as below:*

- Valuing respect to the patient.
- Connecting to the patient.
- Empowering knowledge.
- Finding meaning.
- Genuineness.
- Empowerment and self responsibility.
- Confidentiality.
- Unconditional positive regards.

*Breaking bad news to a patient:*

- To break the bad news to a patient proper preparation is important, e.g. need to sit with the patient in a consulting room and make sure that she is comfortable with the environment inside the room.
- Need to find out from the patient that 'how much she knows about her/his illness including the prognosis of the disease?'
- Need to listen attentively to her all the current concern.



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- Try to get more information from the patient by asking open ended questions.
- Need to find out more that 'How patient will cope present ailments.
- Ensure that patient should get enough support both mental and physical from the loved one or close relatives, as well as from the health care worker.
- Need to involve the multi-disciplinary team problem and concern; such as social welfare officer.
- Need to make sure patient should be free from all the stress and pain.
- If patient need spiritual support e.g. from her/his church or priest, I will make sure or arrange that kind of support as well for her/his.
- Finally, there is a need to discuss with the patient about the hospice and palliative care facilities. If patient wants that service, try to organize that as well.

*Patient background:*

Patient is a 66 years old lady and retired from job as a school secretary. She is known to have metastasis carcinoma of the breast and had mastectomy 2 years ago.

6 months later from the date of her operation, her husband died of cerebral metastasis from the previously undiagnosed carcinoma of the lung.

Her only daughter living in Canada and works as a receptionist at a doctor's clinic over there. Also, the daughter has got her third baby, who was born recently in Canada. Apparently, the patient is staying alone at home and there is no close is nearby to give her support.

*Communication between doctor and in this particular patient (barrier from both side):*

This patient is living alone at home, because her husband died 6 months ago, and the only daughter is not around as well. Therefore, we need to explore from the patient what really, she wants us to do at this moment! Information about the palliative hospice care facility in South Africa and after discussion if she wants to get that service, then doctor can organize for her.

She could have a fear of suffering alone at the end stage of her life, because she has already seen the suffering of her husband who died of undiagnosed cerebral metastasis of lung carcinoma.

Being alone at home probably she frustrated and in anxiety as well, therefore give her mental support and also, can make sure that she is getting it repeatedly. For that if necessary, involve a counsellor to counsel her as per her needs.

She is a retired lady and she may have financial problem also. Therefore, doctor should try to explore that if she needs particularly financial support etc. doctor can try to organize a social grant for her from the state and also, doctor can involve social welfare officer as a multidisciplinary team to support her.

There will barrier from doctor side, doctor needs to consult or involve multidisciplinary team (as palliative care team) and sometimes it will not be possible because of the availability of human resource.

Her daughter is in overseas and she has a little bay to look after. So, there is no love one around her at this stage. Also being alone the patient is missing her daughter and the grand child at this moment. She needs both mental and physical support at this stage. However, it is our duty as a doctor to satisfy her at this stage of her life and to make sure that she is comfortable or happy with the approach of palliative care etc to her.

To disclose her recent condition that the cancer has already metastasis to the bone. It is really very difficult and a barrier for breaking another bad news to the patient as a doctor, because she is already under stress about the death of her husband and who had almost similar kind of illness. To overcome from this particular situation, it is good to follow the steps to break bad news.

*Pain assessment in general as a palliative care physician:*

*Definition of pain:*

*Pain* is an unpleasant and emotional experience associated with actual or potential tissue damage or describes in terms of such damage.

*The perception of pain modulated by the followings:*
Patient's *MOOD.*
Patient's *MORALE.*
*MEANING* of pain by the patients.

Depression, anxiety, fear and low morale can all lead to an increase severity of the perceived pain. The meaning of the pain can also influence perceived severity of pain e.g. the headache due to brain metastasis signifies a threat to the patient's way of life, unlike an everyday headache.

*Total pain has few components:*

- Physical.
- Mental.
- Inter- personal.
- Spiritual.
- Financial.

*Assessment of pain in this particular patient:*

In figure it is shown that the patient has pain at her back, and which is every possibility due to the metastasis from the breast cancer of her.

There are very much need to assess psychological factors for the pain such as follows:

- Anxiety.
- Anger.
- Fear.
- Depression.
- Boredom.



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- Insomnia and tiredness.
- Social isolation.

To check the severity and the total component of pain I follow the mnemonic tools that are PQRSST.

- What are the *precipitating or exacerbating* factors of pain which patient noticed most of the time in her daily life?
- What is factors patient noticed to get relief from the pain?
- What is the *quality* of pain? E.g. the pain is sharp or dull in nature etc.
- Does the *radiate* any other parts of the body?
- To make sure that any other associated *symptoms or signs* rather than nausea and vomiting.
- *Time* and the course of pain.

After assessing the patient thoroughly, I quote the severity of the pain numerically from 0 to 10.

*Examination:*

We need to do both physical and systemic examination to find out the source, nature, severity of pain in her case.

- By due proper examination I will find out that the pain is due compression on the nerves at thoracic or lumber plexuses.
- Need to look for the most localise tenderness as well if there is any.
- Need to look for is the patients is jaundice, anaemic, dehydrated or oedematous etc?
- Need to look for any other abdominal mass or oranomegaly during my systemic examination.
- Are there any signs or symptoms of renal involvement?
- Are there any signs and symptoms of metabolic impairment such as *hypercalcaemia* due to severe bone involvement?
- By doing full neurological examination, I will try to explore is there any nerve compression etc?

*Investigations:*

- Full blood count.
- Blood urea and electrolytes.
- Blood for tumour marker.
- Serum calcium.
- Liver function test.
- X ray of whole spine.
- If necessary, CT or MRI scan.

*Differential diagnosis:* Her pain areas which are all spotted at the back due to the metastasis form the primary cancer and which could be related with the cord compression as well.

*Keywords:*

- Communication.
- Skills.
- Patient's interest.
- Pain.
- Relationship.

## II. Conclusion

Improving communication skills for a health care professional especially doctors and nurses is not an *'option, but it is necessary'*. Learning communication skills in times of change and uncertainty depends on an emotional openness to self and others.

To develop effective interventions to promote better communication, it is useful to explore specific communication patterns within the border context of the type decision making process within which communication is embedded.

Teaching communication should be included at all level of the medical education and even importantly, should be a mandatory element of the medical school curriculum and programme continuing medical education. This can be achieved by the support from the specialist physician policy maker in medical faculty at different university level

Proper pain assessment is very important in patient with suffering from any cancer. To know how to assess the pain properly we need the palliative care skills. It is also important to control pain, because our one of major goal in palliative care medicine.

A holistic approach of pain control is essential, rather only attending to the physical aspect of the pain.

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# Artificial Intelligence (AI) in Pathology- A Summary and Challenges

By Archana Buch & Rohan Kulkarni

*Abstract-* This bibliographic study covers Artificial Intelligence (AI)theory and its applications from the healthcare field and in particular from the discipline of pathology. This review includes basics of AI, supervised and unsupervised machine learning (ML), various supervised ML algorithms, and their applications in healthcare and pathology. Digital Pathology with Deep Machine Learning is more advantageous over traditional pathology that is based on 'physical slide on a physical microscope'. However, various implementation challenges of cost, data quality, multi-center validation, bias, and regulatory approval issues for AI in clinical practice still remain, which are also described in this study.

*Keywords:* *history of artificial intelligence (AI), AI in healthcare, deep learning (DL) in digital pathology (DP).*

*GJMR-K Classification:* *NLMC Code: QY 4*




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# Artificial Intelligence (AI) in Pathology– A Summary and Challenges

Archana Buch [α] & Rohan Kulkarni [σ]

*Abstract-* This bibliographic study covers Artificial Intelligence (AI)theory and its applications from the healthcare field and in particular from the discipline of pathology. This review includes basics of AI, supervised and unsupervised machine learning (ML), various supervised ML algorithms, and their applications in healthcare and pathology. Digital Pathology with Deep Machine Learning is more advantageous over traditional pathology that is based on 'physical slide on a physical microscope'. However, various implementation challenges of cost, data quality, multi-center validation, bias, and regulatory approval issues for AI in clinical practice still remain, which are also described in this study.

*Keywords: history of artificial intelligence (AI), AI in healthcare, deep learning (DL) in digital pathology (DP).*

## I. Introduction

The main objective of this paper is to describe the history of the evolution of Artificial Intelligence over time. The past two decades have shown tremendous progress in the application of artificial intelligence (AI) including in a few medical images based specialties of radiology, dermatology, ophthalmology, and pathology. First, we explore how AI began about 65 years back and its progression in various disciplines including healthcare/medicine and particularly pathology. Second, we review books available on AI in general as well as AI in medicine and in pathology. Next, we define the necessary terms in AI and various AI algorithms that are utilized to get acceptance by the physicians to assist patients in a more efficient fashion. After, we review AI literature pertinent to healthcare and pathology. Finally, the various challenges and barriers AI faces for use in pathological applications are then discussed.

## II. AI Theory in Textbooks

In 1955 Artificial intelligence (AI) was termed by McCarthy et al. as the subdivision of computer science in which machine based methodologies were used to make predictions to imitate what human intellect may do in the identical situation.[1] The origin of Digital Pathology (DP) began in 1966, as Prewitt et al. photographed images from a microscopic field from a blood smear and then transformed the information into a matrix of optical density numbers for mechanized image investigation.[2] The AI field is built on statistics and Vapnik provides a more detailed description of the statistical learning theory in his two books.[3, 4] In 2003, Russell and Norig introduced an idea of an intellectual agent that mechanically plans and performs a sequence of activities to attain a goal as a novel form of AI.[5] Good fellow et al.'s comprehensive textbook on the AI is written by some of the most innovative and prolific researchers in the field.[6] Kelleher explains how deep learning is useful in understanding big data and covers methodologies of Autoencoders, Recurrent neural networks, Generative Adversarial Networks, Gradient descent and Backpropagation.[7]

### a) AI books in medicine and pathology

There are many excellent textbooks on AI's applications in medicine including note taking, drug development, remote patient monitoring, surgery, laboratory discovery, and healthcare delivery.[8, 9, 10, 11, 12, 13]

In this section our emphasis is on review of the latest textbooks on AI in pathology. Sucacet et al. in *Digital Pathology* (DP) discuss how technology over a decade has seen tremendous growth in its applications. They observe that DP offers the hope of providing pathology consulting and educational services to underserved areas of the world that otherwise would not experience high level of services.[14] In *Artificial Intelligence and Deep Learning in Pathology*, Cohen observes how recent advances in computational algorithms, and the arrival of whole slide imaging (WSI) as a platform for combining AI, are assisting both diagnosis and prognosis by transforming pattern recognition and image interpretation. The book focuses on various AI applications in pathology and covers important topics of WSI for 2D and 3D analysis, principles of image analysis, and deep learning.[15] Holzinger et al. in their book describe why AI and Machine Learning (ML) is very promising in the disciplines of DP, radiology, and dermatology. They observe that in some cases Deep Learning (DL) even exceeds human performance and stress the importance that a human expert regardless should always verify the outcome. The authors cover 'biobanks,' which offer large collections of high quality and well labeled samples as big data is required for training and covering a variety of diseases in different organs.[16]Belciug in his book covers theoretical concepts and practical

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techniques of AI and its applications in cancer management. The author describes the impactful role of AI during diagnosis and how it can help doctors make better decisions including AI tools to help pathologists identify exact types of cancer and assist surgeons and oncologists. The book discusses over 20 cancer examples in which AI was used and in particular AI algorithms utilized for them.[17]

## III. AI Basics

In this section we cover Learning theory, important AI terminology, and algorithms for Machine Learning.

*a) Learning theory and machine learning*

Vapnik introduces the learning model from examples using three constituents of a) a creator of random vectors, b) a supervisor that yields an output vector for each input vector, and c) a learning machine qualified of applying a set of functions. The next step is the Risk Minimization Problem. So as to find the best obtainable estimate to the supervisor's reply, one should measure the difference between the reply of the supervisor to a specified input and the answer offered by the learning machine.[18]In 2015, Deo's review on ML found that only a few papers out of thousands applying ML algorithms to medical data have contributed meaningfully to clinical care unlike how ML has been impactful in other industries.[19]Cabitza et al. search for 'laboratory medicine/tests' and 'machine learning' terms found 34 papers in Scopus and three in PubMed showing that it is a relatively new area for AI in laboratory medicine/tests.[20]

*b) Important AI terminology*

In this section we will cover important AI terminology.

a) *Machine learning (ML):* Machine Learning is a discipline of mathematics that combines statistical modeling and computers/machines to learn from available data sets hence its name. ML is classified into categories called 'supervised' and 'unsupervised' learning. ML techniques are widely used in transcribing speech into text, matching news items, and identifying objects in images. In these applications a 'Deep learning' (DL) technique is widely used.

b) *Supervised learning:* In supervised learning the goal is to either predict a known output or target (Y) from input variables (X) using an algorithm to learn the mapping function [Y= f(X)] from the labeled input data to the output. This derived mapping function can then be used for a new input data ($X_1$) to predict its output variable ($Y_1$). Supervised learning based models can be of 'classification' or 'regression' types. In the classification case the output variable is a category e.g. disease or lack of disease. Automated interpretation using pattern recognition of a breast X-ray or an EKG to select from a limited set of diagnoses are examples of supervised learning. In a regression problem the output variable is a real continuous value of e.g. temperature or blood pressure. The concept of bias and variance and their relationship with each other are important determinants of the performance of supervised ML models. To obtain a most Generalizable Supervised ML Model requires finding a right balance between bias and variance.

c) *Unsupervised learning:* In unsupervised learning, unlike supervised learning, there is no output prediction variable. Instead, all input data (X) which is unlabeled, the algorithms in this case learn to understand inherent structure from the available input. E.g., an objective could be to look for data patterns to identify novel disease mechanisms.

d) *Semi-supervised learning:* In semi-supervised learning, some of the available data is labeled and the remaining is not. In this type of learning scientists use a combination of supervised and unsupervised methods. LeCun et al. describe various techniques used in ML such as 'Conventional ML' and 'Deep ML.' They discuss limitations of 'Conventional ML' in their ability to process data in their raw form. In contrast 'Representation learning' permits a computer to be served with the data to find the depictions desired for recognition or categorization. 'Deep learning' are 'Representation learning' approaches with numerous stages of representation acquired by creating non-linear sections which convert the representation at one stage into a representation at a higher but at a more abstract level.[21]

e) *Artificial Neural Networks (ANNs):* Similar to a brain which operates through interconnected, complex network of neurons, an Artificial Neural Network has a set of artificial neurons which are layered and connected, with a definite passage way for how information is transmitted through the network. The Artificial Neural Network allows a means of reaching an output that is the outcome of many nondependent phases of computation and weighting.

f) *Convolutional Neural Networks (CNN or ConvNets)*: ConvNets are deep, feed forward networks that are easier to train and are generalized better than networks with full connectivity between adjacent layers. CNNs are applicable to use information that come in the shape of numerous arrays such as a colour photo consisting three 2D arrays comprising pixel concentrations in the three colour channels. A CNN is designed with the first few steps being constituted of two types of tiers of convolutional and pooling tiers.[22]



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g) *Recurrent Neural Networks (RNN):* RNNs process a given input order of one component at a time while preserving in their concealed parts a 'state vector' which keeps data regarding entire historical components of the arrangement. RNN is appropriate with sequential inputs, such as speech and language. Back propagation is therefore appropriate for training RNNs. Training RNNs can have issues as the back propagated gradients grow/shrink at each step causing them to blow up or become very small.[23]

c) *Algorithms for Supervised ML*

Model building phase of Supervised ML includes splitting of the available data into training and testing sets in order to train the model followed by testing it for validation. The following algorithms are widely used in Supervised ML:

A. *Linear Regression:* Linear regression models find the target by finding the best-fitted "least squares regression line," which has the smallest error sum, amongst the independent continuous variables (features/the cause) and the dependent continuous variables (target/the effect). Aggarwal et al. detail the pitfalls associated with this analysis.[24]

B. *Logistic Regression:* Ranganathan et al. discuss logistic regression examining the relationship of a binary outcome of 'yes/no,' 'alive/dead,' 'success/failure' with one or more predictors being either categorical or continuous. They provide method's limitations in choosing the right predictor variables, avoiding the use of highly correlated variables, restricting the number of variables, and handling continuous input variables.[25]

C. *Convolutional Neural Network or CNN:* Neural Networks attempt to model a neuron which uses certain input features to find and assign appropriate mathematical weights to forecast some output objective. Deep neural network has a sizable number of nodal contacts within its unseen tier and are most appropriate for highly complicated data studies such as images. However, caution is required because of a limitation due to overfitting.

D. *k-Nearest Neighbor or k-NN:* This algorithm is used for data classification and regression tasks of nonparametric clustering. *k* is defined as the square root of the number of occurrences and its distance from a pre-defined point and classification is based on the number of *k* neighbors.[26] Being 'distanced based,' they require normalization of features and work best in the presence of a smaller number of input variables but are sensitive to the outliers.

E. *Support Vector Machine or SVM:* The SVM algorithm classifies available data by defining a hyperplane that best differentiates the presence of two groups. The differentiation for the two groups is maximized by growing the space on either side of the hyperplane and the hyperplane enclosed area with the greatest possible distance is then chosen for the evaluation. It finds an onlinear relationship using a kernel function but has tendency for overfitting.[27]

F. *Naive Bayes:* Naive Bayes approach assumes that the features under evaluation are independent of each other. For simple tasks it can produce good results, but in general their performance is inferior to the other ML algorithms.[28]

G. *Decision Tree and Boosted Tree:* A decision tree comprises a root, nodes, branches, and leaves. The node is where the characteristic is examined and the branch is where the result of this examined query is then assigned. The decision tree provides a set of guidelines that defines the passageway from the root all the way to the leaves. Gradient boosting machine uses weak predictors (a Decision tree) that are boosted, which provide a better performing model (a Boosted tree). This method can work with unbalanced data sets but may produce overfitting.[29]

H. *Random Forest or RF:* Breiman provides how RFs are an effective tool in accurate prediction of classifiers and regressors as it avoids overfitting due to the Law of LargeNumbers.[30] However, it might be more time exhausting and less efficient vs. the nonparametric (SVM and *k*-NN) and parametric (logistic regression) modeling.

## IV. AI Research in Pathology

In this section we cover research in topics of origins of image analysis, computational pathologist, machine learning in pathology, Digital Pathology, Convolutional Neural Network in pathology, and other AI in cancer applications.

a) *Origins of image analysis*

Meijer et al. summarized origins of image analysis in the field of clinical pathology related to routine diagnostic cytopathology, histopathology, and research. They distinguished between three different areas of image analysis namely: a) Evaluating morphological features of tissues/cells/nuclei/nucleoli, b) Counting of tissue/cell constituents, and c) Cytometry and configuration recognition. Further they discussed historical significance of Morphometry (quantitative description of geometric features of structures of any dimension), Planimetry (measurement of geometric features of structures in two dimensions), Stereology (quantitative information about geometric features of structures with a test system of lower dimension than the structure itself), and Counting objects techniques in relation to image analysis. Techniques of Cytometry and DNA Cytometry using visible light, coupled with powerful computers have allowed the development of systems for



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automatic cell classification based on pattern recognition.[31]

*b) Computational pathologist*

Beck et al. developed an ML based method for automatically analyzing cancer images and predicting prognosis called the Computational Pathologist (C-Path). Their image processing structure performed an automated, ranked scene subdivision generating measurements in thousands, comprising standard morphometric descriptors of image objects and upper level contextual, relational, and global image characters. The pipeline comprised of three phases. First, their processing steps included a) separating the tissue from its background, b) partitioning the image into smaller regions with a consistent appearance recognized as superpixels, c) finding nuclei inside the superpixels, and d) constructing cytoplasmic and nuclear characters within the superpixels. Next, within every superpixel they estimated the size, shape, intensity, and texture of the superpixel and its neighbors. Afterwards, to create more biologically significant features, they categorized superpixels as either epithelium or stroma. They used an ML based approach of $L_1$-regularized logistic regression, in which they hand-annotated superpixels from 158 photos and utilized those images to train the classifier. The resultant classifier composed of 31 characters achieved a categorization accuracy of 89% on detained data. The authors using a series of relational characters produced a set of 6,642 features per image. Predicting survival based on the images from patients who were alive 5 years after surgery and also from patients who had died at 5 years after surgery they built the prognostic model. After constructing the model, it then was utilized to a verify set of breast carcinomaphotos which were not part of the model creation to categorize patients as either low or high risk of dying at 5 years. A bootstrap examination on the data set and for each of the 6,642 features the authors obtained a 95% Confidence Interval for the feature's coefficient estimate.[32]

*c) Machine learning in pathology*

To achieve optimum Supervised Machine Learning Model Rashidi et al. proposed four questions: i) Does the endeavor tackle a necessity?, ii) Is enough data accessible which is appropriate type that scrutinized by clinical specialists?, iii) Which Machine Learning method to utilize?, and iv) Are the enhanced ML simulations appropriate and general enough when used with a new data set? The authors support a balanced approach using clinical trial data merged with real world data to optimize ML training. They recommend that pathologists/laboratorians must be sufficiently familiar with available modeling options in order to make meaningful contributions within the team.[33]

Moxley-Wyles et al. introduce the basics of AI in pathology and discuss the future and challenges for the discipline with focuse on surgical pathology instead of cytology. The authors foresee AI's potential to obtain derive novel biological insights by identifying subtle cell changes, which are not recognized by pathologists (using the Haematoxylin and Eosin (H&E) stain) that can predict specific mutations within the cell. Predictions using AI have been proven for Speckle-Type POZ Protein (SPOP) mutation in prostate cancer, *BRAF* in melanoma, and many mutations in lung adenocarcinoma. They observe that with robustly validated AI tools second opinions from other pathologists could become not necessary. The authors expect AI's potential assistance in predicting outcomes of responses to treatments after regulatory approvals. However, in their opinion the use of Artificial Intelligence in diagnostic practice is rare due to some of the limits of Artificial Intelligence including regulatory and validation issues, as well as a high cost.[34]Li et al. used the fluorescence hyperspectral imaging technique to acquire spectral images for the early diagnosis of gastric cancer. They combined DL with spectral-spatial categorization techniques utilizing 120 fresh tissue specimens with an established diagnosis by histopathological assessments. The method was utilized to detect and extract the 'spectral + spatial' characters to create an early cancer diagnosis model. It resulted in the accuracy of 96.5%, specificity of 96%, and sensitivity of 96.3% for non-precancerous lesion, precancerous lesion, and cancer groups.[35]

*d) Digital Pathology (DP)*

Hartman et al. numerate how DP is more advantageous over traditional pathology based on' physical slide on a physical microscope.' This tool development did benefit from 24 public challenges based publications in specific pathological diagnostic tasks. However, there is a true disconnect between the types of organs studied in these public challenges and the large volume of specimens typically available in clinical practice. Even though disciplines of dermatology and gastrointestinal collect a majority of samples in pathology laboratories, so far there are no pathology based dermatology public challenges while only a few in regards to the gastrointestinal field. This mismatch is the key reason there being a limit on the wider adoption of AI in pathology field.[36]

Niazi et al. have developed the generation of synthetic digital slides that can be used for educational purposes to train future pathologists. Their Conditional Generative Adversarial Networks approach contains two main components of the generator and the discriminator. The generator creates fake stained images, while the discriminator tries to catch them. Their approach of distinguishing between 15 real and 15 synthetic images yielded an accuracy of 47.3% amongst



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three pathologists and two image analysts. The authors do see a role for AI in quality assurance by improving the pathologist's performance with the use of intelligent deep learning and AI tools.[37]

DP involving the slide digitization process in some instances does create artifacts that are 'Out-Of-Focus' or OOF. OOF is typically noticed after a careful review which requires a whole-slide rescanning, as the manual screening for OOF affecting only parts of a slide isnot feasible. Kohlberger et al. developed a ConvFocus using a refined semi-synthetic OOF information production process and was assessed using seven slides covering three dissimilar tissue and three dissimilar stain types and then was digitized. For 514 separate regions representing 37.7K 35 μm × 35 μm image patches, and 21 digitized "z-stack" Whole Slide Images containing known Out-Of-Focus patterns, ConvFocus scored Spearman rank coefficients of 0.81 and 0.94 on two separate scanners, and it replicated the expected Out-Of-Focus patterns from z-stack scanning. More importantly the authors observed a decrease in the accuracy with increasing OOF.[38]

Hartman et al. investigated a US healthcare organization with 20+ hospitals, 500 outpatient sites, international affiliations of one hospital in Italy and a lab in China. The organization employs 100+ pathologists, does consultations by telepathology from the Chinese lab, and uses Digitized Pathology scanned over 40,000 slides. Their conclusion for attainment of successful DP is performing a combination of pre-imaging adjustments, integrated software, and post-imaging evaluations.[39] Parwani observed that to attain DP in a lab requires an essential alteration in how tissue is handled and the workflow is harmonized, and the laboratory has attained a digital workflow. It is more than making the workflow to digital and acquiring WSI scanners. He numerates a key advantage the digital workflow provides of reduction in errors in DP and obtaining a second opinion.[40]

In DP problems of color variations do arise in tissue appearance due to the disparity in preparation of tissues, difference in stain reactivity between different batches and different manufacturers, user and/or protocol dissimilarity, and the use of scanners from diverse vendors. Khan et al. present a novel preprocessing approach to histopathology image stain normalization using representation derived from color deconvolution based on non-linear mapping of a source image to a target image. A method of color deconvolution obtains stain intensity values when the stain matrix, which describes how the colour is changed by the stain intensity is made available. Instead of using the standard stain matrices, which might be unsuitable for a specified image, they recommend the utilization of a colour based classifier incorporating a new stain colour descriptor to compute image explicit stain matrix.[41]

Janowczyk et al. developed a tutorial on focusing on the critical components needed by DP experts in automating tasks of grading or investigating clinical hypothesis of prognosis prediction. The authors examined seven use cases of (i) nuclei segmentation, (ii) epithelium segmentation, (iii) tubule segmentation, (iv) lymphocyte detection, (v) mitosis detection, (vi) IDC detection, and (vii) lymphoma classification, and demonstrated how DL can be applied to the most common image analysis tasks in DP using open source framework Caffe. They further subdivided the seven tasks into three categories of detection (mitotic events, lymphocytes), segmentation (nuclei, epithelium, tubules), and tissue classification (IDC, lymphoma subtypes), as the approaches used are similar within each analysis category. With over 1200 DP images used during evaluation produced the following: (i) nuclei subdivision with *F* score of 0.83, (ii) epithelium subdivision with *F* score of 0.84, (iii) tubule subdivision with *F* score of 0.83, (iv) lymphocyte detection with *F* score of 0.90, (v) mitosis recognition with *F* score of 0.53, (vi) invasive ductal cancer recognition with *F* score of 0.77, and (vii) lymphoma categorization with categorization accuracy of 0.97. In many of these cases the results are excellent versus seen from the modern feature-based categorization approaches.[42]

To guide surgical decisions further, intraoperative frozen sections are useful for rapid pathology-based diagnosis. However, the quality of frozen sections is lower compared to formalin fixed paraffin embedded tissue[43] and that they must be diagnosed within 20 min of receipt. In current clinical practice, thyroid nodule surgeries are the most common in requiring intraoperative consultations. However, using traditional approach the sensitivity for diagnosing thyroid nodules from frozen sections is around 75%.[44] Li et al. investigated for the first time if a 'patch-based diagnostic system' with DL methodology can diagnose thyroid nodules from intraoperative frozen sections. They approached the problem as a three-category classification problem of benign, uncertain, and malignant classes. In order to reduce the overall time cost, they applied tissue localization first in the whole slide diagnosis to locate thyroid tissue regions. This rule-based system considered the conservative diagnosis manner of the practical thyroid frozen section diagnosis. Their computerized diagnostic technique demonstrated a precision of malignant and benign of thyroid nodules of 96.7% and, 95.3% respectively, and 100% sensitivity for the unsure category. Moreover, the methodology resulted in diagnosis of a typical Whole Slide Image in less than one min.[45]Paeng's presentation covers limitations of pathology and relative advantages of DP of reproducibility, accuracy, and workload reduction. Key applications of DP are a) Tumor proliferation score prediction – breast resection, and b) Gleason score prediction – prostate biopsy. The



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author's method scored the best in Tumor Proliferation Assessment Challenge. He achieved Gleason score prediction of 83% for core-level performance and discussed overcoming: how to handle gigapixel images, how to handle quality variation between slides, and how to handle ambiguous ground-truth.[46]

*e) Convolutional Neural Network (CNN) in pathology*

Hegde et al. for histopathology images introduced 'SMILY' (Similar Medical Images Like Yours) which is a DL based reverse image search tool. Their tool follows the steps of: a) Create a database of image patches and a numerical portrayal of each patch's image fillings called the embedding, b) Calculate the embedding utilizing a CNN, c) SMILY calculates the embedding of the selected query image and matches it in a proficient manner with those in the database, and in the last step d) SMILY yields the k most similar patches, where k is customizable. To create the database the authors used images from TCGA with the evaluations utilizing127K image patches from 45 slides while the question set included 22.5K patches from additional 15 slides. The CNN algorithm, instead of using large, pixel-annotated datasets of histopathology images, was trained using a dataset of images of people, animals, and manmade and natural objects. In the assessment of prostate specimens for finding similar histologic features, SMILY scored 62.1% on average which is, considerably higher than the random search results score of 26.8% with $p$ *-value* $< 0.001$. SMILY's score for histologic feature match, when queried from multiple organs, was appreciably higher than random with the score of 57.8% vs. 18.3% with *p-value* $< 0.001$.The authors claim that SMILY can be used as a general purpose tool in multiple applications of diagnosis, research, and education even though it will have lower accuracy than an application specific tool.[47]

*f) AI in cancer applications*

*AI in breast cancer:* Stålhammar et al. for prognostic and predictive value categorized breast cancers by using four gene expressions 'Luminal A,' 'Luminal B,' 'HER2-enriched,' and 'Basal-like.' The authors examined 3 cohorts of main breast carcinoma specimens totaling 436 (up to 28 years of survival) and scored them for ER, PR, HER2, and Ki67 rank by Digital Image Analysis (DIA) and manually. DIA approach beat manual scoring in both sensitivity and specificity for the Luminal B subtype, and achieved slightly superior concordance and Cohen's $\kappa$ agreement in reference with PAM50 gene expression assays. The manual biomarker and DIA approaches were close in comparison of each other for Cox regression hazard ratios. In addition DIA faired superior in terms of Spearman's rank-order correlations, and prognostic value of Ki67 scores in terms of likelihood ratio thus adding appreciably more prognostic information to the manual scores. The authors concluded that overall the DIA approach was clearly a better substitute to the method of manual biomarker scoring.[48] A manual process identifying the existence and degree of breast carcinoma by a pathologist is serious for patient administration for tumor staging, including an assessment of treatment response, but it is subject to variability between inter- and intra-reader. As a decision support tool any computerized technique needs to be robust to data acquisition from different sources, different scanners, and different staining/cutting approaches. Cruz-Roa et al.'s CNN approach trained the classifier using 400 exemplars from various sites and using TCGA data to validate it with 200 cases. Their approach attained a Dice coefficient of 75.9%, a PPV of 71.6%, and a NPV or of 96.8% regarding the evaluation for pixel-by-pixel in reference with manually annotated regions of invasive ductal carcinoma.[49]

*Autoencoder (AE) use in breast cancer:* An AE can be described as an ANN with a symmetric construction in which middle tiers encode the entered data and then aim to construct a form of its input onto the yield tier and avoids using a direct copy of the data along with the network.[50] Macías-García et al. developed a structure to process DNA methylation to obtain meaningful data from pertinent genes regarding breast cancer recurrence and tested it using The Cancer Genome Atlas (TCGA) data portal. The method is based on AEs to preprocess DNA methylation and generate AE features to characterize breast cancer recurrence and demonstrated how it improved recurrence prediction.[51]

*AI in cervical cancer:* Out of half million annual cervical cancer cases in the world about 80% occur in low and middle income nations. Hu et al. followed over 9,000 women ages 18 to 94 from Costa Rica over period of seven years from 1993 to 2000 identifying cancers up to 18 years. They developed a DL based visual evaluation algorithm based on digitized cervical images taken with a fixed focus camera (cervicography), which did automatically identify cervical precancer or cancer. The DL method recognized cumulative precancer and cancer cases with higher AUC of 0.91compared to the original cervigram interpretation with AUC of 0.69 or conventional cytology with AUC of 0.71. The authors therefore recommend use of automated visual evaluation of cervical images from contemporary digital cameras.[52]

*AI in prostate cancer:* Ström et al. work noticed the high intra/inter-observer variability in grading resulting in either under or over treatment of prostate carcinoma. To overcome this issue the authors developed an AI method for prostate cancer detection/localization, and Gleason grading. They digitized 6,682 slides from biopsies of 976 randomly selected Swedes aged 50-69 and another 271 slides from 93 men from outside the original study to train deep neural networks. The



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resulting networks were tested with independent 1,631 biopsies from 246 men from STHLM3 for the presence, extent, and Gleason grade of malignant tissue and an exterior data from 73 men of 330 biopsies. They also compare drating performance by 23 pathology experts on grading 87 biopsies. The AI networks attained an AUC of 0·997 for differentiating between benign and malignant biopsy cores on the independent dataset and 0·986 on the external verification data between benign and malignant. The correlation found between carcinoma length predicted by the Artificial Intelligence networks and given by the pathology experts was 0·96 for the impartial data and 0·87 for the external verification dataset. The AI methodology for allotting Gleason grades attained a mean pairwise kappa of 0·62which was within the range of values for the pathology experts of 0·60-0·73. The authors recommend using the AI approach resulting in reduction of the evaluation of benign biopsies and automating the work of determining cancer length in the cases of positive biopsy cores. This AI approach by standardizing grading can be utilized as a second opinion in cancer assessment.[53]

*AI in stomach and colon cancer:* Iizuka et al. in their study utilized biopsy histopathology WSIs of stomach and colon trained CNNs and RNNs to classify them into adenocarcinoma, adenoma, and non-neoplastic. They gathered datasets of stomach and colon consisting of 4,128 and 4,036 WSIs, respectively which were then manually annotated by pathologists. The authors using millions of tiles extracted from the WSIs then trained a CNN based on the Inception-V3 architecture for each organ to categorize a tile into one of the three classification tags. Next they summed the projections from all the tiles in the WSI to acquire a final categorization using two approaches of a RNN and a Max Pooling. The models were successfully evaluated on three independent test sets each and achieved Area Under the Curves (AUCs) for gastric adenocarcinoma and adenoma was 0.97 and 0.99 respectively, and for colonic adenocarcinoma and adenoma of 0.96 and 0.99 respectively. Further they evaluated the stomach model versus a collection of pathology experts and medical scholars that were not part of labeling the teaching set utilizing an investigation set of 45 images (15 WSI of adenoma, 15 of adenocarcinoma, and 15 of non-neoplastic lesions). The categorization time for Whole Slide Image using the educated model ranged from 5-30 seconds. The average accuracy of diagnoses achieved by pathologists was 85.9%, medical school students was 41.2%, while the stomach model achieved an accuracy of 95.6% in a 30 sec assessment.[54]

*AI in lung cancer:* Kriegsmann et al.'s evaluation of CNNs included the classification of the very usual lung carcinoma subtypes of pulmonary adenocarcinoma (ADC), pulmonary squamous cell carcinoma (SqCC), and small-cell lung cancer (SCLC). To validate the appropriateness of the outcomes, skeletal muscle was also integrated in the investigation, as histologically the difference between skeletal muscle and the three tumor entities is unambiguous. They assembled a group of 80 ADC, 80 SqCC, 80 SCLC, and 30 skeletal muscle specimens. TheInceptionV3, VGG16, and Inception ResNetV2 architectures were qualified to categorize the four entities of interest.InceptionV3 based on the CNN model produced the highest classification accuracy and hence was used for the classification of the test set. The final model received an image patch categorization accuracy of 88% in the training as well as in the verification set. In the test set they achieved image patch and patient-based CNN classification results of 95% and 100%.[55] To predict carcinoma in WSIs, Kanavati et al. trained a deep learning CNN founded on the EfficientNet-B3 design, using transfer learning and weakly-supervised learning to calculate carcinoma using a training dataset of 3,554 WSIs from a sole medical establishment. The model was then applied to four independent test sets from distinct hospitals in order to validate its generalization on unseen data. The authors obtained excellent results that did show differentiation amongst lung cancer and non-neoplastic with an elevated Receiver Operator Curve based AUCs on impartial investigation of four sets of 0.98, 0.97, 0.99, and 0.98, respectively. Out of two methodologies to train the simulations of 'fully supervised learning' and 'weakly supervised learning,' the last performed always superior with an improvement of 0.05 in the AUC on the experiment sets.[56]

## V. AI - Regulation

The FDA's vision is that with suitable regulatory oversight, Software as a Medical Device (SaMD) based on AI-ML will deliver safe and effective software functionality that will be able to improve the quality of patient care. Their guidance for software modifications focuses on the risk to patients resulting from the software change. For a traditional application three classes of software alterations that might necessitate a premarket submission include: a) a change that introduces a novel risk or changes an existing risk that can produce significant harm, b) an alteration to risk controls to avoid substantial harm, and c) a modification that considerably affects clinical functionality of the device. For SaMD, any modifications would require a premarket submission to the FDA when the AI/ML software changes significantly, the alteration is to the device's envisioned use, or the alteration introduces a key change to its algorithm. The FDA to date has approved several AI/ML-based SaMD algorithms that are locked before marketing and algorithm modifications will possibly require an FDA pre-market assessment for the modifications beyond the initial approval. However,



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the SaMD has the capability to constantly learn, as the alteration or modification to the algorithm is recognized after the SaMD has learned from real world experience might provide a significantly dissimilar output in contrast to the output originally approved for a specified set of inputs. Therefore, the AI/ML tools require a new, Total Product Life Cycle (TPLC) regulatory approach.[57]

## VI. AI – Issues to be Resolved

Over the last 100 years both The Covid19 and The Spanish Flu pandemics have shown their disproportionate impacts on patients of low income and racial minorities. A combination of diagnostics bias and sample bias have been the culprit for the global healthcare disparities. Evans argues that present diagnostic tools often fail patients who do not fit the prospects of the majority.[58] Even though there is an active effort to involve females in clinical study samples there are many treatment and drug advices that are founded on findings taken from the samples of Caucasian males. The author proposes, going forward, to decode the present and reshape existing practices before implementing AI to avoid existing biases and further increasing health disparities.[59]

Colling et al. propose a UK-wide strategy for AI and DP. If the requirements of proper slide image management software, integrated reporting systems, improved scanning speeds, and high-quality images for DP systems are achieved then it will provide time and cost saving benefits over the traditional microscope based pathology approach and reduce problem of inter-observer variation. The successful introduction of AI and DP tools to the healthcare system will need proper regulatory approved and evidence based validation, and a lowering of the resistance to collaborate between academic and industry developers.[60] Robertson et al.'s work discusses the limitations of deep learning as it works well in supervised learning but not for unsupervised learning. The deep learning approach is not suitable for the discovery of novel biomarkers, as it being an unsupervised learning problem. If the model is educated only by means of images attained from imaging equipment from a single merchant then it may fail to react acceptably to images acquired from the equipment of another merchant. They observe the challenges to having a full digital workflow, a must for deep learning, due to the high costs and the dependence on solid IT support systems.[61] Typically, training of DL models requires many of annotated samples that belong to dissimilar categories. However, in reality it can be hard to collect a balanced dataset for training because of the fact that certain ailments have a low prevalence causing problem of data. Studies have shown that many models that perform well on balanced datasets do not when it comes to their imbalanced counterparts.[62] Most of medical image datasets possess this imbalance problem. One-class classification, which emphases on learning a model using examples from only a single given class, is used as an approach to overcome the problem of imbalance. Gao et al. proposed a novel method which allows DL models to leverage the concept of imaging complexity to optimally learn single-class-relevant inherent imaging features. They then compared the effects of perturbing operations used on images to realize imaging intricacy to boost feature learning, and allowing their method outperforming four advanced methods.[63]

Tizhoosh et al. explore problems that must be solved in order to exploit opportunities for the AI promises in computational pathology. The challenges discussed include: i) Lack of labeled or annotated data can be overcome by using active learning applied to labeling with public datasets, ii) Pervasive variability: infinite number of patterns due to presence of several tissue types (connective tissue, nervous tissue, epithelium, and muscle) required by AI algorithms to be learned, iii) Non-Boolean nature of diagnostic tasks as binary language of 'yes' or 'no' can be possible in only easy pathological cases but is rarity in the clinical practice, iv) Dimensionality obstacle: Use of "Patching" (divide an image into small tiles) as WSI sizes typically are larger than 50Kx 50K pixels, v) Turing test dilemma: A machine can be as intelligent as a human and Turing test for DP is explicitly not known, vi) Uni-task orientation of weak artificial intelligence as Deep ANNs are designed to perform only one task requiring independently training multiple AIs for tasks of classification, segmentation, and search, vii) Affordability of required computational expenses for adoption of DP is a challenge due to high costs of acquisition and storage of gigapixel histopathological scans, viii) Adversarial attacks (Targeted manipulation of a very small number of pixels inside an image can mislead the network) as negligible presence of artifacts produce misdiagnosis, ix) Lack of transparency and interpretability which is not acceptable to the physicians as there is a lack of explanation on why AI made a specific decision in reference to histopathology scans, and x) Realism of AI as the pathology community has yet to buy in fully due to its issues related to ease of use, financial return, and trust. The authors describe multiple opportunities of: a) Deep features – Pretraining is better using Transfer learning instead of training a new network from scratch, b) Handcrafted features (such as gland shape and nuclear size)– Do not forget computer vision as it can be applied in DP to attain high identification accuracies, c) Generative frameworks: Learning to see and not judge as Generative models, focus on acquiring to reproduce data instead of making any decision such as pulmonary disease categorization and for functional MRI analysis, d) Unsupervised learning: When we do not need annotations in self-organizing plots and hierarchical clustering, and



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effectively combine them in the workflow of usual practice of pathology as annotating images is not portion of the everyday work of pathology experts, e) Virtual peer review – Placing the pathologist in the central to both algorithm development and execution: Algorithms extract reliable information from proven archived diagnosed cases similar to the relevant features of the patient, that are diagnosed and treated by other physicians; Comparing for example diagnosis of patient's cervix biopsy to a prior Pap test assessment for real-time cytologic-histopathologic correlation, f) Automation with AI can assist with case triage by performing laborious tasks for example of screening for easily identifiable cancer types or counting mitoses, and with simplification of complex tasks (e.g., triaging biopsies which require immediate action and ordering suitable stains upfront when specified); AI algorithms have attained sensitivity above 92% for breast cancer recognition, g) Re-birth of the hematoxylin and eosin image: combination of computational pathology and emerging technologies of multiplexing and three-dimensional imaging allows analysis of individual pixels of pathological images to understand diagnostic, and theoretically available prognostic information, h) Making data science accessible to pathologists will enhance their accuracy with the use of AI tools to generate/analyze big image data.[64]

To integrate AI based algorithms into the workflow of pathologists, Jiang et al. outlined and discussed various challenges facing their implementation in pathology. The challenges include: i) Validation: AI models are typically established on small-scale data and images from single-center and therefore they need to be sufficiently validated using multi-institutional data before clinical adoption, ii) Interpretability: DL-based AI methods are rightfully perceived as 'black-box' methods due to their lack of interpretability which is an obstacle towards the clinical adoption by doctors, iii) Computing system: Histopathological photo file dimensions are typically 1,000x of an X-ray and 100x of a CT image files requiring powerful computing and storage, and bandwidth to transmit gigapixel-sized images, iv) Attitude of pathologists: Due to the lack of AI based model's interpretability, pathologists are afraid of the change in workflow and worry about how to describe the evidence from AI in the diagnosis report, v) Attitude of clinicians and patients: In order to have both clinicians and patients have trust, AI based diagnostic and prognostic/predictive assays ought to have a high accuracy, and vi) Regulators: The clinical adoption of AI digital pathology needs approval by regulatory agencies and the lack of interpretability limits the approval.[65] Samek et al. present two methods that describe predictions of deep learning models to overcome DL's black box approach. The first method which computes the sensitivity of the prediction with respect to changes in the input and the second approach meaningfully decomposes the decision in terms of the input variables.[66] Some of problems that need to be overcome to achieve the progress of DP and ML in their daily usage in pathology practice are: a) Make interfaces user friendly which currently are not, b) Require a single image format instead of current existence of several proprietary image formats, c) Overcome issue of the large image file sizes using technological advances in storing, and d) Enhance interactions between AI experts and pathologists.[67]

AI machine learning model development, a multi-step process, includes important technical, regulatory, and clinical barriers. The model should overcome these barriers, which collectively define a "translation gap," in order to being accepted in a real world. The translation gap in digital pathology includes a variability caused by the manual nature of the tissue acquisition process and histopathology slide preparation, differences introduced during tissue sampling, tissue fixation, sectioning, and staining. During model development and validation these variations must be accounted for in order to achieve its widespread adoption. Also, since DP is relatively immature, at present only two manufacturers have received FDA approval to market digital pathology systems for primary diagnosis.[68, 69] Similarly Steiner et al. discuss how the low penetration of digital pathology has negatively affected integration of AI into pathologist's diagnostic workflow and validation of algorithms in live clinical settings.[70]

## VII. Conclusion

Artificial Intelligence (AI) has come a long way over the last 65 years. Over the last two decades research in AI has gained traction in healthcare and it is now being applied across many medical subspecialties of dermatology, radiology, and pathology. A nationwide or global strategy for AI and Digital Pathology (DP) will be necessary in order to be used for automated diagnosis, triaging cases for improved workflow, or deriving novel insights for pathologists. If DP system's requirements of proper slide image management software, integrated reporting systems, improved scanning speeds, and high-quality images, are achieved then it will provide time and cost saving benefits over the traditional microscope based pathology approach, offer a second opinion, and in addition it will reduce the problem of inter-observer variation. However, AI approaches including deep learning do face rightful criticism, as their internals to make decisions by design are not known and hence will require legal and regulatory issues worked out to reap the possible benefits. The successful introduction of AI and DP tools to the healthcare system will need proper regulatory approved evidence based validation, and



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lowering of the resistance to collaboration between academic and industry developers.

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# Application of Physical Factors in Complex Etiopathogenetic Therapy Patients with Coronavirus-19

By Bitsoev Vladimir Dodtievich

*Abstract-* Fundamental scientific research of domestic and foreign scientists strongly suggests that the progress of medicine is impossible without the widespread use of modern physical factors in the diagnosis, prevention, treatment and rehabilitation of almost all nosological forms of diseases from newborns to old age of patients.

Each micro-and macro-organism has individual bioenergetic characteristics corresponding to its type, which is the main condition for normal life activity of the organism.
In the case of "alien" bioenergetic characteristics, specific biological processes inherent in this organism are disrupted, which leads to its death [13].

The biopotential of each person is strictly individual in both normal and pathological conditions. The degree of deviation of the biopotential corresponds to the stage of development of the disease, i.e. the formation of intermediate States of the body with a violation of its supramolecular structures.

*Keywords:* *etiopathogenetic therapy, supramolecular structures, coronavirus, COVID-19.*

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# Application of Physical Factors in Complex Etiopathogenetic Therapy Patients with Coronavirus-19

Bitsoev Vladimir Dodtievich

*Abstract-* Fundamental scientific research of domestic and foreign scientists strongly suggests that the progress of medicine is impossible without the widespread use of modern physical factors in the diagnosis, prevention, treatment and rehabilitation of almost all nosological forms of diseases from newborns to old age of patients.

Each micro-and macro-organism has individual bioenergetic characteristics corresponding to its type, which is the main condition for normal life activity of the organism.
In the case of "alien" bioenergetic characteristics, specific biological processes inherent in this organism are disrupted, which leads to its death [13].

The biopotential of each person is strictly individual in both normal and pathological conditions. The degree of deviation of the biopotential corresponds to the stage of development of the disease, i.e. the formation of intermediate States of the body with a violation of its supramolecular structures.

*Keywords: etiopathogenetic therapy, supramolecular structures, coronavirus, COVID-19.*

## I. Introduction

Natural and preformed physical factors occupy an important place in medicine of the XXI century, as they are important for the diagnosis, treatment, prevention and medical rehabilitation of patients.

Medicine should be developed according to this concept:

"The level of medical excellence determines the progress of conservative treatment of patients with any pathology other than traumatology."

Surgery should not be a factor in determining the progress of medicine. It is forced and will yield to the conservative method of treatment constantly with different speed and scale.

Based on the progress of physical and technical Sciences, it is necessary to replace the concept of "mechanism of action of the physical factor" with "mechanism of interaction of the physical factor and the whole organism".[1,4,9]

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Already from the moment of contact of the physical factor and the organism, intermediate States of both sides are formed with the release of energy (for the continuation of the cyclic process).

In the Russian and world literature, we have not found scientific studies of their significance for the diagnosis, effectiveness and correction of treatment, prevention and medical rehabilitation. This is especially important in Oncology for monitoring and managing the treatment process.[3,5]

For the body, any external influence is a violation of its integrity and therefore the system of rapid disposal of it is instantly activated.

Even your own blood outside the vascular bed is a foreign body for the body. That is, there is an instantaneous transfer of the work of all organs and systems of the body to an abnormal mode.[4,5]

It should be noted that at the moment of development of medical science there are no methods for determining the time level of the cycle of each system at the time of exposure to the body of a medicinal substance, in its transition States at the supramolecular level and when all systems return to normal mode of life.[2,15]

In this regard, it is difficult to imagine the advantage of a particular drug, and in particular for a particular patient. The lack of data in the chronological sequence of the drug in its path to achieving the goal calls into question the advantages of drug therapy over physical therapy.

It is known that " the interaction of a drug with the body is studied in two aspects: how it affects the body (pharmacodynamics) and what happens to it in the body (pharmacokinetics). Pharmacodynamics studies the localization, mechanism of action and pharmacological effects of medicinal substances.[2]

Pharmacokinetics studies the patterns of absorption, distribution and elimination of medicinal substances in the human and animal bodies. [2]

At the same time, it should be noted that the speed, scale, content and time of formation of intermediate formations of a pharmacological drug in the body for each patient are strictly individual.

All drugs in interaction with the body before their introduction into medical practice, in accordance with pharmacodynamics, pharmacokinetics should be



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studied by fast, harmless and highly informative methods. [5]

Compliance with this concept contributes to ensuring a high therapeutic effect, primary and secondary prevention of diseases, prevention of complications and side effects on the body.

This is not observed in medical and pharmaceutical practice due to the lack of research methods for pharmacological preparations at the supramolecular level. [6]

The biopotential for each person is strictly individual both in norm and in pathology. In this regard, any nosology in each individual causes a deviation of its biopotential in accordance with the stage of development of the disease, i.e. the formation of intermediate States of the body with certain violations of its supramolecular structures.

This, in turn, determines the clinical picture at the time of examination of the patient and is the leading condition for choosing the right treatment tactics for any specialist doctor, so that the regression of the disease is accompanied by the restoration of destroyed supramolecular structures, excluding new gross violations at any level of the entire body[6,7].

This concept is not the main principle for drug therapy, due to the lack of highly informative research methods: frequency, dose, mechanism of action of pharmacological drugs at the supramolecular level.

It is known that the final characteristic of any drug at the supramolecular level is "energy", which is difficult to dose and regulate for therapeutic purposes.

The impact of energy from any physical factor is dosed and regulated (physiodynamics) using nanotechnology and its path can be freely traced to each molecule of the whole organism (physiokinetics) without disrupting supramolecular structures, without negative consequences by means of a nanosensor.(patents for inventions: Russia # 2675006, Germany # 20 2017 006 896.)

Modern pharmaceutical science does not have such a high level of control over the path of a medicinal substance in the body.

"The conversion of the energy of photons, light particles, into electrical energy takes place in several stages," explains Professor Christoph Well, head of the IFG Institute. First, light is absorbed on the surface of the light-sensitive material.[11]

Under the influence of the energy of photons of light, the electrons leave their places, leaving in their place electronic holes, with which they immediately form quasiparticles called polaritons.

These polaritons exist only for a very short time, moving to the boundaries of the material, where they break up into electrons and holes, which continue to move further on their own.

And the future fate of these charge carriers already depends on the nature of the light-sensitive material used" [11].

In this regard, any therapeutic effect on the body should be considered a trigger for restoring homeostasis, connecting its own internal systems.

After studying the officially proposed and published Russian media medicines designed to combat coronavirus-19, we have to admit not only their ineffectiveness, but sometimes even harm.

Their original assumptions are clearly wrong. In fact, physiotherapy is seen as a more appropriate approach.

It is based not only on the stated considerations, but also on half a century of experience in use.

Highly effective methods of physical therapy include:

i. Light Therapy of the device "BIOPTRON".

Its spectral range-480-3400 nm-reproduces the dominant types of Solar radiation on Earth-visible and IR radiation, under the influence of which the body absorbs and uses radiant energy. Polychromatic visible and infrared polarized (PVIP) light activates the enzymes nicotinamidadenin-dinucleotide phosphate-oxidase (NADP-oxidase) and nucleotide containing biopteroflavoprotein-NO-synthesis, localized in the cell membrane and using the surrounding oxygen produce its active forms-superoxidanion, hydrogen peroxide, hydroxyl radical and nitric oxide (NO). [15]

They conduct a light signal from the surface of the irradiated cell to its nucleus, affecting specialized intracellular mechanisms for conducting the activation signal (protein phospholidation, the state of calcium channels, the content of calcium in the cell, etc.).

The enzymes responsible for the formation of ROS and NO, as themselves and intermediaries, are found in cells and tissues, in all types of white blood cells, platelets, endothelial and smooth muscle cells of blood vessels. It was found that nitric oxide-NO, is an important part of the mechanism of blood vessel dilation and platelet aggregation, without which phototherapy could hardly be highly effective.[10,14]

After daily 5-10 irradiations, the number of mononuclear leukocytes – monocytes and lymphocytes-circulating in the blood increases by 14-17%.

30 minutes after the first exposure to PVIP light, Pro – inflammatory cytokines-tumor necrosis factor (TNF – α), interleukins-IL-6, IL-2, and IL-12-disappear from the circulating blood. So, at the initial increased content of TNF-α, it falls by 30 times, IL-8 – by 4-6 times, IL-2 – by 4-10 times and IL-12-by 12 times, by the end of the course.[14,16]

Simultaneously, the plasma content of anti – inflammatory cytokines-IL – 10 and transforming growth factor-TFR-β1 increases. [14]



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A feature of PVIP-light phototherapy is a rapid 6-fold increase in the blood of the most important immunomodulator – interferon-γ (IFN-γ).

The most important function of this cytokine is to activate cellular immunity (the functional state of monocytes, macrophages, natural killers and cytotoxic T-lymphocytes), which primarily increases the body's antiviral and antitumor resistance.[13]



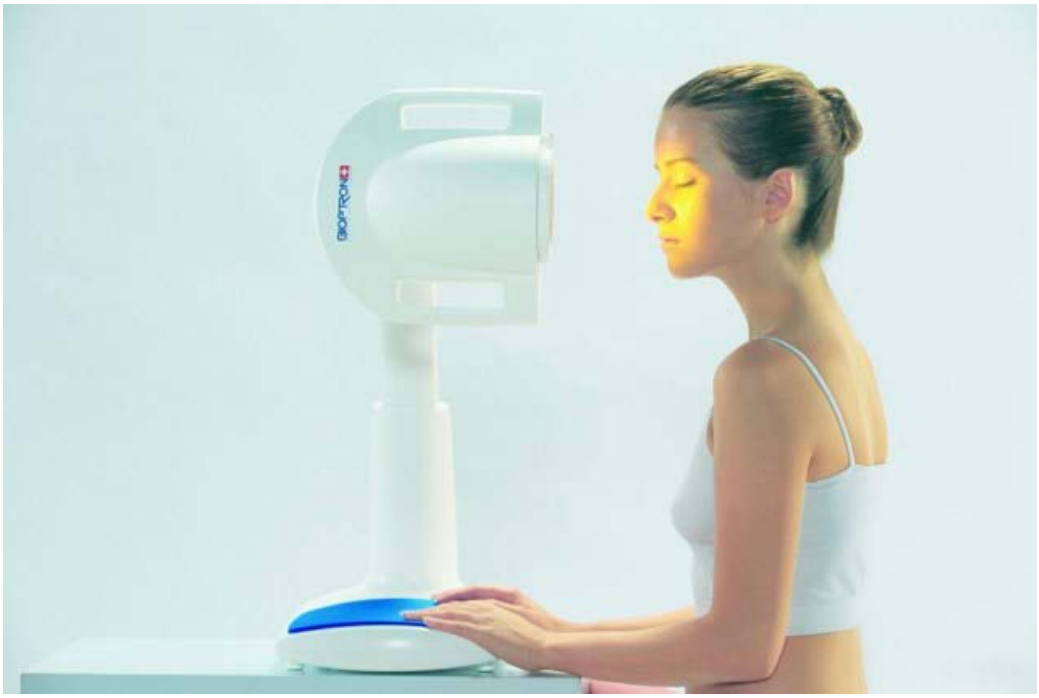
*Fig. 1:* Light Therapy (PVIP) performed by the "BIOPTRON-COMPACT" device-5cm.



*Fig. 2:* Light Therapy (PVIP). The device "BIOPTRON PRO"- 11cm.



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*Puc.3:* Light therapy (PVIP) conducted by the Bioptron PRO apparatus - 11cm.

ii. Application of dry carbon dioxide baths "Reabox".

Dry carbon dioxide baths (SUV) - a method of percutaneous therapeutic action of carbon dioxide on a patient whose body is located up to the neck level in a specially equipped box. Application (SUV) "Reabox" provides non-invasive, i.e. does not violate the integrity of the skin, the introduction of carbon dioxide, which distinguishes this method from CO2 injections. Direct action of carbon dioxide on the respiratory center. The excitation of the respiratory center is not caused by carbonic acid itself, but by an increase in the concentration of hydrogen ions due to an increase in its content in the cells of the respiratory center.



*Fig. 4:* Dry carbon dioxide baths using the "Reabox" device

The specificity of carbonic acid as a respiratory center pathogen was revealed by the experiments of Frederick and Holden, who found that h+ and HCO3 ions pass poorly through the cell membrane, and undifferentiated carbonic acid passes well: undifferentiated H2CO3 diffuses into the cells of the nerve center, which dissociates already in the nerve cells, releasing the irritating H+ion.

Faster diffusion into cells than other acids is a specific feature of carbonic acid, and this is associated with a stronger irritating effect on the respiratory center. [12,15]

The normal ranges of total CO2 in the blood should be as follows.



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| Age range | Conventional units | SI units |
|---|---|---|
| 18–59 | 23–29 mEq / l | 23–29 mmol / l |
| 60–89 | 23–31 mEq / l | 23–31 mmol / l |
| 90+ | 20–29 mEq / l | 20–29 mmol / l |

Hyperventilation for a short time (several tens of minutes) leads to death due to the loss of carbon dioxide by the body.

Humoral regulation of respiration, the role of carbon dioxide, oxygen and blood pH in this process.

The main respiratory stimulant is CO2. Blood pH also plays an important role in the regulation of respiration.

When the pH of arterial blood decreases in comparison with the normal level (7.4), lung ventilation increases, and when the pH increases above the norm, ventilation decreases. Increasing the content of CO2 in the blood stimulates respiration both by reducing the pH and directly by the action of CO2 itself. [12,15]

The effect of CO2 and H+ ions on respiration is mediated mainly by their action on special structures of the brain stem that have chemosensitivity (Central chemoreceptors are part of the blood – brain barrier; low sensitivity threshold).

It was found that a decrease in the pH of the cerebrospinal fluid by only 0.01 is accompanied by an increase in pulmonary ventilation by 4 l / min. [15]

Lack of O2 can be a respiratory stimulant in the case of barbiturates as narcotic drugs, because in this case, the sensitivity of the respiratory center to CO2 is suppressed. Breathing pure oxygen (O2) in patients with reduced sensitivity to CO2 is very dangerous, because when the O2 voltage increases in the arterial blood the last respiratory stimulant (lack of O2) is eliminated in the blood and respiratory arrest may occur. In such cases, it is necessary to use an artificial respiration device.

iii. Extremely high frequency therapy (EHF) is the therapeutic use of millimeter-wave electromagnetic waves

The experience of using it for more than 30 years shows high efficiency in the treatment of a wide range of diseases, including cancer patients.

Extremely high frequencies occupy the range of 30-300 GHz (the wavelength range is 10-1 mm). The peculiarity of this frequency range is that millimeter radiation of cosmic origin is almost absorbed by the earth's atmosphere, so the biological evolution of all living organisms took place with a very small natural EHF electromagnetic background. This, apparently, explains the active influence of low-intensity millimeter radiation on a person.

The following wavelengths are most commonly used in EHF therapy: 4.9 mm (60.12 GHz), 5.6 mm (53.33 GHz), and 7.1 mm (42.19 GHz). [8]

Low-intensity millimeter radiation refers to non-ionizing radiation, i.e. it cannot have a destructive harmful effect on the biological tissues of the body, and therefore it is safe.

A specific feature of EHF exposure is its normalizing nature, i.e. EHF radiation normalizes only the physiological parameters of a number of States of the body that deviate from it: it increases the values of reduced indicators and reduces the values of inflated values. Parameters that are normal do not respond to radiation of the body with a millimeter field.

That is, the features of EHF therapy as non-invasiveness, lack of Allergy to EHF radiation, drug-free therapy contribute to the normalization of intracellular energy of any cell in the whole body.

iv. Multifunctional device for spot infrared and magnetic therapy for effective pain relief (Rayforce)

IR wavelength: 850 nm. Magnet power: 1000 Gauss. Charging: from sunlight and artificial light.

IR-therapy. It is proved that waves of different ranges affect the body in different layers and levels. IR radiation has the greatest penetration depth. In physiotherapy, waves are used in the range from 780 to 1400 nm, i.e. short, penetrating the tissues to a depth of 5 cm. The effect of IR radiation is aimed at accelerating the physical and chemical processes reactions: the processes of tissue repair and regeneration are stimulated, the vascular network expands, blood flow accelerates, cell growth increases, biologically active substances are produced, and white blood cells are sent to the lesion site. The reserve functions of the body are awakened. Permanent magnetic field (PMP) improves microcirculation, stimulates healing processes, activates immunological reactions, has anti-inflammatory and sedative effects.[17] Experimental studies were conducted at the scientific center for fiber optics (ncvo) of the Russian Academy of Sciences, Moscow. New non-toxic, non-hygroscopic silver halide light guides with low optical losses in a wide spectral range of 3-15 microns have been developed by the ntsvo staff, allowing to obtain skin spectra in vivo with a good signal-to-noise ratio even on the uncooled standard DNGS Fourier spectrometer Bruker.



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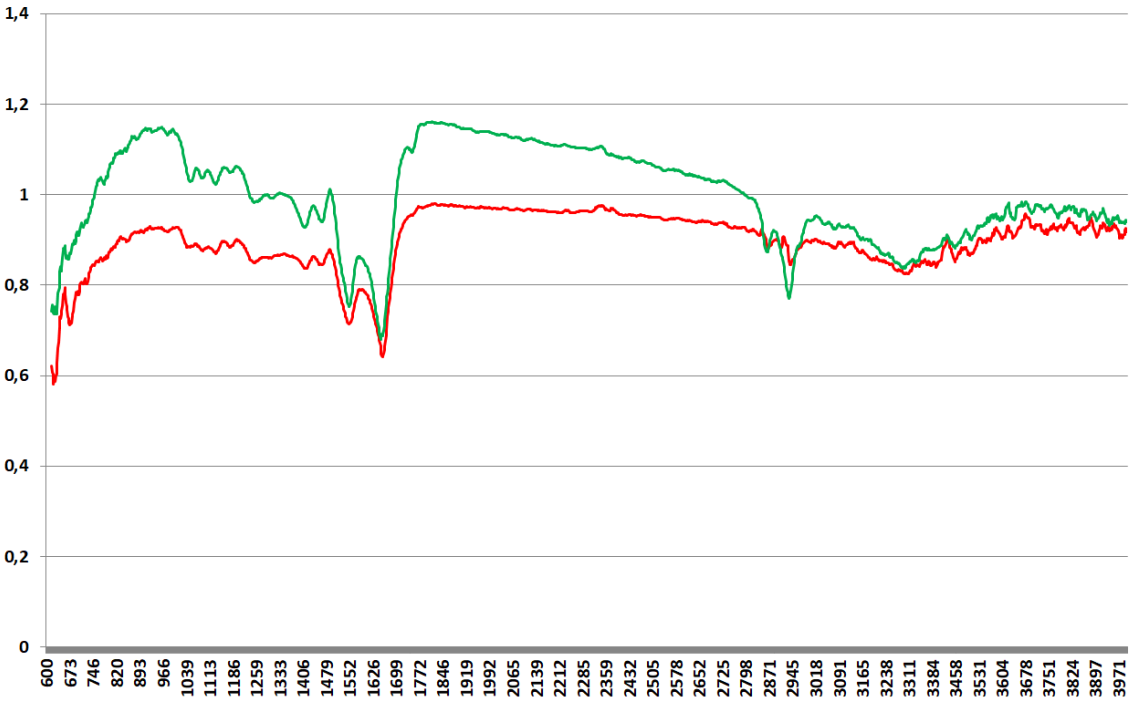



*Fig. 5:* IR spectroscopy of the inner surface of the left elbow joint

spectrum of the left elbow joint area before treatment
spectrum of the left elbow joint area after RayForce treatment



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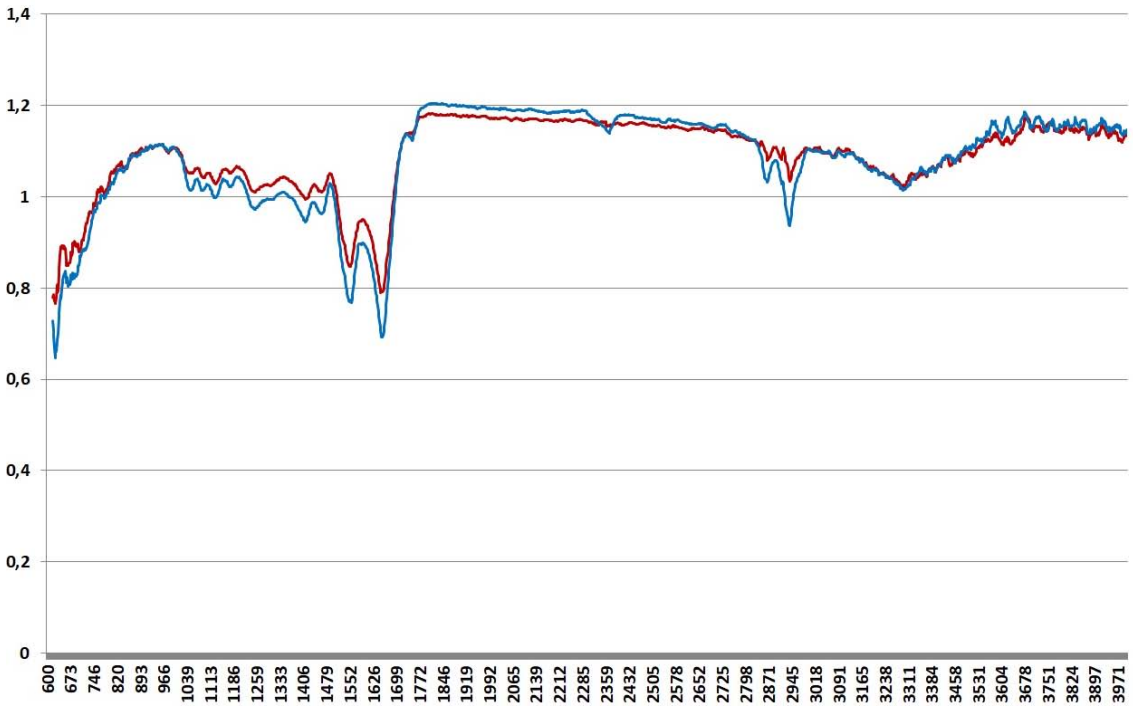



*Fig. 6:* IR spectroscopy of the inner surface of the right elbow

joint. spectrum of the right elbow
joint area before treatment spectrum of the right elbow joint area after RayForce

Results of RayForce treatment effectiveness based on IR spectroscopy data. This experiment confirmed the high therapeutic effectiveness of the RayForce device: For rice.5 IR spectroscopy shows the absence of pain in the left elbow joint after the treatment of RayForce device in the form of a complete restoration of the spectrum in the form and amplitude of light transmission, as well as correction of morphological changes in this area of exposure in the wavelength range of 970 – 1400nm. Based on the data in Fig.6. according to IR spectroscopy, there is reason to assert that the right elbow joint in the experiment was healthy and should be considered IR spectroscopy of the right elbow joint control.

Symptoms of coronavirus, the first signs of COVID-19.

- Elevated temperature.
- Dry cough.
- Dyspnea.
- The tightness in his chest.
- Runny nose.
- Weakness.
- Undue fatigability.

The lung involvement by coronavirus

The structure of human lungs is cellular. They consist of tiny bubbles saturated with air - the alveoli.

Each such alveola is surrounded by capillaries, through which, in fact, carbon dioxide is removed from the blood and oxygen is supplied.

Red blood cells (red blood cells) are responsible for their transport through tissues and organs.

Alveolar cells that participate in gas exchange are of two types: type I. Thin. Oxygen passes through them;

Type II. A surfactant is isolated - a substance that envelops the alveola and protects it from damage. The coronavirus attacks mainly type II cells.

Spiked proteins on its surface are bound by angiotensin converting enzyme 2 (APF2) on their surface.

So the virus "breaks" the protection and gets inside the cell, starting to replicate its RNA.

The host cell soon dies, and the coronavirus spreads to neighboring cells and thus gradually affects the lungs.

Naturally, our immune system does not sit still and actively produces macrophage cells.

The result of this struggle is the death of the alveoli and a decrease in the turnover of gas exchange.

This continues until the so-called alveolar collapse occurs and the acute respiratory distress syndrome begins.

In severe inflammation, fluid rich in inflammatory proteins enters the bloodstream and spreads to other organs and tissues.

This is how the systemic inflammatory response syndrome (SARS) develops, followed by septic shock and multiple organ failure.



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The incubation period of COVID-19 is from 2 to 14 days, during which time there are no symptoms. Preventive physical therapy should be started as soon as a coronavirus infection is suspected.

1. light Therapy with the "BIOPTRON" device:

- impact on the face from 10 cm to 5 minutes;
- on the neck area with 10 cm 5 minutes;
- on the inter-scapular area with 5 cm 10 minutes;
- on the plantar surfaces of the feet from 5 cm to 5 minutes;
- on Palmar surfaces from 5 cm to 5 minutes;
- twice a day, daily, the course of treatment is 14 days.

2. Dry carbon dioxide baths "Reabox":

- CO2 concentration of 18-20%, 15 minutes, 1 time per day, treatment course of 14 days.

3. EHF therapy, the device " Yav»:

- paravertebral inter-scapular area with two points on both sides, the distance between the points is 10 cm;
- epigastric region;
- paravertebral at the level of the VII cervical vertebra;
- emitters: 4.9 mm (60.12 GHz), 5.6 mm (53.33 GHz) and 7.1 mm (42.19 GHz) for 3 minutes per field 1 time per day, daily, 14 days of treatment.

4. Therapeutic breathing exercises 5 minutes, 1 time a day, daily, 14 days of treatment.

In case of complications, the physiotherapist makes a plan of daily physiotherapy with hourly correction individually for each patient according to the state of the clinic.

Physical therapy is performed in combination with medication.

The proposed physiotherapy plan provides indications and contraindications at the supramolecular level, as well as for children from two years of age with a 50% reduction in the exposure time of each method, i.e. if an adult is 5 minutes, then children are 2.5-3 minutes.

When establishing the diagnosis of "pneumonitis", the oxygen-helium mixture should be inhaled according to the developed method of academician A. G. Chuchalin from the AKGS-31 apparatus of the Minsk research Institute of radio materials.

## II. Conclusion

Given the characteristics of coronavirus (COVID-19) infection, its differences from other known viruses are

- suddenness of occurrence;
- high speed, scale and unhindered distribution;
- program selectivity of penetration into the intracellular space;
- consistency of the striking nature at the supramolecular level of chronically weakened organs and systems, taking into account their biological age.

The wave origin of coronavirus-19, that is, based on quantum mechanics (entanglement), should be assumed.

In this regard, it should be argued that a global solution to the problem of neutralizing the damaging insidious actions of the virus (COVID-19) is possible at the level of quantum physics and can only be done by a group of scientific physicists led by professor Lukin Mikhail Dmitrievich of the United States Harvard University.

The physiotherapeutic methods proposed above for the prevention, treatment, and rehabilitation of patients with coronavirus (COVID-19) infection are also consistent with quantum physics, since their mechanism of action on the whole organism is identical to quantum touch, so they should be included in the program for combating coronavirus infection (COVID19).

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Career | Credibility | Exclusive | Reputation




## Certificate

### Certificate, LoR and Laser-Momento

Associates receive a printed copy of a certificate signed by our Chief Author that may be used for academic purposes and a personal recommendation letter to the dean of member's university.

Career | Credibility | Exclusive | Reputation




## Designation

### Get honored title of membership

Associates can use the honored title of membership. The “AMRC” is an honored title which is accorded to a person’s name viz. Dr. John E. Hall, Ph.D., AMRC or William Walldroff, M.S., AMRC.

Career | Credibility | Exclusive | Reputation

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### Better visibility and citation

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Career | Credibility | Reputation

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Career | Financial



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john [AT] globaljournals [DOT] org.

Career | Credibility | Reputation



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Financial

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### Organize seminar/conference

Associates are authorized to organize symposium/seminar/conference on behalf of Global Journal Incorporation (USA). They can also participate in the same organized by another institution as representative of Global Journal. In both the cases, it is mandatory for him to discuss with us and obtain our consent. Additionally, they get free research conferences (and others) alerts.

Career | Credibility | Financial

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Exclusive




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Exclusive | Financial

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Financial

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| Associate | Fellow | Research Group | Basic |
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# Preferred Author Guidelines

**We accept the manuscript submissions in any standard (generic) format.**

We typeset manuscripts using advanced typesetting tools like Adobe In Design, CorelDraw, TeXnicCenter, and TeXStudio. We usually recommend authors submit their research using any standard format they are comfortable with, and let Global Journals do the rest.

Alternatively, you can download our basic template from https://globaljournals.org/Template

Authors should submit their complete paper/article, including text illustrations, graphics, conclusions, artwork, and tables. Authors who are not able to submit manuscript using the form above can email the manuscript department at submit@globaljournals.org or get in touch with chiefeditor@globaljournals.org if they wish to send the abstract before submission.

## Before and during Submission

Authors must ensure the information provided during the submission of a paper is authentic. Please go through the following checklist before submitting:

1. Authors must go through the complete author guideline and understand and *agree to Global Journals' ethics and code of conduct,* along with author responsibilities.
2. Authors must accept the privacy policy, terms, and conditions of Global Journals.
3. Ensure corresponding author's email address and postal address are accurate and reachable.
4. Manuscript to be submitted must include keywords, an abstract, a paper title, co-author(s') names and details (email address, name, phone number, and institution), figures and illustrations in vector format including appropriate captions, tables, including titles and footnotes, a conclusion, results, acknowledgments and references.
5. Authors should submit paper in a ZIP archive if any supplementary files are required along with the paper.
6. Proper permissions must be acquired for the use of any copyrighted material.
7. Manuscript submitted *must not have been submitted or published elsewhere* and all authors must be aware of the submission.

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It is required for authors to declare all financial, institutional, and personal relationships with other individuals and organizations that could influence (bias) their research.

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Plagiarism is not acceptable in Global Journals submissions at all.

Plagiarized content will not be considered for publication. We reserve the right to inform authors' institutions about plagiarism detected either before or after publication. If plagiarism is identified, we will follow COPE guidelines:

Authors are solely responsible for all the plagiarism that is found. The author must not fabricate, falsify or plagiarize existing research data. The following, if copied, will be considered plagiarism:

- Words (language)
- Ideas
- Findings
- Writings
- Diagrams
- Graphs
- Illustrations
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- Printed material
- Graphic representations
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- Any other original work

## Authorship Policies

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2. Drafting the paper and revising it critically regarding important academic content.
3. Final approval of the version of the paper to be published.

**Changes in Authorship**

The corresponding author should mention the name and complete details of all co-authors during submission and in manuscript. We support addition, rearrangement, manipulation, and deletions in authors list till the early view publication of the journal. We expect that corresponding author will notify all co-authors of submission. We follow COPE guidelines for changes in authorship.

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Unless specified in the notification, the Editorial Board's decision on publication of the paper is final and cannot be appealed before making the major change in the manuscript.

**Acknowledgments**

Contributors to the research other than authors credited should be mentioned in Acknowledgments. The source of funding for the research can be included. Suppliers of resources may be mentioned along with their addresses.

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## Preparing your Manuscript

Authors can submit papers and articles in an acceptable file format: MS Word (doc, docx), LaTeX (.tex, .zip or .rar including all of your files), Adobe PDF (.pdf), rich text format (.rtf), simple text document (.txt), Open Document Text (.odt), and Apple Pages (.pages). Our professional layout editors will format the entire paper according to our official guidelines. This is one of the highlights of publishing with Global Journals—authors should not be concerned about the formatting of their paper. Global Journals accepts articles and manuscripts in every major language, be it Spanish, Chinese, Japanese, Portuguese, Russian, French, German, Dutch, Italian, Greek, or any other national language, but the title, subtitle, and abstract should be in English. This will facilitate indexing and the pre-peer review process.

The following is the official style and template developed for publication of a research paper. Authors are not required to follow this style during the submission of the paper. It is just for reference purposes.

***Manuscript Style Instruction (Optional)***

- Microsoft Word Document Setting Instructions.
- Font type of all text should be Swis721 Lt BT.
- Page size: 8.27" x 11'", left margin: 0.65, right margin: 0.65, bottom margin: 0.75.
- Paper title should be in one column of font size 24.
- Author name in font size of 11 in one column.
- Abstract: font size 9 with the word "Abstract" in bold italics.
- Main text: font size 10 with two justified columns.
- Two columns with equal column width of 3.38 and spacing of 0.2.
- First character must be three lines drop-capped.
- The paragraph before spacing of 1 pt and after of 0 pt.
- Line spacing of 1 pt.
- Large images must be in one column.
- The names of first main headings (Heading 1) must be in Roman font, capital letters, and font size of 10.
- The names of second main headings (Heading 2) must not include numbers and must be in italics with a font size of 10.

***Structure and Format of Manuscript***

The recommended size of an original research paper is under 15,000 words and review papers under 7,000 words. Research articles should be less than 10,000 words. Research papers are usually longer than review papers. Review papers are reports of significant research (typically less than 7,000 words, including tables, figures, and references)

A research paper must include:

a) A title which should be relevant to the theme of the paper.
b) A summary, known as an abstract (less than 150 words), containing the major results and conclusions.
c) Up to 10 keywords that precisely identify the paper's subject, purpose, and focus.
d) An introduction, giving fundamental background objectives.
e) Resources and techniques with sufficient complete experimental details (wherever possible by reference) to permit repetition, sources of information must be given, and numerical methods must be specified by reference.
f) Results which should be presented concisely by well-designed tables and figures.
g) Suitable statistical data should also be given.
h) All data must have been gathered with attention to numerical detail in the planning stage.

Design has been recognized to be essential to experiments for a considerable time, and the editor has decided that any paper that appears not to have adequate numerical treatments of the data will be returned unrefereed.

i) Discussion should cover implications and consequences and not just recapitulate the results; conclusions should also be summarized.
j) There should be brief acknowledgments.
k) There ought to be references in the conventional format. Global Journals recommends APA format.

Authors should carefully consider the preparation of papers to ensure that they communicate effectively. Papers are much more likely to be accepted if they are carefully designed and laid out, contain few or no errors, are summarizing, and follow instructions. They will also be published with much fewer delays than those that require much technical and editorial correction.

The Editorial Board reserves the right to make literary corrections and suggestions to improve brevity.



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## Format Structure

***It is necessary that authors take care in submitting a manuscript that is written in simple language and adheres to published guidelines.***

All manuscripts submitted to Global Journals should include:

**Title**

The title page must carry an informative title that reflects the content, a running title (less than 45 characters together with spaces), names of the authors and co-authors, and the place(s) where the work was carried out.

**Author details**

The full postal address of any related author(s) must be specified.

**Abstract**

The abstract is the foundation of the research paper. It should be clear and concise and must contain the objective of the paper and inferences drawn. It is advised to not include big mathematical equations or complicated jargon.

Many researchers searching for information online will use search engines such as Google, Yahoo or others. By optimizing your paper for search engines, you will amplify the chance of someone finding it. In turn, this will make it more likely to be viewed and cited in further works. Global Journals has compiled these guidelines to facilitate you to maximize the web-friendliness of the most public part of your paper.

**Keywords**

A major lynchpin of research work for the writing of research papers is the keyword search, which one will employ to find both library and internet resources. Up to eleven keywords or very brief phrases have to be given to help data retrieval, mining, and indexing.

One must be persistent and creative in using keywords. An effective keyword search requires a strategy: planning of a list of possible keywords and phrases to try.

Choice of the main keywords is the first tool of writing a research paper. Research paper writing is an art. Keyword search should be as strategic as possible.

One should start brainstorming lists of potential keywords before even beginning searching. Think about the most important concepts related to research work. Ask, “What words would a source have to include to be truly valuable in a research paper?” Then consider synonyms for the important words.

It may take the discovery of only one important paper to steer in the right keyword direction because, in most databases, the keywords under which a research paper is abstracted are listed with the paper.

**Numerical Methods**

Numerical methods used should be transparent and, where appropriate, supported by references.

**Abbreviations**

Authors must list all the abbreviations used in the paper at the end of the paper or in a separate table before using them.

**Formulas and equations**

Authors are advised to submit any mathematical equation using either MathJax, KaTeX, or LaTeX, or in a very high-quality image.

**Tables, Figures, and Figure Legends**

Tables: Tables should be cautiously designed, uncrowned, and include only essential data. Each must have an Arabic number, e.g., Table 4, a self-explanatory caption, and be on a separate sheet. Authors must submit tables in an editable format and not as images. References to these tables (if any) must be mentioned accurately.

**Figures**

Figures are supposed to be submitted as separate files. Always include a citation in the text for each figure using Arabic numbers, e.g., Fig. 4. Artwork must be submitted online in vector electronic form or by emailing it.

## Preparation of Eletronic Figures for Publication

Although low-quality images are sufficient for review purposes, print publication requires high-quality images to prevent the final product being blurred or fuzzy. Submit (possibly by e-mail) EPS (line art) or TIFF (halftone/ photographs) files only. MS PowerPoint and Word Graphics are unsuitable for printed pictures. Avoid using pixel-oriented software. Scans (TIFF only) should have a resolution of at least 350 dpi (halftone) or 700 to 1100 dpi (line drawings). Please give the data for figures in black and white or submit a Color Work Agreement form. EPS files must be saved with fonts embedded (and with a TIFF preview, if possible).

For scanned images, the scanning resolution at final image size ought to be as follows to ensure good reproduction: line art: >650 dpi; halftones (including gel photographs): >350 dpi; figures containing both halftone and line images: >650 dpi.

Color charges: Authors are advised to pay the full cost for the reproduction of their color artwork. Hence, please note that if there is color artwork in your manuscript when it is accepted for publication, we would require you to complete and return a Color Work Agreement form before your paper can be published. Also, you can email your editor to remove the color fee after acceptance of the paper.

## Tips for writing a good quality Medical Research Paper

***1. Choosing the topic:*** In most cases, the topic is selected by the interests of the author, but it can also be suggested by the guides. You can have several topics, and then judge which you are most comfortable with. This may be done by asking several questions of yourself, like "Will I be able to carry out a search in this area? Will I find all necessary resources to accomplish the search? Will I be able to find all information in this field area?" If the answer to this type of question is "yes," then you ought to choose that topic. In most cases, you may have to conduct surveys and visit several places. Also, you might have to do a lot of work to find all the rises and falls of the various data on that subject. Sometimes, detailed information plays a vital role, instead of short information. Evaluators are human: The first thing to remember is that evaluators are also human beings. They are not only meant for rejecting a paper. They are here to evaluate your paper. So present your best aspect.

***2. Think like evaluators:*** If you are in confusion or getting demotivated because your paper may not be accepted by the evaluators, then think, and try to evaluate your paper like an evaluator. Try to understand what an evaluator wants in your research paper, and you will automatically have your answer. Make blueprints of paper: The outline is the plan or framework that will help you to arrange your thoughts. It will make your paper logical. But remember that all points of your outline must be related to the topic you have chosen.

***3. Ask your guides:*** If you are having any difficulty with your research, then do not hesitate to share your difficulty with your guide (if you have one). They will surely help you out and resolve your doubts. If you can't clarify what exactly you require for your work, then ask your supervisor to help you with an alternative. He or she might also provide you with a list of essential readings.

***4. Use of computer is recommended:*** As you are doing research in the field of medical research then this point is quite obvious. Use right software: Always use good quality software packages. If you are not capable of judging good software, then you can lose the quality of your paper unknowingly. There are various programs available to help you which you can get through the internet.

***5. Use the internet for help:*** An excellent start for your paper is using Google. It is a wondrous search engine, where you can have your doubts resolved. You may also read some answers for the frequent question of how to write your research paper or find a model research paper. You can download books from the internet. If you have all the required books, place importance on reading, selecting, and analyzing the specified information. Then sketch out your research paper. Use big pictures: You may use encyclopedias like Wikipedia to get pictures with the best resolution. At Global Journals, you should strictly follow here.



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***6. Bookmarks are useful:*** When you read any book or magazine, you generally use bookmarks, right? It is a good habit which helps to not lose your continuity. You should always use bookmarks while searching on the internet also, which will make your search easier.

***7. Revise what you wrote:*** When you write anything, always read it, summarize it, and then finalize it.

***8. Make every effort:*** Make every effort to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in the introduction—what is the need for a particular research paper. Polish your work with good writing skills and always give an evaluator what he wants. Make backups: When you are going to do any important thing like making a research paper, you should always have backup copies of it either on your computer or on paper. This protects you from losing any portion of your important data.

***9. Produce good diagrams of your own:*** Always try to include good charts or diagrams in your paper to improve quality. Using several unnecessary diagrams will degrade the quality of your paper by creating a hodgepodge. So always try to include diagrams which were made by you to improve the readability of your paper. Use of direct quotes: When you do research relevant to literature, history, or current affairs, then use of quotes becomes essential, but if the study is relevant to science, use of quotes is not preferable.

***10. Use proper verb tense:*** Use proper verb tenses in your paper. Use past tense to present those events that have happened. Use present tense to indicate events that are going on. Use future tense to indicate events that will happen in the future. Use of wrong tenses will confuse the evaluator. Avoid sentences that are incomplete.

***11. Pick a good study spot:*** Always try to pick a spot for your research which is quiet. Not every spot is good for studying.

***12. Know what you know:*** Always try to know what you know by making objectives, otherwise you will be confused and unable to achieve your target.

***13. Use good grammar:*** Always use good grammar and words that will have a positive impact on the evaluator; use of good vocabulary does not mean using tough words which the evaluator has to find in a dictionary. Do not fragment sentences. Eliminate one-word sentences. Do not ever use a big word when a smaller one would suffice.

Verbs have to be in agreement with their subjects. In a research paper, do not start sentences with conjunctions or finish them with prepositions. When writing formally, it is advisable to never split an infinitive because someone will (wrongly) complain. Avoid clichés like a disease. Always shun irritating alliteration. Use language which is simple and straightforward. Put together a neat summary.

***14. Arrangement of information:*** Each section of the main body should start with an opening sentence, and there should be a changeover at the end of the section. Give only valid and powerful arguments for your topic. You may also maintain your arguments with records.

***15. Never start at the last minute:*** Always allow enough time for research work. Leaving everything to the last minute will degrade your paper and spoil your work.

***16. Multitasking in research is not good:*** Doing several things at the same time is a bad habit in the case of research activity. Research is an area where everything has a particular time slot. Divide your research work into parts, and do a particular part in a particular time slot.

***17. Never copy others' work:*** Never copy others' work and give it your name because if the evaluator has seen it anywhere, you will be in trouble. Take proper rest and food: No matter how many hours you spend on your research activity, if you are not taking care of your health, then all your efforts will have been in vain. For quality research, take proper rest and food.

***18. Go to seminars:*** Attend seminars if the topic is relevant to your research area. Utilize all your resources.

***19. Refresh your mind after intervals:*** Try to give your mind a rest by listening to soft music or sleeping in intervals. This will also improve your memory. Acquire colleagues: Always try to acquire colleagues. No matter how sharp you are, if you acquire colleagues, they can give you ideas which will be helpful to your research.

***20. Think technically:*** Always think technically. If anything happens, search for its reasons, benefits, and demerits. Think and then print: When you go to print your paper, check that tables are not split, headings are not detached from their descriptions, and page sequence is maintained.

***21. Adding unnecessary information:*** Do not add unnecessary information like "I have used MS Excel to draw graphs." Irrelevant and inappropriate material is superfluous. Foreign terminology and phrases are not apropos. One should never take a broad view. Analogy is like feathers on a snake. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Never oversimplify: When adding material to your research paper, never go for oversimplification; this will definitely irritate the evaluator. Be specific. Never use rhythmic redundancies. Contractions shouldn't be used in a research paper. Comparisons are as terrible as clichés. Give up ampersands, abbreviations, and so on. Remove commas that are not necessary. Parenthetical words should be between brackets or commas. Understatement is always the best way to put forward earth-shaking thoughts. Give a detailed literary review.

***22. Report concluded results:*** Use concluded results. From raw data, filter the results, and then conclude your studies based on measurements and observations taken. An appropriate number of decimal places should be used. Parenthetical remarks are prohibited here. Proofread carefully at the final stage. At the end, give an outline to your arguments. Spot perspectives of further study of the subject. Justify your conclusion at the bottom sufficiently, which will probably include examples.

***23. Upon conclusion:*** Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium though which your research is going to be in print for the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects of your research.

## Informal Guidelines of Research Paper Writing

***Key points to remember:***

- Submit all work in its final form.
- Write your paper in the form which is presented in the guidelines using the template.
- Please note the criteria peer reviewers will use for grading the final paper.

**Final points:**

One purpose of organizing a research paper is to let people interpret your efforts selectively. The journal requires the following sections, submitted in the order listed, with each section starting on a new page:

*The introduction:* This will be compiled from reference matter and reflect the design processes or outline of basis that directed you to make a study. As you carry out the process of study, the method and process section will be constructed like that. The results segment will show related statistics in nearly sequential order and direct reviewers to similar intellectual paths throughout the data that you gathered to carry out your study.

**The discussion section:**

This will provide understanding of the data and projections as to the implications of the results. The use of good quality references throughout the paper will give the effort trustworthiness by representing an alertness to prior workings.

Writing a research paper is not an easy job, no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record-keeping are the only means to make straightforward progression.

**General style:**

Specific editorial column necessities for compliance of a manuscript will always take over from directions in these general guidelines.

**To make a paper clear:** Adhere to recommended page limits.



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*Mistakes to avoid:*

- Insertion of a title at the foot of a page with subsequent text on the next page.
- Separating a table, chart, or figure—confine each to a single page.
- Submitting a manuscript with pages out of sequence.
- In every section of your document, use standard writing style, including articles ("a" and "the").
- Keep paying attention to the topic of the paper.
- Use paragraphs to split each significant point (excluding the abstract).
- Align the primary line of each section.
- Present your points in sound order.
- Use present tense to report well-accepted matters.
- Use past tense to describe specific results.
- Do not use familiar wording; don't address the reviewer directly. Don't use slang or superlatives.
- Avoid use of extra pictures—include only those figures essential to presenting results.

**Title page:**

Choose a revealing title. It should be short and include the name(s) and address(es) of all authors. It should not have acronyms or abbreviations or exceed two printed lines.

**Abstract:** This summary should be two hundred words or less. It should clearly and briefly explain the key findings reported in the manuscript and must have precise statistics. It should not have acronyms or abbreviations. It should be logical in itself. Do not cite references at this point.

An abstract is a brief, distinct paragraph summary of finished work or work in development. In a minute or less, a reviewer can be taught the foundation behind the study, common approaches to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Use comprehensive sentences, and do not sacrifice readability for brevity; you can maintain it succinctly by phrasing sentences so that they provide more than a lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study with the subsequent elements in any summary. Try to limit the initial two items to no more than one line each.

*Reason for writing the article—theory, overall issue, purpose.*

- Fundamental goal.
- To-the-point depiction of the research.
- Consequences, including definite statistics—if the consequences are quantitative in nature, account for this; results of any numerical analysis should be reported. Significant conclusions or questions that emerge from the research.

**Approach:**

- Single section and succinct.
- An outline of the job done is always written in past tense.
- Concentrate on shortening results—limit background information to a verdict or two.
- Exact spelling, clarity of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else.

**Introduction:**

The introduction should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable of comprehending and calculating the purpose of your study without having to refer to other works. The basis for the study should be offered. Give the most important references, but avoid making a comprehensive appraisal of the topic. Describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will give no attention to your results. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here.

*The following approach can create a valuable beginning:*

- Explain the value (significance) of the study.
- Defend the model—why did you employ this particular system or method? What is its compensation? Remark upon its appropriateness from an abstract point of view as well as pointing out sensible reasons for using it.
- Present a justification. State your particular theory(-ies) or aim(s), and describe the logic that led you to choose them.
- Briefly explain the study's tentative purpose and how it meets the declared objectives.

**Approach:**

Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done. Sort out your thoughts; manufacture one key point for every section. If you make the four points listed above, you will need at least four paragraphs. Present surrounding information only when it is necessary to support a situation. The reviewer does not desire to read everything you know about a topic. Shape the theory specifically—do not take a broad view.

As always, give awareness to spelling, simplicity, and correctness of sentences and phrases.

**Procedures (methods and materials):**

This part is supposed to be the easiest to carve if you have good skills. A soundly written procedures segment allows a capable scientist to replicate your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order, but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt to give the least amount of information that would permit another capable scientist to replicate your outcome, but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section.

When a technique is used that has been well-described in another section, mention the specific item describing the way, but draw the basic principle while stating the situation. The purpose is to show all particular resources and broad procedures so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step-by-step report of the whole thing you did, nor is a methods section a set of orders.

**Materials:**

*Materials may be reported in part of a section or else they may be recognized along with your measures.*

**Methods:**

- Report the method and not the particulars of each process that engaged the same methodology.
- Describe the method entirely.
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures.
- Simplify—detail how procedures were completed, not how they were performed on a particular day.
- If well-known procedures were used, account for the procedure by name, possibly with a reference, and that's all.

**Approach:**

It is embarrassing to use vigorous voice when documenting methods without using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result, when writing up the methods, most authors use third person passive voice.

Use standard style in this and every other part of the paper—avoid familiar lists, and use full sentences.

**What to keep away from:**

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings—save it for the argument.
- Leave out information that is immaterial to a third party.



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**Results:**

The principle of a results segment is to present and demonstrate your conclusion. Create this part as entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Use statistics and tables, if suitable, to present consequences most efficiently.

You must clearly differentiate material which would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matters should not be submitted at all except if requested by the instructor.

**Content:**

- Sum up your conclusions in text and demonstrate them, if suitable, with figures and tables.
- In the manuscript, explain each of your consequences, and point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation of an exacting study.
- Explain results of control experiments and give remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or manuscript.

**What to stay away from:**

- Do not discuss or infer your outcome, report surrounding information, or try to explain anything.
- Do not include raw data or intermediate calculations in a research manuscript.
- Do not present similar data more than once.
- A manuscript should complement any figures or tables, not duplicate information.
- Never confuse figures with tables—there is a difference.

**Approach:**

As always, use past tense when you submit your results, and put the whole thing in a reasonable order.

Put figures and tables, appropriately numbered, in order at the end of the report.

If you desire, you may place your figures and tables properly within the text of your results section.

**Figures and tables:**

If you put figures and tables at the end of some details, make certain that they are visibly distinguished from any attached appendix materials, such as raw facts. Whatever the position, each table must be titled, numbered one after the other, and include a heading. All figures and tables must be divided from the text.

**Discussion:**

The discussion is expected to be the trickiest segment to write. A lot of papers submitted to the journal are discarded based on problems with the discussion. There is no rule for how long an argument should be.

Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implications of the study. The purpose here is to offer an understanding of your results and support all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of results should be fully described.

Infer your data in the conversation in suitable depth. This means that when you clarify an observable fact, you must explain mechanisms that may account for the observation. If your results vary from your prospect, make clear why that may have happened. If your results agree, then explain the theory that the proof supported. It is never suitable to just state that the data approved the prospect, and let it drop at that. Make a decision as to whether each premise is supported or discarded or if you cannot make a conclusion with assurance. Do not just dismiss a study or part of a study as "uncertain."

Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work.

- You may propose future guidelines, such as how an experiment might be personalized to accomplish a new idea.
- Give details of all of your remarks as much as possible, focusing on mechanisms.
- Make a decision as to whether the tentative design sufficiently addressed the theory and whether or not it was correctly restricted. Try to present substitute explanations if they are sensible alternatives.
- One piece of research will not counter an overall question, so maintain the large picture in mind. Where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

**Approach:**

When you refer to information, differentiate data generated by your own studies from other available information. Present work done by specific persons (including you) in past tense.

Describe generally acknowledged facts and main beliefs in present tense.

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| ***Methods and Procedures*** | Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads | Difficult to comprehend with embarrassed text, too much explanation but completed | Incorrect and unorganized structure with hazy meaning |
| ***Result*** | Well organized, Clear and specific, Correct units with precision, correct data, well structuring of paragraph, no grammar and spelling mistake | Complete and embarrassed text, difficult to comprehend | Irregular format with wrong facts and figures |
| ***Discussion*** | Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited | Wordy, unclear conclusion, spurious | Conclusion is not cited, unorganized, difficult to comprehend |
| ***References*** | Complete and correct format, well organized | Beside the point, Incomplete | Wrong format and structuring |

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