



## An alternative approach for daily perineal care of patients with indwelling urinary catheterization: Photodynamic inactivation with cationic porphyrin derivatives

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### Abstract


**Background:** Catheter-associated urinary tract infections (CAUTI) constitute a significant portion of healthcare-associated infections. Using antiseptic for routine daily perineal care of patients with IUC may reduce CAUTIs.


**Aim:** This study aimed to examine antimicrobial photodynamic inactivation (aPDI) against clinical isolates for use in the daily perineal care of patients with IUC. In addition, it was also aimed to compare the antimicrobial activities of aPDI and 0.1% chlorhexidine gluconate.


**Methods:** In this *in-vitro* study, cationic porphyrin derivatives (CPDs) were used as photosensitizers in the experiments. CPDs, named PM, PE, PN, and PL were synthesized by the researchers. A diode laser device emitting light with a wavelength of 450 nm (blue light) was used as the light source. Methicillin-resistant *Staphylococcus aureus* (MRSA), *Escherichia coli* and *Klebsiella pneumoniae* with multidrug-resistant (MDR) properties and *Candida albicans* were used. Photosensitizer (PS), aPDI, light (L), and control (C) groups in aPDI experiments; control (C) and chlorhexidine gluconate 0.1% groups were used in the chlorhexidine gluconate experiments. Survival was calculated based on CFU/mL in the control group.

**Results:** In experiments, combinations of 25 J/cm<sup>2</sup> with 6.25 and 3.125 µM PM, PE reduced *E. coli*, *K. pneumoniae*, MRSA, and *C. albicans* survival in the range of 8.70 to 11.53 log<sub>10</sub>. In aPDI experiments performed with 6.25 and 3.125 µM PN and PL concentrations at the same energy density, reductions


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in the range of 4.41 to 0.17 log<sub>10</sub> were observed in all four clinical isolates. In experiments where 1.5625 μM concentration was used, survival decreased in the range of 8.29 to 10.87 log<sub>10</sub> in PM and PE, while antimicrobial activity was limited in PN and PL. In the 0.1% chlorhexidine gluconate experiments, the survival reduction in all four clinical isolates ranged from 8.87 to 10.24 log<sub>10</sub>.

**Conclusion:** For PM and PE, a very strong aPDI was obtained in *C. albicans*, *E.coli*, *K. pneumoniae*, and MRSA at low concentrations and energy density. The same antimicrobial activity was found in experiments using 0.1% chlorhexidine gluconate. In this context, we would like to inform you that aPDI to be performed with a combination of 25 J/cm<sup>2</sup> at 6.25 and 3.125 μM concentrations of PM and PE has the potential to be an antiseptic in the daily perineal care of patients with IUC.

**Keywords:** Indwelling urinary catheterization, catheter-associated urinary tract infections, daily perineal care, antiseptic, antimicrobial photodynamic inactivation, MDR, *E.coli*, *K. pneumoniae*, MRSA, *C. albicans*.

## 1. Introduction

Indwelling urinary catheterization (IUC) is applied to approximately 25% of hospitalized patients and approximately 7% of individuals living in nursing homes (1). The rate of IUC is increased to 75-90% in intensive care units (2). IUC, which is applied for many purposes such as obstruction of urinary flow, surgical interventions, urinary incontinence, bladder irrigation, drug administration, and hourly or daily urine measurement, continues to be the most important source of catheter-associated urinary tract infections (CAUTI), especially in the intensive care units (1–4). During the IUC process, the risk of developing urinary catheter-related daily bacteriuria and or candiduria is 5-7%, and after the 30th day it is considered to be 100% (5,6). It is reported that the role of biofilm-forming bacteria in the CAUTI pathogen is quite high. Especially in long-term IUC, the biofilm formed on 5×10<sup>9</sup> colony-forming unit 1 cm segments (CFU/cm) on the catheter surface causes urinary catheter obstruction, permanent and progressive urinary system infections (7).

CAUTI has been associated with increased disability, death, hospital cost, and length of stay in IUC of short or long duration (>30 days) (5,6,8). It has shown that CAUTIs make up 70-80 % of healthcare-associated infections, costing £1.0-2.5 billion and causing approximately 2100 deaths per year (4). According to the data of the National Healthcare Safety Network (NHSN), the standardized CAUTI rate for 2019 in general acute care hospitals was 0.74 (9).

In Turkey, the standardized CAUTI rate is 0.12-0.41 according to 2017 national surveillance data. Although it decreased by 16% according to 2016 data, it ranked 3rd among healthcare-associated infections with the highest rate (10). In 2019, the rate of CAUTI varied between 0.01 and 5.1 (11). Although many bacterial species and fungi cause urinary tract infections, *Escherichia coli* and *Klebsiella pneumoniae* are reported to cause approximately 90% of these infections (12). In addition to these two pathogens, in epidemiological studies *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Enterococcus* spp., *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *Candida* spp. were found to be among the most frequently encountered agents (12,13).

Microbial pathogens can enter the urinary tract either extraluminal, by migration along the outer side of the catheter in the periurethral mucus sheath or intraluminal by movement from a contaminated collection bag or catheter along the inner lumen of the catheter. It has been associated with extraluminal and intraluminal entry of microbial pathogens that cause CAUTI, violation of asepsis in indwelling bladder catheterization, disruption of the closed catheter drainage system, reflux of urine from the urine collection bag and tube into the bladder, catheter occlusion and meatus colonization and maintenance errors. (6,7,14).

In the prevention of CAUTI, performing the catheterization procedure under aseptic conditions and applying daily perineal care are among the important practices (2,15–18). It is a result of studies that the use of saline and/or tap water and/or water and soap in the daily perineal care,

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which is recommended in the relevant guidelines and currently applied in clinical settings, can not prevent extraluminal transmission (6,19). Academic research has focused on the option of using antiseptics in daily perineal care. Chlorhexidine gluconate and iodine are among the antiseptics tried so far (2,19–24).

We consider it possible to use antimicrobial photodynamic inactivation (aPDI) in the routine daily perineal care of patients with IUCs. aPDI is a treatment method based on the principle of killing microbial cells by using a non-toxic dye or a combination of photosensitizer and low-density harmless visible light that stimulates photosensitizer. aPDI causes damage to bacterial deoxyribonucleic acid (DNA) and cytoplasm membrane with reactive species formed as a result of chemical and physical reactions occurring in two different ways, Type I and Type II and shows its antimicrobial activity by inactivating the transport systems and enzymes in the bacterial membrane. aPDI to be applied with the combination of a photosensitizer with maximal absorption into the bacteria and light of the appropriate wavelength that activates this photosensitizer has the potential to disrupt the structure of the biofilm layer formed by the bacteria and show antimicrobial effects against many bacteria, including multidrug-resistant (MDR) strains that colonize on the surface (25–27).

Today, although efforts to discover photosensitizers that can show a maximal antimicrobial effect against MDR bacteria are still continuing, it has been reported that CPDs have the potential to capture this effect in *in-vitro* and *in-vivo* aPDI experiments on MDR clinical isolates (25–31). In addition, it is reported that singular oxygen ( $^1O_2$ ) formed as a result of CPDs and aPDI on human skin fibroblast cells has a life of microseconds, this life is barely enough for it to diffuse in the cell where it is produced.

In the aPDI experiments we performed using a 665 nm wavelength light source with the CPDs previously synthesized by us, a strong antimicrobial activity was obtained against Gram-negative bacteria (*P. aeruginosa*, *E. coli*, *Acinetobacter baumannii*, and *K. pneumoniae*) and methicillin-resistant *S. aureus* (MRSA) with MDR properties. Bacterial survival reductions of up to 6 log<sub>10</sub> levels were observed in our aPDI experiments (25–27). The photosensitizers did not have antimicrobial activity alone and the results met the condition of being an "ideal photosensitizer" (26). However, the survival reduction of up to 57% in fibroblast cells in live cell toxicity experiments was not a desired result for the photosensitizer. The toxicity was associated with the excess concentrations used in the experiments (27). Therefore, it is predicted that strong antimicrobial activity can be obtained at lower concentrations by using blue light instead of red light.

## 2. Purpose

This study aimed to examine antimicrobial photodynamic inactivation (aPDI) against clinical isolates for use in the daily perineal care of patients with IUC. In addition, it was also aimed to compare the antimicrobial activities of aPDI and 0.1% chlorhexidine gluconate.

## 3. Method and material

### 3.1. Photosensitizers used in experiments

In this study, CPDs synthesized by us as photosensitizers named PM, PE, PN, and PL were used. CPDs can absorb a wavelength ranging from 250 to 800 nm in the broad spectrum and the maximum light absorption is  $422 \pm 3$  nm (27). The antimicrobial activities of CPDs without light exposure are almost non-existent (26).

### 3.2. Microorganism strains used in experiments

In this study, clinical isolates of MRSA, *E. coli*, *K. pneumoniae*, and *Candida albicans*, which differ in their antibiotic resistance profile, were used. The phenotypic characteristics and resistance profiles of these strains were determined by conventional methods and antibiotic susceptibility tests. Antimicrobial susceptibility results of *E. coli*, *K. pneumoniae* can be obtained from the " supplementary

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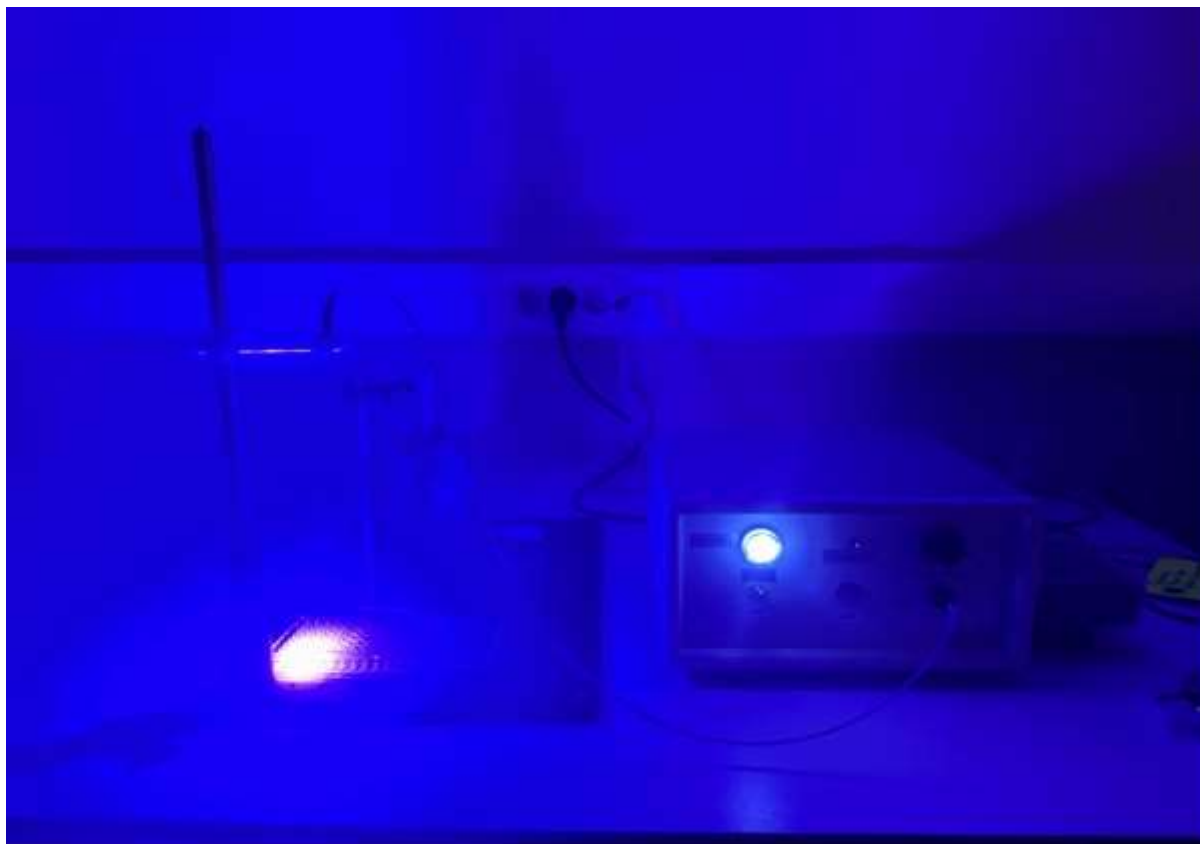
1" file (27), antimicrobial susceptibility results of MRSA from (25).

In the preparation of bacterial suspensions, bacterial strains from stock cultures kept at  $-80\text{ }^{\circ}\text{C}$  were inoculated on tryptic soy agar (TSA) medium (Merck, Germany) and incubated overnight (16-18 hours) at  $37\text{ }^{\circ}\text{C}$ . After incubation, a single colony was taken and inoculated into tryptic soy broth (TSB) (Merck, Germany), and incubated overnight at  $37\text{ }^{\circ}\text{C}$ . After the bacterial cells have been centrifuged (3000 rpm for 10 min at  $4\text{ }^{\circ}\text{C}$ ), the resulting pellet will be suspended in phosphate buffered saline (PBS) and a bacterial suspension was prepared at  $10^8$  CFU/mL (600 nm: 0.6-0.8 optical density) (25–27).

In the preparation of the *C. albicans* clinical isolate used in the experiment, the method described in (32) was used. The clinical isolate of *C. albicans* was cultured on sabouraud dextrose agar (Merck, Germany) plates supplemented with chloramphenicol and incubated at  $35\text{ }^{\circ}\text{C}$  for 18 hours. Next, 5 small colonies from each agar plate were picked with a sterile inoculation loop and suspended in a tube containing sabouraud 2%-dextrose-broth medium (Merck, Germany) by rubbing the loop against the wall of the tube. Suspensions of *C. albicans* strains were incubated at  $35\text{ }^{\circ}\text{C}$  for 3 hours. Finally, the density of the suspensions was adjusted to a turbidity equivalent to the 0.5 McFarland standard, corresponding to an inoculation containing approximately  $10^6$  CFU/mL.

### 3.3. The light source used in the experiment

In the study, a Custom-made diode laser device (Teknofil, Istanbul) emitting light with a wavelength of 450 nm was used as the light source. The distance between the optical table (exposure level) and the end of the fiber is 26 cm. The radius ( $r$ ) of Illumination area on the target is 3 cm. The output power of the laser device was kept constant at 0.4 W, and  $25\text{ J}/\text{cm}^2$  energy densities was used in the experiments (Figure 1).



**Figure 1.** Image of the light source used in the experiment procedure for aPDI.

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### 3.4. Experiment procedure

#### 3.4.1. Experiment procedure for aPDI

The groups and the procedures to be applied to the groups in the aPDI experiments performed by using combinations of CPDs and energy densities at different concentrations are detailed below.

Groups;

- Light Group [L]: In this group, where the toxic effect of light or the presence of a biostimulant effect on the clinical isolate was investigated, clinical isolate suspensions were exposed to light of a certain energy density to be determined in preliminary experiments.
- Photosensitizer Group [PS]: In this group, in which the toxic effect or biostimulant effect of PS on the clinical isolate was investigated, clinical isolate suspensions were incubated with PS at determined concentrations for a certain period of time (15 minutes).
- Antimicrobial Photodynamic Inactivation Group [aPDI]: A mixture of clinical isolate PS incubated with clinical isolates at certain concentrations for 15 minutes was exposed to light at a specific energy density.
- Control Group [C]: Clinical isolate suspensions in this group were incubated with PBS for 15 minutes.

The experiments were performed as follows: Fresh stock solutions of CPDs used in the experiments were prepared at certain concentrations ( $\mu\text{M}$ ) before each aPDI experiment. The stock solutions prepared with PBS were kept in the dark during the experiment. 50  $\mu\text{L}$  of clinical isolate suspension was transferred to specific wells of each of the 96-well plates designated as PS, aPDI, L and C groups. Specific concentrations of PS from 50  $\mu\text{L}$  of stock suspensions were added to the wells of the PS and aPDI group plates with clinical isolate. 50  $\mu\text{L}$  of PBS was added to the wells of L and K group plates with bacteria. All four groups were incubated at 37 °C for 15 minutes in the dark. Plates of group L and aPDI were exposed to light. After light treatment, clinical isolate suspensions in all groups were diluted with PBS using the serial dilution method. From the diluted suspensions, 20  $\mu\text{L}$  of aliquot was taken and plated on tryptic soy agar (TSA) and incubated overnight (18 hours) in the dark at 37°C. In this procedure for *C. albicans*, sabouraud dextrose agar (Merck, Germany) plates supplemented with chloramphenicol was used and incubated for 48 hours in the dark at 37°C. After incubation, cell survival in colony forming unit (CFU) /mL was calculated. Each experiment was repeated three times in triplicate.

#### 3.4.1. Experiment procedure for chlorhexidine gluconate

The antimicrobial activity of chlorhexidine gluconate was determined at a concentration of 0.1%, which is the recommended amount for clinical use (2). Chlorhexidine gluconate solution was prepared from the commercially available "Chlorhexidin Gluconate 20% Chem Pure - 5 LT" (ZAG Kimya, Turkey)". A final 0.1% solution was prepared by diluting the stock solution with sterile distilled water. In these experiments, sterile distilled water was used in all steps instead PBS was used since PBS and chlorhexidine gluconate reacted chemically. As in the aPDI procedure, 50  $\mu\text{L}$  of clinical isolate suspension, 50  $\mu\text{L}$  of chlorhexidine suspension were placed in 96-well plate cells. The plate containing this mixture was incubated at 37 °C for 37 min in the dark area (This time was used to be the same as for the aPDI procedure. Incubation time was 15 min and irradiation time was 22 min in the aPDI procedure.). After 37 minutes of incubation clinical isolate suspensions in all groups were diluted with sterile distilled water using the dilution method. From the diluted suspensions, 20  $\mu\text{L}$  of aliquot was taken and plated on tryptic soy agar (TSA) and incubated overnight (18 hours) in the dark at 37°C. In this procedure for *C. albicans*, sabouraud dextrose agar (Merck, Germany) plates supplemented with chloramphenicol was used and incubated for 48 hours in the dark at 37°C. After incubation, bacterial survival in CFU/mL was calculated. Each experiment was repeated three times in triplicate.

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### 3.5. Research ethics

Ethical approval was not received for this study, which was conducted in 2023, because it was conducted in-vitro.

### 3.6. Statistical analysis

All statistical analyses were carried out using Excel program (Microsoft Office Professional Plus 2016). Bacterial survival in CFU/mL was calculated according to the following formula 1.

Formula 1

$$CFU/mL = \text{Number of colonies per mL on the plate} \times \text{Total dilution factor}$$

The control group was taken as a reference for determining survival reduction of the aPDI, PS, or L or chlorhexidine gluconate groups. Survival reductions were calculated as logarithmic as shown in formula 2.

Formula 2

$$\text{Reduction} = \log_{10} \left( \frac{\text{Number of colonies per mL in the control group}}{\text{Number of colonies per mL in the application group}} \right)$$

## 4. Results

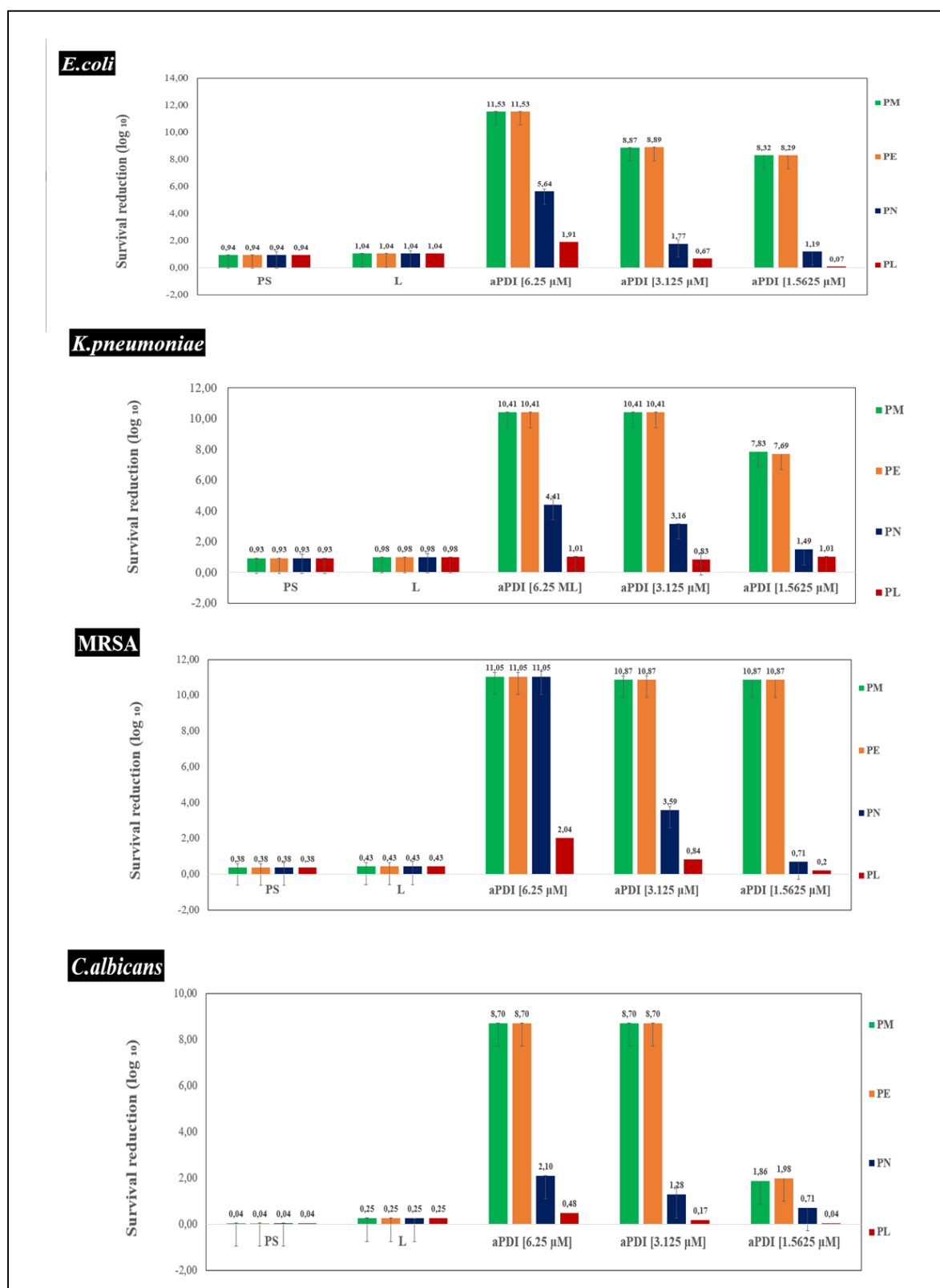
In this study carried out in *in-vitro* conditions the results of the experiment for aPDI against *E. coli*, *K. pneumoniae* and MRSA with MDR properties and *C. albicans* clinical isolates are as seen in Figure 2. The aPDI of CPD combinations at concentrations of 6.25  $\mu\text{M}$ , 3.125  $\mu\text{M}$  and 1.5625  $\mu\text{M}$ , respectively, was investigated, keeping the 25 J/cm<sup>2</sup> energy density constant. Change in survival for each experiment was based on control groups. As can be seen, there was no change in survival in the photosensitizer and light groups.

For PM and PE photosensitizers, a survival reduction of over 11.53 log<sub>10</sub> was found at *E. coli* at the 6.25  $\mu\text{M}$ . When the concentration was reduced to 3.125  $\mu\text{M}$ , the survival reduction was 8.87 log<sub>10</sub> in experiments using PM and 8.89 log<sub>10</sub> in experiments using PE. Similar results were obtained in the aPDI groups for both photosensitizers at the 1.5625  $\mu\text{M}$  concentrations. In experiments using PN, there was a 5.64 log<sub>10</sub> survival reduction at the 6.25  $\mu\text{M}$  concentration, but aPDI efficiency was also reduced when the concentration was lowered. In experiments with any concentration of PL, the reduction in survival was limited to the range of 1.91 log<sub>10</sub> to 0.07 log<sub>10</sub>.

In experiments on *K. pneumoniae* and MRSA, the reduction in survival in the aPDI groups was over 10 log<sub>10</sub> at the 6.25 and 3.125  $\mu\text{M}$  PM and PE concentrations. At the 1.5625  $\mu\text{M}$  concentration, there was a 10.87 log<sub>10</sub> MRSA reduction in both photosensitizers, 7.83 log<sub>10</sub> *K. pneumoniae* reductions in PM and 7.69 log<sub>10</sub> in PE. For *K. pneumoniae* and MRSA, the reduction in survival in the aPDI groups using PN and PL ranged from 4.41 to 0.2 log<sub>10</sub>(Figure 2).

In experiments with *C. albicans*, the reduction in survival in the aPDI groups using 6.25 and 3.125  $\mu\text{M}$  PM and PE was 8.70 log<sub>10</sub> each. The reduction in survival in the aPDI groups was limited to the range of 2.10 to 0.04 log<sub>10</sub> at all three concentrations for PN and PL. Antifungal activity was limited in aPDI groups at concentrations of 1.5625  $\mu\text{M}$  for all four photosensitizers (Figure 2).

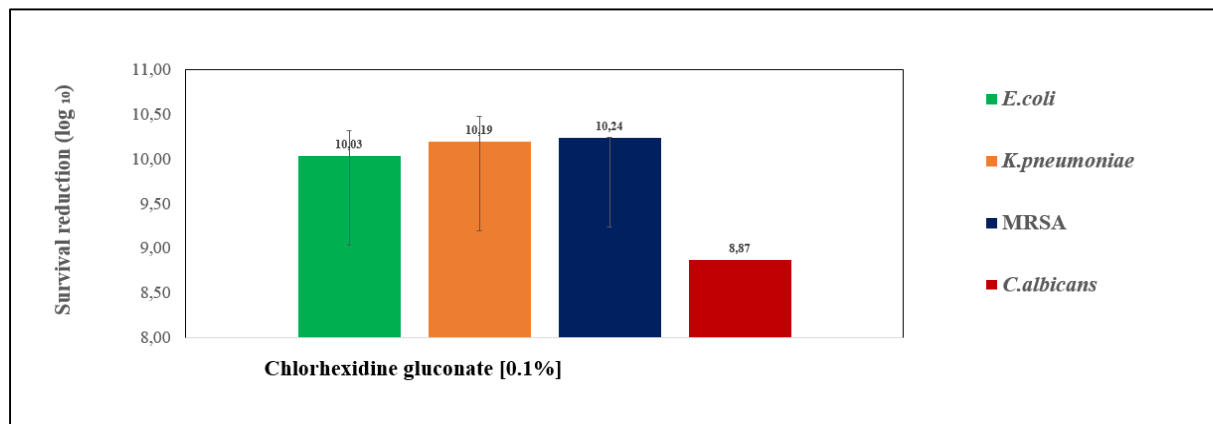
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**Figure 2.** The results of the aPDI experiments on the clinical isolates by selected combinations at 25 J/cm<sup>2</sup> (PS: Photosensitizer; L: Light; aPDI: antimicrobial photodynamic inactivation).

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The antimicrobial results of 0.1% chlorhexidine gluconate based on the concentration used in the perineal care of patients with urinary catheterization in the clinical setting are as seen in Figure 3. The survival reductions in MDR *E. coli*, *K. pneumoniae*, MRSA, and *C. albicans* were 10.03 log<sub>10</sub>, 10.19 log<sub>10</sub>, 10.24 log<sub>10</sub>, and 8.27 log<sub>10</sub>, respectively.



**Figure 3.** The results of the chlorhexidine gluconate experiments on the clinical isolates

## 5. Discussion

Today, CAUTI still remains a problem (1–4). The source of this infection may occur during the IUC, microorganisms pass through the urinary tract from the intraluminal and extraluminal routes (6,7,14). In this context, we think that there is an urgent need for effective applications to prevent extraluminal transition to be used in the clinical setting.

Research results on the antiseptics of the perineal region before IUC and the daily perineal care during the IUC differ from each other. Meta-analysis studies reported that antiseptic agents used for daily perineal care during antiseptics did not significantly change the rates of CAUTI. Although not significant, their efficacy on CAUTI was ranked from one (potentially most effective) to seven "chlorhexidine, clean water, soap and water, iodine, saline, and antibacterial agent," based on probability rankings (24,33,34).

So far, the most prominent antiseptic for daily perineal care of patients with IUC is 0.1% chlorhexidine gluconate. In our *in-vitro* research, it was determined that 0.1% chlorhexidine gluconate had a very strong antimicrobial effect on *C. albicans* and *E. coli*, *K. pneumoniae*, and MRSA with MDR properties. On the other hand, studies examining the use of 0.1% chlorhexidine gluconate in the daily perineal care of patients with IUC, were not found to be superior to distilled water/saline or tap water in terms of preventing CAUTIs (2,20,21,23,24). In addition, it was concluded that the use of chlorhexidine gluconate at different rates (0.05% and 4%) in the daily perineal care of patients with IUC did not affect the CAUTIs rates (20–22).

Another handicap is the toxicity problems of chlorhexidine. In the *in-vitro* evaluation of the effects of 0.2% chlorhexidine gluconate was determined that fibroblast cell reduced cell viability and had a cytotoxic effect on fibroblast cells at short exposure times of 30 seconds and 2 minutes. In experiments performed *in-vitro* and *in-vivo*, concentrations above 0.002% Chlorhexidine gluconate cause toxicity in keratinocytes, fibroblasts, myoblasts, and osteoblasts (35–38). In one study, chlorhexidine gluconate was shown to exhibit cytotoxicity that could disrupt the stable cellular redox balance, resulting in increased levels of free radical formation and subsequent cell death (39).

Therefore, the results regarding chlorhexidine limit its clinical usefulness. Guidelines recommend that the use of antiseptics or chemical-containing solutions for daily perineal care in



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patients with IUC is not appropriate for the prevention of CAUTI, but on the contrary, daily perineal care during daily bathing may be sufficient and appropriate (6,19)

On the other hand, the dramatic ratios in CAUTI in the literature show that the solution to this problem should be focused on (1–4). Microbial colonization was detected in the urinary catheters of all patients included in the sample in our project titled “Microbial Colonization and Related Factors in the Indwelling Urinary Catheter” which is still in the publication proses. In addition, despite perineal care with water twice a day, intense discharge was observed in the meatus of most of the patients, predominantly female during sampling for culture. Therefore, we think that daily perineal care with antiseptic is needed routinely. In this context, there is an urgent need for a non-toxic alternative antiseptic that can be used safely in the routine perineal care of patients with IUC.

In our study, in aPDI experiments with PM and PE, significant antimicrobial activity was observed against *C. albicans*, *E. coli*, *K. pneumoniae* and MRSA clinical isolates at the 6.25  $\mu\text{M}$  and 3.125  $\mu\text{M}$  concentrations, as in 0.1% chlorhexidine gluconate. The same antimicrobial efficacy cannot be mentioned for PN and PL. In the literature, antimicrobial activity was obtained on clinical isolates with wild type or MDR clinical isolates in the aPDI results performed with different types of photosensitizers with blue light (40–45). Similarly, a strong aPDI was obtained on wild-type microorganisms in experiments with blue light and CPDs combinations (42,46–50). In experiments performed under *in-vivo* conditions, a strong aPDI was also detected in MDR clinical isolates (51–54). In addition, it is extremely important that blue light does not show toxicity in living cells in aPDI. Blue light itself induced fibroblast cell growth in live animal experiments *in-vivo* (31). In our study, a very strong antimicrobial was obtained against *C. albicans* and MDR clinical isolates, which are frequently isolated in CAUTIs at very low concentrations and low energy density. These results obtained from experiments carried out in *in-vitro* conditions have given our research uniqueness compared to studies carried out in other *in-vitro* environments.

## 6. Conclusions and recommendations

In this *in-vitro* study, the efficacy of aPDI and 0.1% chlorhexidine gluconate on *C. albicans*, MDR *E. coli*, *K. pneumoniae*, and MRSA, which are among the clinical isolates frequently isolated in CAUTI, were evaluated. For PM and PE, a very strong aPDI was obtained in *C. albicans*, *E. coli*, *K. pneumoniae*, and MRSA with MDR properties at low concentrations and energy density. The same antimicrobial activity was found in experiments using 0.1% chlorhexidine gluconate. Antimicrobial efficacy was limited in all experiments in which PN and PL. In this context, we would like to inform you that aPDI to be performed with a combination of 25  $\text{J}/\text{cm}^2$  at 6.25 and 3.125  $\mu\text{M}$  concentrations of PM and PE has the potential to be an antiseptic in the daily perineal care of patients with IUC. On the other hand, the toxicity of these effective combinations on living cells and perineal microbiota should be investigated under *in-vitro* conditions. In addition, the stability and toxicity of these combinations in aPDI under *in-vivo* conditions should be considered. Our next experiments will be designed around the realization of these goals.

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## Declaration of competing interest

The authors declare no conflict of interest.

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