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AN OVERVIEW OF NEBULIZED DRUG DELIVERY SYSTEM AND THEIR APPLICATION IN DIFFERENT FIELDS

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ABSTRACT

Different technological advancements and developments have been performed worldwide in the avenue of inhalation therapy. Nebulization is a common method for generating medical aerosol and is used worldwide by adults and children. Nebulizer is a electrically powered or battery powered machine that turn liquid medication into a mist so that it can be breathed directly into the lungs. Nebulized Pharmacological therapy is used treatments for patients with asthma and COPD. People suffered from COPD died every year in low- and middle-income countries. Current guidelines emphasized on inhaled pharmacology therapy as the favorable route of administration for treating COPD, asthma and various other pulmonological diseases. A successful pulmonary administration requires a harmonic interaction between the drug formulation, the inhaler device, and the patient. This review describes the various features of nebulizer delivery devices concerning mechanisms of aerosol generation, their use with different formulations, and their advantages and disadvantages.

Keywords: Technological advancement, Inhalation therapy, Aerosol generation, pulmonary problems, COPD, Mist generation.

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INTRODUCTION

Nebulizer is a device that converts liquids into aerosols that can be inhaled into the lower respiratory tract. Nebulizers used in aerosol drug delivery to produce a polydisperse aerosol where the drug delivered in the particle size range 1-5 micrometer in diameter. Nebulizers can be used to relieve symptoms of various lung conditions by administering both quick-relief medicines and long-term control medicines. Most inhaled medications relieve symptoms such as wheeziness, breathlessness, and tightness in the chest. They can also prevent or slow the accumulation of phlegm and mucus. Though some conditions such as asthma and COPD can be treated with an inhaler but condition such as cystic fibrosis, bronchiectasis and various other severe lung injury can be better treated with nebulizers. Though ultrasonic nebulizer tends to be more expensive and are not typically used outside the hospital setting, most nebulizers are small and easy to use. [1,2].

History [3, 4, 5**]**

The first "powered" or pressurized inhaler was invented in France by Sales-Girons in 1858. This device used pressure to atomize the liquid medication. The pump handle is operated like a bicycle pump. When the pump is pulled up, it draws liquid from the reservoir, and upon the force of the user's hand, the liquid is pressurized through an atomizer, to be sprayed out for inhalation near the user's mouth.

Fig. 1: Siegle's steam spray inhaler

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In 1864, the first steam-driven nebulizer was invented in Germany. This inhaler, known as "Siegle's steam spray inhaler", used the Venturi principle to atomize liquid medication, and this was the very beginning of nebulizer therapy. The importance of droplet size was not yet understood, so the efficacy of this first device was unfortunately mediocre for many of the medical compounds. The Siegle steam spray inhaler consisted of a spirit burner, which boiled water in the reservoir into steam that could then flow across the top and into a tube suspended in the pharmaceutical solution. The passage of steam drew the medicine into the vapor, and the patient inhaled this vapor through a mouthpiece made of glass.

The first pneumatic nebulizer fed from an electrically driven gas (air) compressor was invented in the 1930s and called a . As an alternative to the expensive electrical nebulizer, many people in the 1930s continued to use the much more simple and cheap hand-driven nebulizer, known as the Parke-Davis Glaseptic.

In 1956, a technology competing against the nebulizer was launched by Riker Laboratories, in the form of pressurized metered-dose inhalers, with Medihaler-iso (isoprenaline) and Medihaler-epi (epinephrine) as the two first products. In these devices, the drug is cold-fill and delivered in exact doses through some special metering valves, driven by a gas propellant technology (i.e. Freon or a less environmentally damaging HFA).

In 1964, a new type of electronic nebulizer was introduced: the "ultrasonic wave nebulizer". Today the nebulizing technology is not only used for medical purposes. Ultrasonic wave nebulizers are also used in humidifiers, to spray out water aerosols to moisten dry air in buildings.

Some of the first models of electronic cigarettes featured an ultrasonic wave nebulizer (having a piezoelectric element vibrating and creating high-frequency ultrasound waves, to cause vibration and atomization of liquid nicotine) in combination with a vapouriser (built as a spray nozzle with an electric heating element). The most common type of electronic cigarettes currently sold, however, omit the ultrasonic wave nebulizer, as it was not found to be efficient enough for this kind of device. Instead, the electronic cigarettes now use an electric vaporizer, either in direct contact with the absorbent material in the "impregnated atomizer," or in combination with the nebulization technology related to a "spraying jet atomizer" (in the form of liquid droplets being out-sprayed by a high-speed air stream, that passes through some small venturi injection channels, drilled in a material absorbed with nicotine liquid).

Working principle [6]

Nebulizers works mainly based on BERNOULIS PRINCIPLE-

By the mid 19th century the search was on for a device that would turn a solution into a spray. It was believed that such a device would break down the solution into atoms, and in this way the solution could be inhaled. This breakdown was thus referred to as atomization, pulverizing or nebulizing, and the devices created were often referred to as atomizers, pulverizers or nebulizers.

Yet no such machine would have been invented if not for the discovery of the Bernoulli Principle. Daniel Bernoulli observed that when water hits a rock it creates a mist that can be inhaled. He published a book in 1738 where he described that a similar effect could be created by forcing water through a narrow tube.

His concept was based on the fact that the faster water flows through a tube, the less the lateral pressure will be. A decreased lateral pressure is also referred to as a negative side stream pressure. If there is a hole in the side of the tube, the negative pressure will force water into the stream.

This same concept was used in creating the first nebulizers only by using air. Air is forced through a tube, and a hole in the tube is connected to a container with a solution in it that contains the medication. The fluid is basically sucked in due to the negative sidewall pressure, and turned into a spray or mist.

Nebulizer vs inhaler [7]

Inhalers and nebulizers both send medication into your lungs, and both have pros and cons.

A nebulizer is often easier for young children to use because all they have to do is breathe normally. It takes longer to deliver medicine: at least 5 or 10 minutes. And even portable nebulizers can be bulky and hard to carry around. But some people prefer nebulizers because they can see and feel the mist of medication.

Inhalers are often cheaper and tend to have fewer side effects than nebulizers. You can carry one in your pocket or bag. An inhaler can be tricky to use at first, but most people quickly get the hang of it. It delivers an exact dose of medication.

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Types of nebulizer [6,7]

Fig. 2:Inhaler or metered-dose nebulizer [8]

Fig. 3: Jet nebulizer [9]

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Fig. 4: Ultrasonic nebulizer [10]

Table 1: Comparison of three different nebulizers [11]

S. no.	Nebulizers	Working principle	Advantages	Disadvantages
1a)	Jet nebulizers with a corrugated tube	Bernoulli's principle	Cheap, easy to use, Effective in delivering the drugs that cannot be delivered with pMDIs and DPIs	Inefficient, difficult to clean, Need compressed and additional tubing
1b)	Breath-actuated and breath enhanced jet nebulizers	Bernoulli's principle	Drug delivery only during inhalation, easy to use, less medication wasted, more efficient than JNs with tubing	Need sufficient flow to trigger drug delivery, Takes longer to deliver the drug, Not ventilator-enabled expensive
2	Ultrasonic nebulizers	Piezoelectric crystal vibration at high frequencies	Easy to use, more efficient than jet nebulizers	Large residual volume Inability to aerosolize viscous solutions. Degradation of heat sensitive materials
3	Mesh nebulizers	Contraction and expansion of vibration	A fast, quiet, portable, self-contained power source, optimize particle size for specific drugs, more efficient than other nebulizers, easy to use	More expensive, cleaning can be difficult, medication dosage must be adjusted, not compatible with viscous liquids or those that crystallize on drying

Table 2: Marketed formulations of nebulizer [11**]**

S. no.	Brand name	Drug	Innovator name
1	Accuneb ®	Albuterol sulphate	Mylan
2	Xopenex®	Levalbuterol HCl	Oak Pharmaceuticals
3	DuoNeb®	Ipratropium bromide, Albuterol sulphate	Mylan
4	Performist®	Formoterol fumarate	Mylan
5	Cayston®	Aztreonam	Gilead life sciences
6	Aeronab®	Albuterol sulphate and Ipratropium bromide	Nectar therapeutics
7	Micro air NE U-22	Albuterol sulphate and Ipratropium bromide	Omron health care
8	Bethkis®	Tobramycin	Chiesi
9	Brovana®	Arformoterol tartrate	Sunovion Pharma
10	Pulmicort	Budesonide	AstraZeneca

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How to use a Nebulizer [12]

1. Put the nebulizer compressor (the main body of the machine) on a flat surface near an outlet.
2. Make sure each nebulizer piece is clean.
3. Wash your hands prior to preparing the medication.
4. Mix your medication if it hasn't been premixed and add it to the container. Keep the container upright during treatment.
5. Connect the compressor and liquid container with the tubing.
6. Prepare the mouthpiece or mask.
7. Turn your nebulizer on and make sure it's misting.
8. Make sure the mouthpiece or mask isn't leaking. It usually takes about 15 minutes to inhale all of it.

Different parts of nebulizer [12]

Nebulization is done with the help of a nebulizer system or nebulizer kit. Jet nebulizers are the most widely used nebulizers and consist of 4 main parts.

1. **Compressor**

   The compressor is the part which fuels the working of the nebuliser system. It is a device which pumps the ambient/outside air forcefully through the nozzle which is attached to the tubing. The compressor is connected to a power source.

Fig. 5: Compressor

2. Tubing

The tubing delivers the pressurized air from the compressor to the medication cup which converts the liquid medicine into vapour or aerosol or mist form.

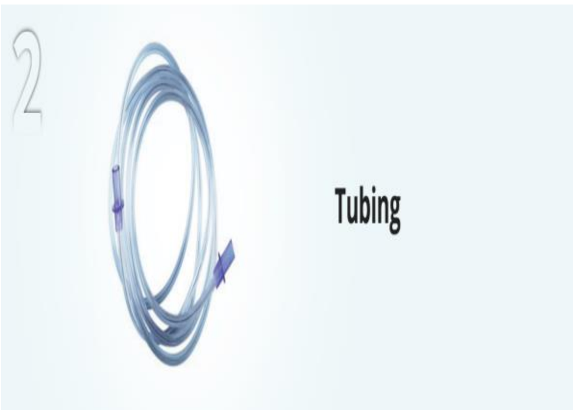

Fig. 6: Tubing

3. Medication cup

This is the unit into which the liquid medicine is poured. In this cup, the liquid medicine is converted into aerosol or mist by the pressurized air pumped by the compressor through the tubing.

Fig. 7: Nebulizing chamber

4. Facemask/Mouthpiece

The face mask or the mouthpiece is the part that is worn by the patient and through which the medicine mist can be inhaled. If a face mask is used, ensure that it fits tightly. In the case of a mouthpiece, ensure that the mouthpiece is held firmly between the teeth with the lips covering it completely.

Fig. 8: Facemask/Mouthpiece

5. Nebulizerfilter

Nebulizer filters are an important part of the nebulizer system. Nebulizers compress and pump the ambient air or oxygen, which helps convert the liquid medicine into an aerosolized medication. This air, before entering the medication cup, passes through the filter, which helps to remove particulate particles in the compressed air. The filter should be checked regularly and replaced when needed.

Fig. 9: Nebulizer filter

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Table 3: Commonly used excipients in nebulizer formulations [13]

S. No.	Category	Role	Example
1	Isotonicity adjustment	Used to adjust the tonicity of the formulation	Sodium chloride, Dextrose
2	pH adjustment	Used to adjust pH same to physiological conditions and maximize drug stability	Sodium hydroxide, hydrochloric acid sulphuric acid
3	Purging	Purging used to reduce oxidation	Nitrogen
4	Antimicrobial preservative	To avoid the microbial growth in the formulation	Benzalkonium chloride, ethanol, propylene glycol, Beczoyl Alcohol, chlorobutanol, Methyl paraben
5	Buffer component	It gives the buffer capacity to formulation at desire Ph	Sodium citrate, Sodium Phosphate, citric acid
6	Surfactant	Increases suspendability and stability of suspension	Polysorbate 80,20
7	Cation chelating agent	Forms chelate with ions present in the formulation and increases the stability	Disodium EDTA
8	Suspending Agents	Increases viscosity and suspendability of suspension	CMC, Na CMC
9	Co-Solvent	Helps to improve solubility	Alcohol, PEG 400, Propylene Glycol
10	Humactant	Used to maintain humidification in the formulation	Glycerin

Characterization of Nebulizer [13]

1. pH

For both inhalation solution and suspension, the pH of the Formulation should be tested and an appropriate acceptance criterion established. Thus the stability can achieve by proper selection of pH of formulation. However, the pH of formulation should be (4.5-6.5) to prevent the sneezing.

2. Osmolality

For formulations containing an agent to control the tonicity or for products having a label claim regarding tonicity, the osmolality of the formulation should be tested and controlled at release. Some existing marketed products have reported osmolality in the range of 300-700 mOsmol/Kg.

3. Impurities and Degradation Products

The levels of impurities and degradation products should be determined by a validated analytical procedure or procedures. Acceptance criteria should be set for individual and total impurities and degradation products. All related impurities appearing at levels of 0.1 percent or greater should be specified according to ICH guideline for impurities.

4. Preservatives and Stabilizing Excipients Assay

If preservatives, antioxidants, chelating agents, or other stabilizing excipients (e.g., benzalkonium chloride, phenylethyl alcohol, and edetate) are used in the formulation, there should be a specific assay for these components with associated acceptance criteria. Acceptance criteria for the chemical content of preservatives at the time of product release and through the product shelf life should be included in the drug product specification.

5. Delivered Dose

Delivered dose testing is carried out to determine the total amount of drug that the patient might be expected to receive during a treatment period. Two discrete metrics are defined and measured: the active substance delivery rate and the total active substance delivered. Reflecting the mode of operation of nebulisers, delivered dose testing is carried out using well-defined breathing profiles for specific patient types. The defined profiles for child, infant and neonate patients are based on significantly smaller volumes, higher breathing frequencies and different inhalation/exhalation ratios.

To measure active substance delivery rate the output from the nebulizer is captured on a filter, under appropriate test conditions, over a specified time (typically 60 seconds). Longer test times are applied to provide sufficient mass (greater than the limit of quantification) for reliable analysis, where delivery rates are low. Replacing the filter and continuing the test until nebulisation stops, because the reservoir is empty, enables calculation of the second metric – total active substance delivered. This is the total mass collected during steps 1 and 2 of the test.

Mean Nebulisation Time (MNT) and Mean Delivered Dose (MDD) determined at the labelled flow rate of 5.5 L/min through such time that mist is no longer coming out of the mouthpiece.

6. Aerodynamic particle size distribution (APSD)

Generally speaking a particle size range of < 5 microns is taken as being optimal for pulmonary deposition. Cascade impaction is the preferred method for APSD measurement because of its ability to provide well-resolved, drug specific particle size data in the size range of interest.

APSD

Cooling of the NGI prior to testing is specified to decrease the evaporation of droplet. The aerodynamic size distribution may be characterised by the fine particle dose (FPD), mass median aerodynamic diameter (MMAD) and the geometric standard deviation (GSD). The MMAD is the most important parameter defining particle size, i.e. drug deposition. Theoretically, a monodisperse aerosol will exhibit a GSD of 1.0, in practice however, a GSD of ≤1.22 is considered as monodisperse.

7. Droplet size distribution

The DSD of a nebuliser is a critical parameter, since it significantly influences the *in vivo* deposition of the drug in the lung. The droplet size is hereby mainly influenced by the formulation and the nebuliser device. If a laser diffraction method is used, droplet size distribution can be controlled in terms of ranges for the D10, D50, D90, span [(D90-D10)/D50], and percentage of droplets less than 10 µm.

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Table 4: Nebulizer advantages and disadvantages [13]

S. No.	Nebulizers	Advantages	Disadvantages
1a)	**Jet nebulizers with corrugated tubing**	• Cheap • Easy to use • Effective in delivering drugs that cannot be delivered with pMDIs and DPIs	• Inefficient • Difficult to clean • Need compressed and additional tubing
1b)	**Breath-actuated & Breath-enhanced jet nebulizers**	• Drug delivery only during inhalation • Easy to use • Less medication wasted • More efficient than JNs with 3tubing	• Need sufficient flow to trigger drug delivery • Takes longer to deliver drug • Not ventilator-enabled • More expensive
2)	**Ultrasonic nebulizers**	• E4asy to use • More efficient than jet nebulizers	• Large residual volume • Inability to aerosolize viscous solutions • Degradation of heat-sensitive materials
3)	**Mesh nebulizers**	• Fast, quiet, portable • Self-contained power source • Optimize particle size for specific drugs • More efficient than other nebulizers • Easy to use	• More expensive • Cleaning can be difficult • Medication dosage must be adjusted • Not compatible with viscous liquids or those that crystallize on drying

Nebulizer after care [14]

1. **Wash your hands:**
 Before beginning, it's a good idea to take a few moments to wash your hands with soap and water or an alcohol-based sanitizer. Washing your hands kills bacterial and other harmful microorganisms on them. Since this method for cleaning the nebulizer doesn't use any soap, you won't want to accidentally transfer these onto the nebulizer by cleaning it with dirty hands.

2. **Take the nebulizer apart, if possible:**
 Most nebulizers consist of a mask or mouthpiece, a section of tubing, a few connecting pieces, and a compressed air machine. Gently take these pieces apart from each other. You only need to clean one or two pieces, not the entire machine, so don't leave them connected unless your nebulizer does not come apart.

- Most nebulizers come in one of two varieties: atomizer jet and ultrasonic. Atomizer jets, the more common variety, use compressed air to disperse your medicine, while ultrasonic nebulizers vibrate the liquid medicine with soundwaves to make it into a vapor. While these two nebulizers use different mechanisms to operate, they both use similar mouthpiece/tubing setups to disperse the medicine, so the cleaning instructions are virtually identical for both.
- Some nebulizers (like, for instance, smaller portable models) may have slightly different configurations. In these cases, do your best to remove the pieces that can be removed. Nearly all nebulizers will have some sort of mouthpiece or mask — this is the most important thing to remove and clean.

3. **Wash the cup or mouthpiece with warm water.** Run some warm (*not hot*) water. Rinse the mouthpiece and any T-shaped connecting pieces that attach to it under the water for about half a minute to one minute, making sure that every part of these pieces gets rinsed.

- Do not rinse the tubing or the compressed air machine with water. The tubing is difficult to dry and the machine itself is not intended to be cleaned this way. You *can*, however, wipe down the outsides of these pieces with a towel.

4. **Let air dry:**
 Shake the excess water off of your mouthpiece (and any T-shaped connector piece you washed) and set it on a clean towel. Allow the water to evaporate naturally. This can

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take anywhere from 20 minutes to an hour or two, depending on the climate.

5. **Put the machine back together and store:**
When the pieces are dry, put the entire nebulizer back together. Run air through the machine for about 10 to 20 seconds to remove any water inside.[7] At this point, you can disconnect the mouthpiece and tubing from the compressed air machine and store both separately.

- A good place to store the mouthpiece and tubing is in a clean ziplock bag. The compressed air machine can be covered with a sheet or towel to keep dust off of it.

6. **Optionally, wash pieces in soapy water at the end of the day:**
Some (but not all) nebulizers will recommend that you disinfect the pieces after each day of use. Consult your model's instructions to determine whether you need to do this. Follow the steps below for this intermediate cleaning method, which is nearly the same as the steps above, but using soap:[8]

- Remove the nebulizer's mouthpiece and any T-shaped connector pieces attached to it. The tubing and compressed air machine should not be washed.
- Run warm water.
- Use mild dishwashing soap or detergent to wash the pieces for about half a minute to one minute, making sure that every part of the pieces is cleaned.
- Rinse for about half an hour and air dry.

Deep cleaning of nebulizer [15]

1. To ensure long-term cleanliness and keep your nebulizer in good working order, it's important to give it regular deep cleanings to kill any bacteria or microorganisms your normal cleaning regimen failed to kill. After you finish using your nebulizer, start by washing it as you normally would. See the section above for more details.
Most manufacturers recommend performing a deep cleaning once or twice per week. If you are unsure how often to deep clean your nebulizer, consult the instructions that came with it.
2. **Get a disinfectant solution (or make your own.):**
Different nebulizer manufacturers will recommend using different products for deep cleaning sessions. Some nebulizers will have a cleaning solution included with them, others will recommend that you buy a commercial cleaning solution from the pharmacy, and others will recommend that you make your own — consult your nebulizer's instructions to be sure which is best for you.
3. **Soak your pieces:**
Put the mask and any T-shaped connector piece in a clean bowl and cover them with the cleaning solution until they are completely submerged. Leave them to sit so that the solution can clean them thoroughly. The amount of time your nebulizer's manufacturer will recommend for soaking can vary from model to model. Typically, however, this is around 20 minutes to an hour. Once again, don't soak the tubing or the compressed air machine.
4. **Rinse well and air dry before storing:**

- Once the nebulizer has finished soaking, finish the cleaning process the same way as you would for a quick-clean in the method above. See below:
- Remove the pieces from the solution and rinse them thoroughly with warm running water for at least 30 seconds.
- Shake the excess water off and set the pieces on a clean towel.
- Allow the pieces to air dry.
- When dry, you may re-connect the pieces and run the compressed air machine briefly to remove any water caught inside them.
- Store the tubing and mask in a clean zip lock bag. Cover the compressed air machine with a towel before storing it.
- Dispose of your leftover cleaning solution — don't reuse it.

Application

1. **IN COPD PATIENTS [16,17]**

Although handheld pMDIs or DPIs are effective in most patients with COPD, cognitively impaired and elderly patients may benefit more from the use of a nebulizer, since these patient populations may have difficulty synchronizing inhalation with inhaler actuation or may be unable to generate a sufficient inspiratory flow rate against the resistance of a breath-activated DPI to generate an effective aerosol. SMIs are compact portable multidose inhalers that use liquid formulations similar to those in nebulizers but, like MDIs and DPIs, require manual manipulation to generate the aerosol and special breathing techniques for effective delivery of the aerosolized medication to the lungs. The choice of therapy, however, ultimately depends on a wide range of factors, including the prescribing physician, the availability of specific drug/device pairings, drug cost, and patient preferences and satisfaction. Each of the delivery devices that are available for administering drugs to patients with COPD.

Table 5: Advantages and disadvantages of different Nebulizers in COPD patient [17]

Inhalation device	Advantages	Disadvantages
DPI	Breath-actuated devices	Requires patient to generate moderate to high inspiratory flow[a]
	Convenient Portable Rapid medication delivery	Elderly patients and those with hyperinflation and flattened diaphragms may have difficulty achieving adequate inspiratory flow
	Single- and multidose devices Counter indicates remaining doses	Can result in high pharyngeal and central airway deposition, which can lead to adverse events
pMDI	Multiple dosing (≥100 doses/canister)	Multiple steps involved Requires adequate patient coordination to synchronize inhalation with pMDI actuation[b]
	Short administration time	High pharyngeal deposition, which can lead to adverse events
	Convenient	Only 10%–20% of dose deposited in lungs from suspension MDIs[c]

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	Portable	While the addition of spacer eliminates the need to coordinate inhalation and reduces oropharyngeal deposition, spacers are bulky and require cleaning
SMI	Multiple dosing (1 month's supply)	Multiple steps involved
	High lung deposition	Not breath actuated
	Portable No propellants Slow-velocity aerosol generated Aerosol persists for 1.5 seconds, increasing ease of synchronizing inhalation with actuation	Not available in most countries
Jet nebulizer	Easy for patients to use	Limited portability
	Requires minimal cognitive ability	Device preparation required
	Does not require hand-breath coordination, manual dexterity, or hand strength	Lengthy administration time Daily cleaning required Not all medications are available in this format May not readily aerosolize drug suspensions
High-efficiency vibrating mesh nebulizer	Portable	High cost
	Quiet	Device preparation required
	Short administration times	Daily cleaning required Not all medications are available in this format May not readily aerosolize drug suspensions Optimal doses need to be defined by additional studies to avoid overdosing

2. IN ASTHMA PATIENTS [17]

Administration of asthma medication via inhalation is advantageous because it allows for drug delivery directly to the site of action, resulting in faster onset of action, smaller doses, reduced systemic absorption, and fewer systemic adverse events compared with oral administration.' However, proper and effective administration of inhaled asthma medication to infants and young children is challenging

Children's abilities to use different inhalation delivery devices vary, thus affecting the dose of medica tion that reaches the airway. The efficacy of inhaled medication is highly contingent on the patient's ability to use an inhalation device correctly. Device selection should include consideration of the child's ability to use the device properly, the types of med ication being prescribed (eg, rescue, controller, or both), and preferences of the caregiver and patient. and Incorrect use of pMDIs is common," infants and young children may lack the coordination to use a pMDI correctly and effectively. Incorrect use of inhalers may lead to undertreat ment with inhaled corticosteroids (ICSs), resulting in overtreatment with oral corticosteroids and inhaled ß-adrenergic agonists for asthma that is not well controlled. Therefore each child should be assessed as to his/her ability to produce the necessary effort and coordination required for a specific device. Parents/guardians also should be able to help the child administer the medication properly.

3. NEBULIZED ANTICOAGULANT IN LUNG INJURY [18]

The efficacy of nebulized activated protein C, antithrombin, heparin and danaparoid has been tested in diverse animal models of direct (for example, pneumonia-, intra-pulmonary lipopolysaccharide (LPS)-, and smoke inhalation-induced lung injury) and indirect lung injury (for example, intravenous LPS- and trauma-induced lung injury). Nebulized anticoagulants were found to have the potential to attenuate pulmonary coagulopathy and frequently also inflammation. Notably, nebulized danaparoid and heparin but not activated protein C and antithrombin, were found to have an effect on systemic coagulation. Clinical trials of nebulized anticoagulants are very limited. Nebulized heparin was found to improve survival of patients with smoke inhalation-induced ALI. In a trial of critically ill patients who needed mechanical ventilation for longer than two days, nebulized heparin was associated with a higher number of ventilator-free days. In line with results from preclinical studies, nebulization of heparin was found to have an effect on systemic coagulation, but without causing systemic bleedings.

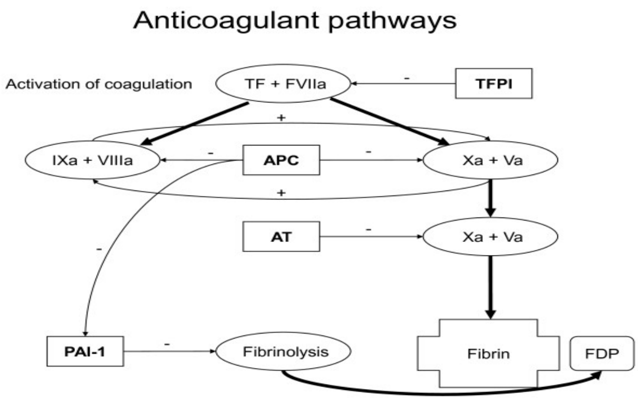

Fig. 10: Anticoagulant pathway

4. AEROSOL THERAPY SYSTEM DURING INVASIVE VENTILATION [19]

All patients receiving at least one aerosol treatment were on ventilators with bias flow settings during invasive ventilation. The most commonly utilized aerosol generator was the pneumatic jet nebulizer, which was used in 67.2% (84/125) of the patients, followed by a vibrating mesh nebulizer (15.2%), a metered-dose inhaler (MDI) (12.8%), and an ultrasonic nebulizer (4.8%). For the pneumatic jet nebulizers, 63.1% (53/84) of the individuals were driven by the ventilator to generate aerosol synchronized with inspiration (breath-synchronized nebulizer) and 64.2% (34/53) were placed close to the Y piece on the inspiratory limb. The remaining 31 individuals on the jet nebulizers were powered by an external compressed gas source operated continuously (continuous nebulizer), with 71% (22/31) of them placed close to the Y piece in the

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inspiratory limb, and 12.9% (4/31) being placed 20–30 cm away from the Y piece in the inspiratory limb. The vibrating mesh nebulizer and ultrasonic nebulizer were both placed close to the Y piece in the inspiratory limb for patients receiving aerosol with MDI. Among patients who used an MDI (n=18), only 1 (5.6%) patient used a spacer chamber.

5. NEBULIZATION IN PEDIATRIC PATIENTS [20]

Doctors may prescribe nebulizers for chronic conditions in infants. Asthma, for example, is a condition that causes an immune response that irritates the airways. Other conditions a doctor may prescribe a nebulizer for include:

Croup:

Croup is the result of one of the viruses that causes the common cold. It causes airway swelling that leads a child to develop a barking cough, runny nose, or fever.

Cystic fibrosis:

This genetic_disease can cause thick mucus to build up in the airways, clogging them and making it harder to breathe.

Epiglottitis:

This rare__condition is a result of the *Haemophilus influenzae* type B bacteria that can cause pneumonia. It causes severe airway swelling that leads to an abnormal, high-pitched sound when breathing.

Pneumonia:

Pneumonia is a severe illness involving inflamed lungs. It usually requires hospitalization in babies. Symptoms include fever, shortness of breath, and changes in a baby's alertness.

Respiratory syncytial virus (RSV):

RSV is a condition that often causes mild, cold like symptoms. While severe symptoms aren't common in older children, infants can develop inflammation of the small airways (bronchiolitis).

Nebulizers can be an alternative to inhalers. These devices deliver short bursts of medication when a person inhales.

Nebulizers deliver medication over a course of time, usually 10 to 15 minutes. They don't require a baby to cooperate to take the medicine in.

While inhalers can be fitted with masks and used even with young infants, nebulizers are preferred, depending on the medication and why it's being used.

While some of the elements of using a nebulizer depend on the specific type, here's a general example of the nebulizer process:

- Collect the medication for the nebulizer. Some are available in liquid form that has the medicine added. Others are a liquid or powder that must be mixed with sterile water or saline solution. Read the directions carefully before pouring the medication in the cup.
- Connect one end of the tubing to the cup of medication and the other to the nebulizer.
- Connect the mask or pacifier to the cup.
- Hold the mask to your child's face. While many of the infant masks come with strings to put around a baby's head, most babies don't tolerate these strings very well. It may be easier to gently hold the mask touching the child's faced and cover their nose and mouth.
- Turn the nebulizer on.
- Hold the mask to your child's face while the treatment bubbles and creates a mist inside the mask.
- You'll know when the treatment is complete when the mist becomes less noticeable and the little cup appears almost dry.
- Clean the mask and nebulizer after each use.

6. NEBULIZATION THERAPY IN COVID-19 PANDEMIC [21]

Nebulization and some of the other procedures performed on patients with known or suspected COVID-19 could generate infectious aerosols or have the potential to do so. In the absence of enough data on their safety or risk involved, they continue to be a potential source of infection. Such procedures that pose a risk should be performed cautiously and avoided if possible. However, based on the available data, nebulizer administration in patients with COVID-19, likely represents a lower infection risk than other AGPs, but close-range viral aerosol generation remains to be a possibility.

Based on this potential risk, the CDC and Minnesota Department of Health recommend the following guidance to minimize risk to HCPs:

- If patient can tolerate and properly use, switch to MDI with a dedicated spacer
- HCPs should wear a N-95 facemask along with an eye protection, gloves, and a gown during treatment
- The number of HCP present during the procedure should be limited to only those essential for patient care and procedure support. Visitors should not be present for the procedure
- Close patient's room door when providing nebulizer treatment
- Upon the setup of nebulizer, have HCPs maintain a safe distance (6 feet or greater), possibly outside the door
- Clean and disinfect procedure room surfaces promptly with recommended disinfectants
- AGPs should preferably be performed in airborne infection isolation rooms, if available
- Patients do not need to be transferred to a higher level of care solely for the purpose of providing nebulizer treatment.

The guidance further notes that HCP should use appropriate hand hygiene when helping patients remove nebulizers and oxygen masks. Only disposable single-use nebulization units should be used for the purpose of nebulization of a patient in a health-care facility which in no case must be reused. The driving gas to run the unit could be either oxygen or compressed air according to the need in the particular case. These units must be disposed of properly after every use.

7. HOME NEBULIZATION [22]

Doctors prescribe home nebulizer therapy for a variety of health issues, but primarily for problems affecting the lungs, such as:

- chronic obstructive pulmonary disease (COPD)
- cystic fibrosis
- asthma
- emphysema
- chronic bronchitis
- Currently, there are two basic types of nebulizer:

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- The jet nebulizer uses compressed air to turn medication into a mist.
- The ultrasonic nebulizer achieves the same outcome by using ultrasonic vibrations.

Medication labels may specify the best nebulizer for their particular formulation. Some manufacturers offer nebulizers specifically for children.

Home nebulizer therapy does not require the person to coordinate their breathing with the machine, which makes it easier to use than other devices, such as inhalers. For this reason, doctors often recommend nebulizers for people who may have difficulty using inhalers, such as children, older adults, and people on ventilators.

In addition, home nebulizer therapy delivers medication more deeply into the lungs than some people can manage on their own.

8. FUTURE TRENDS IN NEBULIZED THERAPY IN PULMONARY DISEASES [23]

Aerosol therapy is a key modality for drug delivery to the lungs of respiratory disease patients. Aerosol therapy improves therapeutic effects by directly targeting diseased lung regions for rapid onset of action, requiring smaller doses than oral or intravenous delivery and minimizing systemic side effects. In order to optimize treatment of critically ill patients, the efficacy of aerosol therapy depends on lung morphology, breathing patterns, aerosol droplet characteristics, disease, mechanical ventilation, pharmacokinetics, and the pharmacodynamics of cell-drug interactions. While aerosol characteristics are influenced by drug formulations and device mechanisms, most other factors are reliant on individual patient variables. This has led to increased efforts towards more personalized therapeutic approaches to optimize pulmonary drug delivery and improve selection of effective drug types for individual patients. Vibrating mesh nebulizers (VMN) are the dominant device in clinical trials involving mechanical ventilation and emerging drugs. In this review, we consider the use of VMN during mechanical ventilation in intensive care units. We aim to link VMN fundamentals to applications in mechanically ventilated patients and look to the future use of VMN in emerging personalized therapeutic drugs.

Other Nebulized Therapies [24-38]

Alpha-1 antitrypsin (AAT)-

The role of nebulized AAT as an anti-inflammatory treatment in CF is currently being investigated.

Magnesium sulphate-

Various studies have assessed the role of magnesium sulfate in asthma exacerbation. A recent Cochrane review did not find significant improvements when magnesium sulfate was added to beta-agonist treatment.

Lidocaine-

Lidocaine is a drug used as a local anesthetic and antiarrhythmic agent. In addition to its topical use to suppress coughing during fibrobronchoscopy, nebulized lidocaine has been used to treat difficult-to-control cough and asthma. Although it is not commercially available for nebulization, lidocaine hydrochloride solution for injection satisfies the requirements for use in nebulized form.

Furosemide-

This has also been used to relieve dyspnea via nebulized administration. It has been effective in patients with advanced cancer and severe dyspnea who do not respond to opiates. Various studies reviewing the effects of nebulized furosemide in patients with airway obstruction have found that it has a slight bronchodilator effect, or at least is capable of arresting bronchoconstriction.

Prostanoids-

In pulmonary arterial hypertension (PAH), there are 2 drugs within the prostanoid group that can be inhaled.

Tuberculostatics-

Some attempts have been made to treat multi-resistant tuberculosis via the inhaled route, such as with dry powder capreomycin, or formulations of various tuberculostatics such as liposomal capreomycin, isoniazide or rifampicin that have shown good levels via aerosol delivery in experimental animals.

Surfactant-

One meta-analysis that analyzed the administration of exogenous surfactant in ARDS found that it might improve oxygenation but not mortality. However, a wide variety of routes of administration were used in this meta-analysis, which concluded that the bronchoscopic route may be most promising, as the rate of pulmonary deposition using the nebulized route only reaches 4%–5%.

CONCLUSION

Nebulized drugs are an effective therapeutic alternative in multiple respiratory diseases. Effective, rapid administration nebulization devices are currently available. The future will doubtless bring innovative drugs and new evidence that will allow us to resolve the many uncertainties that still exist.

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