Volume 1, Issue 1, December 2021 - ISSN 2812-4898

مركز الأكاديمية للنشر
ACADEMY Publishing Center

AMPDR

Advances in Medical, Pharmaceutical and Dental Research Journal

Academy Publishing Center
Advances in Medical, Pharmaceutical and Dental Research (AMPDR)
First edition 2021

Volume 1, Issue 1, (Dec.2021) eISSN: 2812-4898 pISSN: 2812-488X

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Re-enforcing Bridges between Different Medical Research Fields

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Dr. Amira Senbel is a Professor of Pharmacology & Toxicology, College of Pharmacy, and currently holds the position of Vice-Dean for Educational Affairs, and for Training and Community Service at College of Pharmacy, Arab Academy for Sciences and Technology, Alexandria, Egypt. Dr. Senbel is graduated from Faculty of Pharmacy Alexandria University (AU) in 1998. She was appointed as Academic staff Assistant at Faculty of Pharmacy AU in 1999 and got her full Professorship in 2017. Vascular and smooth muscle Pharmacology and Toxicology is her major scientific research interest. She worked as a research scientist at Imperial College London, University of Rome 1, and INSERM U1148 University Paris 13.

Welcome to the first issue of "Advances in Medical, Pharmaceutical and Dental Research, AMPDR", a new international, peer-reviewed journal published by the Arab Academy for Science Technology & Maritime Transport (AASTMT) Publishing Centre. The journal comprises three main sections: Medical and Clinical Research section which serves all fields of medical and clinical practice, Advanced Research in Pharmaceutical Sciences, and Experimental and Applied Dental research. Original research papers, review articles and case reports are welcomed. The journal equally encourages recommendations for special issues covering hot medical topics and findings of national and international importance.

As the title suggests, the AMPDR journal welcomes contributions from various health-related fields, but more importantly, inter- and multi- disciplinary research in these fields along with technological advances which nowadays contribute to all fields of research. Recently, AASTMT embarked on establishing faculties in various medical sciences such as Medicine, Pharmacy and Dentistry. Fortunately, this couldn't come at a better time now that the emergence of COVID-19 pandemic showcased how advances in medical research could be the center of attention worldwide. This calls for establishing AMPDR to highlight the ever-increasing demand to publish findings in different specialties related to healthcare and medical field.

Based on the growing support of the Interdisciplinary research as having as a main goal to "advance fundamental understanding or to solve problems whose solutions are beyond the scope of a single discipline or area of research practice" [1], we believe that combining and presenting contemporary research findings by different teams from different medical research interests not only give change to widen the scope of knowledge but also provides chance to integrate information, techniques, perspectives, concepts, and/or theories, for the advancement of medical practice.

AMPDR has an ultimate goal to become a major international publication hub for medical sciences. Our journal has compiled a list of renowned scientists as member of the editorial board, which contribute and enrich the journal with their vast experience in different fields of interest. As editorial team, we give special and indispensable respect to academic integrity, ethics in clinical studies to be in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki [2] and its later amendments, as well as welfare of experimental animal use in research and 3Rs (Reduce, Refine, Replace) principle [3].

By the launch of this journal, AASTMT also continues its everlasting efforts in embracing the sustainable development goals of UN,

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
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by not only promoting health and well-being, medical care, sports facilities, healthy environment, national and international cooperation in the field of health promotion and education, but also by supporting research, innovation and exchange of professional expertise in this field and present it nationally and internationally.

We are committed to make AMPDR a leading international journal in all aspects of medical fields, and we rely on our valued contributing authors, reviewers and eminent members of our editorial and advisory board. Thank you for considering AMPDR in your professional reading list and for your next contribution.

References

[01] Gohar, F., Maschmeyer, P., Mfarrej, B., Lemaire, M., Wedderburn, L. R., Roncarolo, M. G., & van Royen-Kerkhof, A. "Driving Medical Innovation Through Interdisciplinarity: Unique Opportunities and Challenges." Frontiers in medicine, 6, 35, 2019.https://doi.org/10.3389/fmed.2019.00035.

[02] Declaration of Helsinki: Medical Research Involving Human Subjects. World Medical Association.https://www.wma.net/wp-content/uploads/2018/07/DoH-Oct2008.pdf.

[03] Hubrecht, R. C., & Carter, E. "The 3Rs and Humane Experimental Technique: Implementing Change." Animals : an open access journal from MDPI, 9(10), 754, 2019. https://doi.org/10.3390/ani9100754

Prof. Senbel won the prestigious "L'Oréal-UNESCO For Women in Sciences" Fellowship prize in 2013, as well as various national and international awards during her career path. Her biography is included in "Who's Who in the World" and in "2000 Outstanding Intellectuals of the 21th Century", Cambridge, England, as well as "Women of Egypt", 2017.

She is an active member of many national and international scientific Societies such as the prestigious British Pharmacological Society (BPS), and International Society for the Study of Xenobiotics (ISSX). She is the author of more than 30 publications in international peer-reviewed journals as full-text articles and conference presentations. She is a scientific reviewer for Biovision- Bibliotheca Alexandrina, Science Technology and Development Fund (STDF), L'Oreal Unesco Young Talents Sub-Saharan Fellowship- Africa, as well as for many highly-ranked international journals.

Prof. Senbel has more than 15 years-experience in Quality Assurance, Accreditation and strategic planning in Higher Education. She held the position of Deputy Director of the Quality Assurance Center (AU) managing and auditing the implementation of highest academic (education, research and facilities) standards in all Faculties and Research Institutes of AU.

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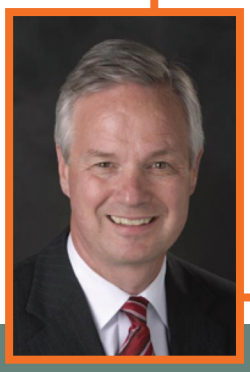
The Journey to Advanced Clinical Pharmacy Practice: Global Collaboration Will Accelerate the Pace



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Paul Bush is the Vice President for Global Resource Development and Consulting for the American Society of Health-System Pharmacists (ASHP). He has held the positions of Chief Pharmacy Officer for Duke University Hospital in Durham, NC, Director of Pharmacy Services for Medical University of South Carolina, St. John Hospital and Medical Center and Detroit Osteopathic Hospital and was Corporate Director for Clinical Pharmacy Services for Horizon Health System.

Dr. Bush received his B.S. in Pharmacy from the University of Michigan and Pharm.D. and M.B.A. from Wayne State University in Detroit, Michigan. He serves on the faculty of University of North Carolina Eschelman School of Pharmacy and Campbell University College of Pharmacy and Health Sciences. He previously served on the faculty of the Medical University of South Carolina (1999-2009) and Wayne State University (1984-1999) and served as Clinical Associate Dean for Medical Center and Health Systems for the South Carolina College of Pharmacy.

He has served as presidential officer, board member and Chair of the Board of Directors of ASHP. Dr. Bush is Past-Treasurer of the Michigan Pharmacists Association. He has served on the Michigan Society of Health System Pharmacists Board of Directors and held the position of President-elect.
He co-authored Managing and Leading – 44 Lessons Learned for Pharmacists, and chapters in Building a Successful Ambulatory Practice, Financial Management Basics for Health System Pharmacists, Handbook of Institutional Pharmacy Practice, and the Pharmacy Certified Technician Training Manual.

Dr. Bush was awarded the John W. Webb Lecture Award by Northeastern University and ASHP, an honorary Doctor of Science degree from Campbell University, the Distinguished Alumnus Award from the Wayne State University Pharmacy Alumni Association, the Dean Golod Award from MUSC Health, the Distinguished Service Award by the ASHP Section of Pharmacy Practice Managers and the NCAP Pharmacy Ambassador Award

The Arab civilization's early contribution to pharmacy was recognized in the late 700's when pharmacy attained a professional identity and independent pharmacy practice was established through the introduction of the pharmacy shop.[1] In the ninth century pharmaceutical educational was formalized in the Arab world and pharmacy achieved recognition as a profession. [1]

The pharmacist was responsible for preparing and dispensing medications based on prescriptions enhancing the safety of the medication use process. Pharmacy practice in the Arab world has continuously evolved and today there are many centers with progressive pharmacy programs with comprehensive clinical services. As an example of progress, in 2008, a clinical pharmacy program became part of pharmaceutical education in Egypt and pharmacy schools began to prepare pharmacists for clinical practice.[2]

The movement from a product orientation to a patient focused clinical role has progressed at varying paces around the globe. The model was initially described as clinical pharmacy - defined as the branch of pharmacy that involves the provision of patient care with the use of medications to optimize the health outcomes of patients. [3] In the late 1990's the term pharmaceutical care was popular and today, the model is often referred to as medication management.

The journey from a product preparation and dispensing orientation to a patient focused clinical role has occurred in the United States during my 40-year professional career. While a pharmacy student at the University of Michigan in the mid-1970s I gained practice experience at a community hospital on weekends as a pharmacy intern. Services were limited to review of new medication orders, preparation, dispensing, and provision of drug information when requested. We introduced our first clinical service, a consult-based aminoglycoside pharmacokinetic dosing service in 1980 and deployed our first clinical pharmacist to an acute care patient unit to "provide convenient and specialized pharmacy services". The pharmacist participated with the care team, provided drug information, patient drug-profile monitoring, intravenous therapy consultation, code team response, medication order review and first-dose dispensing. This is just one example of the movement toward clinical practice underway in the US at the time.

The vision of pharmacy leaders was for the pharmacy profession to provide efficient, effective, and safe medication accessibility with extensive deployment of clinically trained pharmacists working collaboratively with physicians, nurses and other clinicians to improve patient outcomes. To create momentum several consensus conferences were convened. In 1985, Directions for Clinical Practice

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
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in Pharmacy – Hilton Head Conference was convened to assess the current state of clinical practice of pharmacy, set goals and identify practical ways to advance clinical practice. Then four years later the Pharmacy in the 21st Century Conference was held. Participants examined major issues that would confront the profession in the ensuing 15-20 years and identified strategies to address opportunities and responsibilities in pharmaceutical care. The term pharmaceutical care became widely used in the 1990's and was viewed to encompass both the clinical role of the pharmacist, as well as other activities of pharmacists, including medication preparation and dispensing.

It was defined as the direct, responsible provision of medication-related care for the purpose of achieving definite outcomes that improve a patient's quality of life.[4] In 1993, more than 200 participants met in San Antonio at the ASHP Conference on Implementing Pharmaceutical Care. Participants identified critical skills needed to provide pharmaceutical care, the need for a departmental strategic plan, personal commitment of the entire pharmacy staff, and support of boards of pharmacy to enable pharmacists to provide pharmaceutical care. To support the movement, schools of pharmacy adopted the Doctor of Pharmacy curriculum, and the hospitals dramatically increased the number of post-graduate residency programs.

Significant practice changed was underway, but it became clear the "practice model" utilized in health system pharmacy would need to change for pharmacists to realize their full potential in providing direct patient care. In 2010, ASHP convened the Pharmacy Practice Model Initiative (PPMI) Summit to create passion, commitment, and action among hospital and health-system pharmacy practice leaders to significantly advance the health and well-being of patients. The objectives of the PPMI were to create a framework for the practice model, determine services, identify emerging technologies, develop a template, and identify specific actions pharmacy leaders and staff should take to implement practice model change. The PPMI stimulated the action and change needed. Many departments transitioned to an integrated practice model, pharmacists enhanced their clinical capabilities, the pharmacy technician's role expanded, and information and automation technology was adopted.

The journey continues in the US. Most health systems have adopted an integrated practice model with pharmacists deployed to patient care units or assigned to teams. Today's focus is further deployment of clinical pharmacists to additional patient care units and ambulatory clinics. The leadership and support provided by professional societies has been key to successful progress. The ASHP Practice Advancement Initiative (PAI) 2030 provides momentum and a path forward with 59 recommendations on providing optimal, safe, and effective medication use, aspirational guidance serving as a roadmap to pharmacy advancement and a future-focused set of concepts looking beyond today's barriers to change. PAI 2030 themes for practice change focus on optimizing care via pharmacist-provided comprehensive medication management, integrating the pharmacy enterprise for convenient and cost-effective care, advancing pharmacy technician roles, and adopting personalized, targeted therapies.[5]

Globally, pharmacy practice is evolving to patient focused interprofessional team-based care. The pace of change varies from region to region, but the vision of pharmacy as a clinical profession is constant. What is different today and has been a game-changer is the robust capability of willing and engaged pharmacists across the globe to communicate, share strategies and collaborate using information technology. Social media, video calls and web-based meeting capability has dramatically improved global communication and collaboration.
I have shared the journey in the US to illustrate that practice change takes time and coordinated effort. What I have described is not unique to the US and has been occurring in countries around the world. The pace of change varies from one country to the next for unique but important reasons. Pharmacy leaders across the globe can enhance the pace of change by working together to identify barriers, design solutions, and implement change.

References

[01] D. L. Cowen and W. H. Helfand, *Pharmacy: an illustrated history*. New York : Harry N. Abrams, Inc, 1990.
[02] M. M. Abdel-Latif and K. Sabra, "Clinical pharmacy practice in Egyptian hospitals." *American Journal of Hospital Pharmacy*, Vol. 73, pp. 63-66, 2016.
[03] "American College of Clinical Pharmacy. The definition of clinical pharmacy." *Pharmacotherapy*; Vol. 28, no. 6, pp. 816–817, 2008.
[04] "American Society of Hospital Pharmacists. ASHP statement on pharmaceutical care." *American Journal of Hospital Pharmacy*, Vol. 50, pp. 1720–1723, 1993.
[05] "ASHP Practice Advancement Initiative 2030: New recommendations for advancing pharmacy practice in health systems." *American Journal of Health-System Pharmacy,* Vol. 77, pp. 113– 121, 2020.

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http://dx.doi.org/10.21622/AMPDR.2021.01.1.005

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Stem Cells Era in Maxillofacial Surgery

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Prof. Amr Bayoumi is currently: - Professor and Consultant of Oral and Maxillofacial Surgery, Faculty of Dentistry, Alexandria University, Egypt, and King Abdulaziz University, KSA.

Education:

Undergraduate:

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Post graduate:

- Master's degree in Oral and Maxillofacial Surgery with a "very good" grade, Alexandria University (1988).

- Ph.D. in Oral and Maxillofacial Surgery, Alexandria University (1991)

- Completed a course in Oral and Maxillofacial Radiology provided by the British government in King's College, London University, London, 1989, and a clinical training course of Oral & Maxillofacial surgery provided by Mount Vernon hospital, London, England.

Stem cells provide a new era for oral and maxillofacial surgery and reconstruction. Stem cells are colonlogic cells that have the ability to renew themselves and form various predecessors. They are found in common tissues used for wound healing and recovery after injuries. Large numbers of these cells are known to be instantly accessible; no immunological denial or rejection; do not have host disease against graft; Tumorigenesis do not occur; but there are some small ethical problems; The predictable differentiation potential for tissue separation and integration is not surprising.

There are two basic types of stem cells, depending on their origin:
• Embryonic Stem Cells (ESCs): ESCs are initiated by a fetus that has been fertilized in an in vitro fertilization clinic (100,200 organized cell blastocysts). They are called a pluripotent cell population and are characterized by the ability to maintain the karyotype. ESCs can be divided into the three embryonic cotyledons (ectoderm, endoderm, and mesoderm); and in a culture; they form in colonies. These important highlights make ESCs affordable for future use in regenerative medicine and pharmaceuticals. Still; ethical discussions about the use of human embryos cannot be decided entirely; because in addition to scientific and practical questions, it is also dealt with through religious laws and philosophical reflections on the nature of human life.

• Adult stem cells: Adult stem cells are found in fetal and postnatal tissues; They are more specialized (multipotent) cells that participate in the repair and restoration of tissues, as well as in the maturation and aging processes. There are numerous sources of adult stem cells such as bone marrow (BMMSC); Adipose tissue (ATMSCs); Liver; Umbilical cord; and muscles. The intraoral sources are the dental pulp; The periodontal ligaments can also be a source of adult stem cells.

Fat and bone marrow stem cells are successful and are produced in the context of restorative work and aesthetics. However, ATMSCs have been less easily obtained without harmful effects on patients. Adipose tissue contains a population of mesenchymal stem cells that can be isolated and differentiated into various cell lines, including osteocytes; Fat cells; and myocytes depending on the culture conditions. These cells are called adipose derived stem cells (ASC).

The question arises here is: what do stem cells do? And the answer is so simple when you know that 10 million cells in your body die every minute every day and your own stem cells replace them so you can continue living.

Both undifferentiated ATMSC and BMMSC have osteogenic; chondrogenic and lipogenic differentiation potential. Both produce markers that help repair the deformity and have the same morphology; spindle shaped cells. Both appeared to work positively when used in reconstructive treatments. There are some contrasts between them; but the main imperative is; the ease of collection and the lower morbidity on the part of the donor. These two variables were extremely critical and favor the choice between fat and bone

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2021.01.1.005

marrow for repair. ATMSCs and BMMSCs may be suitable replacements for the traditional intrusive method in the future. A better understanding of stem cell types, different platforms, and the influence of developmental components on the tissue design of different scaffolds, and how growth factors affect the tissue engineering pathway, opens opportunities to monitor recovery of bones and soft defects in the future, thus providing an alternative and innovative treatment for patients with soft / hard tissue defects.

- Lectured in many national & international scientific meetings.
- Published 43 articles in peer reviewed and international journals.
- Member of the IADR.
- Member of the Egyptian Society of Oral and Maxillofacial Surgery.
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  1-The journal of Oral and Maxillofacial surgery: clinics in Surgery.
  2- The International journal of Dentistry and oral science.
  3-The world journal of surgery and surgical research.
- Reviewer for the International journal of Dentistry and Oral Health.
- Reviewer for the Alexandria Dental Journal.
- Reviewer for the Saudi medical Journal.
- Reviewer for the Annals of Maxillofacial Surgery.

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2021.01.1.007

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Inhalable nano-embedded microspheres as an emerging way for local treatment of lung carcinoma: Benefits, Methods of preparation & characterizaton

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Received on, 28 October 2021 - Accepted on, 1 December 2021 - Published on, 16 December 2021

Abstract:

Lung cancer is the leading cause of cancer deaths worldwide, and this makes it an attractive disease to review and possibly improve therapeutic treatment options. The extreme lethality of lung cancer is ascribed to the lack of early diagnostic strategies as in almost 50 % of the cases the disease is confirmed in stage IV, leaving low chance of survival. The inaccessibility to the deeper portions of the lung for conventional therapy further adds up to the complication in the treatment process. Surgery, radiation, chemotherapy, targeted treatments, and immunotherapy separate or in combination are commonly used to treat lung cancer. However, these treatment types may cause different side effects, and chemotherapy-based regimens appear to have reached a therapeutic plateau. Hence, effective, better-tolerated treatments are needed to address and hopefully overcome this conundrum. Nanocarriers through inhalational route offer many advantages like; 1) they achieve uniform distribution of drug among the alveoli, 2) better solubilization of the drug, 3) sustained drug release which subsequently decreases dosing frequency, 4) better patient compliance, 5) lesser side effects, and 6) improved drug internalization to the cells. Therefore, targeted inhalable NP delivery to the lungs is a potential area of research in cancer nanotechnology that catches the attention of many formulation scientists, oncologists, and biomedical researchers. Based on this literature review, we will discuss the development, characterization, and benefits of inhalable nanocarriers for local treatment of lung carcinoma.

Key words: *Nanocarriers- lung carcinoma- microparticles*

1. INTRODUCTION

1.1. Incidence and etiology of lung cancer

Lung cancer now accounts for 23% of all cancer-related deaths globally, outnumbering the combined deaths from breast, colon, and prostate cancer [1,2]. It can start in the cells lining the bronchi and parts of the lung such as the bronchioles or alveoli. Further, it is thought to start as areas of pre-cancerous changes in the lung.

1.2. Different categories of lung cancer

Lung cancer is mainly categorized into two forms; namely non-small-cell lung carcinoma (NSCLC) (the most frequent kind of lung cancer, accounting for 85 percent of cases) and small-cell lung carcinoma (SCLC)[3]. NSCLC is further categorized as epidermoid, large cell, bronchoalveolar, adenocarcinoma, and squamous cell carcinoma [2]. These NSCLC forms are histologically distinct from each other. It responds to the chemotherapy; but, their response varies according to treatment protocol. On the other hand, SCLC rarely occurs but shows fast metastasis and aggressive growth, with average survival of merely 4 months if not treated [4].

1.3. Conventional ways for lung cancer treatment

Till date, chemotherapy, radiotherapy, and/or invasive surgical procedures have been the most common modalities of cancer treatment. Such conventional therapy, does not distinguish between cancer and healthy cells, resulting in significant side effects as well as a poor tumour response to treatment due to nonspecific bioavailability of the administered anticancer agent. Thus, the lack of efficacy of intravenous chemotherapy against lung tumors results from a combination of (usually) late diagnosis, and inadequate drug access to lung tissue following intravenous administration [5]. Despite the introduction of targeted and tailored therapies to patients according to individual biological tumor characteristics, the overall survival rates have failed to meet the expected progression-free survival or overall survival[6]. Moreover, acquired resistance to cytotoxic agents has been observed, mainly involving the apoptotic mechanism in NSCLC cell lines[7]. In SCLC, acquired resistance has been observed and five-year survival remains less than 10 %, despite the use of various drug combinations. Therefore, novel therapies are in great demand.

Thus, the complete eradication of lung cancer requires a new approach such as utility of nano-scale materials. It is by the virtue of nanoscale dimension of lung cancer therapeutic and/or diagnostic system that they are capable of effectively transcending bronchial epithelium

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2021.01.1.007

barrier and accumulating in deep lung regions. Some of such nanoscale formulations that have given promising results include nanogels or nano-sprays which are intratracheally administered into the lungs, and the results have confirmed that intratracheal means of drug delivery for lung cancer therapy are much better than the parenteral route [8]. In one such approach, inhalable deoxycholic acid-modified glycol chitosan (DOCA-GC) nanogels containing palmityl acylated exendin-4 (Ex4-C16) were synthesized for treatment of hyperglycemia.

The therapeutic efficacy of this nanogel formulation was monitored in type 2 diabetic db/db mice, and the cytotoxicity associated with them was established by using A549 and Calu-3 cell lines. The use of chitosan-based nanogels for pulmonary delivery did not instigate any immune response and prolonged hyperglycemic effect even at lower concentration of drug. This work established the possibility of using such nanogel-based pulmonary delivery system for delivery of anticancer drugs specifically to lung cancer cells [9,10].

1.4. Emerging applications of nanoparticles for lung cancer diagnosis and therapy

Since, nanoparticles (NPs) have attractive characteristics like small particle size, large surface area, and the capability of tailoring their surface properties, they therefore have several advantages over other delivery systems[11]. Additionally, it has been proven that NP-based drug delivery systems assure passive (size-based targeting due to their size up to ~100 nm) as well active targeting (surface functionalization by targeting ligand) and enhanced therapeutic efficacy of anticancer agents [12].

The applications of these nanoparticles in cancer therapies have been effective to a great extent owing to their inherent small dimensions which enable them to specifically accumulate in tumor cells as they permeate through the leaky vasculature in the vicinity of tumor cell mass (enhanced permeability and retention effect, EPR).

The poorly developed lymphatic drainage also contributes indirectly to NP accumulation at the site of the tumor. Another benefit of nanoscale systems is that they may efficiently overcome kidney clearance and thus give adequate blood circulation time for the drugs they transport. In other words, NPs can limit the biodistribution profile of anticancer medications and focus them to tumour areas, increasing therapeutic efficiency and lowering nonspecific toxicity [11].

2. Local versus systemic treatment of lung carcinoma

The majority of chemotherapeutics come in intravenous (iv) forms. Furthermore, some important chemotherapeutics used to treat lung malignancies are extremely lipophilic, necessitating greater doses and/or surfactant-based solubilization to improve systemic drug availability. In addition, oral administration of cancer chemotherapeutics is often limited due to first-pass metabolism [13]. However, systemic drug bioavailability is not the only concern here, as even at higher dose or systemic availability, only limited quantity of drugs is delivered to lung tumor. The majority of chemotherapeutics act on normal tissues due to their non-targeting nature, causing side effects. Nevertheless, drugs already being used for systemic administration have been successfully administered regionally in various types of cancer. The concept of local drug delivery is proposed as a method for delivering high drug concentrations to the target site while preventing exposure of vital organs to toxic drug concentrations in the systemic circulation. In this way, local delivery can play an important role in safer chemotherapy with better patient compliance and minimized systemic side effects. The respiratory system has a large surface area, thin alveolar epithelium, rapid absorption, lack of first-pass metabolism, high bioavailability, and the capacity to absorb large quantities of drug, making it an optimal route of drug administration. In addition, it is considered as a needle-free approach that offer better comfort to the subjects [13].

3. Targeted inhalable nanoparticle for lung carcinoma

Pulmonary delivery via inhalation is a common technique of drug administration to patients with a variety of lung diseases. But the airway geometry of the lungs poses a challenge for delivery into the alveoli [14,15]. However, delivery of individual nanoparticles to the lungs appears to be a problematic, as due to their small sizes ($< 1\mu m$) which increased their probability of exhalation before deposition [16].

Therefore, to successfully deliver nanoparticles by inhalation, they first have to be transformed into micro-scale nanocomposite structures having theoretical aerodynamic diameter between 1 and $5\mu m$ [17]. There are three clinically successful pulmonary inhalation pharmaceutical dosage forms based on device classes; namely, nebulizers (Nebs), pressurized metered dose inhalers (PMDIs) and dry powder inhalers (DPIs). DPIs are breath-actuated devices that deliver a dry powder drug through shear-induced aerosolization. They may contain respirable powdered drugs alone or blended with non- respirable carriers.

DPIs offer many advantages including high encapsulating ability, long term stability, no coordination of actuation and inhalation, no liquid propellant, an extended release profile, improved tolerability, reduced toxicity, easy to use and non-invasiveness. Based on the mechanisms of particle dispersion and aerosolization, the DPI devices are further categorized as passive or active devices. DPI is a rapidly growing sector of the pulmonary inhalation pharmaceutical market which is evident by the increasing number of successful products in the market. DPIs have two potential problems concerning relatively low fine particle fraction (FPF) and emitted dose (ED) which can be attributed to insufficient particle dispersion by the patient or DPI device, aerosol dispersion inefficiency, or the powder formulation itself [15].

Over the past decade, a new direction in nanotechnology has been raised to focus on targeting to lung diseases including cancer. The focus is to combine the nanotechnology-based therapeutic delivery with pulmonary/ inhalational route of administration. This strategy has been encouraged due to the possible usefulness of lung as a portal for drug entrance, including peptides and proteins. The lungs are well-organized entrance for drugs to the bloodstream as they have large surface area for absorption (~100 m2), with very thin absorption membrane (0.1–0.2 μm). Furthermore, the lungs show comparatively lesser local metabolic activity, and unlike the oral route of drug administration, pulmonary/ inhalation route is not vulnerable to first-pass metabolism [18].

Nanocarriers through inhalational route offer many advantages like; 1) they achieve uniform distribution of drug among the alveoli, 2) better solubilization of the drug, 3) sustained drug release which subsequently decreases dosing frequency, 4) better patient compliance, 5) lesser side effects, and 6) improved drug internalization to the cells [11]. Therefore, targeted inhalable NP delivery to the lungs is a potential area of research in cancer nanotechnology that catches the attention of many formulation scientists, oncologists, and biomedical researchers. Here, we discuss the challenges in delivery of chemotherapeutics to lung cancer, the significance of applying inhalable NPs in lungs cancer drug targeting, and the concern of toxicity in using this approach. Nevertheless, to our knowledge there is no approved inhalation product for local treatment of lung cancer yet available in the international market.

4. Dry powder inhalers and nanoparticulate powders for inhalation

Nanoparticles are considered to be promising carriers for pulmonary drug delivery. The differences between microparticles and nanoparticles extend beyond just the size, having larger surface area to volume ratios. Nanoparticles can have a higher drug loading capacity, using less polymers, better cross permeability barriers, increased cellular uptake, longer lung retention and in airway nanoparticles have better chances of mucus penetration [14]. This improves dissolution properties where decreasing the particle size increases the solubility and intracellular drug delivery potential.

Studies have also demonstrated that particles with decreased size are better internalized by cells. Microspheres or in another term nanocomposite particles consist of drug-loaded nanoparticles and excipients. Nanoparticles are combined with a matrix to form micro-size particles, the 3μm size of which is the most effective to deposit deeply into the lung site. Upon deposition in the lung and exposure to the humid environment and the lung lining fluid, the matrix dissolves and readily decomposes into primary drug-loaded nanoparticles in the surface layer of alveoli as shown in Figure 1 [14].

Nanoparticles can escape mucociliary clearance and recognition of alveolar macrophages. Therefore, after depositing to the surface layer of the alveoli, drug-loaded nanoparticles will immigrate near the epithelial cells and be taken up by them. Yang et al.[19], successfully formulated a salmon calcitonin adsorbed polymeric PLGA nanospheres which was coated onto a lactose carrier to form nanocomposites. The nanocomposite particles had efficient lung deposition and a rapid release of salmon calcitonin occurred. Another interesting aspect was explored by *Yang et al*.[17], who developed DPI formulation of hybrid nanoparticles composed of PLGA and soybean lecithin as the polymer and lipid constituents, respectively. The hybrid nanoparticles are transformed into inhalable micro-scale nanocomposite structures by a novel technique based on electrostatically-driven adsorption of nanoparticles onto the polysaccharide chitosan carrier particles.

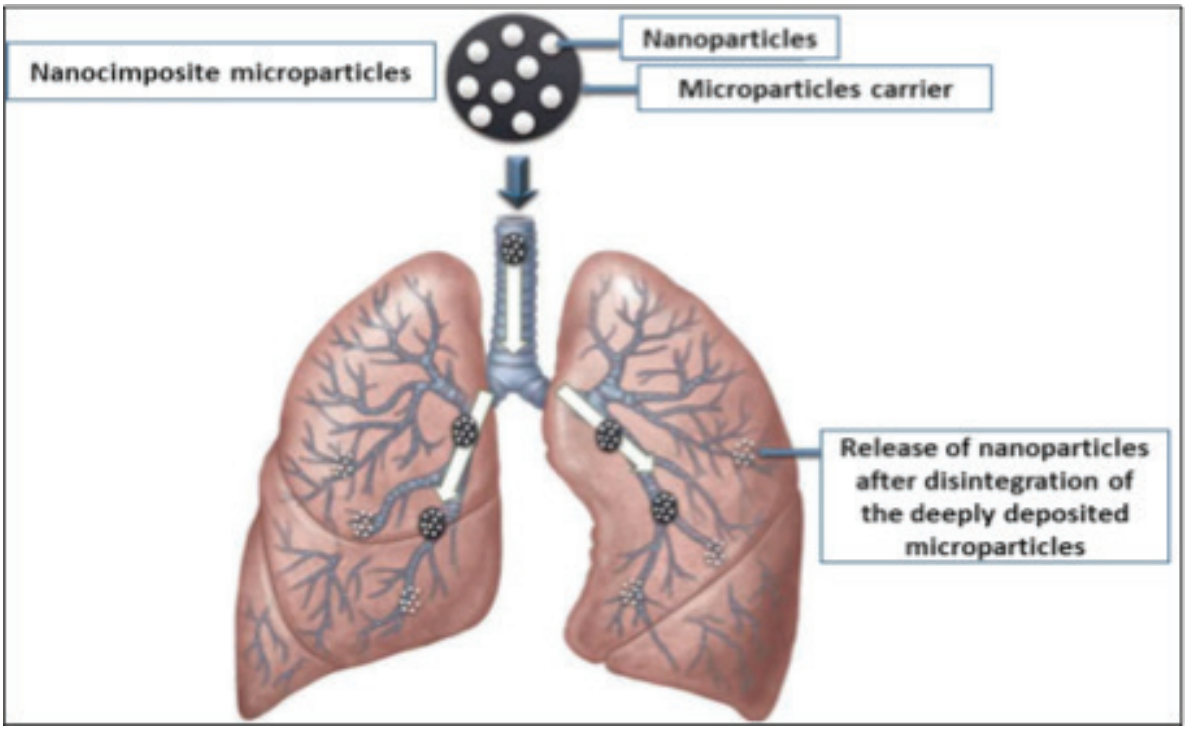

Figure 1: Decomposition of nanocomposite microparticles into primary nanoparticles upon administration [14] .

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http://dx.doi.org/10.21622/AMPDR.2021.01.1.007

4.1. Engineering of nanocomposite powders for inhalation as DPIs

Particles with aerodynamic diameters ranging from 1-5 μm are optimal for lung deposition. The complex nature of interparticulate interactions on the low micron-sized scale, together with the extensive application of dry powder formulations and the specific of aerodynamic behavior within the inhaler device and the respiratory system, have hindered the development of such a dosage form. The pharmaceutical industry has adopted a variety of techniques to incorporate desirable characteristics into inhalable multiparticulate systems, including narrow particle-size distribution, improved dispersibility, enhanced drug stability, optimized bioavailability, sustained release and/ or precise targeting [20]. The most sophisticated and advanced manufacturing technologies utilized are:

4.1.1. Milling process

Milling is a common pharmaceutical processing procedure for reducing primary particle size and producing a dry powder with the desired particle size range [21]. Vibration milling, ball milling and, in particular, jet-milling (fluid energy) are well-established and well validated techniques used to manufacture dry powders for inhalation. A ball mill is essentially a rotating cylinder loaded with a drug and the "milling media" (i.e., balls that grind the drug between each other as they tumble inside the mill). Ball milling is time consuming and poorly scalable process. On the other hand, jet milling is the most widely used method for producing respirable aerosol particles in the solid-state. The basic procedure of jet-milling is to grind a bulk crystallized particles into small particles by one of the following mechanical forces: pressure, friction, attrition, impact, or shear. Particles with diameters down to approximately 1 μm can be produced using this technique. Although no approved inhaled drugs have been produced from the milling process to date, the process has been explored with several inhaled drugs, including beclomethasone dipropionate, fluticasone propionate and ciclosonide [22]. In a recent study conducted by Onoue *et al.*[23], tranilast, an anti-allergic agent was prepared as a nanocrystal solid dispersion which was freeze dried. The resulting solid-state particles were micronized by gas-jet milling to render them into the respirable size range and blended with large (50 μm) non-respirable lactose monohydrate carrier particles. These particles produced dry powder inhalation aerosols with 97.9% emitted dose (ED) and 59.4% fine particle fraction (FPF) values. The in *vivo* characteristics showed a notable anti-inflammatory performance of the formulation.

4.1.2. Spray drying

Spray drying is a pharmaceutical manufacturing process used to efficiently produce respirable colloidal particles in the solid-state. In this process, the drug solution or suspension is introduced at a high pressure via an atomizing nozzle with spray-air into a heated chamber where, the solvent evaporates and the solid dries out followed by separation of the particles using a cyclone separator. Compared to milling, spray drying produces more spherical particles. Such particles are characterized by a lower area of contact and smaller, more homogeneous particle-size distribution that results in a higher respirable fraction than mechanically micronized drugs. Nevertheless, particles from spray drying process are not always spherical and may have convoluted surfaces, holes and voids [24]. In fact, the shape is influenced by the drying rate, surface tension and viscosity of the liquid. One of the principal purposes of aerosolizing spray- dried powders is to achieve particle diameters of several micrometers with a narrow particle size distribution. This ensures, assuming an appropriate aerodynamic diameter, a maximum deposition of the embedded drug in the tracheo-bronchial and deep alveoli regions at normal inhalation rates [25]. The principal advantages of spray drying with respect to pulmonary drug delivery are the ability to manipulate and control a variety of parameters such as solvent composition, solute concentration, solution and gas feed rate, temperature and relative humidity and droplet size. This allows optimization of particle characteristics namely; size, size distribution, morphology and density, in addition to macroscopic powder properties such as bulk density, flowability and dispersibility. Moreover, spray dryers are available at different production scales and industrial scale up is easy. However, degradation during the spray drying process may be a problem for some macromolecules as a result of a number of factors such as thermal stress during droplet drying, high shear stress in the nozzle and peptide/ protein adsorption at the greatly expanded liquid/air interface of the spray solution [25].

4.1.3. Spray-freeze drying

Spray freeze drying is an advanced particle engineering method which combines spray drying and freeze-drying processing steps. This technique involves the atomization of an aqueous drug solution into a spray chamber filled with a cryogenic liquid (liquid nitrogen) or halocarbon refrigerant such as chlorofluorocarbon or fluorocarbon [26]. Since the normal boiling point for such a liquid is very low, the droplets are quickly frozen. Lyophilizing these frozen droplets results in porous spherical particles suitable for inhalation. Cheow *et al.*[27], prepared spray freeze dried poly-caprolactone nanoparticles containing levofloxacin. This method produced inhalable particles with low density, smooth surface morphology and good aqueous redispersibility. Furthermore, they proved that polyvinyl alcohol and mannitol as suitable adjuvants can be processed with spray freeze drying. Unlike spray drying, spray freeze drying is conducted at sub ambient temperature, and has, therefore, been used to formulate a significant number of thermolabile and highly potent therapeutic proteins/ peptides into dry powder inhalation products[27]. Wang et al.[28], performed comparative studies of employing spray drying and spray freeze drying to produce inhalable dry powder form of levofloxacin-loaded lipid/ polymer hybrid nanoparticles. Results showed the superiority of spray freeze drying over spray drying technique as it produces nano- aggregates of larger aerodynamic diameter resulting in easier physical handling, higher yield and reconstitutibility, better flowability, as well as higher ED and FPF. However, spray freeze drying is not as commonly used as spray drying due to complexity, time consuming and cost involved.

4.1.4. Supercritical fluid technology

Supercritical fluids are known as compressed gases or liquids above their critical pressures and temperatures, which possess several fundamental advantages as solvents or non-solvents for pharmaceutical manufacturing. Carbon dioxide is the most commonly used solvent in this technology. The three main supercritical fluid processes are precipitation from supercritical solutions composed of supercritical fluid and solutions, precipitation from gas saturated solutions and precipitation from saturated solutions using supercritical fluid as antisolvent. All three techniques allow production of inhalable particles with a narrow particle size distribution and less charge which allows them to flow more freely and to be more easily dispersed following discharge from a DPI. Despite its potential, supercritical fluid is still an emerging technology that is not much exploited in DPI products because of complicated and expensive high-pressure equipment, low solubility of many pharmaceutical compounds in CO^2 and a lack of experience on scaling-up problems [24].

4.2. Excipients in Dry Powder Inhalers

In general, excipients are used to enhance the physical or chemical stability of the active pharmaceutical ingredient, its mechanical and pharmaceutical properties such as dissolution and permeation. In fact, excipients are inactive ingredients that are intentionally added to therapeutic products to improve their delivery or efficacy [18]. The FDA favors the use of commercially established excipients as well as "generally recognized as safe" (GRAS) substances. It should be noted that the current excipients approved for respiratory drug delivery are very limited in number (Table 1).

Table 1:
List of accepted or interesting additives for DPI formulations [18]. Excipients Description Status

Sugars • **Lactose** • **Glucose** • **Mannitol** • **Trehalose**	Coarse/fine carrier	• Approved and commonly used • Approved (Bronchodual®)** • Approved (Exubera®)** • Promising alternative
Hydrophobic additives • **Magnesium stearate**	Protection from moisture	• Approved (SkyeProtect)**
Lipids • **DPPC*,DSPC*, DMPC*, cholesterol**	Used in liposomes, matrix, coating	Biocompatible and biodegradable, very interesting excipients
Amino acids • **Leucine, trileucine**	Improved aerosol efficiency	Endogenous substance but no data on lung toxicity
Surfactants • **Poloxamer** • **Bile salts**	Production of light and porous particles	• May not be pro-inflammatory at low dose. • Endogenous substances, may be accepted but at low dose (2–5%, w/w).
Absorption enhancers • **Chitosan, trimethylchitosan** • **Hydroxypropylated-β- CD*, natural-γ- CD**	Absorption for proteins & peptides	• Pro-inflammatory effect observed • Promising results
Biodegradable polymers • **PLGA***	Used in sustained release formulations	• Immunogenicity effect observed

***DPPC**; Dipalmitoyl phosphatidyl-choline, **DSPC**; Distearoyl phosphatidyl-choline **DMPC**; Dimyristoyl phosphatidyl-choline, **CD**; Cyclodextrin, **PLGA**; Poly-lactic-co-glycolic acid.
****Examples of marketed products containing approved excipients.**

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
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5. Models for studying deposition patterns of inhaled therapeutics

It is important to study the patterns of deposition of microparticles upon pulmonary administration. Some models are attempted to simulate the lung airway structure and have routinely been used to determine the particle deposition patterns in laboratory setup [29]. Lung cast models have long been used for long time to study various characteristics of the lungs. Lung cast models of human, rat, hamster, monkey and dog have been developed using various materials including rubber, resin, metal, alloy and wax. However, because of the higher degree of complexity and the lack of expertise required for those models, they are not widely used. Impactors, including twin-stage impinger, multi-stage liquid impinger, Andersen cascade impactor and next generation impactor are the most widely used instruments to measure the size and the deposition patterns of particulate formulations delivered via the pulmonary route. However, impactors are not considered as *in vitro* simulators of lungs, chiefly, due to the discrepancy in the flow rate when compared with that of a functional lung. It is important to keep in mind that the impactor operates at constant flow rate but human lungs have a varying flow rate originating from the breathing cycle [29].

Nevertheless, impactors comprised of different number of stages that are constructed in a pattern such that larger particles having sufficient inertia will impact upon particular stage collection plate as the aerosol stream passes through, whereas relatively smaller particles with insufficient inertia will be carried in the air stream and pass to the next impaction stage [30] (Figure 2).

Thus, impactors can provide useful information regarding particle size on the basis of aerodynamic diameter and can predict the deposition patterns of particulate drug carriers in the respiratory tract. Impactors are useful in predicting *in vivo* deposition of particles, and hence are important tools in the development and quality control of new pharmaceutical products. However, these methods have some limitations as they do not adequately mimic the upper and lower respiratory tracts [31]. An approach to resolve this problem could be capturing images of particulate drug carriers *in vivo* by means of various methodologies such as gamma scintigraphy, single photon emission computed tomography, positron emission tomography, magnetic resonance image and fluorescence imaging [29]. Currently used *in vivo* imaging techniques can measure total lung deposition and oropharyngeal deposition of particles directly by using radionuclides, non- ionizable radiation and fluorescent dyes [32]. Deposition patterns can be examined directly by taking images of lungs or by autoradiography after sacrificing and dissection of animal lungs.

Overall, the use of *in vivo* imaging techniques is beneficial over *in vitro* techniques as they can provide an actual picture of regional deposition of particles in the lungs. Moreover, these techniques can be used to evaluate both qualitative and quantitative aspects of particle deposition in the lungs and can be a useful means to understand the relation between deposition of drugs in the lungs and their clinical effects. However, these techniques have some drawbacks including high cost, higher radiation doses, safety hazards, and specialized training required in handling of radio- labelled isotopes.

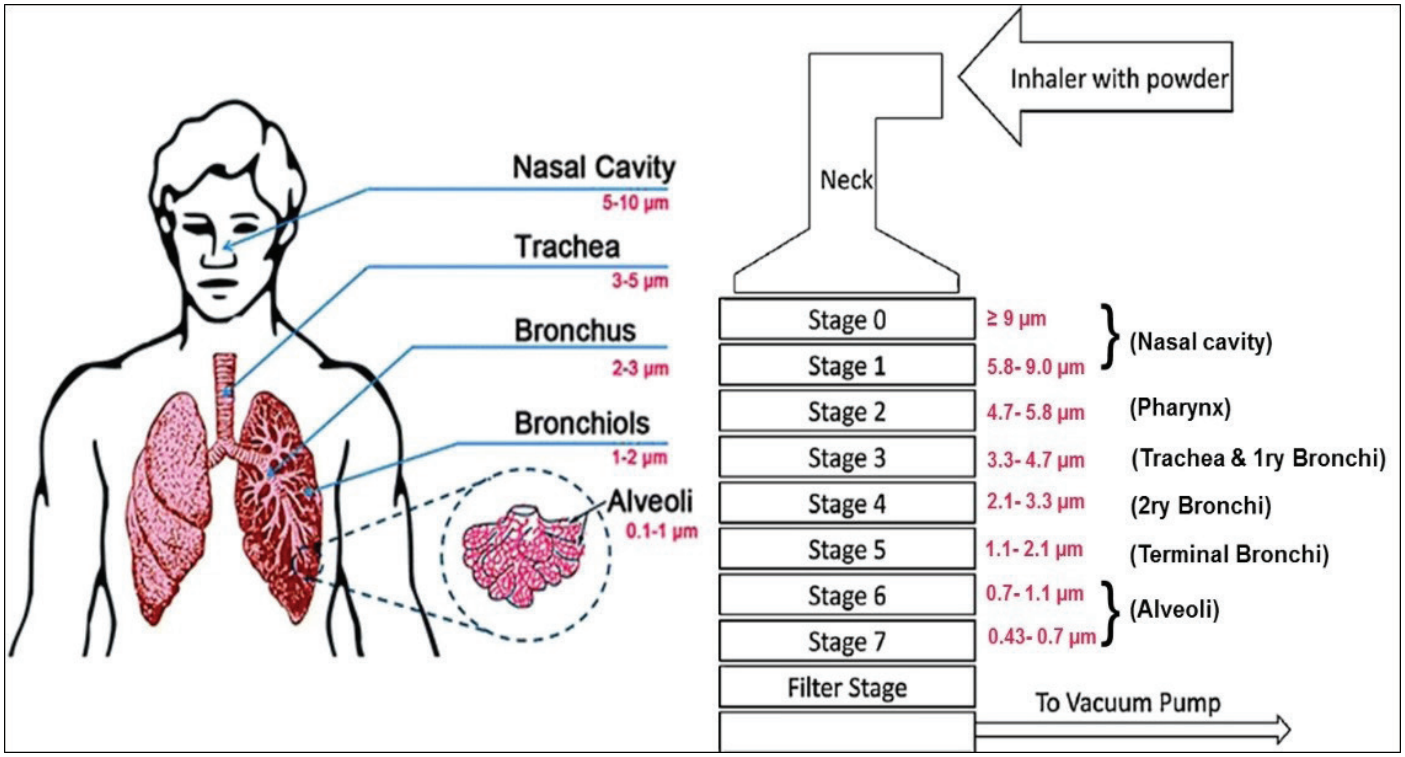

Figure 2: Schematic presentation showing particle deposition using Andresen cascade impactor (ACI) according to MMAD in comparison to real particle deposition.

6. Models to study drug absorption following pulmonary administration

The absorption profiles of drugs administered via the pulmonary route are evaluated for both locally and systematically acting drugs. For locally acting drugs, pulmonary absorption profiles are determined to assess the amount of drug that is likely to enter the systemic circulation. Pulmonary absorption profiles also give information regarding the amount of drug that would be available locally to produce therapeutic effect in the lungs and overall systemic exposure of the drug.

6.1. *In vitro* cell culture models

In vitro cell culture models have been used extensively to study the uptake, transport and metabolism of drugs by the lungs as they mimic microenvironment of the tissue [15]. The cell lines used include A549, HBE14o and the Calu-3 line. A549 cell line represents the alveolar type II pulmonary epithelial cell, and has been reported to be an ideal model to study the metabolic and macromolecular mechanisms of drug delivery at the alveolar pulmonary epithelium due to the endocytic ability of the pulmonary epithelium and localization of cytochrome P450 systems. Calu-3 and HBE14o model the upper airways (bronchi) which have been utilized extensively in the literatures. For example, the permeability data of small lipophilic molecule (e.g. testosterone) and high molecular weight substance (e.g. fluorescein isothiocyanate-transferrin) across Calu-3 cell line has been examined [33]. The authors demonstrated that this cell line is useful for studying the contributions of bronchial epithelial cells to the mechanism of drug delivery at the respiratory epithelium. Similar conclusions were drawn when the apparent permeability of the glucocorticosteroid budesonide and fluticasone propionate was investigated [34]. However, the main drawbacks of cell culture models are time- consuming isolation and cultivation as well as limited cell lifespan.

6.2. *Ex vivo* tissue models

Ex vivo tissue models are isolated perfused tissue models, which allow studying the mechanism of drug transport, deposition and efficacy in the isolated organ while maintaining its structural and functional integrity [8]. Isolated perfused tissue models provide a more realistic correlation with the *in vivo* studies compared to the single cell monolayer models. They have been developed for rodents such as rats and rabbits, while attempts have also been made to establish human lung perfusion models. The isolated perfused rat lung model has been used for studying absorption and deposition of inhaled pharmaceutical formulations (Figure 3).

This method involves surgical removal of the lung and placing it in an artificial thoracic chamber supplied with atmospheric air and perfusion media. The surgical procedure for isolation of the lungs is fairly complex and requires an extra caution to prevent any tissue damage. Following surgery, drug or formulations can be administered either in perfusate or directly into the lungs using suitable delivery devices in order to evaluate various pharmacokinetic parameters without the influence of the whole body. Following drug administration, continuous sampling is possible from the perfusate outlet from the lungs. This method allows regulation of lung volume, ventilation rates and respiratory patterns [35]. However, there are several limitations associated with isolated perfused lung models. One of the main concerns is the viability of tissues over a period of time. Keeping the lungs viable for more than 2–3 h at 37 °C has been quite challenging, chiefly due to edema formation.

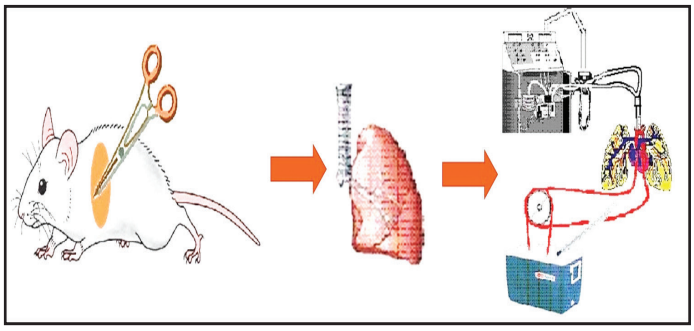

Figure 3: Steps of Ex vivo study on isolated perfused lung models in rats.

6.3. *In vivo* animal models

In vivo intact animal models are mainly used for studying the absorption, distribution and pharmacodynamics of inhaled pharmaceuticals. In earlier methods, the drug was administered to the lungs using an intratracheal tube after surgical exposure of the trachea (Figure 4). However, the proposed method required destructive tissue sampling for each time point which was considered as major limitations for studying pharmacokinetics in intact animals [36]. Recently, this method has largely been replaced by a non-invasive method that uses aerosolizers or insufflators for small animals. For administration of drugs using these devices, the trachea of anesthetized animals is visualized by using a small animal laryngoscope for inserting dry powder insufflator inside the trachea. Drug is spray-instilled into the lungs by pushing the syringe plunger of the device. These devices can deliver liquid or powder in the form of aerosolized droplets or particles to ensure deep lung deposition [37].

In this method, blood sampling is performed by means of surgical catheterization or tail vein without sacrificing animals. However, non-invasive intratracheal administration suffers from a number of limitations. This method does not reflect normal physiological conditions because drugs are administered to anesthetized animals. Moreover, as this method uses anesthetized animals, multiple dosing is not recommended and repeated insertion of inhalation device may cause injury of the trachea. Limitations of direct administration of drugs to anesthetized animals can be overcome by using passive administration chambers such as whole body, nose only and head only exposure chambers. These chambers allow administration of drugs directly to conscious animals thus mimicking a more physiological condition [38]. The difference between 3 models to study drug absorption *in vivo* is shown in Figure 5.

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2021.01.1.007

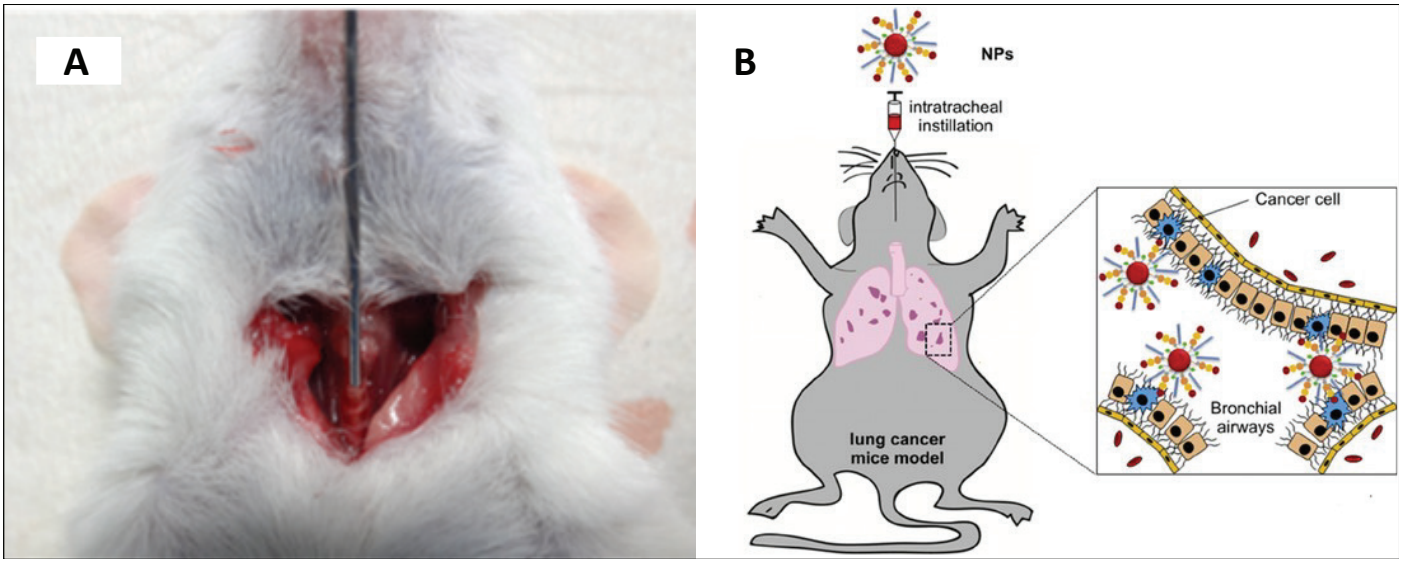

Figure 4: Intratracheal instillation of NPs for local treatment of lung cancer in mice model [39].

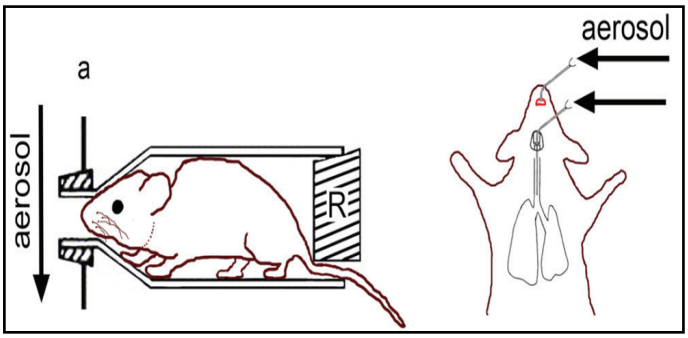

Figure 5: Exposure of rodents to aerosols with 3 different models. A) Intratracheal instillation, B) Oropharyngeal aspiration using insufflators and C) Passive administration chamber with nose-only exposure [40].

Conclusion:

Cancer is a leading cause of death worldwide. Lung, female breast, colorectal and stomach cancers accounted for more than 40% of cancer cases diagnosed worldwide; with the World Health Organization reporting an estimated 14.1 million new cancer cases worldwide in 2012. Among them, lung cancer is one of the most common, with 16.7% of all new cases diagnosed in men. Lung cancer is the most common cause of cancer-related death for men and women and the financial burden to the healthcare system is estimated at >100 million dollars annually in Australia. Notably, lung cancer has the highest mortality rate of all common cancers and a miserable dismal rate of less than 5 years. Out of the 8.2 million deaths caused by cancer in 2011 globally, mortality from lung cancers contributed the highest, with 1.3 million deaths alone.

Surgery, chemotherapy and radiation are standard treatment options for lung cancer depending on the stage of malignancy, resectability and overall performance. Chemotherapy is a first-line treatment for advanced stage of lung cancer in which chemotherapeutic drugs are usually administered intravenously for systemic circulation. The use of chemotherapeutic drug is based on the principle of toxic compounds to inhibit the proliferation of cells growing at an abnormal rate. However, it should be noted that the majority of chemotherapeutic drugs is associated with side effects such as pain, nerve damage and skin allergic reactions. Therefore, minimizing the side effects of chemotherapy drugs remains a challenge in the field of cancer chemotherapy. Lung offers numerous advantages as a delivery route for noninvasive drugs for localized therapy of lung cancer. Compared to other delivery methods such as oral or intravenous injection, it is envisaged that the bioavailability of drugs in lung could be enhanced using pulmonary delivery since lung possesses limited intracellular and extracellular drug metabolizing enzyme activities unlike gastrointestinal tract and liver. On top of that, this option also reduces non-reversible tissue damage caused by drugs' cytotoxicity. In addition, higher absorption rate, reduced drug doses and rapid onset of action are among the advantages of pulmonary administration.

References:

[01] Conway EM, Pikor LA, Kung SH, Hamilton MJ, Lam S, Lam WL, Bennewith KL. "Macrophages, inflammation, and lung cancer." American journal of respiratory and critical care medicine. vol. 193, issue, 2, pp. 116-130, Jan 2016.

[02] Ramalingam SS, Owonikoko TK, Khuri FR. "Lung cancer: New biological insights and recent therapeutic advances." CA: A Cancer Journal for Clinicians, vol. 61, issue 2, pp. 91-112, Feb 2011.

[03] Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. "Global cancer statistics." CA: A Cancer Journal for Clinicians, vol. 61, issue 2, pp. 69–90, Feb 2011.

[04] Ahmad J, Akhter S, Rizwanullah M, Amin S, Rahman M, Ahmad MZ, et al. "Nanotechnology-based inhalation treatments for lung cancer: State of the art." Nanotechnology, Science and Applications, vol. 8, pp. 55-66, Nov 2015.

[05] Wauthoz N, Rosière R, Amighi K. "Inhaled cytotoxic chemotherapy: Clinical challenges, recent developments, and future prospects." Expert opinion on drug delivery, vol. 18, issue 3, pp. 333-354, Mar 2021.

[06] Kang J-H, Song K-H, Jeong K-C, Kim S, Choi C, Lee CH, et al. "Involvement of Cox-2 in the metastatic potential of

chemotherapy-resistant breast cancer cells." BMC cancer, vol. 11, issue 1, pp. 1-13, Dec 2011.

[07] Otterson GA, Villalona-Calero MA, Sharma S, Kris MG, Imondi A, Gerber M, et al. "Phase I study of inhaled Doxorubicin for patients with metastatic tumors to the lungs." Clinical Cancer Research, vol. 13, issue 4, pp. 1246-1252, Feb 2007.

[08] Sukumar UK, Bhushan B, Dubey P, Matai I, Sachdev A, Packirisamy G. "Emerging applications of nanoparticles for lung cancer diagnosis and therapy." International Nano Letters, vol. 3, issue 1, pp. 1-7, Dec 2013.

[09] Lee J, Lee C, Kim TH, Lee ES, Shin BS, Chi S-C, et al. "Self-assembled glycol chitosan nanogels containing palmityl-acylated exendin-4 peptide as a long-acting anti-diabetic inhalation system." Journal of Controlled Release, vol. 161, issue 3, pp. 728-734, Aug 2012.

[10] Paranjpe M, Muller-Goymann CC. "Nanoparticle-mediated pulmonary drug delivery: A review." International Journal of Molecular Sciences, vol. 15, issue 4, pp. 5852-5873, Apr 2014.

[11] Mottaghitalab F, Farokhi M, Fatahi Y, Atyabi F, Dinarvand R. "New insights into designing hybrid nanoparticles for lung cancer: Diagnosis and treatment." Journal of Controlled Release, vol. 295, pp. 250-267, Feb 2019.

[12] Akhter S, Amin S, Ahmad J, Khan S, Anwar M, Ahmad MZ, et al. "Nanotechnology to Combat Multidrug Resistance in Cancer." Resistance to Targeted ABC Transporters in Cancer, vol. 4, pp. 245-272, 2015.

[13] Tseng C-L, Wu SY-H, Wang W-H, Peng C-L, Lin F-H, Lin C-C, et al. "Targeting efficiency and biodistribution of biotinylated-EGF-conjugated gelatin nanoparticles administered via aerosol delivery in nude mice with lung cancer." Biomaterials, vol. 29, issue 20, pp. 3014-3022, Jul 2008.

[14] Elsayed I, AbouGhaly MHH. "Inhalable nanocomposite microparticles: preparation, characterization and factors affecting formulation." Expert Opinion on Drug Delivery, vol. 13, issue 2, pp. 207-222, Feb 2016.

[15] Muralidharan P, Malapit M, Mallory E, Hayes D, Mansour HM. "Inhalable nanoparticulate powders for respiratory delivery." Nanomedicine: Nanotechnology, Biology, and Medicine, vol. 11, issue 5, pp. 1189-1199, Jul 2015.

[16] Lee W-H, Loo C-Y, Traini D, Young PM. "Development and evaluation of paclitaxel and curcumin dry powder for inhalation lung cancer treatment." Pharmaceutics, vol. 13, issue , pp. 1-19, Jan 2021.

[17] Yang Y, Cheow WS, Hadinoto K. "Dry powder inhaler formulation of lipid–polymer hybrid nanoparticles via electrostatically-driven nanoparticle assembly onto microscale carrier particles." International Journal of Pharmaceutics, vol. 434, issue 1-2, pp. 49-58, Sep 2012.

[18] Pilcer G, Amighi K. "Formulation strategy and use of excipients in pulmonary drug delivery." International Journal of Pharmaceutics, vol. 392, issue 1-2, pp. 1-19, Jun 2010.

[19] Yang M, Yamamoto H, Kurashima H, Takeuchi H, Yokoyama T, Tsujimoto H, et al. "Design and evaluation of poly (DL-lactic-co-glycolic acid) nanocomposite particles containing salmon calcitonin for inhalation." European Journal of Pharmaceutical Sciences, vol. 46, issue 5, pp. 374-380, Aug 2012.

[20] Zhang J, Wu L, Chan HK, Watanabe W. "Formation, characterization, and fate of inhaled drug nanoparticles." Advanced Drug Delivery Reviews, vol. 63, issue 6, pp. 441–455, May 2011.

[21] Zhou QT, Leung SSY, Tang P, Parumasivam T, Loh ZH, Chan H-K. "Inhaled formulations and pulmonary drug delivery systems for respiratory infections." Advanced Drug Delivery Reviews, vol. 85, pp. 83-99, May 2015.

[22] Chiang P-C, Hu Y, Blom JD, Thompson DC. "Evaluating the suitability of using rat models for preclinical efficacy and side effects with inhaled corticosteroids nanosuspension formulations." Nanoscale Research Letters, vol. 5, issue 6, pp. 1010-1019, Jun 2010.

[23] Onoue S, Aoki Y, Kawabata Y, Matsui T, Yamamoto K, Sato H, et al. "Development of inhalable nanocrystalline solid dispersion of tranilast for airway inflammatory diseases." Journal of Pharmaceutical Sciences, vol. 100, issue 2, pp. 622-633, Feb 2011.

[24] Gradon L, Sosnowski TR. "Formation of particles for dry powder inhalers." Advanced Powder Technology, vol. 25, issue 1, pp. 43-55, Jan 2014.

[25] Alhajj N, O'Reilly NJ, Cathcart H. "Designing enhanced spray dried particles for inhalation: A review of the impact of excipients and processing parameters on particle properties." Powder Technology, vol. 384, pp. 313-331, May 2021.

[26] Yu S, Pu X, Ahmed MU, Heidi HY, Mutukuri TT, Li J, et al. "Spray-freeze-dried inhalable composite microparticles containing nanoparticles of combinational drugs for potential treatment of lung infections caused by Pseudomonas aeruginosa." International Journal of Pharmaceutics, vol. 610, pp. 121160-121169, Dec 2021.

[27] Cheow WS, Ng MLL, Kho K, Hadinoto K. "Spray-freeze-drying production of thermally sensitive polymeric nanoparticle aggregates for inhaled drug delivery: effect of freeze-drying adjuvants." International Journal of Pharmaceutics, vol. 404, issue 1, pp. 289-300, Feb 2011.

[28] Wang Y, Kho K, Cheow WS, Hadinoto K. "A comparison between spray drying and spray freeze drying for dry powder inhaler formulation of drug-loaded lipid–polymer hybrid nanoparticles." International Journal of Pharmaceutics, vol. 424, issue 1-2, pp. 98-106, Mar 2012.

[29] Nahar K, Gupta N, Gauvin R, Absar S, Patel B, Gupta V, et al. "In vitro, in vivo and ex vivo models for studying particle deposition and drug absorption of inhaled pharmaceuticals." European Journal of Pharmaceutical Sciences, vol. 49, issue 5, pp. 805-818, Aug 2013.

[30] Mitchell JP, Nagel MW. "Cascade impactors for the size characterization of aerosols from medical inhalers: their uses and limitations." Journal of Aerosol Medicine, vol. 16, issue 4, pp. 341-377, Dec 2003.

[31] Chow MYT, Tai W, Chang RYK, Chan H-K, Kwok PCL. "In vitro-in vivo correlation of cascade impactor data for orally inhaled pharmaceutical aerosols." Advanced Drug Delivery Reviews, vol. 177, pp. 113952-113961, Oct 2021.

[32] Yi D, Price A, Panoskaltsis-Mortari A, Naqwi A, Wiedmann TS. "Measurement of the distribution of aerosols among mouse lobes by fluorescent imaging." Analytical Biochemistry, vol. 403, issue 1-2, pp. 88-93, Aug 2010.

[33] Mansour HM, Rhee YS, Wu X. "Nanomedicine in pulmonary delivery." International journal of nanomedicine, vol. 4, pp. 299-319, Dec 2009.

[34] Borchard G, Cassará ML, Roemelé PEH, Florea BI, Junginger HE. "Transport and local metabolism of budesonide and fluticasone propionate in a human bronchial epithelial cell line (Calu-3)." Journal of Pharmaceutical Sciences, vol. 91, issue 6, pp. 1561-1567, Jun 2002.

[35] Selg E, Ewing P, Acevedo F, Sjöberg C-O, Ryrfeldt Å, Gerde P. "Dry powder inhalation exposures of the endotracheally intubated rat lung, ex vivo and in vivo: the pulmonary pharmacokinetics of fluticasone furoate." Journal of Aerosol Medicine and Pulmonary Drug Delivery, vol. 26, issue 4, pp. 181-189, Aug 2013.

[36] Sakagami M. "In vivo, in vitro and ex vivo models to

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2021.01.1.007

assess pulmonary absorption and disposition of inhaled therapeutics for systemic delivery." Advanced Drug Delivery Reviews, vol. 58, issue 9, pp. 1030-1060, Oct. 2006.

[37] Doan TVP, Grégoire N, Lamarche I, Gobin P, Marchand S, Couet W, et al. "A preclinical pharmacokinetic modeling approach to the biopharmaceutical characterization of immediate and microsphere-based sustained release pulmonary formulations of rifampicin." European Journal of Pharmaceutical Sciences, vol. 48, issue 1, pp. 223-240, Jan 2013.

[38] Rundfeldt C, Steckel H, Scherliess H, Wyska E, Wlaź P. "Inhalable highly concentrated itraconazole nanosuspension for the treatment of bronchopulmonary aspergillosis." European Journal of Pharmaceutics and Biopharmaceutics, vol. 83, issue 1, pp. 44-53, Jan 2013.

[39] Conde J, Tian F, Hernández Y, Bao C, Cui D, Janssen K-P, et al. "In vivo tumor targeting via nanoparticle-mediated therapeutic siRNA coupled to inflammatory response in lung cancer mouse models." Biomaterials, vol. 34, issue 31, pp. 7744-7753, Oct 2013.

[40] Fröhlich E, Salar-Behzadi S. "Toxicological assessment of inhaled nanoparticles: role of in vivo, ex vivo, in vitro, and in silico studies." International Journal of Molecular Sciences, vol. 15, issue 3, pp. 4795-4822, Mar 2014.

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2021.01.1.017

December 2021
Volume 1
Issue 1

COVID-19: Dentistry related aspects

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Received on, 17 November 2021 - Accepted on, 27 November 2021 - Published on, 10 December 2021

Abstract:

The coronavirus disease 2019 (COVID-19) is a highly contagious transmittable disease caused by a recently discovered coronavirus, SARS-CoV-2. The COVID-19 is associated with a global "pandemic" health situation. In humans, the effects of SARS-CoV-2 range from flu (influenza) like symptoms to severe respiratory tract infections and sometimes death. Some oral manifestations associated with this virus have also been reported. This literature overview provides a description of pathophysiology, the clinical aspects of COVID-19 and transmission. Because SARS-CoV-2 is highly infective through airborne contamination, dental professionals play great roles in the transmission of this virus in dental environment. In this review, we also discussed various preventive and control measures during dental practice to combat COVID-19 effectively. Furthermore, we described and highlighted the potential of tele dentistry as a new approach during the COVID-19 crisis.

Key words: *COVID-19, Coronavirus, dentistry, SARS-CoV-2, dental environment; Personal protective equipment, tele dentistry.*

Background:

In 1968, a Nature publication by Almeida et al. first described a newly discovered single-stranded RNA virus with a diameter of 120 nanometers [1]. They decided to name this new group of viruses "corona viruses" due to their appearance under the electron microscope with their distinguishing fringe of projections on the outer surface of the virus which reminded the scientist of solar corona. Coronaviruses are prone to mutation and recombination, and therefore, around 40 different variations of coronaviruses have been recognized mostly infecting human and non-human mammals and birds [2].
Coronaviruses are a large family of viruses that usually cause mild to moderate upper-respiratory tract illnesses, like the common cold. However, three new coronaviruses have emerged from animal reservoirs over the past two decades and caused serious and widespread illness and death. Those viruses jump to humans— called a spillover event—and can cause more serious, even fatal, disease. The coronavirus (SARS-CoV) emerged in November 2002 and caused severe acute respiratory syndrome (SARS). That virus disappeared by 2004. Middle East respiratory syndrome (MERS) is caused by the MERS coronavirus (MERS-CoV). It is transmitted from an animal reservoir (camels). MERS was identified in September 2012 and continues to cause sporadic and localized outbreaks. The third novel coronavirus has emerged in late 2019 [3].

COVID-19:

A highly infectious pneumonia started to spread in Wuhan, China, from 12 December 2019 [4]. In early January 2020, the officials announced the novel coronavirus as the causative pathogen of the disease [5]. This novel viral pneumonia was named "Corona Virus Disease (COVID-19)" by the World Health Organization (WHO) [6].The name "SARS CoV-2" was also given for this novel coronavirus by the International Committee on Taxonomy of Viruses (ICTV) [7]. Soon, it turned into one of the toughest public health challenges in the modern world having spread in over 200 countries across the globe [8]. In March 2020, the **World Health Organization** (WHO) officially declared it as a global pandemic [9].

The most updated epidemiological and genetic studies performed on infected Chinese patients revealed that this pandemic originated from a zoonosis [10]. Some evidence suggests that the pathogen of COVID-19 originated in some species of bats first, and it was then spread to intermediate hosts such as wild dogs, snakes, and pangolins. The spread to human is thought to have happened via contaminated meat products from traditional wildlife market in Wuhan [11, 12].

Viral structure and pathogenesis:

A SARS-CoV-2 virion is approximately 50–200 nm in diameter. This virus has a +ssRNA genome of approximately 29.9 kb in length. It has four structural proteins, known as the S (spike), E (envelope), M (membrane), and N (nucleocapsid) proteins; the N protein holds the RNA genome, and the S, E, and M proteins together create the viral envelope [13].

Host cell binding and entry are mediated by the spike glycoprotein-S. The first step in infection is virus binding of S protein to a host cell through its target receptor angiotensin-converting enzyme 2 (ACE2). SARS-CoV-2 then uses serine proteases TMPRSS2 (transmembrane protease serine 2) for S protein priming by cleavage of the S proteins at the S1/S2 and S2 sites. This cleavage step is necessary for the virus host cell membrane fusion and cell entry to start its replication cycle[14]. After viral entry, the initial inflammatory response attracts virus-specific T cells to the site of infection, where the infected cells are eliminated before the virus spreads, leading to recovery in most people. In patients who develop severe disease, SARS-CoV-2 elicits an aberrant host immune response. This leads to accumulation of cytokines in multiple organs and causes extensive tissue damage, or a cytokine release syndrome (cytokine storm), resulting in capillary leak, thrombus formation, and multi organ dysfunction [15, 16](figure 1).

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2021.01.1.017

For example, postmortem histology of lung tissues of patients who died of covid-19 have confirmed the inflammatory nature of the injury, with features of bilateral diffuse alveolar damage, hyaline-membrane formation, interstitial mononuclear inflammatory infiltrates, and desquamation consistent with acute respiratory distress syndrome (ARDS), and is similar to the lung pathology seen in severe Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) [17, 18].

A distinctive feature of covid-19 is the presence of mucus plugs with fibrinous exudate in the respiratory tract, which may explain the severity of covid-19 even in young adults [19].

Furthermore, ACE-2 receptors present at high concentrations in lungs, myocardial cells, endothelial cells of blood vessels, kidney, liver and intestines, as well as on oral mucosa (especially of the salivary glands and tongue)[20, 21]. These structures have been considered as early targets of Sars-CoV-2 [22]. These findings also indicate that the virus directly affects many organs[23].

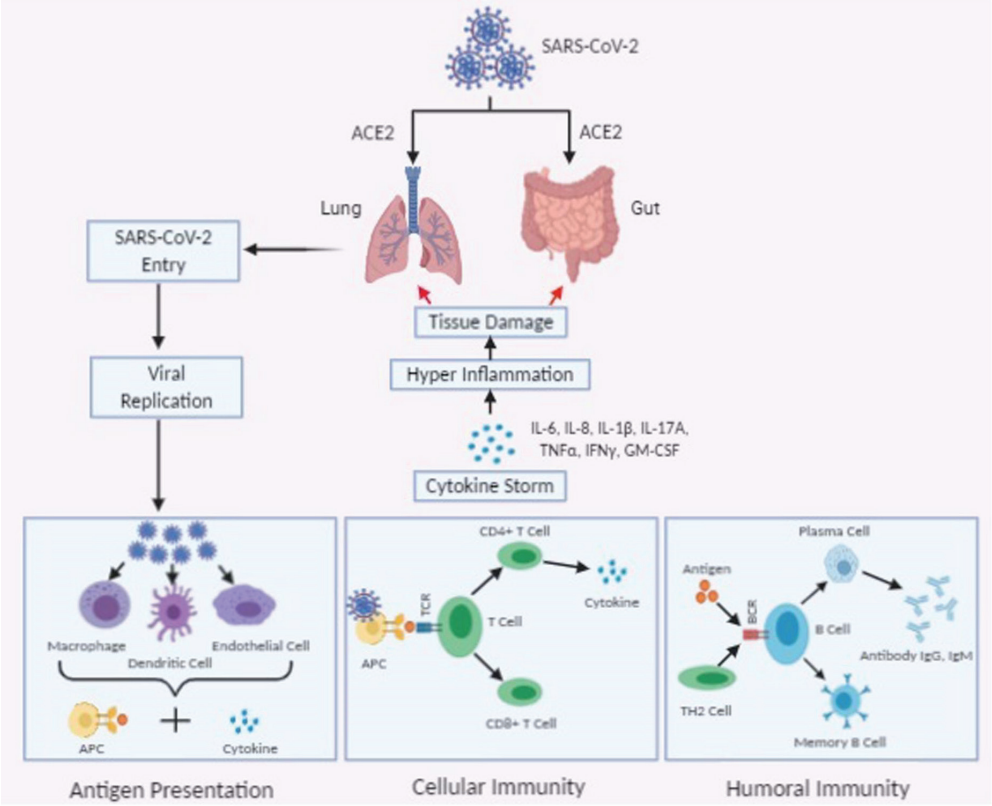

Figure 1: Schematic representation of immunopathogenesis of SARS-COV-2 (23).

Symptoms:

The incubation period of SARS-CoV-2 varies between 3 and 14 days; however, a 24-day incubation period has also been reported [24]. In most instances, the infection brought on by this new coronavirus is asymptomatic or causes few symptoms [2]. Clinical symptoms can vary from case to case. Infected patients mainly exhibit night fever, continuous dry cough, sore throat and asthenia, myalgia or fatigue. Patients with more severe disease can exhibit dyspnea as well as multi organ involvement and dysfunction. The most severe symptoms occur in 15%–25% of infected patients, with a relevant impairment of respiratory function that leads to hospitalization and assisted ventilation[10].

The fatality rate is found to be significantly higher in patients with hypertension, diabetes, and cardio-vascular diseases (CVD) [25-27]. The cause behind this could be the substantial increase in the expression of ACE2 in diabetic and hypertensive patients, treated with ACE inhibitors and angiotensin II type-I receptor blockers (ARBs). This consequently promotes SARS-CoV-2 infection severity [28].

Although loss of sense of smell (anosmia) and taste (ageusia) were not initially evidenced as symptoms of COVID-19, these symptoms are now the earliest indicators of COVID-19 patients [29]. Additionally, there is some new evidence on the impact of COVID-19 on the central nervous system. It suggests that SARS-CoV2, could target the central nervous system, possibly infecting neurons in the nasal passage and disrupting the senses of smell and taste [29].

These symptoms are slightly different from those of severe acute respiratory syndrome (SARS) caused by SARS coronavirus which was widely spread in early 2000s. The differences between SARS and COVID-19 are hidden in their transmissibility and severity pyramids. The transmissibility rate of COVID-19 is reported to be higher than that of SARS [30]. Additionally, in comparison with SARS, a larger population of COVID-19 positive patients demonstrated mild or no symptoms which makes it challenging to diagnose the patients clinically during the incubation period, and therefore, spread of infection can occur at an accelerated rate [31].

Oral manifestations:

Oral manifestations associated with COVID-19 have been reported. Oral mucosal lesions presented multiple clinical aspects, including, white and erythematous plaques, irregular ulcers, small blisters, petechiae, gingival inflammation and desquamative gingivitis, xerostomia and cracked teeth. Tongue, palate, lips, gingiva, and buccal mucosa were mostly affected. In mild cases, oral mucosal lesions developed before or at the same time as the initial respiratory symptoms; however, in those who required medication and hospitalization, the lesions developed approximately seven to 24 days after onset symptoms [32, 33].

Many physicians continue to question the direct link between SARS-CoV-2 and oral disease. Studies suggested that the mouth might be the most vulnerable area to this virus. The abundance of the ACE2 (angiotensin) receptor in oral tissue could be the main cause. In addition, a new preprint study found that cells of the salivary glands, tongue, and tonsils carry an enzyme called TMPRSS (transmembrane protease, serine 2), which allows the virus to fuse its membrane with that of the host cell and slip inside[34, 35]. Xerostomia may be due to mouth breathing caused by mask use. The surface receptors (ACE2) found in the salivary glands may contribute also to xerostomia [36].

Moreover, bruxism caused by psychological stress from the pandemic could have a major role in stress-related tooth fracture [37]. Despite that, several studies stated that some oral conditions could be secondary to the deterioration of systemic health or due to treatments for COVID-19. They are more likely to present as co-infection. The new coronavirus could have the ability to alter the balance of the oral microbiota, which is added already to a depressed immune system. This would allow opportunistic infections colonization [38-40]. It has been established that correct oral hygiene could decrease the incidence and severity of the main complications of COVID-19 [40, 41].

The most common oral manifestation is Gustatory impairment. As previously mentioned, the mechanism behind this loss is viral disruption of cranial nerves 1, 7, 9, and 10, as well as the supporting cells of neural transmission. In addition, because the tongue has an abundance of ACE2 receptors which provide a direct viral entry into tongue cells[42, 43].

Transmission pathways:

The COVID-19 has similar transmission pathways, but not identical, to those of other SARS-CoV infections, being mainly through the respiratory system. Transmission through droplets and fomites (objects or materials which are likely to carry infection) are the main modes of transmission of SARS-CoV-2. Airborne infection occurs through aerosols and droplets released by infected individuals through coughing, sneezing, exhalation, or speech (figure 2). Direct-contact infection occurs through contact with contaminated surfaces and subsequent touching of eyes, nose or mouth [44, 45].

Dental procedures by their nature have a high risk of COVID-19 infection due to close contact with the patient's oral cavity. Consequently, there is a risk of contact with saliva, blood, and other biological fluids. In addition, the presence of bacteria and viruses in the aerosols created by dental instrumentation such as using a high-speed handpiece or ultrasonic instruments [45]. Therefore, both patients and dental professionals are at a bilateral risk of being exposed to viral pathogens that can be transmitted through the oral cavity and respiratory tract during dental visits [46].

A study performed on a mannequin fitted with phantom jaws, and seated on a dental chair, showed that the highest levels of aerosol contaminants can be found within 60 cm from the patient's head, mainly on the right arm of the dentist, on their mask, and around their nose and eyes [47]. Clinical studies indicated that most of the dental procedures involving use of rotary handpieces generate considerable amount of contaminated and potentially infectious aerosol and droplets [48]. An in vitro study showed that SARS-CoV-2 maintained viability in the air for at least 3 hours and its viability half-life was nearly 1 hour [49].

Moreover, SARS-CoV-2 demonstrates persistent adherence, for a maximum of 9 days, to various surfaces [45, 50]; therefore, all surfaces and instruments in a dental clinic should be considered as potential sources of virus transmission because infected droplets from saliva or aerosols could land on any exposed surface [46, 47]. The cross-contamination between the attendees to the dental surgery is highly possible in the absence of effective and rigorous cross-infection control protocols[51].

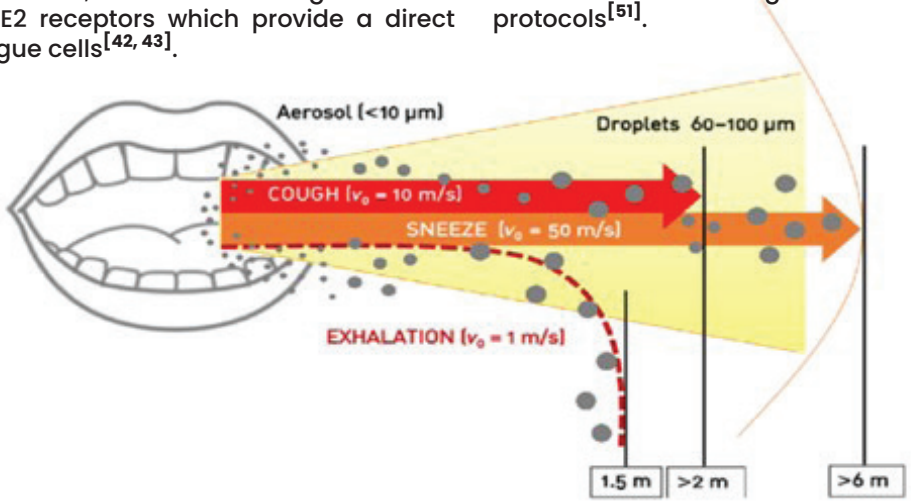

Figure 2: Exhalation distances of aerosol microparticles and large droplets (52).

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2021.01.1.017

The protocol followed in dental office during pandemic:

During the pandemic, updated local guidelines have suggested avoidance of dental treatments, except for patients with emergencies [22]. These dental emergency categories included: • Severe and uncontrolled pain; • Spreading, recurrent or continuing infection; • Avulsed permanent tooth; • Severe trauma [53].
Only urgent treatment for these dental conditions can be performed during the COVID-19 outbreak taking into consideration pharmacological management as the first line and contagion-reduced minimally invasive emergency treatment as the secondary and final management [54].

According to the recommended guidelines during COVID-19, the protective measures that should be undertaken in a dental setting can be categorized into three phases: 1) prior to dental treatment, 2) during the dental procedure, and 3) after dental treatment [54].

Pre-dental treatment measures:

Patient triage is mandatory for initial evaluation of patients. This is for identification of possible suspects, delay of non-urgent dental care and management of dental appointments [54] (figure 3). Dental professionals must be able to screen and identify potential high-risk COVID-19 patients to prevent the spread of the infectious disease. The first screening measure would be taking the body temperature of each patient using a contact-free forehead thermometer. Patients should fill in a questionnaire answering questions to determine if they have had COVID-19 symptoms such as fever, persistent cough and difficulty breathing within the past two weeks. Any contacts with individuals who had tested positive for COVID-19 should be recorded. Patients should also report if they have had contact with at least two people who demonstrated fever or respiratory symptoms within the last two weeks. The social history and any participation in gatherings and meetings need to be noted as well [45] (figure 4).

Patients answering 'yes' to any of the survey questions and who have a body temperature of >37.5 °C (99.5 °F) should be confined to their home or hospitalized.
Patients answering 'yes' to any of the survey questions to the survey and who have a body temperature of <37.5 °C (99.5 °F) should not be treated for at least 14 days. Patients who have recovered from COVID-19 can be treated 30 days after symptom remission. Patients answering 'no' to the survey questions and who have a body temperature of <37.5 °C (99.5 °F) can be treated, but procedures that cause aerosol production should be avoided [45, 55].

Decrease in the number of patients attending for dental treatment and their accompanies as well as management of social distancing in the waiting room are among the protective protocols that should be considered [54].

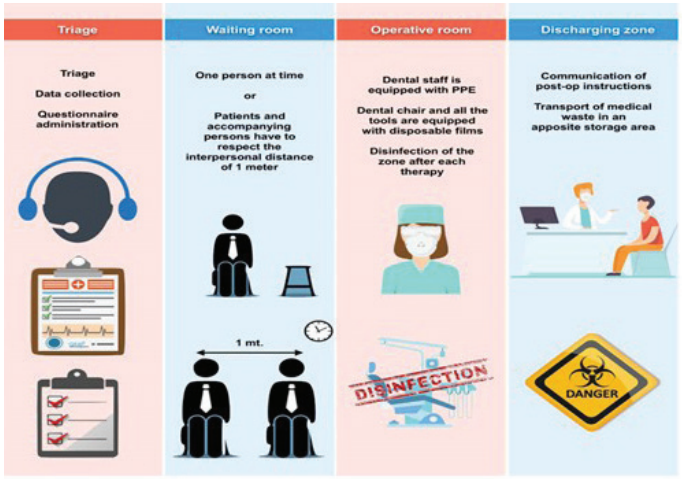

Figure 3: The protocol followed in dental office during pandemic (56).

1. Do you have any fever?	Yes ☐ No ☐
2. Do you have any upper respiratory symptoms?*	Yes ☐ No ☐
3. Do you have conjunctivitis?*	Yes ☐ No ☐
4. Do you or any of your family members or close contact suffer from these same symptoms?*	Yes ☐ No ☐
5. Did you have any contact with patients confirmed with coronavirus disease in the last 14 days?*	Yes ☐ No ☐
6. Have you travelled to outbreak areas of the coronavirus disease in the last 14 days?*	Yes ☐ No ☐

Figure 4: Questionnaire of COVID-19 in dental practice (57).

During dental procedures:

Protective personalized equipment (PPE)

Currently, there is not a practical solution to avoid generation of aerosols mixed with patient's blood and saliva. Therefore, the use of Personal Protective Equipment (PPE), such as disposable waterproof scrubs and bonnets, gloves, eyewear protection, face shields, disposable shoe-covers, and masks, is highly recommended. All dental patients should be considered as potentially infected [58].

In dentistry, the most indicated PPE for airway protection is the Filtering Facepiece (FFP) mask. They are designed to protect the wearer and are divided into the following different categories based on their filtration efficiency towards powders ≥0.3 μm in diameter. The COVID-19 particles are estimated to be 0.06–0.14 μm. According to US standards, FFPs are classified to N95 (95% minimal total filtration efficiency), N99 (99% minimal total filtration efficiency) and N100 (99.97% minimal total filtration efficiency) [46, 59]. In addition to the filtration efficacy, facepieces can be further distinguished as valved or non-valved respirators. Valved respirators can filter the entering air, but do not filter the wearer's exhaled air. Nonvalved respirators provide good two-way protection by filtering both inflow and outflow of air [60]. In dental procedures, it is suggested to use a mask with the highest filtration efficacy without a valve, or a valved mask covered by a surgical mask and the mean surgical period should not exceed 2 hours. The mask also should be considered as disposable [22].

The ocular pathway is known to be one of the most frequent routes of infection with SARS-CoV-2, so eyewear is required during dental procedures. Plastic shields may be preferred to glasses because of their greater capacity to protect the face from aerosol droplets [45].

Disinfection and sanitization

Hand hygiene is considered the most important preventive measure to reduce the risk of transmission of microorganisms between dentists and patients. Soap and cleansers must be rubbed extensively on both hands, until the appearance of abundant foam. Friction with an alcoholic hand sanitizer is suggested after handwashing. These actions have been shown to dissolve the lipid sheath around the viruses, causing dispersion and decomposition of viral molecules [61].

A valid method to reduce the microbial load in the patient's oral cavity is rinsing before dental procedures. There remains controversy regarding the effectiveness of chlorhexidine against coronavirus. Because SARS-CoV-2 is sensitive to oxidation, mouth rinses containing 1% hydrogen peroxide or 0.2% povidone iodine have been proposed [62].

It is crucial that medical and dental teams follow an effective and strict disinfection protocol for both clinical and communal areas. All surfaces in the clinical areas must be cleaned and disinfected to the highest standard according to the local guidelines and requirements. Each potentially contaminated surface should be cleaned and then disinfected with 62%–71% ethanol, 0.5% hydrogen peroxide or 0.1% sodium hypochlorite. Coronaviruses can persist on plastic, glass and metal surfaces and remain infective for a maximum of 9 days, with a mean infective period of 4–5 days. The authors found that coronavirus could be effectively eliminated in 1 minute when the surfaces were disinfected [50]. Installation of enhanced air ventilation systems in dental clinics and centers can also help to facilitate removal of airborne pathogens from clinical environments and reduce the risk of infection [63]. Ozone is a natural gas, and one of the most effective systems for environmental sanitization. It provides highly reactive free radicals that can oxidize bacteria, viruses [64]. Germicidal ultraviolet (UV) radiation also represents a valid sterilization option. Ultraviolet light can damage microbial DNA and RNA, thus preventing reproduction of microbes and reducing the harmful effects of infectious organisms [65].

Mechanisms to reduce spread of COVID-19 in the dental environment.

Handpieces with an anti-retraction system should be used during the COVID19 pandemic. When handpieces or ultrasonic devices must be used, the use of a rubber dam is indicated as this significantly reduces the amount of aerosol containing saliva and/or blood. Rubber dam usage also provides a 70% reduction of droplets around the surgical field [54]. When isolation using a rubber dam is not possible, manual instrumentation is preferred over high-speed handpieces [45]. Simultaneous assembly of two ejectors (e.g., a high-speed ejector and a high-volume evacuator) is highly recommended to achieve considerable reduction of droplet spread during dental procedures. When possible, it is recommended to avoid dental procedures that could cause cough and regurgitation [22].

Orthopantomography (OPG) or cone beam computed tomography (CBCT) are preferred; periapical X-rays should be avoided because they could provoke hypersalivation, coughing or vomiting [55].

After dental treatment:

Clinical Waste Management

Clinical waste should be stored in a safe temporary storage area, and all reusable instruments and items should be pre-treated, cleaned, sterilized, and properly stored in accordance with the local protocols. The clinical waste generated after treatment of COVID-19 positive patients must be regarded as infectious clinical waste and stored in clinical waste bags within a designated area. The surface of the package bags should be marked and disposed according to the local regulations and requirement for the management of medical waste [45].

COVID-19 Testing:

There are various methods available for COVID-19 testing, and the decision to carry out a test on suspected individuals should be made based on clinical symptoms and epidemiological factors. It would be beneficial if dental practices were provided with fast COVID19 detection kits in order to test the high-risk and suspicious patients. This way, they can take necessary precautions in reducing the spread of the virus [31].

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2021.01.1.017

RT-PCR

Also called a molecular test, this COVID-19 test detects genetic material (RNA) of the virus. As per WHO guideline, the RT-PCR test should be done in asymptomatic or mildly symptomatic patients and those who have had contact with COVID-19 positive cases. A swab is normally utilized to gather specimen from inside the nose or posterior part of throat [66].

Serological or Antibody Testing

Another method of investigation in an ongoing pandemic is serological survey of cases. This test detects antibodies produced by the immune system in reaction to viral infection. This method tests whether a suspected individual has been infected by COVID-19 and has produced antibodies. The immunological reactions to the SARS-CoV-2 can take several weeks to happen, and some studies show that antibodies to COVID-19 may take 14 days to appear. Therefore, a serology test before this period may result in an unhelpful negative. Antibody test requires a blood sample from the patient [67].

Antigen test

This COVID-19 test detects certain proteins in the virus. A fluid sample is obtained by long nasal swab. There is an increased chance of false-negative results. The doctor may recommend a PCR test to confirm a negative antigen test result [68].

Medical imaging

The CT scan may present some findings even before the onset of symptoms [60]. Bilateral multilobed ground-glass opacifications associated with a peripheral asymmetric and posterior distribution is the typical feature of the CT in COVID-19 positive cases. A comparative study conducted in Wuhan suggests that CT is significantly more sensitive than PCR test; however, it is less specific as many of its imaging characteristics overlap with other types of pneumonia [69].

Treatment of COVID-19:

Potential interventions including pharmacologic treatments for novel coronavirus (COVID-19) disease have been comprehensively and systematically reviewed. General supportive treatments such as vitamins (A, B, C, D and E),
Immuno-enhancers including interferons and antiviral medications such as ribavirin, remdesivir and nelfinavir are examples [70, 71]. A large number of clinical trials are currently underway in many countries globally to investigate the suitability of some of these interventions individually or as combination therapies against COVID-19 [31].
Yet, the U.S. Food and Drug Administration (FDA) approved an emergency use authorization (EUA) for the monoclonal antibody "bamlanivimab" and the antiviral drug "remdesivir" for treatment of adult and pediatric patients with COVID-19 [72, 73]. Remdesivir provides only a modest benefit to patients [74].
Still, the pandemic's biggest puzzle is that why some people with coronavirus have no symptoms and others get extremely ill? A study in Nature of more than 2,200 intensive care patients has identified specific genes that may hold the answer. This is done by sequencing of patients' genes. A mutation in gene called TYK2 makesthe immune response to go into overdrive, putting patients at risk of damaging lung. Genetic differences were also found in a gene called DPP9, which plays a role in inflammation, and in a gene called OAS, which helps to stop the virus from making copies of itself [75].

Variations in a gene called IFNAR2 were also identified in the intensive care patients. The gene IFNAR2 is linked to interferon, which helps to start the immune response to the infection. This mutation causes too little production of the interferon which can give the virus an early advantage, allowing it to quickly replicate, leading to more severe disease [75]. Two other recent studies published in the journal Science have also implicated interferon in COVID cases, through both genetic mutations and an autoimmune disorder that affects its production [76, 77]. Interferon was given as a treatment, but a World Health Organization clinical trial concluded that it did not help very sick patients [74].

The findings from these genetic studies will help to identify particular molecular pathways that could be targets for therapeutic intervention [75]. Additionally, large-scale clinical trials are required to approve the efficacy of these target therapies.

Vaccines of COVID-19:

Multiple vaccine development strategies such as virus vaccines, recombinant protein subunit vaccines and nucleic acid vaccines are being evaluated for their safety and efficacy [78].
Researchers are currently testing 63 vaccines in clinical trials on humans, and 18 have reached the final stages of testing. At least 85 preclinical vaccines are under active investigation in animals [79]. The F.D.A. has authorized **PfizerBioNTech** vaccine and Moderna's vaccine for emergency use on 11 December and 18 December, 2020, respectively [80].

Tozinameran (INN), codenamed BNT162b2, commonly known as the Pfizer–BioNTech COVID-19 vaccine is an RNA vaccine composed of nucleoside modified mRNA (modRNA) encoding a mutated form of the spike protein of SARS-CoV-2, which triggers an immune response against infection [81]. Moderna's technology is also modRNA compound named mRNA-1273, which induces immunity to SARS-CoV-2 by encoding a prefusion stabilized spike (S) protein naturally present on the surface of SARS-CoV-2 particles. The drug delivery system of mRNA-1273 uses a PEGylated lipid nanoparticle drug delivery (LNP) system [82].
Both the Pfizer and Moderna use technology known as mRNA, which introduces into the body a messenger sequence that contains the genetic instructions of the virus. The vaccinated person's own cells produce the antigens and generate an immune response. Moderna vaccine has higher mRNA amount per dose (100 micrograms) compared with Pfizer vaccine containing 30 micrograms of mRNA perdose [83].

Potential Long-Term Impact of COVID-19 on Dentistry

Authors' observations and evaluation of the current situation suggest that the costs of providing dental treatment may increase in the future because of several reasons. The need for additional resources such as PPE, dental practice modifications would primarily raise the treatment costs. The need for segregation of patients in the waiting areas resulting in a reduced number of patients that can be seen daily. Additionally, due to an increased occupational health risk to the practitioners arising from carrying out aerosols generating procedures, the cost of specialist services may possibly increase [54].

There could be a general fear of visiting dentists among the public after the COVID-19 outbreak settles down. Consequently, some patients will pay more attention to their oral and dental health by improving their oral hygiene practice and following preventive recommendations [31]. Higher levels of oral hygiene could decrease the need for a person to attend a dental clinic; and at the same time, it can significantly help the person to remove the virus from the body in the early contamination phase [84]. Good oral hygiene also reduces the bacterial load in the mouth and the risk of bacterial superinfection especially in patients who are prone to altered biofilms due to diabetes, high blood pressure or CVDs [85].

Furthermore, Due to overall economic impact of COVID-19, extended lockdown measures and closure of dental clinics and centers, it is predicted that there could be further uncertainty for the profession, reduced incomes, and more job loss in the future. Some small to medium-size dental related businesses may not survive a long-term lockdown [54].

Tele-dentistry:

Tele dentistry is a great innovation to minimize the risk of increased COVID19 dissemination and cross infections at medical or dental offices. Tele-medicine (TM) is a new concept of healthcare to deliver care across distance using advanced communication technologies (smartphones, tablets, and laptops) [86, 87]. The TM completely modified the traditional medical approach of working. The American Dental Association (ADA) describes tele dentistry as "a broad variety of technologies and tactics that deliver virtual medical, health and education services" [88].

There are different (but not limited) key modalities of tele dentistry as described by ADA. These include the following: 1) Synchronous: Live video, two-way interaction between the patient and the tele dentist by utilizing audio-visual telecommunication. 2) Asynchronous: Recorded medical and dental information such as clinical photographs, radiographs and videos are sent by secure telecommunication to the clinician for evaluation and advice. 3) Remote patient monitoring (RPM): Personal medical and dental data collected from an individual in one location is transmitted to the provider by secure telecommunication in a different location. 4) Mobile Health: Use of mobile communication devices for public healthcare, education, and practice [88].

During this ongoing global COVID-19 pandemic, tele dentistry is a viable care option in efforts to help 'flatten the curve'. It is the dental health professional's ethical and professional obligation to limit that risk and prevent the spread of COVID-19 in vulnerable patients and act in accordance with regulatory requirements. It is therefore imperative for dental practitioners to understand that tele dentistry is the practice of online dentistry and that they have a duty of care to the patient [89]. More recently a study utilizing tele dentistry has shown that this allowed monitoring of all patients with reduction in cost and limiting human contact [90].

One of the most significant advantages of tele dentistry or telemedicine include real-time consultations and assessments, storage of data, a reduction in travel for patients and clinicians saving time and cost. In addition, it provides faster access to dental and specialist care, collaborative, and educational tool by giving an opportunity to discuss with family members or fellow clinicians (after patients consent) as well as improved access of care to rural community who are unable to travel to larger cities. Meanwhile, disadvantages can include the exchange of sensitive information, the commitment to confidentiality, the commitment to security and access to a large volume of data stored [88]. It is assumed that the COVID-19 pandemic may cause a permanent transformation in dentistry with the advancement of tele-dentistry [91].

Conclusion:

The COVID-19 has spread worldwide in a pandemic way and infection control measures are mandatory to limit contagion, especially for healthcare professionals who meet potentially infected patients. To date, there is a consensus in providing only emergency dental services, but the situation is constantly evolving. In any case, the reduction of infectious risk remains a challenge for dentists, among the most exposed health professionals.

References

[01] J.D. Almeida, D.A. Tyrrell, "The morphology of three previously uncharacterized human respiratory viruses that grow in organ culture", The Journal of general virology. vol.1, issue 2, pp.175-178, 1967.

[02] K. McIntosh, "Coronaviruses: a comparative review", Current Topics in Microbiology and Immunology/ Ergebnisse der Mikrobiologie und Immunitätsforschung: Springer, p. 85-129, 1974.

[03] National institute of allergy and infectious diseases. (2020). Coronaviruses [Online] Available: https://www.niaid.nih.gov/diseases-conditions/coronaviruses.

[04] Y-R. Guo, Q-D. Cao, Z-S. Hong, Y-Y. Tan, S-D. Chen, H-J. Jin, et al. "The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak – an update on the status", Military Medical Research, vol.7, issue 1, p. 11, 2020.

[05] Q. Li, X. Guan, P. Wu, X. Wang, L. Zhou, Y. Tong, et al. «

Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia", The New England journal of medicine, vol. 382, issue 13, pp. 1199-207, 2020.

[06] J. Rothschild, "Ethical considerations of gene editing and genetic selection", Journal of General and Family Medicine, vol. 21, issue 3, pp. 37-47, 2020.

[07] A.E. Gorbalenya, S.C. Baker, R.S. Baric, R.J. de Groot, C. Drosten, A.A. Gulyaeva, et al. (2020). "Severe acute respiratory syndrome-related coronavirus: The species and its viruses – a statement of the Coronavirus Study Group", bioRxiv [Online]. Available: 2020.02.07.937862.

[08] E. Mahase, China coronavirus: WHO declares international emergency as death toll exceeds 200. BMJ (Clinical research ed). 2020;368:m408.

[09] World Health Organization (WHO). (2020). WHO announces COVID-19 outbreak a pandemic. [Online] Available: https://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/news/news/2020/3/who-announces-covid-19-outbreak-a-pandemic.

[10] N. Chen, M. Zhou, X. Dong, J. Qu, F. Gong, Y. Han, et al, "Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study", The Lancet. vol.395, issue 10223, pp. 507-513, 2020.

[11] P. Zhou, X.L. Yang, X.G. Wang, B. Hu, L. Zhang, W. Zhang, et al, "A pneumonia outbreak associated with a new coronavirus of probable bat origin", Nature, vol.579, issue 7798, pp.270-273, 2020.

[12] T. Zhang, Q. Wu, Z. Zhang. (2020). "Pangolin homology associated with 2019-nCoV", bioRxiv [Online]. Available: 2020.02.19.950253.

[13] M. Kumar, S. Al Khodor. "Pathophysiology and treatment strategies for COVID-19", Journal of Translational Medicine, vol.18, issue 1, p. 353, 2020.

[14] M. Cevik, K. Kuppalli, J. Kindrachuk, M. Peiris. "Virology, transmission, and pathogenesis of SARS-CoV-2", BMJ (Clinical research ed), vol.371, p. m3862, 2020.

[15] N. Mangalmurti, C.A. Hunter, "Cytokine storms: understanding COVID-19", Immunity, 2020.

[16] C. Wu, X. Chen, Y. Cai, X. Zhou, S. Xu, H. Huang, et al, "Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China", JAMA internal medicine, 2020.

[17] L. Carsana, A. Sonzogni, A. Nasr, R.S. Rossi, A. Pellegrinelli, P. Zerbi, et al, "Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study", The Lancet Infectious Diseases, 2020.

[18] Z. Xu, L. Shi, Y. Wang, J. Zhang, L. Huang, C. Zhang, et al, "Pathological findings of COVID-19 associated with acute respiratory distress syndrome", The Lancet respiratory medicine, vol.8, issue 4, pp.420-2, 2020.

[19] C. Wang, J. Xie, L. Zhao, X. Fei, H. Zhang, Y. Tan, et al, "Alveolar macrophage dysfunction and cytokine storm in the pathogenesis of two severe COVID-19 patients", EBioMedicine. Vol.57, p.102833, 2020.

[20] H. Xu, L. Zhong, J. Deng, J. Peng, H. Dan, X. Zeng, et al, "High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa", International journal of oral science. vol.12, issue 1, pp.1-5, 2020.

[21] R. Yan, Y. Zhang, Y. Li, L. Xia, Y. Guo, Q. Zhou. "Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2", Science, vol.367, issue 6485, pp. 1444-1448, 2020.

[22] V. Checchi, P. Bellini, D. Bencivenni, U. Consolo, "COVID-19 dentistry-related aspects: a literature overview", International dental journal, 2020.

[23] S.K. Chatterjee, S. Saha, M.N.M. Munoz, "Molecular Pathogenesis, Immunopathogenesis and Novel Therapeutic Strategy Against COVID-19", Frontiers in Molecular Biosciences, vol.7, issue 196, 2020.

[24] M. Balla, G.P. Merugu, M. Patel, N.M. Koduri, V. Gayam, S. Adapa, et al, "COVID-19, Modern Pandemic: A Systematic Review From Front-Line Health Care Providers' Perspective", Journal of Clinical Medicine Research. Vol.12, issue 4, p. 215, 2020.

[25] F. Zhou, T. Yu, R. Du, G. Fan, Y. Liu, Z. Liu, et al, "Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study", The lancet, 2020.

[26] Z. Wu, J.M. McGoogan, "Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention", JAMA, vol.323, issue 13, pp. 1239-1242, 2020.

[27] B. Li, J. Yang, F. Zhao, L. Zhi L, X. Wang, L. Liu, et al, "Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China", Clinical Research in Cardiology, vol.109, issue 5, pp. 531-538, 2020.

[28] L. Fang, G. Karakiulakis, M. Roth, "Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection?", The Lancet Respiratory Medicine, vol.8, issue 4, p. e21, 2020.

[29] J.R. Lechien, C.M. Chiesa-Estomba, D.R. De Siati, M. Horoi, S.D. Le Bon, A. Rodriguez, et al, "Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study", European archives of oto-rhino-laryngology: official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS): affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery. vol.277, issue 8, pp. 2251-2261, 2020.

[30] Y. Liu, A.A. Gayle, A. Wilder-Smith, J. Rocklöv, "The reproductive number of COVID-19 is higher compared to SARS coronavirus", Journal of Travel Medicine. vol.27, issue 2, 2020.

[31] P. Barabari, K. Moharamzadeh, "Novel Coronavirus (COVID-19) and Dentistry–A Comprehensive Review of Literature", Dentistry Journal, vol.8, issue 2, pp. 53, 2020.

[32] R. Wadia, "COVID-19 - oral manifestations", British Dental Journal. vol.229, issue 10, p. 669, 2020.

[33] A-G. Chaux-Bodard, S. Deneuve, A. Desoutter, "Oral manifestation of Covid-19 as an inaugural symptom?", J Oral Med Oral Surg, vol.26, issue 2, p.18, 2020.

[34] M. Gheblawi, K. Wang, A. Viveiros, Q. Nguyen, J-C. Zhong, A-J. Turner, et al, "Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system: celebrating the 20th anniversary of the discovery of ACE2", Circulation research, vol.126, issue 10, pp.1456-1474, 2020.

[35] N. Huang, P. Perez, T. Kato, Y. Mikami, K. Okuda, R.C. Gilmore, et al. (2020) "Integrated Single-Cell Atlases Reveal an Oral SARS-CoV-2 Infection and Transmission Axis", medRxiv [Online].

[36] J. Xu, Y. Li, F. Gan, Y. Du, Y. Yao. (2020). "Salivary glands: potential reservoirs for COVID-19 asymptomatic infection", Journal of Dental Research, Available: 0022034520918518.

[37] T. Chen. (2020). The New York Times. [Online]. Available: https://www.nytimes.com/2020/09/08/well/live/dentists-tooth-teeth-cracks-fractures-coronavirus-stress-grinding.html. Updated September 11 2020.

[38] J. Amorim dos Santos, A.G.C. Normando, R.L. Carvalho da Silva, A.C. Acevedo, G. De Luca Canto, N. Sugaya, et al. (2020). "Oral Manifestations in Patients with COVID-19: A Living Systematic Review". Journal of Dental Research [Online]. Available:0022034520957289.

[39] J. Amorim dos Santos, A.G.C. Normando, R.L. Carvalho da Silva, R.M. De Paula, A.C. Cembranel, A.R. Santos-Silva, et al, "Oral mucosal lesions in a COVID-19 patient: New signs or secondary manifestations?", International Journal of Infectious Diseases. vol.97, pp.326-328, 2020.

[40] M. Díaz Rodríguez, A. Jimenez Romera, M. Villarroel, "Oral manifestations associated with COVID-19", Oral diseases, 2020.

[41] V. Sampson, N. Kamona, A. Sampson, "Could there be a link between oral hygiene and the severity of SARS-CoV-2 infections?", British dental journal, vol.228, issue 12, pp. 971-975, 2020.

[42] A.A. Agyeman, K.L. Chin, C.B. Landersdorfer, D. Liew, R. Ofori-Asenso, "Smell and Taste Dysfunction in Patients With COVID-19: A Systematic Review and Meta-analysis" Mayo Clinic Proceedings, 2020.

[43] D.H. Brann, T. Tsukahara, C. Weinreb, M. Lipovsek, K. Van den Berge, B. Gong, et al, "Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia", Science Advances, p. eabc5801, 2020.

[44] C. Rothe, M. Schunk, P. Sothmann, G. Bretzel, G. Froeschl, C. Wallrauch, et al, "Transmission of 2019-nCoV infection from an asymptomatic contact in Germany", New England Journal of Medicine, vol.382, issue 10, pp. 970-971, 2020.

[45] X. Peng, X. Xu, Y. Li, L. Cheng, X. Zhou, B. Ren, "Transmission routes of 2019-nCoV and controls in dental practice", International Journal of Oral Science, vol. 12, issue 1, pp. 1-6, 2020.

[46] M. Montevecchi, V. Checchi, P. Felice, L. Checchi, "Management rules of the dental practice: individual protection devices", Dental Cadmos, vol.80, pp. 247-263, 2012.

[47] H. Veena, S. Mahantesha, P.A. Joseph, S.R. Patil, S.H. Patil, "Dissemination of aerosol and splatter during ultrasonic scaling: a pilot study", Journal of infection and public health, vol.8, issue 3, pp. 260-265, 2015.

[48] J. Wei, Y. Li, "Airborne spread of infectious agents in the indoor environment", American Journal of Infection Control, vol.44, suppl.9, pp. S102-108, 2016.

[49] N. Van Doremalen, T. Bushmaker, D.H. Morris, M.G. Holbrook, A. Gamble, B.N. Williamson, et al, "Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1", New England Journal of Medicine, vol.382, issue 16, pp. 1564-1567, 2020.

[50] G. Kampf, D. Todt, S. Pfaender, E. Steinmann, "Persistence of coronaviruses on inanimate surfaces and their inactivation with biocidal agents", Journal of Hospital Infection. vol.104, issue 3, pp. 246-251, 2020.

[51] J.L. Cleveland, S.K. Gray, J.A. Harte, V.A. Robison, A.C. Moorman, B.F. Gooch, "Transmission of blood-borne pathogens in US dental health care settings: 2016 update", Journal of the American Dental Association (1939), vol.147, issue 9, pp. 729-738, 2016.

[52] X. Xie, Y. Li, A. Chwang, P. Ho, W. Seto, "How far droplets can move in indoor environments-revisiting the Wells evaporation-falling curve. Indoor air", vol.17, issue 3, pp. 211-225, 2007.

[53] Management of Acute Dental Problems DuringCOVID-19 Pandemic: Scottish Dental Clinical Effectiveness Programme; (2020) [Online]

[54] M. Banakar, K.B. Lankarani, D. Jafarpour, S. Moayedi, M.H. Banakar, A. Mohammad Sadeghi, "COVID-19 transmission risk and protective protocols in dentistry: a systematic review", BMC oral health, vol.20, issue 1, pp. 1-12, 2020.

[55] L. Meng, F. Hua, Z. Bian, "Coronavirus disease 2019 (COVID-19): emerging and future challenges for dental and oral medicine", Journal of Dental Research, vol.99, issue 5, p. 487, 2020.

[56] A. Giudice, F. Bennardo, A. Antonelli, S. Barone, L. Fortunato, "COVID-19 is a new challenge for dental practitioners: advice on patients' management from prevention of cross infections to telemedicine", The Open Dentistry Journal, vol.14, issue 1, 2020.

[57] P.C. Passarelli, E. Rella, P.F. Manicone, F. Garcia-Godoy, A. D'Addona A, "The impact of the COVID-19 infection in dentistry", Experimental Biology and Medicine, vol.245, issue 11, 940-944, 2020.

[58] J.H. Verbeek, B. Rajamaki, S. Ijaz, R. Sauni, E. Toomey, B. Blackwood, et al, "Personal protective equipment for preventing highly infectious diseases due to exposure to contaminated body fluids in healthcare staff", Cochrane Database of Systematic Reviews, vol.2020, issue 4, 2020.

[59] L.J. Radonovic, M.S. Simberkoff, M.T. Bessesen, A.C. Brown, D.A. Cummings, C.A. Gaydos, et al, "N95 respirators vs medical masks for preventing influenza among health care personnel: a randomized clinical trial", JAMA, vol.322, issue 9, pp. 824-833, 2019.

[60] M. Loeb, N. Dafoe, J. Mahony, M. John, A. Sarabia, V. Glavin, et al, "Surgical mask vs N95 respirator for preventing influenza among health care workers: a randomized trial", JAMA, vol.302, issue 17, pp. 1865-1871, 2009.

[61] M.D. Hillier, "Using effective hand hygiene practice to prevent and control infection", Nurs Stand, vol.35, issue 5, pp. 45-50, 2020.

[62] P. Abedi Elkhichi, M. Aslanimehr, M. Niazadeh, "Stability of SARS-CoV-2 in Different Environments and the Effect of Disinfectants on its Survival", The Journal of Qazvin University of Medical Sciences, vol.24, issue 2, pp. 178-189, 2020.

[63] J.M. Villafruela, I. Olmedo, F.A. Berlanga, M. Ruiz de Adana, "Assessment of displacement ventilation systems in airborne infection risk in hospital rooms", Plos on, vol.14, issue 1, p.e0211390, 2019.

[64] M. Martinelli, F. Giovannangeli, S. Rotunno, C.M. Trombetta, E. Montomoli, "Water and air ozone treatment as an alternative sanitizing technology", Journal of Preventive Medicine and Hygiene, vol.58, issue 1, p. E48, 2017.

[65] Z. Qureshi, M. H Yassin, "Role of ultraviolet (UV) disinfection in infection control and environmental cleaning", Infectious Disorders-Drug Targets (Formerly Current Drug Targets-Infectious Disorders), vol.13, issue 3, pp.191-195, 2013.

[66] A. Tahamtan, A. Ardebili, "Real-time RT-PCR in COVID-19 detection: issues affecting the results" Taylor & Francis; 2020.

[67] D. Jacofsky, E.M. Jacofsky, M. Jacofsky, "Understanding antibody testing for covid-19", The Journal of Arthroplasty, 2020.

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2021.01.1.017

[68] C.H. Chau, J.D. Strope, W.D. Figg, "COVID-19 Clinical Diagnostics and Testing Technology", Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, vol.40, issue 8, pp. 857-868, 2020.

[69] T. Ai, Z. Yang, H. Hou, C. Zhan, C. Chen, W. Lv, et al, "Correlation of chest CT and RT-PCR testing in coronavirus disease 2019 (COVID-19) in China: a report of 1014 cases", Radiology, vol.200642, 2020.

[70] J.M. Sanders, M.L. Monogue, T.Z. Jodlowski, J.B. Cutrell, "Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review", JAMA, vol. 323, issue 18, pp. 1824-1836, 2020.

[71] L. Zhang, Y. Liu, "Potential interventions for novel coronavirus in China: A systematic review", Journal of Medical Virology, vol.323, issue 5, pp. 479-490, 2020.

[72] U.S Food and Drug administration (FDA). (2020). Coronavirus (COVID-19) Update: FDA Authorizes Monoclonal Antibody for Treatment of COVID-19. [Online]. Available: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-monoclonal-antibody-treatment-covid-19.

[73] U.S Food and Drug administration FDA. (2020). FDA Approves First Treatment for COVID-19. [Online]. Available: https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-covid-19.

[74] World Health Organization (November 2020). Therapeutics and COVID-19: living guideline. [Online] Available:///C:/Users/Hagar%20Alaa/Downloads/WHO-2019-nCov-remdesivir-2020.1-eng%20(2).pdf.

[75] E. Pairo-Castineira, S. Clohisey, L. Klaric, A.D. Bretherick, K. Rawlik, D. Pasko, et al, "Genetic mechanisms of critical illness in Covid-19", Nature, 2020.

[76] Q. Zhang, P. Bastard, Z. Liu, J. Le Pen, M. Moncada-Velez, J. Chen, et al, "Inborn errors of type I IFN immunity in patients with life-threatening COVID-19", Science, vol.370, issue 6515, p. eabd4570, 2020.

[77] P. Bastard, L.B. Rosen, Q. Zhang, E. Michailidis, H-H. Hoffmann, Y. Zhang, et al, "Autoantibodies against type I IFNs in patients with life-threatening COVID-19", Science, vol.370, issue 6515, p. eabd4585, 2020.

[78] W-H. Chen, U. Strych, P.J. Hotez, M.E. Bottazzi, "The SARS-CoV-2 Vaccine Pipeline: an Overview", Current Tropical Medicine Reports, vol.7, issue 2, pp. 61-64, 2020.

[79] The New York Times. (2020). Coronavirus Vaccine Tracker. [Online]. Available: https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html.

[80] U.S Food and Drug administration (FDA2020). (2020). COVID-19 Vaccines. [Online]. Available : https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-vaccines.

[81] E.E. Walsh, R.W. Frenck, A.R. Falsey, N. Kitchin, J. Absalon, A. Gurtman, et al, "Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates", New England Journal of Medicin, vol.383, issue 25, pp. 2439-2450, 2020.

[82] L.A. Jackson, E.J. Anderson, N.G. Rouphael, P.C. Roberts, M. Makhene, R.N. Coler, et al, "An mRNA Vaccine against SARS-CoV-2 — Preliminary Report", New England Journal of Medicine, vol.383, issue 20, pp. 1920-1931, 2020.

[83] C. Gaebler, M.C. Nussenzweig, "All eyes on a hurdle race for a SARS-CoV-2 vaccine", Nature Publishing Group, 2020.

[84] O. Lucaciu, D. Tarczali, N. Petrescu, "Oral healthcare during the COVID-19 pandemic", Journal of Dental Sciences, vol.15, issue 4, pp.399-402, 2020.

[85] V. Sampson, "Oral hygiene risk factor", British Dental Journal, vol.228, issue 8, p. 569, 2020.

[86] T. Greenhalgh, J. Wherton, S. Shaw, C. Morrison, "Video consultations for covid-19", BMJ (Clinical research ed), vol.368, p. m998, 2020.

[87] A. Giudice, F. Bennardo, A. Antonelli, S. Barone, L. Fortunato, "COVID-19 is a New Challenge for Dental Practitioners: Advice on Patients' Management from Prevention of Cross Infections to Telemedicine", The Open Dentistry Journal, vol.14, issue 1, pp. 298-304, 2020.

[88] M. Khan, S. Ghafoor, "Teledentistry and COVID-19; Today and Tomorrow", vol.36, pp. 74-76, 2020.

[89] A. Villa, V. Sankar, C. Shiboski, "Tele(oral)medicine: A new approach during the COVID-19 crisis", Oral diseases, 2020.

[90] A. Giudice, S. Barone, D. Muraca, F. Averta, F. Diodati, A. Antonelli, et al, "Can Teledentistry Improve the Monitoring of Patients during the Covid-19 Dissemination? A Descriptive Pilot Study", Int J Environ Res Public Health, vol.17, issue 10, p. 3399, 2020.

[91] M. Estai, Y. Kanagasingam, D. Xiao, J. Vignarajan, B. Huang, E. Kruger, et al, "A proof-of-concept evaluation of a cloud-based store-and-forward telemedicine app for screening for oral diseases", Journal of Telemedicine and Telecare, vol.22, issue 6, pp. 319-325, 2015.

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Advances in Medical, Pharmaceutical and Dental Research Journal

ACADEMY Publishing Center

Volume 1, Issue 1, December 2021 - ISSN 2812-4898