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PDT- versus – Superbugs: The clinical struggle

Nearly 10 years ago PD-PDT published a paper authored by Professor Mark Wainwright, an expert in phenothiazinium photosensitizer- mediated Photodynamic Therapy, entitled 'Photo antimicrobials - so, what's stopping us?' In that paper Wainwright refers to the emergence of increasing multi-drug resistant bacteria and the need for new drugs or novel methods of decontamination to combat the trend [1]. In questioning "what's stopping us?", he was drawing attention to the colossal amount of scientific laboratory and preclinical work which had been undertaken on anti-microbial PDT and his paper was a call to arms, for the setting up of translational clinical studies.

Wainwright was neither the first nor the only scientist to assert the need for new anti- microbial agents or methods to counteract the trend in resistant organisms and to combat local infection by resistant micro-organisms- *superbugs* [2,3]. The topic has been an ongoing issue ever since the discovery of penicillin [4].

At the sharp end of clinical practice, many Physicians and Surgeons have had the painful experience of losing patients through serious infection resulting from organisms which are resistant to all or most available antimicrobial agents.

The many thousands of laboratory and preclinical publications, as well as a few clinical studies, bear testimony to the efficacy and safety of PDT in antimicrobial and localized infection. S0 - to repeat - 'what's stopping us?' in envisaging using PDT in patients with localized, surgical site, infection or, at least to start with, setting up a pilot clinical study.

Fundamentally, clinical research in the 21st Century has too many barriers to negotiate. Regulations and costs are prohibitive factors common to all medical research. Regulatory science [5] is a double edge sword which is intended to protect and set standards, yet it can delay the deployment of innovations urgently needed in health-care or to prevent the use of new treatments.

In the case of PDT in its antimicrobial indication, there are also other concealed difficulties. Concealed because the multitude of studies and their publications, at first sight, suggest that laboratory and preclinical studies can easily be translated to the clinical situation. The impression conveyed by many publications by reputable investigators tends to suggest that the passage from laboratory to the clinic merely requires a well-intentioned clinician with PDT experience to make the final push. This, unfortunately, is not the case. In this instance there seems to be a disconnect between science and the clinical use of PDT in its antimicrobial application, which only becomes apparent when a clinical translational study is being planned.

Some of these difficulties emanate from the fact that, in a great many laboratory studies, PDT is carried out on the culture of organisms in the milieu of a Petri dish. Basically, the results of PDT on a culture of organisms within a Petri dish cannot be replicated in the purulent milieu of living tissue. Therefore, such laboratory results cannot easily be used as a guide and are of limited relevance to a clinical setting.

Another prohibitive issue for the clinical researcher in PDT antimicrobial is related to the lack of clear evidence to show that there is discriminative microbial cell death in PDT and that the host's cells, important in salutary effects of inflammatory reaction, are unharmed [6,7]· Other difficulties relate to the 'tools' of PDT such as the photosensitizer (PS/drug) and its method of delivery, light source and dose appropriate for a given local infection.

There are literally hundreds of PS's which are reported in the literature and are used in laboratory experiments in PDT antimicrobial. Of these, a few have been used in the in vivo setting [8–10] and only a few in clinical studies. Methylene Blue and its relatives in the Phenothiazine group of chemical compounds have been used in a limited number of patients in specific local clinical infection, namely periodontitis. The following is an illustration of the issue under discussion.

Azarpazhooh et al [11], in a literature review of PDT for periodontitis, identified 24 papers of which only 5 were suitable for their final analysis. Their objective was to ascertain the antimicrobial role of PDT either with or without debridement [scaling and root planing (SRP)]. The PS used in all cases was Phenothiazine compounds; nevertheless, the PSs, though within phenothiazine chemical compounds, did not have the same chemical formulation. Also, the reader is not provided with a vital piece of information about the licensing status of the drug used. Further scrutiny reveals that only one of the PSs, the Methylene blue, was partially licensed to be used clinically in Canada and the FDA license was pending.

It follows that, in reality, none of the PSs used in periodontitis - which is a nearest example to a *surgical site infection* - can be used easily without further experimental work. Also, the other essential tool of PDT - the light source and its dose used in preclinical and limited clinical cases - cannot be replicated, basically because of lack of consistently clear methodology in the available published work.

So, to quote Winston Churchill in his time of need in World War II, (speech of February 1941)

"Give us (the clinicians) the tools and we will finish the job."

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