Replacing antibiotics and antivirals

A continuation of the 2016 NEXUS article, "Silver Iontophoresis: Antibiotics Replaced"

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Background and New Insights

This report forms the second part of the NEXUS vol. 23, no. 5, 2016 article that focused on silver iontophoresis delivered by a very small, skin-permeable direct electric current, and its potential to replace these pharmaceutical drugs for infection treatments. Our understanding has since advanced from further clinical experiences and biomedical engineering research and development. We have new insights into the mechanisms and modes of action of this new medical technology, especially relating to the involvement of low intensity direct current (LIDC) in the treatment of both surface and internal infections. The medical and biomedical engineering technology of silver iontophoresis and therapeutic LIDCs for bacterial and viral infection treatments has passed the examination process to be granted a standard Australian patent in February 2020. In addition, our research into electrically stimulating cell phenotype changes, has given further insights into these phenomena as originally documented in the journal articles and two USA patents by electromedical pioneer, Robert O. Becker. These two seemingly unconnected fields of study and clinical methodologies might also have a shared, underlying basis, explored in this article.

Low Intensity Direct Current

An electric current is the movement ("flow") of electrically charged particles. The intensity of an electric current is the rate of flow of the charged particles per unit

time. When any electric current has a repeating cycle of rising and falling intensity, the rate at which that alternating cycle of intensity occurs is the frequency of that electric current. Whereas, when the intensity of any very large or tiny electric current is constant and non-cycling over time, it is a constant direct current (DC) that has no frequency. Electric currents of low microampere (millionths of an ampere) intensities are generally described as being in the low intensity direct current (LIDC) range and those of nanoampere (billionths of an ampere) intensities can be termed ultra LIDCs. A constant LIDC produced through an animal body consists of a stable flow of charged electrons or biomolecules per unit time moving through conductive interstitial fluid (that surrounds the cells of the body) and tissue pathways.

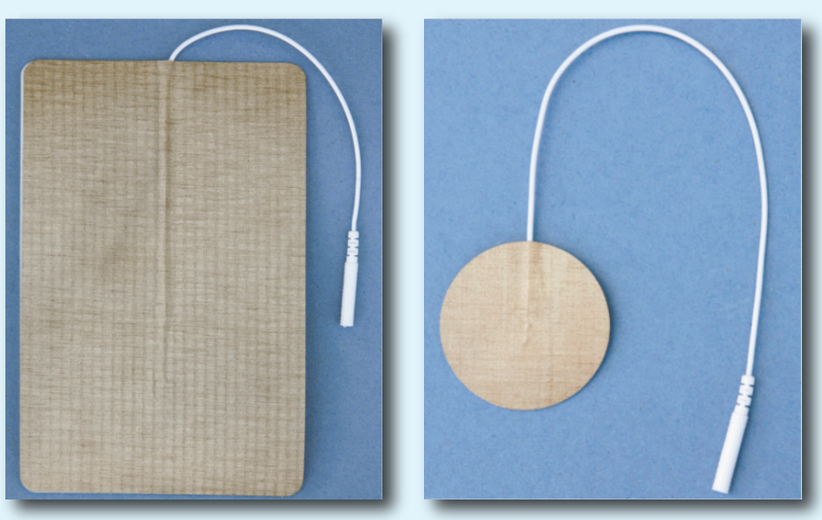
Equipment and Materials

To achieve stable and uninterrupted silver iontophoresis, the specialised electrical stimulator device is a constant-current source that outputs and maintains a constant LIDC through the body even with the fluctuating total electrical resistance of the entire bioelectrical circuit. Electrical resistance is the reciprocal of electrical conductance. The total electrical resistance to the flow of the LIDC is the sum of the electrical resistances of the electrotherapy electrode pad material properties, the electrode–skin interfaces, and the internal body fluids and tissues through which the LIDC flows.

Each of these components of the total electrical resistance are variable and dynamic. Most cutaneous electrotherapy electrode pads (including standard defibrillator pads, TENS pads, etc.) are constructed with a skin-contacting, sticky hydrogel layer. As with Becker's research work and clinical electromedical applications, the skin contacting material of the silver iontophoresis stimulator (SIS) electrotherapy electrode pad is 99 per cent purity silver (Ag) plated nylon, which is wetted with clean water before applying to the skin and then held in place with standard medical fixation tape. The superior electrical conductivity and continuity properties of the hybrid "wet-dry" SIS electrotherapy electrode pad is critical for silver iontophoresis and for maintaining an uninterrupted LIDC over sub-second timeframes. A pair of SIS electrode pads also contributes between 4–400 times (and typically 40 times) less electrical resistance to the total electrical resistance of the entire bioelectrical circuit, compared with a pair of standard hydrogel electrotherapy electrode pads. These very superior conductivity properties enable the LIDC to be generated by very low electrical voltages; a necessary condition for the extended clinical applications needed in order to achieve strong therapeutic effects.

Models and Experiments

We have gained new understanding about infection treatments using LIDC technology. Most of the transcutaneous passage of the therapeutic constant LIDC through the skin's natural resistance to the flow of electricity is via the skin's "conductive appendages"—the sweat glands (well over 100 per square centimetre in the abdomen and six times as high in the palms of the hand) and what we understand as their narrow, bell curve shaped electrophysiological gates of LIDC conductivity [see vol. 23, no. 5, 2016 article]. Once past the skin's naturally high electrical resistance, the underlying tissues are far more conductive to the flow of electric current. However, from numerous clinical experiences and specifically designed tests with infected internal tissue targets, based on the anatomical structures, pathways and physiological properties of the different tissues aligned between the electrically (+) positive and (-) negative paired SIS electrode pads, we reasoned that it was highly unlikely that end-to-end silver cation (Ag^+) iontophoresis was occurring and the active agent providing the confirmed therapeutic effect for these infection treatments. From these tests we had to gradually formulate a new theoretical electrotherapeutics model. In treatments of surface infections of the skin and superficial tissues using the SIS electrode pads, Ag^+ delivery (iontophoresis) is probably, at least in part, the active therapeutic factor; at the same time there is a constant LIDC consisting of a flow of negatively charged electrons and/or anions (electrically negative charged biomolecules) moving in the opposite direction to the Ag^+s that might be an additive or the primary



Left: SIS 10cm×15cm (4×6 inch) Large rectangular silver plated electrode
Right: SIS 4.7cm (1.87 inch) diameter Small round silver plated electrode
(Images: https://siselectromed.com)

therapeutically active factor. Whereas, in treatments of internal infections, using exactly the same equipment, the LIDC flow through the internal infected tissues is on its own the active therapeutic factor; there is very little or no penetration of Ag^{+}s into and through the deeper tissues.

After many such investigations that indicated this LIDC electrotherapeutics model, we finally tested the latter hypothesis by flipping over the silver-plated nylon skin-contacting material of the SIS electrode pad. Its silver (Ag) plated surface was now facing away from the skin, and put in direct contact with the electrode wire—thereby still providing the high electrical conductivity and continuity necessary for the constant LIDC flow. The reverse side of the electrode pad material that has a highly conductive polyurethane coated surface was now in skin contact. The electrode pad was connected to the same, regularly used SIS electrical stimulator device that generates the LIDC.

Model M250: Infection Treatments

We then re-tested the narrow, bell-curve shaped, discrete ranges of therapeutically effective LIDCs normally applied for bacterial and viral infection treatments, which we have confirmed clinically hundreds of times (see Figure 2B for a graphical example of a bell curve). We found that only very small changes (less than five per cent) to these LIDC ranges—graphically shifting the bell curves left or right along the horizontal (x axis) scale of electric current intensities—were needed to achieve the same therapeutic effects for both deep and surface infected tissue targets. These minor LIDC range adjustments were obviously necessary due to the slight resultant changes in the electrical conductivity properties of the SIS electrode pad with the flipped over skin contacting material. This final test validated and confirmed the new LIDC electrotherapeutics model for infection treatments.

These basic technical and therapeutic parameters are also important to note for the reason that attempts to reproduce LIDC infection treatments using different equipment without due attention to these critical details will likely fail; thereby also generating confusing clinical trial results data in the future, and so reducing the potential for the wide and general introduction of LIDC therapeutic technology into the medical field. The study design for many electrotherapeutic applications across various fields of medicine have exactly such confusions and shortcomings, consequent erroneous efficacy data acquisition, analysis and multiple study meta-analysis.

Mechanisms and Modes of Action

For several reasons, we cannot (presently) have complete knowledge of the mechanisms of actions of LIDC infection treatments, and the subject partly remains a "black box". Firstly, the complexity of interactions, happening at multiple physical and physiological scales, is gigantically complex and extremely difficult to investigate, especially in real-time *in vivo* studies. Secondly, there are multiple effects, not one single effect; one or many of these effects might be the active factors, simultaneously, synergistically and in combination, in molecular and cellular scale microenvironments with higher densities of pathogenic viral particles, compared to different single or multiple effects being the active factors in the same very small anatomical spaces with higher densities of pathogenic bacterial or other microorganism species.

Starting from the medical scientific literature we do know what some of the LIDC mechanisms are and modes of action, specifically those that are active factors in bacterial infection:

- Electrolytic (breaking) production of disinfecting hypochlorous acid (HOCl) from physiologic saline has been shown and is also produced naturally in neutrophils—immune system white blood cells involved in infection response and tissue repair;
- Production of increased reactive oxygen species (chemicals) such as hydrogen peroxide (H_2O_2) inside a bacterium as part of its stress response to the LIDC that eventually lead to its dysfunction or death;
- Disruption of a bacterium's membrane including electroporation effects that increase its permeability;
- Reduction of the formation of the biofilms made by grouping bacteria.

Strong LIDC effects on viral infection have also been reported in the medical scientific literature, which may eventually provide more detailed information as the physical scale of effects is far lower (viruses being 1–2 orders of magnitude smaller than bacteria), though these mechanisms of action have so far been less studied.

Complete inactivation of herpes family viral activity has been shown *in vitro* after ten minutes of LIDC exposure (stimulation), with no significant effects on the health and behaviour of the host infected cells (Roohandeh and Bamdad, 2011); the mechanisms of action resulting in the viral inactivation were not investigated. Ninety per cent HIV-1 inhibition has been shown after three minutes

stimulation by a LIDC generated by a one volt electric potential, with "virtually undetectable" harmful changes to the infected cells (Kumagai et al., 2011). Similarly to instances of higher densities of pathogenic bacteria in human biological microenvironments, there are most probably multiple, simultaneous and combined LIDC mechanisms and modes of action in instances of higher densities of pathogenic viral particles in these microenvironments, yet to discovered. These observations where the pathogenic viruses are inactivated or inhibited but not destroyed are also consistent with the actions of the body's newly discovered "co-operative defence system", discussed below.

LIDC and Electrostatic Field Effects

The SIS constant-current source electrical stimulator device creates a LIDC flow via probably multiple, simultaneous and near parallel conductive pathways through the body along and around which static electric fields are produced (Figure 1)—if those pathways are modelled as stationary resistive wires (Assis et al., 1999). The strength of the electrostatic field is proportional to the intensity of the LIDC, and most probably a primary active factor in infection treatments.

If electrically charged objects are brought within an electric field (EF), then they will variously change the EF lines around them depending on their own sum electrical properties; and in the two-way relationship, these same electrically charged objects will have a force exerted on them by the EF. During LIDC biological stimulation, living cells and biomolecules are these charged objects within the electrostatic fields along and around the LIDC conductive tissue pathways through the body.

Cells themselves have biologically significant and dynamic electrical properties. They have plasma membrane resting surface electric charge and dielectric capacitance—being electric charge polarisable and holding energy as an electric field. Both natural endogenously generated and clinically applied EFs thereby interact with and can exert biologically strong effects on cells as well as on biomolecules. These effects can be instructional molecular and cellular scale signals, as discussed further below. The infection of a cell by viral particles changes the composition and morphology of its plasma membrane; these changes result in a lowered membrane dielectric capacitance of around 25 per cent (Archer et al., 1999). This dynamic cell membrane bioelectric property from viral infection has been shown with cell electrorotation techniques used in the field of dielectric spectroscopy (Berardi et al., 2009). Taking these phenomena together towards understanding the mechanisms of action of LIDC infection treatments, the electrostatic fields along and around the conductive pathways of LIDC flow through the body, will certainly have different or altered effects on a virally infected cell than on a non or less infected cell.

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Low strength EFs and LIDCs are also instructional signals to macrophages—immune system white blood cells that are critical for innate immunity and modulating the inflammatory response. These electrical cues significantly enhance and instruct macrophage microbial clearance functions, and the direction of their physical migration is controlled by the electric charge topography and specific EF strength signal range (Hoare et al., 2016). Both B and T type lymphocytes—adaptive immune system cells—also actively and directionally migrate in

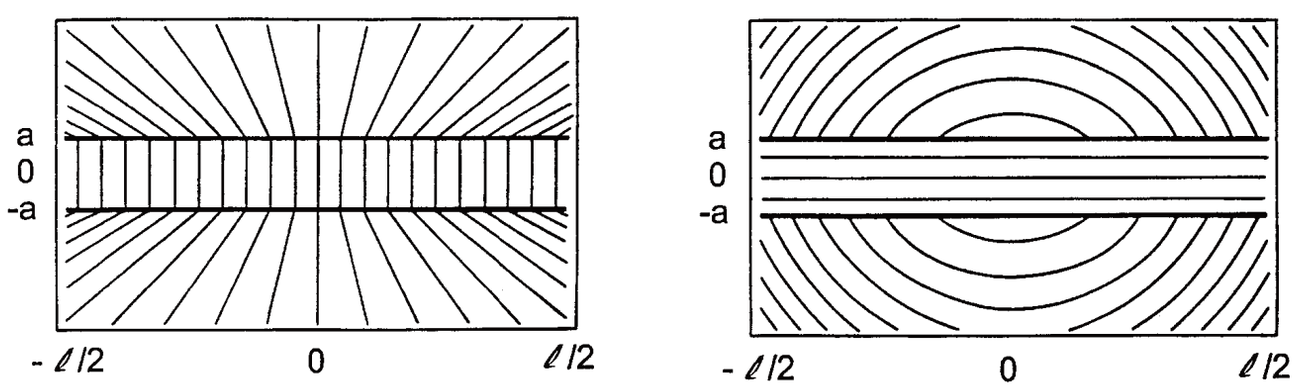
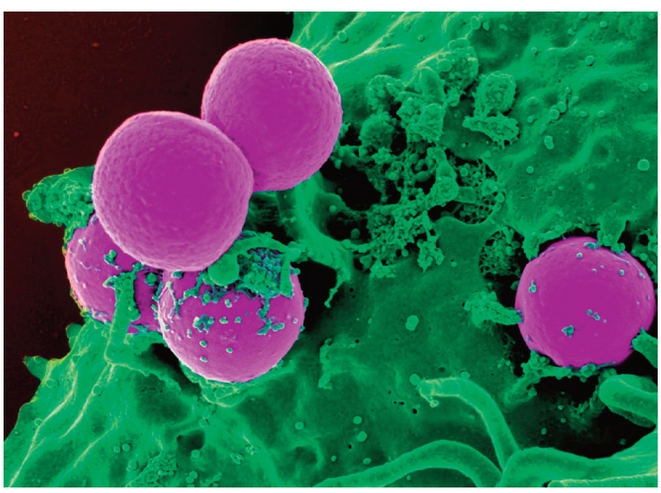


Figure 1. Longitudinal and radial EF lines produced from a constant current flow through a resistive wire. (From: Assis AKT, Rodrigues Jr WA, Mania AJ. The Electric Field Outside a Stationary Resistive Wire Carrying a Constant Current. Foundations of Physics, Vol . 29, No. 5, 1999.)

response to LIDC signalling (Lin et al., 2008). These directed physical migrations mean that the clinically applied LIDCs effectively instruct the positioning of these immune system cells within infected and damaged tissues. Basic calculations and comparisons between the clinically effective LIDCs generated by the SIS constant-current electrical stimulators, and the ranges of the LIDCs induced through interstitial fluid that signal to macrophages and lymphocytes, shows the same order of magnitude and overlapping microampere LIDCs, and that these effects are also probable modes of action of the clinically applied LIDCs for infection treatments.



Normalising Infection with Low Intensity Direct Current

Both bacteria and viruses are present in the healthy human body in at least the same order of magnitude or higher than the number of human cells (Sender et al., 2016). The most abundant microbes that live in and on our bodies are viruses. Pathogenic microorganisms, including viruses, can be present in our bodies for a lifetime without causing clinical symptoms. The physiological determinants of a symptomatic infection are multiple and extremely complex. "How a host responds to a pathogen determines outcome of infection, and the long-standing belief was that a host needed to kill an invading pathogen in order to survive"; but recent discoveries in microbiology show that a host can employ disease tolerance responses carried out by its co-operative defence system that limits pathology and promotes host survival while having *no destructive effect* on the pathogen (McCarville and Ayres, 2018). This new understanding has most recently been applied to COVID-19 infection (Ayres, 2020).

LIDC infection treatments are in fact extremely clinically effective, as illustrated by one highlight medical case of a large and deep post-operative wound with multiple antibiotic resistant infections, where the LIDC treatments completely resolved those infections thereby preventing a whole leg amputation that was urgently recommended to save the patient's life by the hospital surgical and infectious disease team after months of non-resolving response of the infection condition to conventional microbicidal drug treatments. Several bits of understanding can now be synthesised to broadly theorise and describe the overall mode of action of LIDC infection treatments. The first is that instructional signalling from LIDC electric energy and force mediated effects can enhance and instruct localised immune system cell responses. The second is that LIDC is also highly effective for viral infection treatments but that a virus is not alive as a bacterium is and so there is no killing involved. The last is the growing knowledge of the body's co-operative defence system that does not destroy pathogenic microorganisms in infection scenarios. Then combining this information together: the constant LIDC and electrostatic fields along and around its conductive pathways through the body between the (+) positive and (-) negative SIS electrode pads, correct or supplement instructional cues and signals normally produced by the cells and biomolecules in those infected microenvironments, thus promoting and restoring their overall homeostatic normalcy. Whereas in contrast, orthodox Western medicine still over-simplistically approaches these microenvironments as being only infected; and in this current prevailing model of infectious disease care, the clinically effective LIDC infection treatments must instead be comprehended as providing a solution that is underlyingly based on a simple killing or inhibiting effect.

Cell Phenotype Modification

Ultra LIDCs can trigger cell phenotype modification. Cellular phenotype is the conglomerate of multiple cellular processes involving gene and protein expression that result in the elaboration of a cell's particular morphology and function (Sul et al., 2009). Electromedicine pioneer, Robert O. Becker discovered cell modification via electrical stimulation effects. A reader of Becker's 1985 book, *The Body Electric: Electromagnetism and the Foundation of Life*, may have the understanding that this discovery is only related to the effects on cells of electrically generated silver cations (Ag^+s). But Becker's first laboratory experiment report of electrically mediated cell changing effects predates his later discovery of cell modification from interactions with electrically generated Ag^+s (Berger et al., 1976). In his original paper on the subject (Becker and Murray, 1967), he reported his finding that a non-uniform EF, inducing an ultra LIDC, triggered cell phenotype conversion. With these 1967 experiments, he intended to replicate and compare his earlier measurements of voltage potentials and electric currents taken directly across the periosteum (the membrane covering the outer surface of bones) directly above and immediately after bone fractures; in turn, these bone fracture experiments followed on from

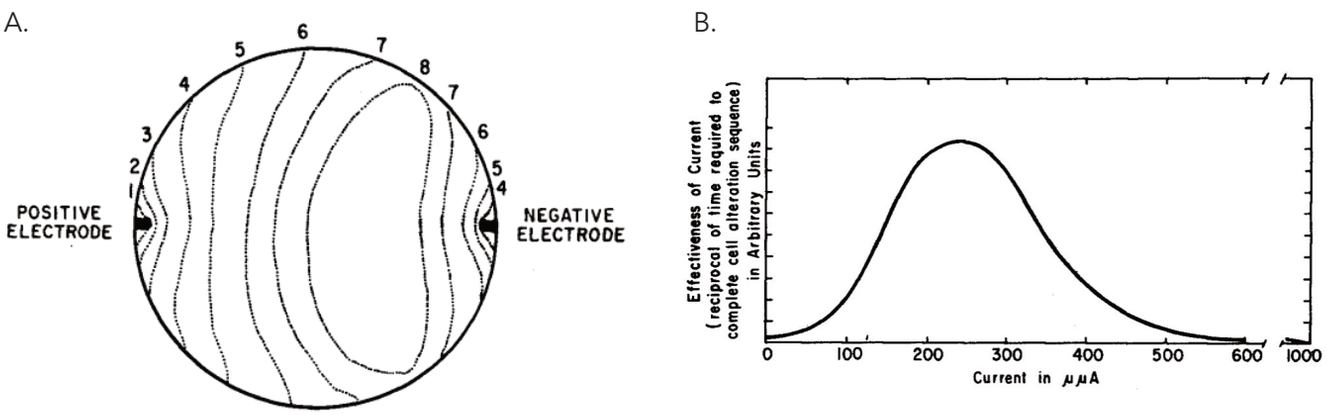


Figure 2. A: Spatial distribution of cellular changes from the EF; the numbering indicates the spatiotemporal sequence of morphological changes.
B: Relative effects of various intensities of ultra LIDC; the vertical axis is the reciprocal of the elapsed time for the morphological changes.
(Source: Becker R.O., Murray D.G. A method for producing cellular dedifferentiation by means of very small electrical currents. Trans N Y Acad Sci. 1967 Mar;29(5):606-15.)

his earlier studies of the autologous "current of injury" naturally generated by salamanders during limb regeneration.

The cells under observation in the 1967 study were held in labware dishes within standard Ringer's physiologic solution that consists of several dissolved salts in water that mimic the chemical composition of the body's interstitial fluid. Becker's experimental design allowed him to test and confirm that there was no Ag^+ nor other ionic flow through the solution that was triggering the cellular changes. In one key variation of his experimental set-up, platinum (Pt) electrodes were used with no contact between the electrodes and the cell-containing solution, and cell phenotype conversion effects were still produced. The observed cell self-modifications (dedifferentiations) were a direct result of the applied voltage and the induced ultra LIDC (Figure 2A). Another key finding in 1967 was that the observed cell modification effects did not correspond to the intensity of the induced ultra-LIDC in a linear dependency: a discrete bell curve relationship was actually observed (Figure 2B).

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Just as with the probable modes of action of clinically applied LIDCs on molecular and cellular scale microenvironments for infection treatments, the cell phenotype conversion effects observed by Becker were the results of the externally applied voltage and the induced ultra-LIDC and its electrostatic field, having very different but still highly (cell) specific, instructional, signalling effects; they were not general or noxious cellular influences of any kind. This was seen when only erythrocytes (red blood cells) responded to the electrical stimulation; leukocytes (immune system white blood cells) did not self-modify their phenotype from stimulation by any tested combination of ultra LIDCs and electrodes of different metals. Becker had discovered a narrow erythrocyte-specific phenotype converting instructional ultra-LIDC range.

We recently had the research opportunity to independently test and confirm EF and ultra LIDC effects on some specialised *in vivo* cell behaviours, maturations and phenotype conversions involved in scar formation and tissue regeneration that we have reported (Malter and Woessner, 2019). We methodically and conclusively determined that the externally applied voltage and induced ultra-LIDC were the effectors as the cellular effects were achieved with the electrical stimulation equipment using stainless steel electrodes. Furthermore, using temperature-calibrated direct electronic measurement with very low nanoampere resolution, we also found a narrow bell-curve shaped effective ultra-LIDC range (compare Figure 2B) in the same order of magnitude and with a maxima very close to (~minus 25 per cent) the peak effect ultra LIDC range reported by Becker in his 1967 paper, which we think confirms our 2019 and his research experiments performed half a century earlier.

Summary

The bioelectrochemical and bioelectric instructional cues and signals between cells and intercellular proteins

and molecules in normal physiology and various pathologies are extensively and continuously studied phenomena; and with far more still to be discovered than is presently known to medical science—the bioelectricity inside cells is still virtually unknown. Logically, there must be very many different (sets of) electrostatic field and LIDC cues and signals, dynamically communicating different information and instructions between the different cell types and biomolecules within the enormously complex, and possible spatiotemporal configurations and patterns, of molecular and cellular scale microenvironments. Several specific LIDCs and the electrostatic fields along and around their conductive pathways through the body, proven as powerfully clinically effective for infection treatments, might very well mimic and belong to specialised sets of these endogenous signals that can normalise those microenvironments with higher than optimal localised densities of pathogenic microorganisms.

LIDC electromedical technology for non-invasive infection treatments is actually very efficient, low cost with reusable electronic equipment, portable, fast acting, has no known side effects, and is quick and easy to apply. Additionally, any regulatory concerns that long-term safety studies have not been done for silver nanoparticles can be avoided with clinical LIDC applications since mechanisms of action are now better understood as not dependent on Ag^+ interactions. LIDC technology has the immediate potential to revolutionise infectious disease and probably several other fields of medical care.

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