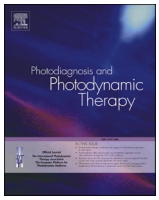
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Photodiagnosis and Photodynamic Therapy 40 (2022) 103158

Contents lists available at ScienceDirect

Photodiagnosis and Photodynamic Therapy

journal homepage: www.elsevier.com/locate/pdpdt



Editorial

Clinical acceptance of antimicrobial photodynamic therapy in the age of WHO global priority pathogens: So what we need to move forward?

While the world continues to face the COVID-19 pandemic crisis, a silent threat related to the spread of antimicrobial resistance is emerging backstage. COVID-19 has fuelled the massive use of antibiotics to treat secondary bacterial infections or co-infections that can worsen the outcome of critically ill patients. Additionally, the prolonged stay in healthcare settings and concomitant increase in invasive procedures have also created a perfect opportunity for antibacterial-resistant pathogens to emerge and disseminate [1].

Over the last decades, the dissemination of antibacterial-resistant bacteria has been a red-alert threat that keeps the global public health authorities awake due to high morbidity and mortality rates [2]. In this regard, a recent systematic analysis revealed that more than 1.2 million people died in 2019 as direct causes of antibiotic-resistant bacterial infections previously treatable in the past, becoming more lethal than malaria or HIV/AIDS [2]. More critically, it is estimated that antibacterial-resistant pathogens would kill about 10 million humans per year by 2050 [3], overcoming deaths caused by cancer or the COVID-19 pandemic during its worst moments. Although some disagreements regarding these forecasts have occurred, the World Health Organization (WHO) recognizes that a globally coordinated action to reduce the rapid dissemination of antibiotic-resistant pathogens is urgently required.

To face this unprecedented global health crisis, the WHO has published a global priority list of antibiotic-resistant bacteria in which discovery, research, and development of new antibiotics are immediately needed [4]. In this list, the most clinically important antibiotic-resistant bacteria were ranked based on mortality, health-care and community burden, the prevalence of resistance, a 10-year trend of resistance, transmissibility, preventability in the community setting, preventability in the health-care setting, treatability, and pipeline. Aside from multidrug-resistant (MDR) and extensively-resistant (XDR) *Mycobacterium tuberculosis*, the WHO pathogens priority list stratified other antibacterial-resistant pathogens as follows: Critical priority (carbapenem-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, and carbapenem-resistant or third-generation cephalosporin-resistant *Enterobacteriaceae*); High priority (vancomycin-resistant *Enterococcus faecium*, vancomycin-resistant or methicillin-resistant *Staphylococcus aureus*, clarithromycin-resistant *Helicobacter pylori*, fluoroquinolone-resistant *Campylobacter* spp., fluoroquinolone-resistant *Salmonella* spp., third-generation cephalosporin-resistant or fluoroquinolone-resistant *Neisseria gonorrhoeae*); Medium priority (penicillin non-susceptible *Streptococcus pneumoniae*, ampicillin-resistant *Haemophilus influenzae*, fluoroquinolone-resistant *Shigella* spp.) [4].

Although the list did not include other microorganisms (*i.e.,* fungi, viruses, and protozoa), the scientific community is also paying careful attention to some emerging drug-resistant pathogens. *Candida* spp., especially the superbug fungus *Candida auris*, is emerging as a public health concern worldwide due to its resistance to multiple antifungal drugs [5]. Indeed, the resistance problem is not just a problem limited to bacteria since many microbial species have the potential to mutate and acquire resistance to new classes of antimicrobials, making them useless. Therefore, the ideal antimicrobial platform used to overcome this challenge should act upon multiple targets to avoid a novel emergence of drug-resistant phenotypes.

The use of light-based technologies in clinical practice began with Niels Finsen who was awarded the Nobel Prize in Medicine and Physiology for showing effective results against cutaneous tuberculosis. Antimicrobial photodynamic therapy (aPDT) involves the use of light and a photosensitizing drug to promote cell killing by oxidative stress and has proven to be effective against a broad range of microorganisms. Since the first *in vitro* study performed by Oscar Raab at the beginning of the last century, many peer-reviewed articles have been published proving aPDT efficacy against multiple microorganisms, including those resistant to clinically important antimicrobials. In addition, there have been no reports concerning the selection of resistant microorganisms following aPDT.

Although it seemed promising, the idea of using light-based antimicrobial therapies was almost forgotten following the introduction of the sulfa and beta-lactam drug classes in the 1930s and 40s. Since then, the effectiveness of antibacterials has been threatened by the emergence and rapid spread of resistant pathogens. As a direct consequence, the expensive development of novel antibacterial classes with short obsolescence periods has led pharmaceutical companies to quit this area of research. Indeed, less than 40 new antibacterial compounds are advancing in the clinical trial phases, and all of those targeting the WHO priority pathogens belong to existing antimicrobial classes. However, none of the new compounds in the clinical development pipeline are promising against WHO critical priority pathogens [6].

The difference in the mode of action and variety of cellular targets makes the development of resistance to aPDT unlikely. It is known that drug-resistant pathogens are, in general, equally susceptible to aPDT as their drug-sensitive counterparts [7]. Additionally, in some specific circumstances, aPDT led to the reduction of virulence factors, inhibited *in vivo* pathogenicity, and enhanced sensitivity to previously ineffective antibiotics of MDR bacteria [8]. Indeed, we have demonstrated the direct inhibition of the most clinically relevant β-lactamase enzymes (*i.e.,* those utilized by critical-priority pathogens) by aPDT, indicating that

https://doi.org/10.1016/j.pdpdt.2022.103158
Received 16 September 2022; Received in revised form 11 October 2022; Accepted 12 October 2022
Available online 13 October 2022

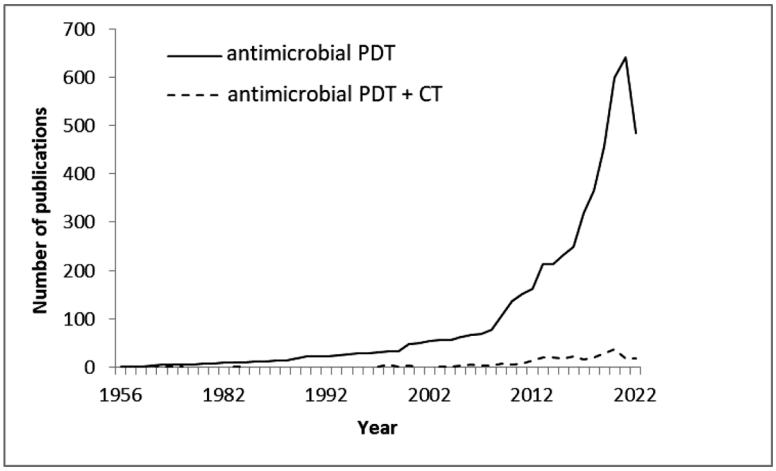


Fig. 1. Number of studies and clinical trials (CT) of antimicrobial photodynamic therapy published. Data were retrieved from the PubMed database via the National Center for Biotechnology Information (NCBI) interface (http://www.ncbi.nlm.nih.gov/RefSeq/) (accessed on September 16, 2022).

synergistic effects may be possible when combined with classic antimicrobial chemotherapy [9]. These features make aPDT very attractive for clinical use. So isn't it time for aPDT to move from laboratory to clinical practice?

Unfortunately, although the literature on aPDT is rich, most of the studies are pre-clinical, *i.e., in vitro* or animal models. There are more than 2000 articles in the literature, but aPDT still has not gained meaningful clinical acceptance and only 200 clinical trials have so far been published (Fig. 1). For decades, aPDT has proven to be highly effective against MDR bacteria, and, as noted, this includes most of the current WHO global priority pathogens. Typical, but not limiting examples, are the studies that demonstrate the ability of aPDT to inactivate vancomycin-resistant *E. faecium*, vancomycin- and methicillin-resistant *S. aureus* (VRSA and MRSA), and carbapenem-resistant *Enterobacteriaceae, A. baumannii* and *P. aeruginosa in vitro*. Moreover, the aPDT effectiveness against *in vivo* infections caused by these bacterial pathogens has been already proved in some studies. On the other hand, clinical studies regarding the use of aPDT to treat infections caused by WHO global priority pathogens in humans are scarce.

In this respect, so far as we could establish, there is only a clinical study, in which aPDT was used in diabetic patients. APDT was applied using both a broadband light source ($400 < \lambda < 725$ nm) and a light-emitting diode (LED, $\lambda = 640 \pm 50$ nm) to cover absorbance of two photosensitizers (PSs): toluidine blue ($\lambda_{max} = 630$ nm) and methylene blue (MB, $\lambda_{max} = 660$ nm). It is important to highlight that all enrolled patients received the same treatments: antibiotic therapy (depending on bacterial culture) and debridement. However, all patients in the control group had foot amputation. In contrast, aPDT prevented amputation in 17 out of 18 patients [10]. Worth noting, at least two of the cured patients had positive cultures for resistant bacteria such as MDR *P. aeruginosa* and carbapenem resistant *K. pneumoniae*, and no intravenous antibiotic was prescribed [10].

An additional case report in veterinary medicine reported the successful use of aPDT mediated by MB and a red laser in unilateral otitis externa caused by carbapenemase (VIM-2)-producing *P. aeruginosa* in a dog [11]. The authors reported a complete resolution of the clinical signs 7 days after aPDT. No positive cultures for VIM-2-producing *P. aeruginosa* were noticed in the 7 and 14 days following aPDT.

Current data and future trends of global mortality by MDR bacteria have been mostly attributed to systemic infections. Even though, infections that progress to sepsis frequently start in the lung, urinary tract, skin, or gastrointestinal tract. Particularly skin and soft tissue infections caused by MDR, including some WHO global priority bacteria, have been increasingly reported [12]. Since aPDT has been extended to include prophylaxis in the decolonization of carriers (*e.g.*, MRSA in pre-operative patients) it might also be used to fight opportunistic pathogens such as MDR *P. aeruginosa*, delaying bacteremia so that medical intervention may be more efficient to prevent sepsis [13].

Besides, although aPDT against MDR bacterial infections has been only used for local and/or topical application, more recent studies have suggested its potential to treat bloodstream infections by using either PS-functionalized or PS-loaded nanoparticles [14,15]. Indeed, systemic infections remain the main limitation of aPDT today and require further evidence *in vivo*.

The lack of robust and large-scale clinical trials confirming the efficacy, safety, and absence of side effects represents a bottleneck that slows down the adoption of aPDT by healthcare professionals. Indeed, similarly to other promising alternative therapies, the scarcity of clinical trials left aPDT open to criticism by mainstream medicine. After more than a century of gathering pieces of evidence of aPDT effectiveness against a broad range of pathogens, it is time to look to this approach as a potential ally against difficult-to-treat infections. In these dark times, we need to shed light and move forward with clinical trials so that the benefits, limitations, and clinical recommendations of aPDT might be firmly established. Thus, perhaps, it could be finally embraced by health professionals, since dedicated LED-based light sources may be readily developed. This alert is a recommendation to financial agencies to open proposals and embrace clinical trials that could improve our knowledge about the clinical scope of aPDT, especially for the treatment of localized infections. Last but not least, scientific journals should also pay attention to this appeal and look carefully at new therapeutic opportunities in the field of infectious diseases.

CRediT authorship contribution statement

Fábio P. Sellera: Conceptualization, Formal analysis, Supervision, Writing – original draft, Writing – review & editing. **Caetano P. Sabino:** Conceptualization, Writing – original draft, Writing – review & editing. **Silvia C. Núñez:** Conceptualization, Writing – original draft, Writing – review & editing. **Martha S. Ribeiro:** Conceptualization, Formal analysis, Supervision, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

No potential conflict of interest was reported by the authors.

Acknowledgments

FPS thanks CAPES for his scholarship (grant # Finance code 001).

References

[1] B.D. Huttner, G. Catho, J.R. Pano-Pardo, C. Pulcini, J. Schouten, COVID-19: don't neglect antimicrobial stewardship principles!, Clin. Microbiol. Infect. 26 (2020) 808–810, https://doi.org/10.1016/j.cmi.2020.04.024.

[2] Antimicrobial Resistance Collaborators, Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis, Lancet 399 (2022) 629–655, https://doi.org/10.1016/S0140-6736(21)02724-0.

[3] J. O'Neill, Antimicrobial resistance: tackling a crisis for the health and wealth of nations, Rev. Antimicrob. Resist. Chaired Jim O'Neill (2014). Available atamr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf (accessed 29 June 2022).

[4] E. Tacconelli, E. Carrara, A. Savoldi, S. Harbarth, M. Mendelson, D.L. Monnet, et al., Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis, Lancet Infect. Dis. 18 (2018) 318–327, https://doi.org/10.1016/S1473-3099(17)30753-3.

[5] K.E. Pristov, M.A. Ghannoum, Resistance of *Candida* to azoles and echinocandins worldwide, Clin. Microbiol. Infect. 25 (2019) 792–798, https://doi.org/10.1016/j.cmi.2019.03.028.

[6] M. Miethke, M. Pieroni, T. Weber, M. Brönstrup, P. Hammann, L. Halby, et al., Towards the sustainable discovery and development of new antibiotics, Nat. Rev. Chem. 5 (2021) 726–749, https://doi.org/10.1038/s41570-021-00313-1.

[7] C.P. Sabino, M. Wainwright, M.S. Ribeiro, F.P. Sellera, C. Dos Anjos, M.D. S. Baptista, et al., Global priority multidrug-resistant pathogens do not resist photodynamic therapy, J. Photochem. Photobiol. B 208 (2020), 111893, https://doi.org/10.1016/j.jphotobiol.2020.111893.

[8] J. Chibebe Junior, B.B. Fuchs, C.P. Sabino, J.C. Junqueira, A.O. Jorge, M.S. Ribeiro, et al., Photodynamic and antibiotic therapy impair the pathogenesis of *Enterococcus faecium* in a whole animal insect model, PLoS One 8 (2013) e55926, https://doi.org/10.1371/journal.pone.0055926.

[9] C. Dos Anjos, F.P. Sellera, M.S. Ribeiro, M.S. Baptista, F.C. Pogliani, N. Lincopan, et al., Antimicrobial blue light and photodynamic therapy inhibit clinically relevant β-lactamases with extended-spectrum (ESBL) and carbapenemase activity, Photodiagn. Photodyn. Ther. 32 (2020), 102086, https://doi.org/10.1016/j.pdpdt.2020.102086.

[10] J.P. Tardivo, F. Adami, J.A. Correa, M.A. Pinhal, M.S. Baptista, A clinical trial testing the efficacy of PDT in preventing amputation in diabetic patients, Photodiagn. Photodyn. Ther. 11 (2014) 342–350, https://doi.org/10.1016/j.pdpdt.2014.04.007.

[11] F.P Sellera, M.R. Fernandes, C.P. Sabino, L.M. de Freitas, L.C.B.A. da Silva, F. C. Pogliani, et al., Effective treatment and decolonization of a dog infected with carbapenemase (VIM-2)-producing *Pseudomonas aeruginosa* using probiotic and photodynamic therapies, Vet. Dermatol. 30 (2019) 170–e52, https://doi.org/10.1111/vde.127.

[12] J.F. Jabbour, S.L. Sharara, S.S. Kanj, Treatment of multidrug-resistant Gram-negative skin and soft tissue infections, Curr. Opin. Infect. Dis. 33 (2020) 146–154, https://doi.org/10.1097/QCO.0000000000000635.

[13] M.C. Hashimoto, R.A. Prates, I.T. Kato, S.C. Núñez, L.C. Courrol, M.S. Ribeiro, Antimicrobial photodynamic therapy on drug-resistant Pseudomonas aeruginosa-induced infection. An *in vivo* study, Photochem. Photobiol. 88 (2012) 590–595, https://doi.org/10.1111/j.1751-1097.2012.01137.x.

[14] J. Wang, H. Wu, Y. Yang, R. Yan, Y. Zhao, Y. Wang, et al., Bacterial species-identifiable magnetic nanosystems for early sepsis diagnosis and extracorporeal photodynamic blood disinfection, Nanoscale 10 (2017) 132–141, https://doi.org/10.1039/c7nr06373c.

[15] M. Raschpichler, M.R. Agel, S.R. Pinnapireddy, L. Duse, E. Baghdan, J. Schäfer, et al., *In situ* intravenous photodynamic therapy for the systemic eradication of blood stream infections, Photochem. Photobiol. Sci. 18 (2019) 304–308, https://doi.org/10.1039/c8pp00267c.

Fábio P. Sellera[a,b], Caetano P. Sabino[c], Silvia C. Núñez[d], Martha S. Ribeiro[e,*]

[a] *Department of Internal Medicine, School of Veterinary Medicine and Animal Science, University of São Paulo, São Paulo, Brazil.*

[b] *School of Veterinary Medicine, Metropolitan University of Santos, Santos, Brazil.*

[c] *BioLambda, Scientific and Commercial LTD, São Paulo, Brazil.*

[d] *Department of Bioengineering, Brasil University, São Paulo, Brazil.*

[e] *Center for Lasers and Applications, Nuclear and Energy Research Institute (IPEN-CNEN), Av. Lineu Prestes, 2242, São Paulo, SP 05508-000, Brazil.*

[*] Corresponding author.
E-mail address: marthasr@usp.br (M.S. Ribeiro).