Saudi Journal of Biological Sciences 28 (2021) 5561–5567

Contents lists available at ScienceDirect

Saudi Journal of Biological Sciences

journal homepage: www.sciencedirect.com

Original article

The effect of antibiotics and photodynamic therapy on extended-spectrum beta-lactamase (ESBL) positive of *Escherichia coli and Klebsiella pneumoniae* in urothelial cells

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ARTICLE INFO

Article history:
Received 14 November 2020
Revised 25 May 2021
Accepted 27 May 2021
Available online 2 June 2021

Keywords:
Pathogen
Antibiotics
PDT
ESBL
E. coli
K. Pneumonia
UTI

ABSTRACT

Background/aim: Urinary tract infections are commonly caused by the bacteria *Escherichia coli* and *Klebsiella pneumoniae* (UTI). The emergence of extended-spectrum -lactamase (ESBL)-producing bacteria strains has made UTI treatment more difficult.

Materials and methods: The aim of this study was to characterize *E. coli* and *K. pneumoniae* strains' cytotoxic effects, antibiotic sensitivity, interaction with urothelial cells, and reaction to photodynamic therapy.

Results: As demonstrated by the higher number of colonies formed, the ESBL + *E. coli* and *K. Pneumonia* showed a higher degree of binding with human urothelial cells. With the urothelial cells, *K. Pneumonia* had the highest binding ability. The cytotoxicity of non-ESBL generating E. coli and *K. Pneumonia*, on the other hand, was higher. With longer incubation, the discrepancy between the cytotoxic effects of non-ESBL producer and ESBL + *E. coli* decreased. *K. Pneumonia* was the opposite. The concentration of ESBL-negative *E. coli* was easily decreased by photodynamic therapy; however, after a two-hour incubation period, the number of *E. coli* ESBL + colonies increased from 124 percent to 294 percent.

Conclusion: With the duration of the incubation period, the number of non-ESBL-producing *K. Pneumonia* increased. Even with longer incubation times, the number of *K. Pneumonia* ESBL + colonies decreased, contrary to expectations. The findings show that the two bacterial species differed in terms of cytotoxicity, interaction with urothelial cells, and photodynamic therapy response.

1. Introduction

The rise in bacterial resistance is a well-known fact as well as a long-standing problem. Despite the availability of new antibiotics, multidrug-resistant microorganisms are becoming increasingly common (Nisha et al., 2015). In urinary tract infections, the bacteria *Escherichia coli* and *Klebsiella pneumoniae* are the most popular etiologic agents. These infections pose a threat to public health and society, as studies show that approximately 40% of women and 12% of men will experience at least one UTI during their adult lives (Wang et al., 2009). The infection has a high rate of recurrence, and if proper antibiotic treatment is not developed, it may quickly progress to serious sepsis or death. *Escherichia coli* is the most common pathogen, accounting for 70 to 95 percent of community-acquired UTIs (CA-UTIs).

There are several treatment options available that can partially or completely stop microorganisms from multiplying and growing in the urinary tissues. Antibiotics (chemicals developed by microorganisms), chemotherapeutics (lab-created substances or structurally modified microbial products), and photodynamic therapy (use of photosensitizing agents, light, and oxygen to trigger cell regression) are some of the therapies available (Cavalieri and Snyder, 1982). The use of these chemicals has changed the way infections are treated, and their success has given rise to a lot of hope for the prevention and treatment of infectious diseases (Yousef et al., 2018). Antimicrobial drug resistance is not a new phenomenon. The discovery of -lactamase in Gram-positive and Gram-negative bacteria dates back to the early 1940s, before penicillin became widely used (Bayraktar et al., 2019). The development of -lactamase enzymes, which hydrolyze the beta-lactam ring by breaking the amide bond and thus lose their ability to inhibit bacterial cell wall synthesis, has been identified as a key mechanism of resistance to -lactam antibiotics (Amer, El-Baghdady, Kamel and El-Shishtawy, 2019). The advent of extended spectrum beta lactamases (ESBLs), which are plasmid-mediated enzymes that can hydrolyze penicillin, oxythino-cephalosporins, extended

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https://doi.org/10.1016/j.sjbs.2021.05.074
1319-562X/

spectrum cephalosporins, and aztreonam, has gradually limited therapeutic options for UTIs caused by *E. coli*. Furthermore, organisms that produce ESBL can develop resistance to other antibiotics such as aminoglycosides, tetracyclines, trimethoprim/sulfamethoxazole, and quinolones (Logan et al., 2014). ESBLs are enzymes found in gram-negative bacteria, mainly enterobacteria including *Escherichia coli* and *Klebsiella pneumoniae*. Gram-positive bacteria have extracellular beta-lactamases, while Gram-negative bacteria have them in the periplasmic region (Boo et al., 2005). Other beta-lactams known as -lactamase inhibitors, such as sulbactam, tazobactam, and clavulanic acid, inhibit these enzymes, making the strains that produce them susceptible to combinations of -lactam antibiotics and -lactamase inhibitors (Rouschop et al., 2006). Even though all -lactamases catalyze the same reaction, only a few forms have been isolated and characterized. The primary structure (classes A to D), as well as functional and biochemical properties, are used to classify these enzymes (group I to IV). Penicillin's and cephalosporins are hydrolyzed by enzymes classified as class A or group II; carbapenems are hydrolyzed by enzymes classified as class B or group III; cephalosporins are hydrolyzed by enzymes classified as class C or group I; penicillin's and cloxacillin are hydrolyzed by enzymes classified as class D; and penicillinases are hydrolyzed by enzymes classified as group IV penicillin a (Elsharkawy et al., 2013; Boo et al., 2005). The enzyme's effects are dependent on the distribution of the enzyme in different bacterial species, the prevalence of lactamase activity within each species, and the prevalence of pathogenic bacteria (Boo et al., 2005). In light of these three considerations, plasmid-mediated class A enzymes are regarded as the most significant in terms of their clinical implications (Hancock et al., 2010). Uropathogenic *E. coli* has been shown to produce a variety of virulence factors and strategies to control their growth and recurrence in the host's urinary tract tissues (Wiles et al., 2008). The adhesion of type P and type 1 pili to the host tissues is the cause of binding and invasion (Cavalieri and Snyder, 1982). Bacteria produce substances such as hemolysin and proteases after adhesion, which aid invasion and multiplication. Hemolysin is a peptide that damages other cells when causing erythrocyte lysis (Nisha et al., 2015). The development of bacterial endotoxins causes paralysis of the ureteral smooth muscle, causing peristalsis to be blocked and bacterial ascent to the kidneys to be favored (Amer et al., 2019). The aim of this study is to look at the sensitivity, interaction with urothelial cell lines, cytotoxic effect on urothelial cells, and response to photodynamic therapy of *Escherichia coli* and *Klebsiella pneumoniae* bacteria, both ESBL producing and non-producing strains (PTD).

2. Materials and methods

The study was conducted at Microbiology division of Biology Department at Faculty of Science, King Abdul-Aziz University.

2.1. Reagent's preparation

The Cysteine lactose electrolyte deficient (CLED) and 10% sodium dodecyl sulphate (SDS) was prepared. The preparation of 0.1% Ethylene diamine tetra acetic acid (EDTA) was done by adding 0.1 g into 100 ml of buffered phosphate saline. The 70% of ethanol by adding 350 ml of absolute ethanol into 150 ml water. 25 mg of Trypsin inhibitor (TI) was and keratinocyte growth medium 2 was also prepared.

2.2. Bacterial identified and Urothelial cells culturing

The strains were collected from the clinical microbiology laboratory at King Abdul-Aziz University Hospital. Samples of *E. coli and K. pneumonia* strains isolated from Urine and identified by BioMérieux Vitek 2 protocol. The bacterial strain was grown in Luria-Bertani (LB) broth overnight at 37C^{o} in the O2 incubator (Alsam et al. 2006). The optical density of bacteria in LB broth was measured by spectrophotometer with wavelength 595 nm and optical density 0.22 was obtained (OD 595 0.22 = ~10^{8} bacteria/ml). Isolated Urothelial cells were also cultured according to different protocols based on Chapman Et Al. (2006).

2.3. Bacteria dilution and association assay

The bacterial association assay was performed following the protocol of Alsam et al. (2006) and the bacterial cultures were grown in LB broth and monitored at OD of 595.0 nm. When the OD was 0.22, 50 μl of this initial bacterial culture was mixed with 450 μl of PBS to obtain a concentration of 10^{-1}

The same was done in 24-well plates where the urothelial cells were placed but 500 μl of PBS was added to controls of cells, 475 PBS with 25 μl 10% SDS for bacteria with cells, 25 μl SDS for controls of bacteria. After mixing well, 7 μl of cells were placed in the haemocytometer to count the number of cells in 1 ml media. The association percentage was finally computed as:

$$Percentage\ (\%)\ of\ bacteria\ associated\ with\ cells = \frac{number\ of\ recovered\ bacteria}{aggregate\ number\ of\ urothelial\ cells} \times 10$$

2.4. Cytotoxicity of bacteria

Two plates of cells were prepared with 24 and 48 h growth. After the growth medium of the cells was discarded, 2 μl of bacteria in 98 μl of nutrient broth was added. After one hour incubation, the supernatants were transferred to Eppendorf tubes and stored in the refrigerator. The cytotoxicity that relates to supernatants was taken through a measurement associated with the release of lactate dehydrogenase (LDH). This constitution is following the set recommendations provided by a manufacturer in terms of the utilised cytotoxicity detection referred to as (Roche). Again, the experiments were done at least three times where the followed computation was:

$$(Percentage\ (\%)\ cytotoxicity = \frac{[sample\ value - low\ control\ value]}{[High\ control\ value - low\ control\ value]} \times 100)$$

2.5. Photodynamic therapy

Three 96-well plates were prepared for each treatment duration (0, 1, and 2 h). The dilution of the cultures was at 10^{-5} where a spread was done on the CLED agar plates for the purpose of determining viability of the cells. An incubation was done for the period of overnight where it was then possible to compute the PDT effects percentage through the application of the following formula:

$$percentage\ (\%)\ of\ PDT = \frac{(count\ of\ cell\ control - \ amount\ of\ cells\ in\ sample)}{count\ of\ cell\ control} \times 100$$

2.6. Statistical analysis

All data analyzed by SPSS v.22. One-way ANOVA was used for significant differences between groups. A P value < 0.05 was accepted as statistically significant.

3. Results

3.1. Association between bacteria and urothelial cells

The association assay indicated that both strains producing the extended spectrum β-lactamase (ESBL) enzyme were more associated with the urothelial cells where the representation is shown in the (Fig. 3.1) below.

The outcomes showed that degrees of association *E. coli* were at 64.50%, ESBL + at 118.42%, *K. pneumoniae* at 64.50%, *K. pneumoniae* ESBL + at 134.00%. *K. pneumoniae* ESBL + bacteria that is found in the urothelial cells is the one with the most concentration. However, ESBL + was the one following the *K. pneumoniae* at the level 118.42% level.

3.2. Antibiotic sensitivity of the bacteria strains

Highly sensitivity was observed *ESBL-negative E. coli*. Except for nalidixic acid (NA), which increased the zone of inhibition, there was less inhibitory effect of the antibiotics on the growth of ESBL-positive *E. coli*. The ESBL negative concentration was only observed at NA 30 μg with 4 cm inhibition. Nonetheless, the IPM 10 μg showed the highest level with regards to inhibition measured in 'cm' at 4.3. Therefore, the main implications achieved in the outcome is that there is present resistance between ampicillin (amp) as well as trimethoprim (W). The statistics also showed that there were no clearly achieved differentiation in terms of the zones of inhibitions with regards to antibiotics. Another illustration from the results that the ESBL-positive tend to increase when in the surrounding of CAZ, AMC, as well as TZP (Fig. 3.2).

Both *K. pneumoniae* and *K. pneumoniae* ESBL^{+} strains showed resistance to ampicillin (amp) and Trimethoprim (W) Unlike *E. coli*, there were no marked differences in the zones of inhibition due to the antibiotics (Fig. 3.3).

3.3. Cytotoxic effect of bacteria on urothelial cells

The determination of cytotoxic impacts of bacteria was assessed at 24 and 48 h. The overall outcome depicted in (Fig. 3.4) is that bacteria tend to show higher cytotoxicity at the 48 h incubation

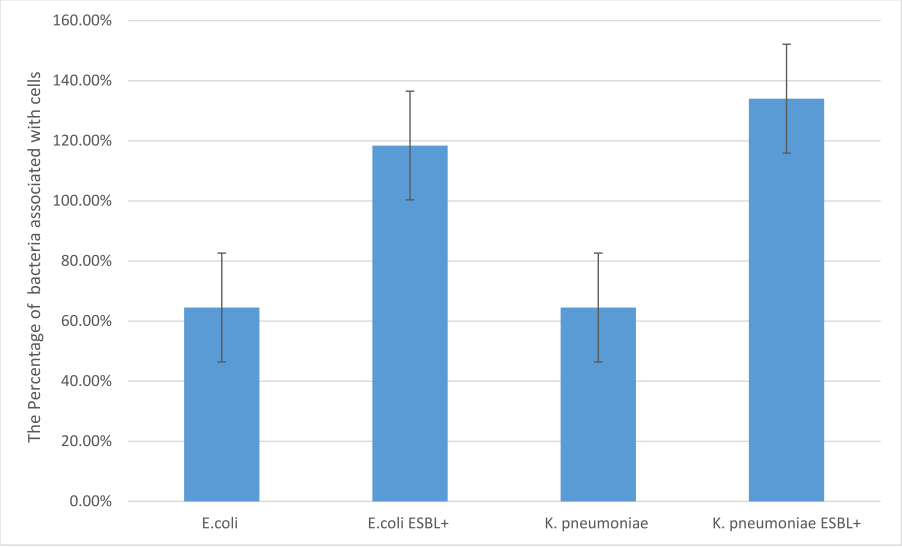

Fig. 3.1. Percentage of bacterial cells that were associated with the human urothelial cells. Error bars represent standard error.

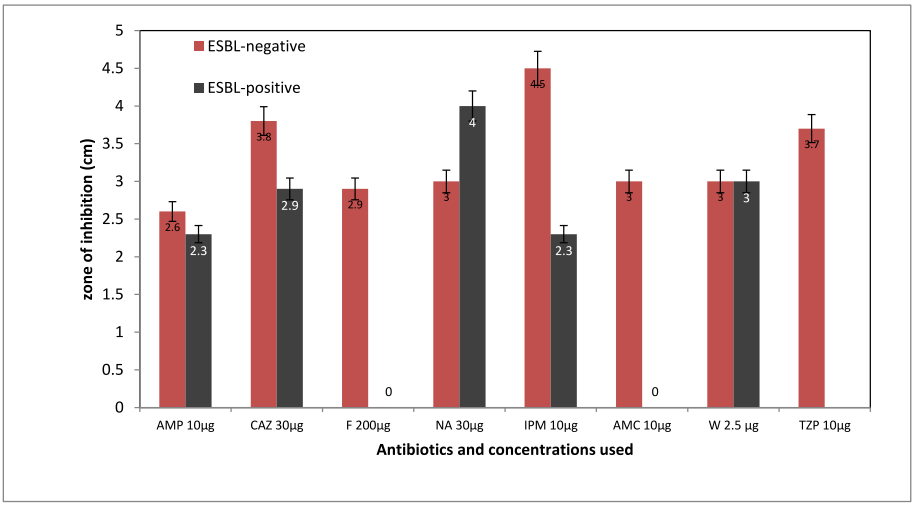

Fig. 3.2. Zones of inhibition produced by the different antibiotics on the growth of *E. coli* strains. Error bars represent standard error.

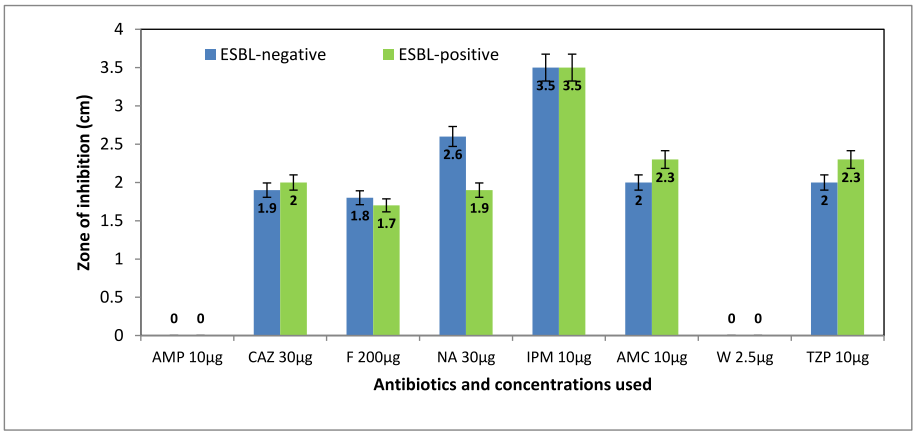

Fig. 3.3. Zones of inhibition produced by the different antibiotics on the growth of *Klebsiella* strains. Error bars represent standard error.

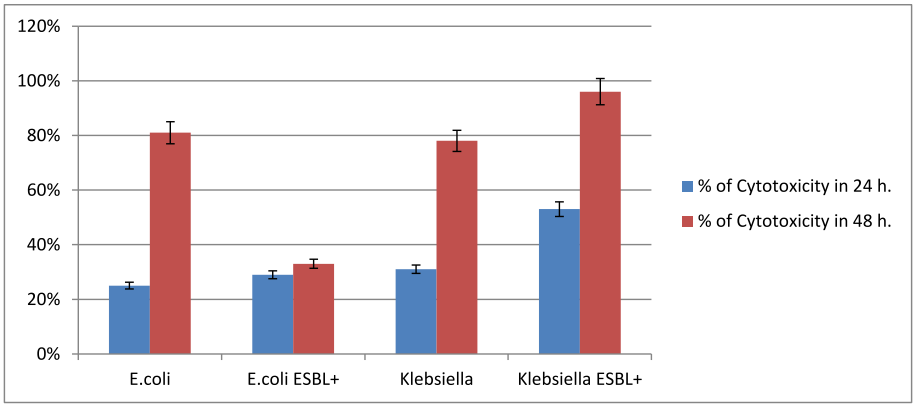

Fig. 3.4. Cytotoxicity of the four bacterial strains after 24 and 48 h of incubation with urothelial cells. Error bars represent standard error.

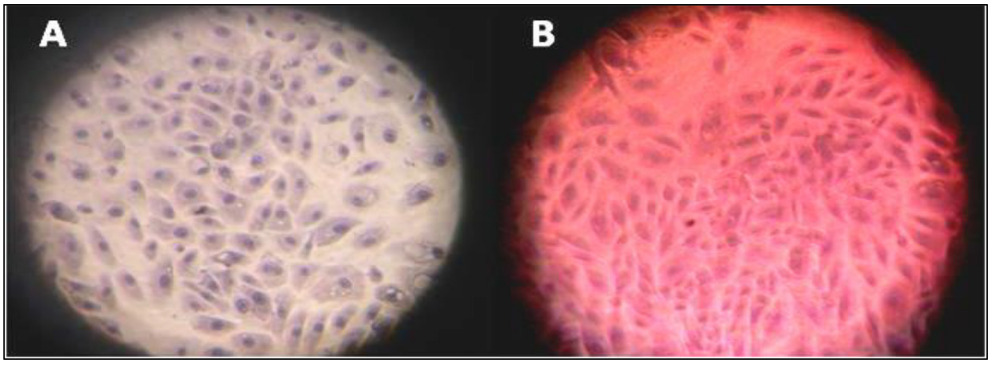

Fig. 3.5. Urothelial cells stained with (A) trypan blue and (B) hematoxylin.

level. This way the cytotoxicity was amplified at the strains *E. coli*, *K. pneumoniae*, and *K. pneumoniae* ESBL$^+$. Based on the derived outcomes, ESBL positive was derived to show that cytotoxic levels were high despite the period of incubation. The results showed that *E. coli, K. Pneumonia,* and *K. Pneumonia* ESBL$^+$ and ESBL positive strains were more cytotoxic irrespective of the incubation time in (Fig. 3.5); it appears to be more dead cells as indicated by the intensity of the stain. (Fig. 3.5), shows that a low number of nuclei were stained.

The number of live and dead cells counted with time can be summarized as shown (Fig. 3.6) below.

3.4. The effect of photodynamic therapy on bacterial viability

The photodynamic therapy increased the viability of ESBL-positive *E. coli.* Increased time of exposure to the photosensitizer increased the viability of ESBL-negative *Klebsiella* but decreased the viability of *Klebsiella* ESBL$^+$. The summary of the outcome is as shown in the (Fig. 3.7) below.

The analysis shows that the efficacy of *E. coli* in reaction to photodynamic therapy is tending to degrade. This aspect is based on the achieved figure at 17% at two hours, which was a very low number as compared to initial value at zero hours that was at

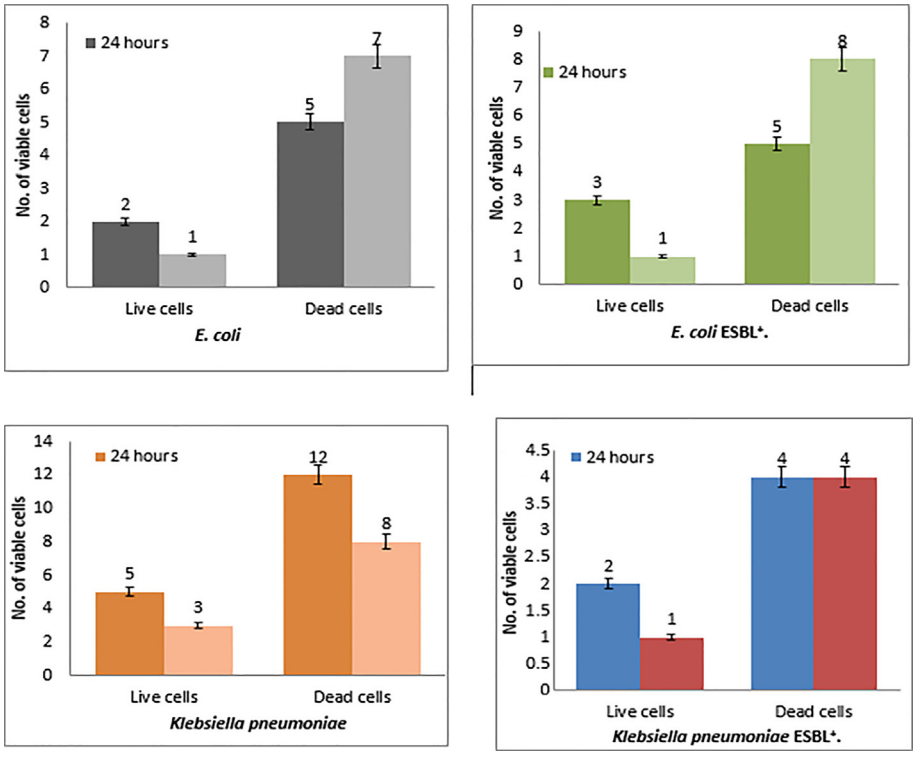

Fig. 3.6. The number of surviving and dead urothelial cells after exposure to bacteria strains. Error bars represent standard error.

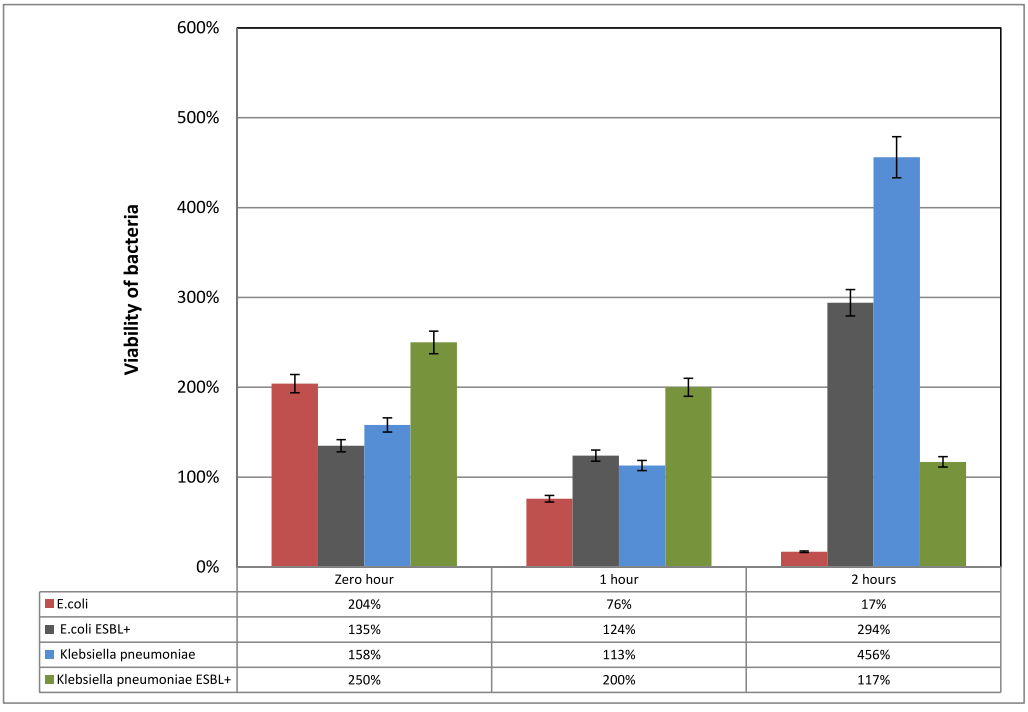

Fig. 3.7. The effect of incubation time with the photosensitizer m-THBPC on the viability of bacterial strains after exposure to light. Error bars represent standard error.

204%. These outcomes are different from the ones for klebsiella pneumoniae where the viability at zero hours was at 158% and the end of exposure to photosensitizer the viability was at 456%. In summary the outcomes showed that the ESBL negative *K. pneumoniae* has the highest resistance to the photo-dynamic treatment, where viability of ESBL-negative *E. coli* was most affected.

4. Discussion

The antibiotic sensitivity of the bacteria strains showed that ESBL-negative *E. coli* were more sensitive than the ESBL-positive *E. coli*. The rational is that ESBL-negative *E. coli* did not have any antibiotic activating mechanism and therefore the growth were

inhibited (Dhakal and Mulvey, 2009). The ESBL-positive *E. coli* demonstrated to have the ability to inhibit the antibiotic activity. The ESBL-positive *Escherichia coli* strain indicated a reduction in the colonies growth with the presence of imipenem, ampicillin, and ceftazidime antibiotics. The antibiotics that presented lowest impact were nitrofurantoin, amoxicillin and. The ampicillin and ceftazidime contain clavulanic and tazobactum acid, respectively, which are inhibitors of a various types of plasmid-mediated β-lactamases. It was notice that both *K. pneumoniae* and *K. pneumoniae* ESBL$^+$ bacteria strains hydrolysed ampicillin (β-lactam antibiotic) and Trimethoprim (dihydrofolate reductase inhibitor). The findings shows that the two species of bacteria present different characteristics concerning antibiotic resistance. This may be due to many classes of ESBL that are characterized and identified according to their chemical structure, range of action and specificity (Boo et al., 2005).

Both ESBL-positive strains of bacteria (*E. coli* and *K. pneumonia*) showed growth in bacterial colonies which means that the ESBL-positive bacteria have good adherence to urinary tracts cells as compared to ESBL-negative strains. According to Trinchina (2003), most of uropathogenic strains of *E. coli* bind very specifically to receptor which are residual carbohydrates of the structure of glycoproteins or glycolipids. Type 1 fimbriae have as glycoprotein receptors with mannose residues, while P-fimbriae receptors have glycosphingolipids and globotriosylceramide (Imming, 1995). This event affects the molecular properties that lead to bacterial adhesion of urinary infections. Zhou et al. (2001) also claim that urinary infections are the result of the interaction of the virulence of bacteria and a series of specific and nonspecific factors of host defences related to ESBL enzymes. The possibility of a colonization and subsequent infection is due to the contact between a series of bacterial structures, called adhesins (fibric or non-fibrical), and receptors or ligands on the surface of the urinary epithelium.

The results indicate that ESBL-positive bacterial strains had less cytotoxic activity than the non-ESBL producing strains. As explained by Härtlein et al. (1983), virulence aspects such as toxins have the ability to reduce viability of host cell and difference in observed between two strains of bacteria can be partially attributed to the expressions of the toxins. Haemolysin, secreted autotransporter toxin (SAT) and Cytotoxic necrotizing factor 1 (CNF1), are all known to have less prevalence in ESBL-positive than the ESBL-negative strains (Sen and Bagchi, 2001).

The different species of bacteria responded distinctively to the photodynamic treatment. For the *E. coli*, the photodynamic treatment reduced the viability of the bacteria cell with sustained contact with photosensitizer. The decrease indicate that the bacterial cells were killed. For the ESBL-positive *Escherichia coli*, the cell viability was increased with increase in photosensitizer exposure. The ESBL-negative *K. pneumoniae* exhibited growth while the non-ESBL producing *K. pneumoniae* indicate somewhat decreased growth. The results seemed to be inconsistent with our expectations as the non-ESBL producing *E-coli* was noticed to be mostly affected by the photodynamic therapy while ESBL-negative producing *K. pneumoniae* was noticed to be more resistant (Rouschop et al., 2006). It showed that different bacteria species and even strains do react differently to photodynamic therapy (Gerlach et al., 1989). Several factors pay part in the success of a PDT and may include photosensitizer concentration and laser power. Other studies have found that increasing PDT light exposure time considerably increases the bactericidal effect (Van Duijnhoven et al., 2005).

5. Conclusion

The findings showed that more colonies in the urothelial cells with *K. pneumoniae* ESBL$^+$ exhibiting higher binding compared to the ESBL-negative strains. The ESBL non-producing bacterial strains have high bacterial cytotoxicity. It was also found that photodynamic therapy (PDT) is the most effective treatment for eradicating the majority of bacteria strains that cause UTI. PDT, on the other hand, was found to be incapable of inhibiting or eradicating ESBL-producing *E. coli*. Future studies in PTD could aim to quantify the length, ideal laser power parameters, and photosensitizer concentration needed in vivo applications.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

I would like to Thank the staff of Clinical Microbiology laboratory at King Abdul-Aziz University Hospital and Microbiology laboratory in Biology Department. At King Abdul-Aziz University for their help during collection data.

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