Drug concentrations in the air and their influencing factors in a pediatric intensive care unit

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Aerosolized drug therapy is a common approach in treating respiratory diseases in clinical practice. This study aimed to assess air quality in the pediatric intensive care unit (PICU) of the medical center and investigate variations in drug concentration relative to the patient’s position during aerosolized drug treatment. To monitor air quality and aerosolized drug concentrations in the PICU, we conducted bi-weekly 24-hour samplings over a month. Monitored air quality parameters included temperature, relative humidity (RH), carbon dioxide (CO₂), particulate matter (PM), total volatile organic compounds (TVOCs), and aerosolized drug levels in the air. The study also used a small volume nebulizer (SVN) to analyze the relationship between aerosolized drug concentration and distance from a simulated patient. This study revealed that the average concentrations of CO₂, PM₁₀ (an aerodynamic diameter equal to or less than 10 μm), and PM₂.₅ (an aerodynamic diameter less than 2.5 μm) in the PICU met Taiwan’s Ministry of Environment (MOENV) indoor air quality standards. However, the hourly average concentration of TVOCs in the PICU was almost twice the MOENV standard. The concentration of acetylcysteine in the air showed a positive association with both RH and CO₂ concentration. Additionally, drug concentrations measured at 1 m, 1.6 m, and 3 m from the SVN were significantly lower than those measured at 0.1 m from the SVN. Continuous monitoring of TVOCs and CO₂ in the PICU is necessary. During
aerosol therapy, it is crucial for medical staff and family members to maintain a safe
distance or integrate a HEPA (high-efficiency particulate air) filter into the ventilator
circuit system. This precautionary step aims to minimize unwarranted exposure and
maintain hospital air quality.

Keywords: hospital, air quality, particulate matter, volatile organic compound, airborne
drug, aerosol therapy.
Aerosolized drug therapy is a prevalent method used in the treatment of respiratory diseases. The goal of aerosolized drug therapy is to deliver drug-containing particles, generated by a nebulizer, to the respiratory tract and deposit them at the intended target sites. Factors that influence the dosage of inhaled drugs include the type of drug, inspiratory time (Bauer et al., 2009), inspiratory flow, inspiratory–expiratory ratio (Pedersen et al., 2006), type of inhaler (Saeed et al., 2017), type of interface (McGrath et al., 2019), use of a heated humidifier (Yang et al., 2018), and nebulizer setting mode during ventilation (Wan et al., 2014).

An in vitro study was conducted to investigate the inhalation dose of aerosolized drugs, revealing that approximately 40% of the albuterol drug was deposited in the nebulizer or released into the indoor air (Ari et al., 2016). Concurrently, factors such as the size of the drug storage chamber (holding chamber) (Abdelrahman et al., 2020) and the design of the exhalation hole on the aerosol mask also play a role in influencing the quantity of drug escape (Hui et al., 2014). Furthermore, during drug inhalation, particles smaller than 1 μm were expelled when the patient exhales (Clara et al., 2023). The literature underscores that escaped aerosolized drugs, sputum expulsion, and cleaning activities constituted the primary sources of airborne particulates in the pediatric intensive care unit (PICU). Notably, these particulates have been observed to rapidly
disseminate to other areas (He et al., 2017). The exposure concentration of aerosolized
drugs among individuals in close proximity to a patient employing such treatment is
influenced by factors such as the air exchange rate, the proximity between the patient
and the medical staff during drug inhalation, the patient’s inspiratory flow, and the type
of protective masks worn by individuals (Olier et al., 2019).

During the administration of aerosolized drug treatments, the escape of these drugs
can increase the risk of unintended drug exposure for medical personnel and individuals
in their vicinity (Saeed et al., 2017; Tsai et al., 2015), potentially leading to health
hazards. Research indicates that anticancer drugs, such as cyclophosphamide, 5-
fluorouracil, cisplatin, bleomycin, and doxorubicin, can induce genetic damage in
surrounding exposed workers (Roussel et al., 2019). Moreover, medical staff exposed
to anticancer drugs face an elevated risk of breast and rectal cancer (Ratner et al., 2010).
Furthermore, exposure to aerosolized medications, such as Atrovet, Budesonide, and
salbutamol sulfate commonly used in asthma and COPD (chronic obstructive
pulmonary disease) treatments, can result in bronchospasm and anaphylaxis in
healthcare workers (Chang et al., 2020; Dubus et al., 2003). The risk of occupational
asthma among healthcare workers was also found to be associated with their exposure
to aerosolized drugs (Delclos et al., 2007).

Until now, there have been limited studies examining drug concentrations in
hospital air and investigating variations in drug concentration at different distances from a patient undergoing aerosolized drug therapy. Therefore, in addition to conducting air quality assessments within the PICU of the medical center to understand the distribution of drug concentrations in the air, we conducted additional *in vitro* experiments. These experiments aimed to explore changes in drug concentration at different positions relative to the patient during aerosolized drug treatment, representing a crucial step toward improving hospital air quality.

2 METHODS

2.1 Air quality monitoring in the PICU

This study was conducted in the PICU of a medical center in northern Taiwan. Air sampling locations included the nursing station and the walkway outside the ward, with the primary consideration being to avoid disrupting personnel entering and exiting. These sampling locations are illustrated in Fig. 1. To monitor changes in air quality and aerosolized drug concentrations in the PICU, we conducted sampling twice a week over the course of a month, with each sampling period lasting 24 hours. All sampling instruments were positioned at a height of 1.2–1.5 meters to simulate the breathing zone of humans. Additionally, sampling instruments were placed at least 45 cm away from walls and other samplers to prevent interference.
In this study, we utilized a suspended particulate analyzer (Grimm 1.109, Ainring, Germany) to measure concentrations of PM$_{10}$, PM$_{2.5}$, PM$_{1}$ (an aerodynamic diameter less than 1 $\mu$m), and PM$_{\geq0.5}$ (an aerodynamic diameter equal to or larger than 0.5 $\mu$m). Furthermore, we employed a nanoparticle counter (NanoTracer XP, Eindhoven, Netherlands) to monitor PM$_{0.01-0.3}$ (an aerodynamic diameter between 0.01 $\mu$m and 0.3 $\mu$m) concentration variability. Temperature, RH, and CO$_2$ concentrations within the PICU were analyzed using an indoor air quality monitoring instrument (TSI 7575, Shoreview, US), along with a portable volatile organic gas meter (ppbRAE 3000, San Jose, US) to measure TVOC concentrations.

In addition, this study employed a three-piece cassette containing a polytetrafluoroethylene filter to sample aerosolized drugs in the air, which included bronchodilators (terbutaline and combivent®), expectorant (acetylcysteine), antibiotics (colistin), and vasoconstrictor (epinephrine). The sampling flow rate was set at 10 liters per minute (L min$^{-1}$). To understand the correlation between the concentration of aerosolized drugs in the air and changes in air quality, this study recorded the types and times of aerosolized drug treatments performed on the day of sampling. Filter paper samples were immediately transported to the laboratory and stored at –80°C in a freezer after air sampling. Subsequent drug analysis was conducted as quickly as possible. All filter samples were extracted with sterile deionized water and analyzed using a full-
spectrum spectrophotometer (Model SpectraMax Paradigm, San Jose, US) under optimal absorption wavelength conditions. These optimal conditions were as follows: terbutaline: 273 nm, Combivent®: 276 nm, acetylcysteine: 260 nm, colistin: 242 nm, and epinephrine: 260 nm. In cases where the analyzed drug concentration fell below the detection limit, the actual concentration of the sample was estimated by dividing the lowest detected concentration by 2 (Failla et al., 2006).

2.2 Analysis of drug concentrations in a simulation experiment within a demonstration ward

This study employed a SVN to investigate the correlation between aerosolized drug concentration and distance from a patient. The test drug administered was 2.5 mL of Salbutamol, diluted in a 1:1 ratio with sterile normal saline for testing purposes. The primary goal was to simulate a scenario in which a patient sat by the bedside and inhaled the medication. Aerosols were sampled at distances of 0.1 (n = 3), 1 (n = 4), 1.6 (n = 4), and 3 (n = 4) meters from the SVN. Air sampling was conducted using a three-piece cassette containing a polytetrafluoroethylene filter. The sampling setup was positioned 1.2 meters above the ground, with a sampling flow rate of 10 L min⁻¹. Throughout the sampling period, the air conditioner, doors, and windows remained closed, and changes in environmental temperature and RH were monitored. Filter samples were extracted
using sterile deionized water, followed by centrifugation at 150 rpm for 10 minutes. Drug concentration analysis was performed using spectrophotometry at a wavelength of 276 nm.

2.3 Statistical analysis

Statistical analyses were conducted using the SPSS version 28.0 software (SPSS, Chicago, Illinois, USA), and graphical representations were created using GraphPad Prism 5.0 software (GraphPad Software, Inc., San Diego, CA, USA). The significance level was set at $P < 0.05$. In addition to descriptive statistical analysis, we utilized the Kruskal–Wallis test and Mann-Whitney U test to compare differences in the concentration of aerosolized drugs at various distances from the SVN. Furthermore, Spearman’s correlation analysis was employed to assess the relationships between indoor air quality indices and concentrations of aerosolized drugs.

3 RESULTS AND DISCUSSION

3.1 Air quality assessment in the PICU

This study reveals that the average temperature and RH in the PICU were 22.81°C and 53.88%, respectively (Fig. 2). Additionally, the concentrations of $\text{CO}_2$ (750.88 ppm), $\text{PM}_{10}$ (4.59 $\mu$g m$^{-3}$), and $\text{PM}_{2.5}$ (1.99 $\mu$g m$^{-3}$) all met the indoor air quality standards set by Taiwan’s Environmental Protection Agency. However, the average
concentration of TVOCs (1,067.88 ppb) exceeded the indoor air quality standard value of 560 ppb by approximately twofold (Fig. 2). Analysis of the trend chart demonstrates that CO₂ concentrations gradually decreased after 8 o'clock in the evening, followed by a gradual increase after 6 o'clock in the morning. TVOC concentration followed a similar trend, with a slight rise at 5 o'clock in the morning. Moreover, the concentration trends of PM₁₀, PM₂.₅, PM₁, and PM₀.₀₁₋₀.₀₃ in the PICU exhibited similarities. Notably, peak changes in these PM concentrations occurred at 8 a.m., 4 p.m., and midnight.

In terms of indoor air quality in the PICU, it was found that the average concentrations of CO₂, PM₁₀, and PM₂.₅ were below Taiwan’s MOENV standards (CO₂: 1,000 ppm, PM₁₀: 75 µg m⁻³, PM₂.₅: 35 µg m⁻³) (TMOENV, 2023). However, the hourly average concentration of TVOCs in the PICU was nearly twice as high as Taiwan’s MOENV standard (560 ppb). It could be related to the frequent use of alcohol and other cleaning agents for environmental disinfection. Long-term exposure to these VOCs may cause symptoms such as dizziness, headache, drowsiness, weakness, and chest tightness (Health Canada website, 2023), thereby affecting the work efficiency of medical staff and potentially reducing the quality of medical care.

In this study, the CO₂ concentration fluctuated with time, and after 10 o'clock at night, the value was significantly lower than during the day. This could be attributed to fewer treatment items and reduced movement of medical staff during the night, along
with the absence of cleaning staff to perform cleaning and disinfection activities. A similar trend with three peaks—namely, at 8 a.m., 4 p.m., and 12 midnight—was observed in the concentrations of PM$_{10}$, PM$_{2.5}$, PM$_1$, and PM$_{0.01-0.3}$. It was speculated that PM concentration was elevated by medical staff during shift changes, when handling instruments, or when moving around. Additionally, the indoor temperature and RH showed no significant change, likely because the hospital utilized a central air conditioning system for ventilation.

In addition, the study found that the mean (range) frequency of inhaler uses and drug concentrations measured in the PICU within the sampling days were as follows: 9 (0–19) times and 0.05 pg m$^{-3}$ of terbutaline, 3 times (0–13) and 0.063 pg m$^{-3}$ of Combivent®, 15.75 (0–30) times and 0.009 pg m$^{-3}$ of acetylcysteine, 4.13 (0–14) times and 0.004 pg m$^{-3}$ of colistin, and 5.25 (0–13) times and 0.008 pg m$^{-3}$ of epinephrine.

This study explored the correlation between drug concentration in the air and air quality indices in the PICU. The results found that only the concentration of acetylcysteine in the air was positively associated with RH ($r_s = 0.783$, $P = 0.022$) and CO$_2$ concentration ($r_s = 0.747$, $P = 0.033$), while a significant negative correlation was found between the concentration of acetylcysteine and PM$_{10}$ concentration ($r_s = -0.759$, $P = 0.029$). Other drug concentrations in the air showed no correlation with air quality indices and the frequency of inhaler use.
During the study period, the concentrations of colistin and acetylcysteine drugs in the air detected in the PICU were extremely low. It is speculated that the low concentrations were possibly due to the aerosolized drugs exhaled by the patients being filtered by the breathing circuit filters. Additionally, the frequency of aerosolized drug spraying was not found to be correlated with the drug concentration in the air of the PICU. The lack of correlation could be attributed to both the low spraying frequency and the dilution of aerosolized drug concentrations by the air conditioning system. Moreover, a notable finding was the high positive correlation between acetylcysteine and CO₂ concentration. This suggests that indoor ventilation conditions can significantly influence drug concentrations in the air. Therefore, maintaining optimal indoor ventilation is crucial to effectively regulating drug concentrations.

### 3.2 Airborne drug concentrations at various distances from a simulated patient

In terms of simulation research, the analytical results showed that the indoor temperature during the experiment ranged from 19.14°C to 24.32°C, while the RH ranged from 61.6% to 88.5%. Additionally, it was found that the aerosolized drug concentrations were not related to the ambient temperature \( (r_s = 0.32, P = 0.24) \) and RH \( (r_s = -0.22, P = 0.43) \). To evaluate the relationship between changes in aerosolized drug concentrations and different distances from simulated patients inhaling Salbutamol
drugs, the analytical results showed that the drug concentration was 220 pg m$^{-3}$ (sd = 8.3 pg m$^{-3}$) at a distance of 0.1 m when patients inhaled drugs from an SVN. The drug concentration decreased as the distance increased (1 m: 32.4 pg m$^{-3}$, 1.6 m: 4.91 pg m$^{-3}$, 3 m: 3.76 pg m$^{-3}$) (Fig. 3). Furthermore, the results showed that the drug concentrations measured at 1 m, 1.6 m, and 3 m away from the SVN were significantly lower than the drug concentrations measured at 0.1 m away from the SVN. Additionally, the drug concentrations measured at 1.6 m and 3 m away from the SVN were also significantly lower than those measured at 1 m away from the SVN. However, there was no difference between the drug concentrations measured at 1.6 m and 3 m away from the SVN.

When using SVN for aerosol therapy in a clinical setting, it is recommended to maintain a gas flow rate between 6 and 10 L min$^{-1}$. Higher flow rates result in the production of smaller particles, allowing them to disperse over a greater distance (Crowley, et al. 2022; Dellweg, et al. 2021). This simulation study revealed that in environments without air conditioning, the drug concentration in the air at a distance of 1 m from the SVN was significantly lower than the drug concentration directly measured at the SVN. Furthermore, the drug concentration at 1.6 m and 3 m from the SVN was significantly reduced. Currently, healthcare facilities specify a separation of 1 m between beds in general wards and 1.6 m in intensive care units. These distances
are considered relatively safe concerning nearby patient exposure. Moreover, considering the presence of a ventilation system within the hospital, it is plausible to expect lower drug concentrations escaping into the air within the wards. However, caution should still be exercised when in close contact with patients undergoing SVN treatment due to the risk of drug exposure. In such situations, medical staff or family members should consider wearing N95 masks for personal protection. Additionally, installing a highly efficient particulate air (HEPA) filter at the expiratory limb of the ventilator circuit can provide an added layer of safety. Furthermore, maintaining appropriate ventilation conditions is essential for both general wards and intensive care units to ensure optimal indoor air quality.

4 CONCLUSIONS

The study demonstrated that the concentration of TVOCs in the PICU exceeded established standards. A correlation was observed between CO₂ concentration and aerosolized drug concentration, emphasizing the importance of vigilant monitoring of ventilation conditions within the environment. Furthermore, during aerosol therapy treatment for patients, it is imperative for medical staff and family members to maintain a safe distance or incorporate a HEPA filter into the ventilator circuit system. This precautionary measure aims to minimize unwarranted exposure and uphold the air
quality within the hospital.
FIGURE LEGENDS

Fig. 1. The layout of the pediatric intensive care unit

Fig. 2. The trend of air quality in the pediatric intensive care unit

Fig. 3. Concentration distribution of aerosolized drugs at different distances
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CRediT authorship contribution statement

HYT: Methodology, Data curation, Writing – original draft. YTT: Methodology, Investigation. YSS: Investigation, Formal analysis. PPP: Investigation, Data curation. GHW: Conceptualization, Methodology, Data curation, Visualization, Writing – review & editing, Funding acquisition

Declaration of Competing Interest

The authors declare no conflict of interest.


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Table 1. Associations between air quality indices and aerosolized drug concentration in the pediatric intensive care unit

<table>
<thead>
<tr>
<th></th>
<th>Absorbance</th>
<th>Temperature</th>
<th>RH</th>
<th>CO₂</th>
<th>TVOCs</th>
<th>PM₁₀</th>
<th>PM₂.₅</th>
<th>PM₁</th>
<th>PM₀.₀₁⁻₀.₃</th>
<th>Spray frequency</th>
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<td><strong>Bronchodilator</strong></td>
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<tr>
<td>Terbutaline</td>
<td>273 nm</td>
<td>-0.255</td>
<td>0.108</td>
<td>-0.024</td>
<td>-0.530</td>
<td>-0.482</td>
<td>-0.446</td>
<td>-0.325</td>
<td>0.615</td>
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<td>Combivent</td>
<td>276 nm</td>
<td>-0.346</td>
<td>0.110</td>
<td>-0.074</td>
<td>-0.602</td>
<td>-0.503</td>
<td>-0.503</td>
<td>-0.466</td>
<td>0.565</td>
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<td><strong>Expectorant</strong></td>
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<tr>
<td>Acetylcysteine</td>
<td>260 nm</td>
<td>-0.139</td>
<td>0.783*</td>
<td>0.747*</td>
<td>-0.096</td>
<td>-0.759*</td>
<td>-0.699</td>
<td>-0.301</td>
<td>-0.157</td>
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<td>Colistin</td>
<td>242 nm</td>
<td>-0.414</td>
<td>0.368</td>
<td>0.638</td>
<td>-0.012</td>
<td>-0.491</td>
<td>-0.430</td>
<td>-0.135</td>
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<td><strong>Vasoconstrictor</strong></td>
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<tr>
<td>Epinephrine</td>
<td>260 nm</td>
<td>0.102</td>
<td>0.218</td>
<td>-0.171</td>
<td>-0.452</td>
<td>-0.296</td>
<td>-0.296</td>
<td>-0.265</td>
<td>0.483</td>
<td>-0.039</td>
</tr>
</tbody>
</table>

*: P < 0.05.
Fig 1. The layout of the pediatric intensive care unit
Fig 2. The trend of air quality in the pediatric intensive care unit
Fig 3. Concentration distribution of aerosolized drugs at different distances