scientific reports

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Space disinfection using TiO2 photocatalyst reduces the incidence of febrile neutropenia in cancer patients

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Febrile neutropenia (FN) is life-threatening condition, and airborne microorganisms have been identified as one of the potential transmission routes. The objective of this study was to evaluate spatial sterilization using photocatalytic oxidative decomposition reactions which are effective to prevent FN. An air purifier equipped with a platinum-added titanium dioxide photocatalytic and LED light source (LED-TiO2 device) was installed in hospital rooms (per 21.5–35 m3) to investigate changes in FN incidence and airborne microorganism counts. Airborne microorganisms in the hospital rooms matched those responsible for nosocomial infections. The incidence of FN was significantly reduced after installation of the LED-TiO_2 device [9/13 vs. 2/12, P-value (P) = 0.015]. The LED-TiO_2 device decreased the number of airborne microorganisms in patient-free rooms by approximately 75% after 2 h [P < 0.001]. When patient was in the room, the number of airborne microorganisms increased with medical procedure. However, after 20 min of procedure, the number of airborne microorganisms was approximately 50% lower than without the device room [P = 0.019]. The LED-TiO_2 device successfully achieved spatial disinfection of hospital rooms, and reduced the incidence of FN. Spatial disinfection using photocatalysts is considered an effective new infection prevention measure for patients with severe neutropenia undergoing cancer treatment.

Keywords Febrile neutropenia, Infection of chemotherapy patients, TiO2 Photocatalyst-Mediated Spatial disinfection, Low-immunity patients

Febrile neutropenia (FN) is a serious chemotherapy-induced complication, lead to in-hospital mortality of approximately 10%[1,2], which can even exceed 20% in patients with multiple or severe comorbidities[1,2]. Therefore, standard precautions and prophylactic antimicrobial therapy are recommended to prevent FN development[3]. In addition, administration of granulocyte colony stimulating factor (G-CSF) is recommended for patients at high risk of developing FN during chemotherapy[3]. However, complete prevention of FN onset is difficult, and inhalation of airborne microorganisms (such as bacteria, fungi, and viruses) is one of the possible causes. A study revealed that the number of airborne Staphylococcus aureus (S. aureus) correlated with the rate of nosocomial S. aureus infection[4]. Additionally, airborne Aspergillus is known to be involved in FN development[5,6]. A previous study showed that installing of laminar air flow (LAF) units with high-efficiency particulate air (HEPA) filters in hospital rooms reduced pathogenic airborne bacteria[7], and lowered infection-related morbidity and mortality compared with those by antimicrobial prophylaxis alone in neutropenic patients who were treated for leukemia[8,9]. Based on these studies, air disinfection using HEPA filters is recommended to prevent infection in patients undergoing hematopoietic stem cell transplantation and intense chemotherapy. However, HEPA filters are expensive and not available in sufficient numbers.

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Recently, TiO2-photocatalyzed reactions have garnered attention because of their strong oxidative degradation ability against various bacteria, fungi, and viruses[10–17], and they can be applied for infection prevention. Upon light irradiation, TiO2 generates strongly oxidizing holes and electrons internally and on its surface[18]. When H2O present in airborne microorganisms and oxygen in the air molecules interact with these holes and electrons, hydroxyl radicals and superoxide are formed[18]. These free radicals and the processes decompose microorganisms[19,20]. In studies on airborne bacteria and fungi, an ultraviolet (UV)-A-irradiating device has been used onto a photocatalyst (TiO2) to inactivate 99.8% of Escherichia coli[12], 97% of Staphylococcus aureus[14], 93% of Legionella pneumophila[15] and 75–90% of Aspergillus niger[16] in aerosols. However, these studies use UVA as a light source, which may involve the risk of skin and eye serious damage. Several studies, the photocatalytic activity of TiO2 under visible light (wavelength > 400 nm) was enhanced by adding platinum[17,21]. We developed an air purifier (light-emitting diode [LED]-TiO2 device), which can irradiate platinum-added TiO2 with 405 nm wavelength LED, which is harmless to the human body and exhibits a strong oxidative degradation effect. The LED-TiO2 device inactivated aerosolized SARS-Cov-2 viruses in a 120-L acrylic box in 20 min[22].

Herein, we investigated the effects of a LED-TiO2 device installed in a hospital ward on the incidence of FN and airborne microorganisms responsible for FN.

Methods

Patients

This study was conducted in accordance with the declaration of Helsinki and was approved by the Ethics Committee of Nihon University Itabashi Hospital (IRB # RK-210713–2 ; https://www.itabashi.med.nihon-u.ac.jp/cr/pdf/RK-210713-2.pdf). Informed consent was obtained in the form of opt-out on the web-site. Those who rejected were excluded. This retrospective study included patients admitted to hospital rooms with LED-TiO2 devices at Nihon University Itabashi Hospital between December 8, 2020, and February 8, 2021. The incidence of nosocomial infections and FN between patients hospitalized for more than 48 h in the 30-day period before installing the TiO2 photocatalyst (from December 8, 2020, to January 8, 2021) and after installation (from January 8 to February 8, 2021, respectively) was determined.

The patients received itraconazole or fluconazole as an oral prophylactic antimicrobial (PA). Additionally, patients with malignant lymphoma received sulfamethoxazole–trimethoprim (ST), and patients with acute leukemia were administered levofloxacin (LVFX). G-CSF was not administered to patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) without complete remission.

LED-TiO_2 device

The simple structure of the LED-TiO_2 device (KL-W01; Width 44.1 × depth 8.3 × height 43.6 cm, Kaltech Co., Japan) is shown in Supplemental Fig. 1a and b. HEPA filter is not used in the LED-TIO_2 device. The LED-TiO2 device comprised a Platinized rutile TiO_2 [Pt/TiO_2 (band gap 3.2 eV, excitation wavelength approximately 410 nm)] coated sheet (25 cm × 25 cm) and 48 LED (405 nm) sources. The LED was placed 2 cm above the Pt/Tio2 sheet, which was irradiated with 10 mW light (Supplemental Fig. 1b). One LED-TiO_2 device was placed per 21.5–35 m^3 of space at a height of 1.5 m at the midpoint between the window and entrance to the hospital room (Supplemental Fig. 2a–d). The LED-TiO_2 devices were operated at a total air flow rate of 72 m^3/h, linear velocity of 2.67 m/s, and flow residence time of 0.09 s, and the air in the rooms was treated approximately once every 30 min.

Culture and identification of bacteria and fungi

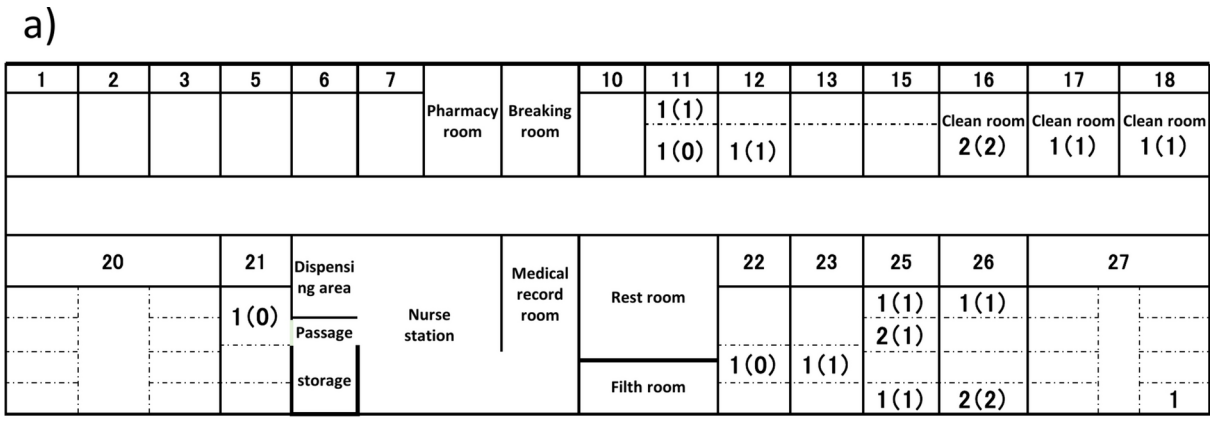
After 5-day incubation at 22–25 ℃ in blood culture bottles(Becton, Dickinson and Company), bacteria were cultured on the blood agar medium (Becton, Dickinson and Company) and fungi were cultured on the potato dextrose agar (Becton, Dickinson and Company) and CHROM agar Candida medium (KANTO CHEMICAL CO.,INC.). After colonization, pure cultures were prepared from individual bacterial and fungal isolates. The obtained pure culture was subjected to 1 µL of 70% formic acid and overlaid with 1 µL of α-cyano-4-hydroxycinnamic acid matrix portion (Bruker Daltonics, Japan). Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF–MS; Microflex LRF, Bruker Daltonics, Japan) was used to identify the bacterial and fungal strains. The MALDI-TOF MS spectra were analyzed using the database (MALDI Biotyper mass spectrum profile MSP Iidentification Sstandard Mmethod 1.1). Fungi were further confirmed by visual morphological observation using lactophenol cotton blue staining combined with blood antigen testing.

Viable count of airborne microorganisms

The number of airborne microorganisms was measured using a BioTrak real-time viable particle counter (BioTrak 9510-BD, TSI Inc., USA). The specifications of this counter have been validated by the U.S. Food and Drug Administration[23], and its performance has been validated according to the U.S. Pharmacopeia (USP) protocol < 1223 > [24], USP < 1116 > [25], and the European Pharmacopoeia (Ph. Eur. Chapter 5.1.6)[26], and the standards of the Parenteral Drug Association (PDA Technical Report)[27]. The counter initially irradiated a 405-nm UV laser to measure and categorize the particles based on their size (diameter range = 0.5–25 µm)[28]. The number of viable airborne microorganisms was measured by detecting two fluorescence emission wavelengths induced by UV-irradiated tryptophan, nicotinamide adenine dinucleotide + hydrogen, and riboflavin, which are major metabolites associated with cell viability[28]. In this study, measurements using the BioTrak counter consisted of 60 cycles of 1-min measurements followed by 1-min pauses.

Statistical analysis

The clinical characteristics and incidence of infections in hospitalized patients before and after the installation of the LED-TiO_2 device were compared based on Fisher's ratio. The length of stay, the number of days when the



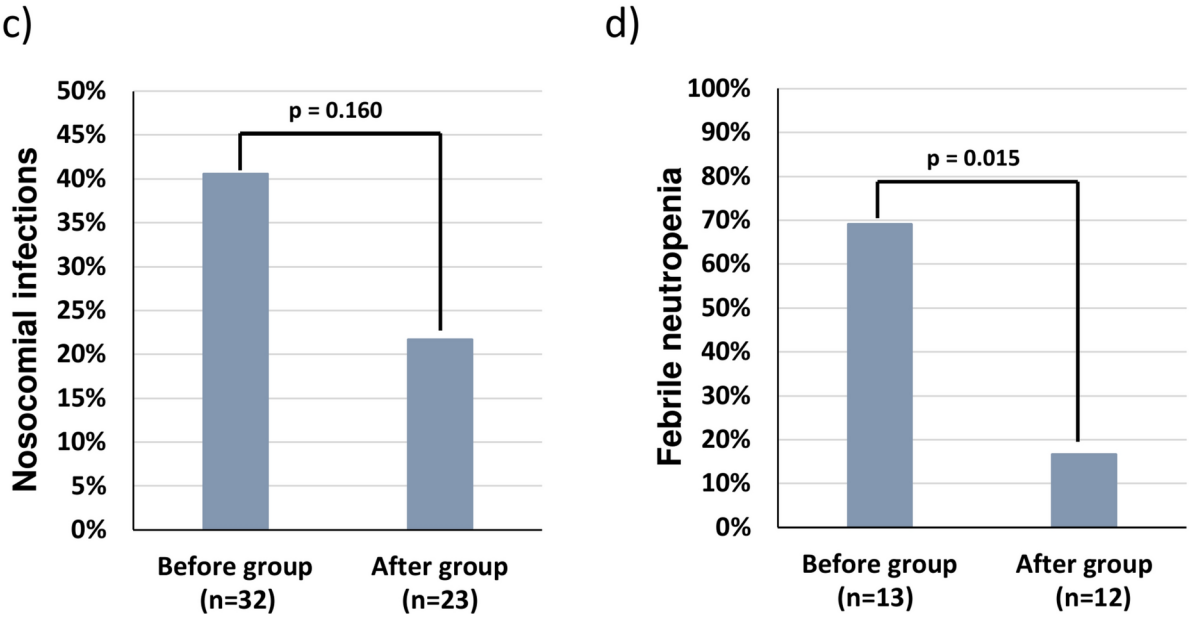


Fig. 1. Hospital rooms where nosocomial infections and febrile neutropenia (FN) developed. The LED-TiO2 device was installed in the rooms indicated in gray. Numbers are expressed as the number of patients with nosocomial infections (number of FN patients) (e.g., 2(1)). (**a**) Number of infected patients in the month before installation of air purifier equipped with a mechanism to irradiate LED to TiO_2 (LED-TiO_2 device) (Before group), (**b**) Number of infected patients in the month after installation of LED-TiO_2 device (After group). (**c**) Incidence of nosocomial infections: Before group vs. After group = 13/32(40.6%) vs. 5/23(21.7%), P = 0.160. (**d**) Incidence of FN (nosocomial infections in patients with neutrophils < 500/μL): Before group vs. After group = 9/13(69.2%) vs. 2/12(16.7%), P = 0.015.

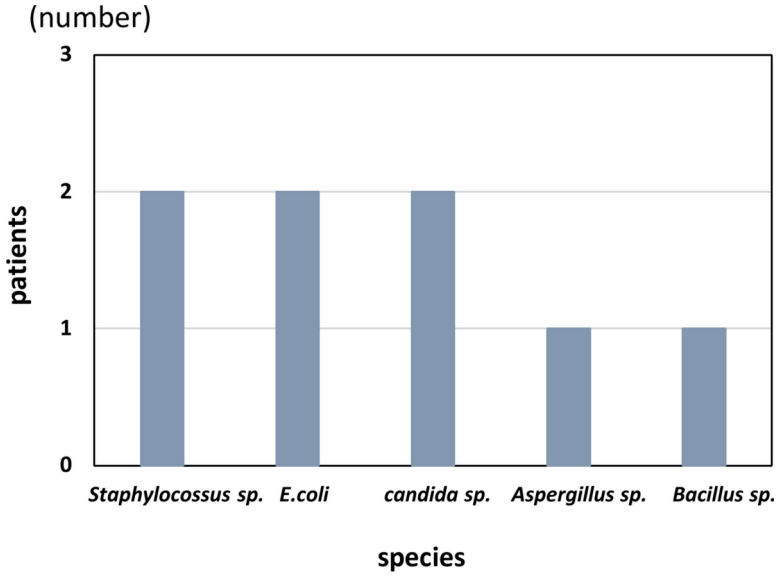


Fig. 2. Causative organisms of febrile neutropenia (FN), Blood cultures of bacteria were analyzed by Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS). Blood cultures of fungi were analyzed by MALDI-TOF MS, morphological observation, and antigen tests were performed.

neutrophils count was < 500/μL, and the number of bacteria and fungi in the room space were compared through the Mann–Whitney U test. P-values (P) < 0.05 were considered statistically significant.

Results

Patients

The patient backgrounds before and after installation of the LED-TiO_2 device are shown in Table 1. There were no significant differences in the length of hospital stay, underlying disease, treatment intensity (risk of FN), frequency or duration of G-CSF use, or PA therapy (Table 1) between the groups before (Before group, n = 32) and after (After group, n = 23) device installation. The number of patients with neutrophils < 500/μL, a risk for FN, was 13 in the Before group and 12 in the After group, and there was no difference the length of stay in LED-TiO_2 device installation room (median [range]; Before group 6^{3-18} days vs. After group 7^{3-17} days, P = 0.956, Table 1). All but one patient in both groups with a neutrophil count < 500/μL received PA.

Decrease in the incidence of nosocomial infections

Figure 1 shows the number of patients with nosocomial infections and FN in the rooms before (Fig. 1a) and after (Fig. 1b) the installation of the LED-TiO_2 device. The incidence of nosocomial infections showed a decreasing trend in the After group compared to Before group, but the difference was not significant (Fig. 1c; 13/32 vs. 5/23, P = 0.160). There was no difference in patients with neutrophil counts > 1000/μL (3/32 vs. 2/22, P = 1.000) and those with neutrophil counts 500–1000/μL (1/14 vs. 1/14, P = 1.000). However, patients with a neutrophil counts < 500/μL showed a significant decrease in the incidence of FN (Fig. 1d; 9/13 vs. 2/12, P = 0.015). Among the FN cases, pneumonia occurred in 4/13 patients before group and 0/12 patients after group (P = 0.096). G-CSF administration induced no significant difference in the incidence of FN between the Before and After groups (2/5 vs. 0/4, P = 0.444). However, when G-CSF was not administered due to AML/MDS before complete remission, there was a significant decrease between the Before and After groups (7/8 vs. 2/8, P = 0.041).

FN causative and airborne microorganisms

The causative bacteria and fungi identified in the blood cultures and fungal antigen tests performed on patients with FN are shown in Fig. 2. The causative organisms of FN were *Staphylococcus sp.*, *Escherichia coli*, *Candida sp.*, *Aspergillus sp.*, and *Bacillus sp*. Four of these organisms (*Staphylococcus sp.*, *Candida sp.*, *Aspergillus sp.*, and *Bacillus sp.*) were detected as airborne microorganisms in the hospital rooms (Table 2, Supplemental Fig. 3a,b). Three of five cases (60%) the FN-causing cultured bacteria were resistant to ST combination, and 2/5 cases (40%) were resistant to LVFX.

Decrease in airborne microorganism count due to the LED-TiO2 device in a patient-free room

Figure 3a shows the results of a 2-h operation of the LED-TiO_2 device in a patient-free room. When the LED-TiO_2 device was not in operation, the number of airborne microorganisms hovered around a certain level from after 60 min (number of airborne microorganisms, median [range]: 60–70 min vs. 110–120 min = 105.5 [83–130]/ft^3 vs. 100.0 [85–108]/ft^3, P = 0.485). In contrast, when the LED-TiO_2 device was operated, the number of airborne microorganisms tended to decrease even beyond 60 min [number of airborne microorganisms, median (range); 60–70 min vs. 110–120 min = 31.5 (18–45)/ft^3 vs. 24.5 (6–39)/ft^3, P = 0.094].

Number (Total 66)	Before installing the device (32)	After installing the device (23)	p value
Male, n (%)	18 (56.3)	15 (62.5)	0.785
Age, median (range)	65 (18-83)	66.0 (18-80)	0.914
Hospital stay, median (range)	15 (3-31)	14 (3-31)	0.738
Diagnosis			
Hematological malignancy*			
AML/MDS	6	6	0.530
ALL	4	1	0.387
ML	4	5	0.467
MM	6	5	1.000
AA	1	1	1.000
Malignant solid tumor			
Lung cancer	6	4	1.000
Seminoma	2	1	1.000
Unknown primary	1	0	1.000
Pneumothorax	1	0	1.000
FN** risk of chemotherapy			
<10% : Low risk	6	5	1.000
10-20%: intermediate risk	8	3	0.326
>20% : High risk	15	15	0.272
G-CSF (granulocyte colony stimulating factor)	13	8	0.781
Neutro <500/μL			
Number of patients	13	12	
Days, median (range)	6 (3–18)	7(3–17)	0.956
PA***, number	12	11	1.000
G-CSF	5	4	1.000

Table.1. Characteristic of patients **AML/MDS* acute myeloid leukemia/ myelodysplastic syndrome, *ALL* Acute lymphoblastic leukemia, *ML* Malignant lymphoma, *MM* Multiple myeloma, *AA* Aplastic anemia. ***FN* Febrile neutropenia (FN). ****PA* prophylactic oral antimicrobial regimens.

No.	Becteria	Score Value
1	Staphylococcus epidermidis	2.16
2	Roseomonas mucosa	2.48
3	Micrococcus luteus	2.05
4	Bacillus flexus	2.11
5	Paenibacillus glucanolyticus	2.33
6	Paenibacillus lautus	2.21
7	Proteus hauseri	2.27
8	Proteus penneri	2.20
9	Proteus vulgaris	2.19

Table2. Airborne bacteria in the patient room

Comparing the numbers of microorganisms in 1 ft^3 of space measured six times during 110–120 min, the median was 24.5 (6–39) with LED-TiO_2 device operation and 100 (85–108) without it, showing a decrease of 75.5% ($P < 0.001$). When a larger unit with 8 folds the photocatalytic contact area was installed, the number of airborne microorganisms after 60 min of operation was comparable to that in a sterile room with a LAF unit whose entire wall was composed of HEPA filters (LED-TiO2 device vs. sterile room, median [range]; $3^{1-5}/ft^3$ vs. $2[0-8]/ft^3$, $P = 0.651$; Fig. 3b).

Decrease in exposure to airborne microorganisms due to LED-TiO2 device operation while the patient is in the room

Figure 4 shows the change in the number of airborne microorganisms while the patient was in the room. Regardless of whether the device was in operation, the number of airborne microorganisms increased during the medical procedure (Figs. 4a; device was operated, Fig. 4b; device was not operated). However, when the device was operated, the number of airborne microorganisms decreased rapidly (Fig. 4c). After the medical procedure, in which the number of airborne microorganisms increased to approximately $350/ft^3$, microorganism counts

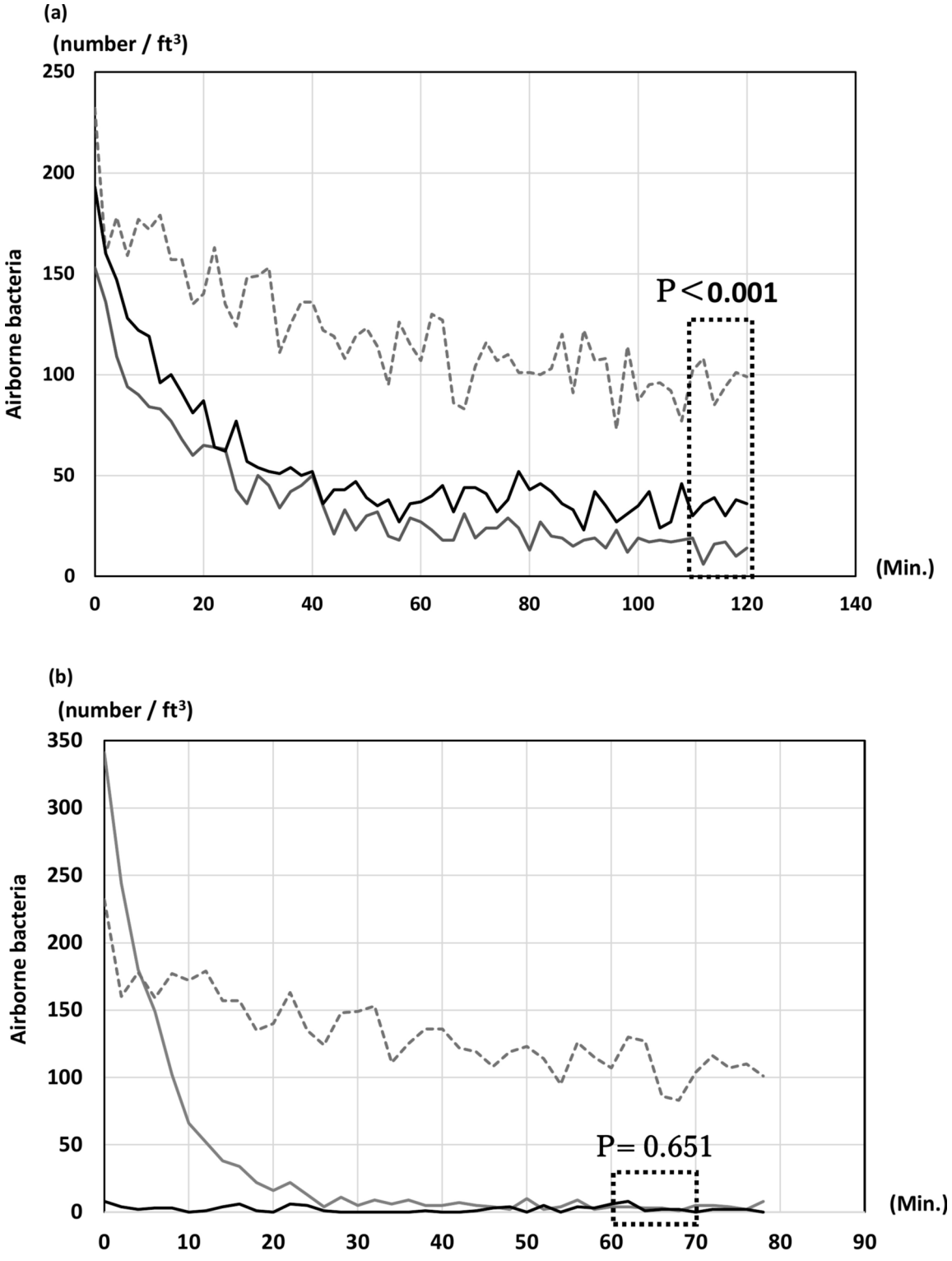


Fig. 3. Airborne microorganism counts in 1 ft^3 (28.3 L) of air in a patient-free room. (**a**) Gray dotted line (control): No operation of an air purifier (LED-TiO_2 device) equipped with a mechanism to irradiate LED toTiO_2. Solid black line: First operation of LED-TiO_2 device. Gray solid line: Second operation of LED-TiO2 device. The number of airborne microorganisms in $1ft^3$ after 110–120 min (the area enclosed by dotted line in the figure) showed a decrease of approximately 75.5% ($P < 0.001$): control vs. LED-TiO_2 device, median (range): 24.5 (6–39) vs. 100 (85–108). (**b**) Gray dotted line: No LED-TiO_2 device in operation. Solid black line: Sterile room without LED-TiO_2 device. Gray solid line: Operation of a large LED-TiO2 device with 8 times larger photocatalytic contact area. Airborne microorganism counts after 60–70 min of operation were similar in the sterile room and the large LED-TiO_2 device operating, median (range); 3(1–5) vs. 2(0–8) ($P = 0.651$).

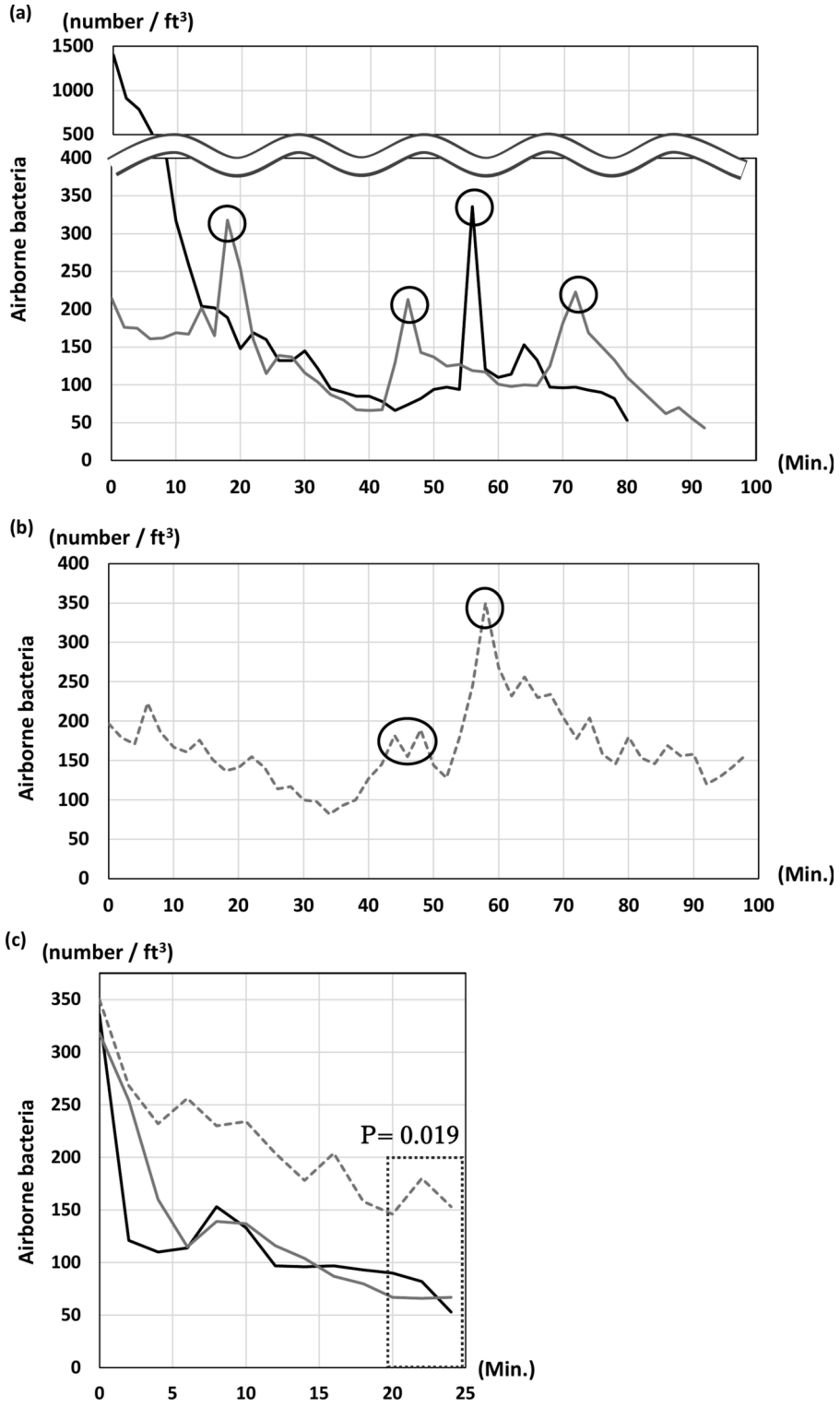


Fig. 4. Airborne microorganisms counts in 1 ft^3 (28.3 L) of air in a patient's room, ○: Peaks of airborne microorganisms during a medical procedure. (**a**) Gray solid line: First operation of air purifier equipped with a mechanism to irradiate LED to TiO_2 (LED-TiO_2 device). Solid black line: Second operation of LED-TiO_2 device. (**b**) Gray dotted line: No LED-TiO_2 device operation. (**c**) Change in the number of airborne microorganisms over time after medical procedure. The number of airborne microorganisms 20–24 min after medical procedure was significantly lower in the rooms where LED-TiO_2 device was operated [without LED-TiO2 device operation vs. with LED-TiO_2 device operation, median (range): 153 (146–180) vs. 74.5 (53–93) P = 0.019].

for 20–25 min were performed three times. The results showed a median of 74.5 (53–93) cells/ft^3 when the device was in operation, which was approximately 50% lower than when the device was not in operation (153 [146–180] cells/ft^3) (P = 0.019; Fig. 4c). Additionally, there was a significant decrease, even compared to the number of airborne microorganisms after 110–120 min in an empty room, where the device was not operating (74.5 [53–93] organisms/ft^3 versus 100.0 [85–108] organisms/ft^3, P = 0.008).

Discussion

Recent studies have reported that photocatalytic oxidative degradation can inactivate airborne microorganisms[12,14–16,22]. This study used oxidative reactions of LED and a photocatalyst (Pt-TiO2) for space sterilization in actual clinical practice. As a result, the device decreased airborne microorganisms and FN.

Importantly, in the hospital room installed with the LED-TiO_2 device, the number of airborne microorganisms that increased after the medical procedure quickly decreased (vs. device off, P = 0.019). Airborne microorganisms in hospital rooms have been reported as FN-causing organisms with the exception of Penicillium sp and Paenibacillus sp[29–32]. In addition, the airborne microorganisms in the patient room included Staphylococci and other bacteria, which have contact infection as the primary route of transmission. Previous studies have reported that the number of airborne microorganisms correlates with the number of fallen microorganisms[33] and the rate of nosocomial infections (such as S. aureus[4]). This suggests that the reduction in patient exposure to not only airborne microorganisms but also number of bacteria adhering to hospital equipment led to the decrease incidence of FN. In the fact, reported using HEPA filters, in which isolation of patients in hospital rooms with LAF units reduced not only pneumonia and lower respiratory tract infections but also urinary tract infections and rectal abscesses in neutropenic patients[9,34], and it also reduced infectious deaths compared with PA alone[9,35]. In addition, patients with FN in this study also decreased in not only pneumonia but also enteritis, urinary tract infection, and cellulitis in the post-treatment group.

A previous study using an LAF unit also reported a reduced rate of infection in patients with neutrophil counts < 1000/μl[36]. In this study, infections were reduced in patients with neutrophils < 500/μl (P = 0.015). In this study, the majority of airborne microorganisms in hospitals was commonly present microorganisms with less pathogenicity; hence, spatial eradication is particularly effective for patients with severely compromised immunity.

HEPA filters capture more than 99.97% of 0.3 μm particles (Japanese Industrial Standards, JIS Z 8122), but not kill microorganisms. Therefore, the longer the HEPA filter is used, the lower its performance in capturing microorganisms. Furthermore, when the filter is replaced, the bacteria float in the air again, posing a risk of secondary infection. In contrast, photocatalyst-mediated oxidative decomposition reactions inactivate and degrade microorganisms[16,22], thus reducing the risk of secondary infection and maintaining antibacterial effects. In this study, the number of airborne microorganisms remained constant at 60–70 min and 110–120 min in hospital rooms where the LED-TiO_2 device was not operating (P = 0.485). In contrast, a decreasing trend in the number of microorganisms was observed with the LED-TiO_2 device operating (photocatalysis) (P = 0.09). Furthermore, spatial disinfection using photocatalyst has a detoxifying effect on endotoxins of gram-negative bacteria such as *Escherichia coli* and *Legionella sp*[37,38]. In addition, maintenance of the LED-TiO_2 device is simple, requiring only filter cleaning with water, and is economically superior.

In this study, a real-time counter was used to measure the number of airborne microorganisms. In the colony-forming unit (CFU) method, researchers have to enter and leave the room to collect airborne microorganisms, which creates air convection and affects the number of airborne microorganisms. This makes it challenging to count airborne microorganisms at short intervals (every few minutes) without external influences. Furthermore, the CFU method involves many culture procedures and is prone to errors; has different detection sensitivities for each species depending on the culture medium; and gives variable results, such as unclear cell counts in each colony[39,40]. On the other hand, the BioTrak used in this study does not require researchers to enter or leave the room, but instead measures the number of airborne microorganisms count automatically, eliminating the aforementioned challenges. Therefore, we were able to accurately count in the hospital room the number of airborne microorganisms changes, verify the effectiveness of spatial disinfection using the LED-TiO2 device.

Currently, the emergence of resistant strains to PA regimens in many institutions has led to concerns about decreasing prophylactic efficacy[41,42] and spatial disinfection has become more important. In this study, approximately half of the bacteria cultured were multidrug-resistant. Photocatalytic inactivation and degradation of bacteria is also effective against resistant bacteria[43,44].

FN is a serious problem that often forces discontinuation or change in cancer treatment. The reduction of FN in this study suggests that advanced spatial disinfection using photocatalysts can easily provide an environment that reduces the risk of infection for patients undergoing cancer treatment. This may be a factor in enabling aggressive chemotherapy with strongly myelosuppression.

Data availability

The datasets generated and/or analyzed during the current study are not publicly available because many cases are also used in other studies. However, it is available from the corresponding author upon reasonable request (iizuka.kazuhide@nihon-u.ac.jp).

Received: 13 March 2024; Accepted: 3 December 2024
Published online: 14 March 2025

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Acknowledgements

We would like to thank Editage (https://www.editage.jp/) for English language editing.

Author contributions

KI designed this study, collected, analyzed the data, culture and identification of bacteria and fungi, and drafted the initial manuscript. HO collected the clinical data, and reviewed and edited the manuscript. JS designed the LED-TiO2 device. YI analyzed the data, and reviewed and edited the manuscript. YT culture and identification of bacteria and fungi. ST, HU, KM, HN, TN, YA, YH, MT reviewed and/or edited the manuscript.

Funding

KI is supported by Kaltech Corporation in this study. They had no role in gathering, analyzing, or interpreting the data. Another study by YA was supported by the Kaltech Corporation and belongs to an endowed chair. They also had no role in gathering, analyzing, or interpreting the data. In addition, YA receives annual compensation received from Japan Racing Association.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-024-82229-6.

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