Antimicrobials: old tools, new approaches

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Appropriate antibiotic use is one of the main goals of the medical community. Overuse of antimicrobial agents has been described worldwide in both community and hospital settings. In addition to the effect on patients, antibiotic misuse can provoke the emergence of bacterial resistance and increase healthcare costs. It is evident that optimizing antibiotic use is a challenge that deserves to be undertaken. In the late 1960s, the medical need for new antibiotics began to be questioned, and the pharmaceutical industry shifted its emphasis of antimicrobials from that of a therapeutic leader to a low-priority research area. Although infectious diseases, in particular those caused by bacterial infections, are still among the top causes of mortality in the world, industrial support continues to wane. The shift from this important area of antimicrobial research has been attributed to a combination of science, medical, marketing and business reasons. This decline in antimicrobial drug discovery, coupled with increased risk as a result of infections caused by drug-resistant microorganisms, represents a clear public health threat. A promising approach is host modulation therapy, which, as the name suggests, aims to modulate the host by suppressing the inflammatory response and the benefits of local application include high and sustained concentrations at the site of infection where local physiological changes may hinder the efficacy of systemic antibiotics.

Keywords: Antimicrobials, host-modulating drugs, drug delivery, doxycycline.

Old ideas are being resurrected, such as the use of lytic bacteriophages, but with little evidence of clinical effectiveness. New approaches, such as defensins, targeted monoclonal antibodies, agents designed to interrupt mechanisms of pathogenesis have yet to fulfill their therapeutic potential. Considered by many as the father of chemotherapy, by his contributions to immunology, Paul Ehrlich was one of the most notable figures in the world of science. This paper outlines some of his most important findings, including those that led him to create the concept of famous “magic bullets”, precursors of the current chemotherapeutic agents.

Essentially, even as we are forced to revisit treatments that are more than 30 years old while waiting desperately for new research to bear fruit, we sense a pervasive belief in the scientific community that increasing resistance is the new norm. This is a misleading and costly attitude, both in human and economic terms [1].

Those leading these international efforts urgently need to develop an understanding and recognition of the most successful approaches, wherever they are working, so that these strategies can be repeated and spread. Since the net present value of antibiotics is low, the development of new antibiotics is not a high priority for pharmaceutical companies. New approaches to overcoming the barrier to drug development have been proposed, including orphan drug benefits, government support for antibiotic development, prolonged patents, expedited approval, and other strategies [1].

However, there are various problems arising with the use of antimicrobials such as local tissue irritation, interference with wound healing process, hypersensitivity reactions, systemic toxicity, narrow antimicrobial spectrum, emergence of resistance. So the increasing clinical importance of drug-resistant microbial pathogens has lent additional urgency in microbiological and antifungal research [2].

Different techniques have been used for increasing the drug load and controlled release. Drug delivery remains the controlled and extended delivery of medication in a therapeutically relevant concentration. Several benefits including increased the bioavailability, prolonged residence time, improved patient compliance, higher efficiency and low side effects are accounted for contact lenses in the literature, compared to conventional dosage forms. The soft contact lenses possess multiple advantages such as ease of application, convenient for long term therapy due to their excellent biocompatibility, provides continuous drug delivery, unproductive systemic absorption, higher patient compliance [3].

A promising approach is host modulation therapy, which, as the name suggests, aims to modulate the host by suppressing the inflammatory response [4]. Traces the evidence on other host modulation agents for treating diseases, including nonsteroidal anti-inflammatory drugs, cytokine receptor antagonists and other novel pharmacotherapeutics. While these and other inflammatory mediator inhibitors have yet to complete the regulatory steps needed for general market use, they represent a new equilibrium in infectious diseases intervention [5].

An estimated 4 million cases of community-acquired pneumonia (CAP) occur each year. Approximately 20% of these cases require hospitalization, and 12% of the patients die. Despite advances in antimicrobial therapy and supportive care, the mortality rate for patients with severe CAP admitted to the intensive care unit (ICU) remains high, ranging from 22% to 54%. Cytokines and mediators of inflammatory response play a key role in the pathogenesis and prognosis of severe infections and sepsis-related organ failure. Several studies have demonstrated that moderate doses of corticosteroids blunt the systemic pro inflammatory cytokine response in patients with severe sepsis and suppress pulmonary inflammation in patients with severe pneumonia and acute lung injury. Two recent studies revealed decreased mortality rates in patients with severe CAP who were treated with systemic corticosteroids. Conversely, two
small randomized controlled trials (RCT) did not find decreased mortality rates in patients with severe CAP. However, these studies included small populations of patients with severe CAP who required mechanical ventilation. Therefore, we evaluated the clinical data in patients who required mechanical ventilation for severe CAP and compared survival with and without the use systemic corticosteroids [6].

The tissue damage stimulates the inflammatory response by several pathways and mechanisms, which in turn may contribute to the proliferation of microorganisms, mainly bacteria and hinders the diffusion of antimicrobial agents in this environment. The use of modulators of the inflammatory response has been to facilitate the action of antimicrobial improving their efficiency by offering greater patient comfort postoperatively.

Although cytokines are essential for the resolution of infection and injury, prolonged production may result in host tissue and organ damage. Several antibiotics, including quinolones and macrolides, have been shown to have modulatory effects on cytokine release. Clearly, it is important to define the immunomodulatory activity of antibiotics and other drugs used to treat patients since these properties may have clinical significance, particularly in patients who are immunodeficient or patients on the intensive care unit [7-11].

In addition, both quinolone (ciprofloxacin and moxifloxacin) and macrolide (clarithromycin) antibiotics have marked effects on T helper (Th) cell cytokines, with implications for immune responses and recovery after severe infection. The mechanisms of such effects are not known, but since the antibiotics only exert their effects after cell stimulation, recently identified so-called ‘master switches’ for Th cell cytokine control may represent targets for future investigation of antibiotic action [12].

Polymorphonuclear leukocytes, fibroblasts, keratinocytes, macrophages and endothelial cells is capable, when activated by various cytokines, arachidonic acid metabolites and growth factors, of producing a battery of different matrix metalloproteinases. Cytokines and growth factors are endogenous transcriptional regulators secreted by inflammatory and mesenchymal cells. Generally, they stimulate enzyme production. Responses may differ for varying cell types and for different cytokines and growth factors [13].

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The matrix metalloproteinases are an important family of zinc- and calcium-dependent endopeptidases secreted or released by a variety of host cells (such as polymorphonuclear leukocytes, macrophages, fibroblasts, bone, epithelial and endothelial cells) that function at neutral pH and utilize the various constituents of the extracellular matrix as their substrates. These proteinases are involved in a number of physiological events such as embryonic development, involution of the post-partum uterus, tissue remodeling, salivary gland morphogenesis and tooth eruption, in addition to various pathological processes such as (but not limited to) periodontal disease, arthritis, cancer, atherosclerosis, diabetes, pulmonary emphysema and osteoporosis [13].

The evidence for the role of matrix metalloproteinases in periodontal destruction has accumulated for over three decades. It has been shown that an imbalance between activated matrix metalloproteinases and their host-derived endogenous inhibitors leads to pathological breakdown of the extracellular matrix during periodontitis and numerous other diseases [14].

To block or retard the proteolytic destruction of connective tissues is of therapeutic significance. Conceptually, this can be accomplished with the use of drugs that can: (i) inhibit the synthesis and/or release of these enzymes; (ii) block the activation of precursor (latent) forms of these matrix metalloproteinases; (iii) inhibit the activity of mature matrix metalloproteinases; (iv) stimulate the synthesis of endogenous tissue inhibitors of matrix metalloproteinases; or (v) protect the host’s endogenous inhibitors from proteolytic inactivation [15].

Clearly, a matrix metalloproteinase inhibitor might not only help in the management of periodontitis, which has been associated with these systemic diseases, having an indirect effect on these processes but may also directly aid in the treatment and prevention of cardiovascular disease, diabetic complications and premature labors [15].

Preclinical and clinical studies have demonstrated that inhibition of these matrix metalloproteinases, as a host modulatory approach, results in favorable changes in biochemical markers of the disease as well as clinical markers of therapeutic efficacy [15].

Surgical practice often includes the use of topical or local antimicrobial agents applied to the operative site to minimize post-operative surgical infections, especially SSI. Compared with systemic antibiotic therapy, topical or local delivery of an antibiotic has many potential advantages, as well as some disadvantages, as outlined in a review by Lipsky and Hoey, 2009 [16]. The benefits of local application include high and sustained concentrations at the site of infection where local physiological changes may hinder the efficacy of systemic antibiotics [15].

Antibiotics may be delivered locally in the form of intraoperative washes or injections, locally applied lotions, solutions, powders, gels, creams or ointments, and antibiotic-impregnated beads or collagen implants. The more commonly used antibiotics include cephalosporins, aminoglycosides, glycopeptides, chloramphenicol and bacitracin. The pharmacodynamic/pharmacokinetic profiles vary depending on the antibiotic, the dose and the method of delivery.
Consequently, it is difficult to establish which antibiotic to use, as well as how much, for how long and in what form, for prophylaxis in a particular type of surgery [15].

Sub-antimicrobial dose doxycycline as adjunctive treatment for periodontitis with a promising approach is host modulation therapy, which, as the name suggests, aims to modulate the host by suppressing the inflammatory response. As discussed above, periodontitis is characterized by detrimental inflammatory processes that destroy periodontal tissue. Matrix metalloproteinases, many of which are produced by infiltrating neutrophils, mediate this tissue destruction by degrading plasma membrane proteins and extracellular matrix proteins such as collagen [17].

Additionally, it has long been known that members of the tetracycline family of antibiotics possess the ability to inhibit matrix metalloproteinases, independently of their antimicrobial activities. Doxycycline was found to be the most potent inhibitor of matrix metalloproteinases [17].

Other benefits include the limited potential for systemic absorption and toxicity, reduced volumes of antibiotic use, and, possibly, less potential for the development of antibiotic resistance (as there is likely to be less of an effect on, e.g. bowel flora). Novel agents that are not available systemically may also be used. A potential benefit of delivery locally antimicrobials treatment over systemic antibiotic therapy, is reduced systemic antibiotic exposure and associated systemic adverse effects [18].

Specifically, sub-antimicrobial doses of doxycycline used as an adjunct to scaling and root planing showed a clinical attachment level gain that was 0.3–0.4 mm greater than when scaling and root planing were used alone. These results are similar to those seen for adjunctive use of locally administered antimicrobial therapies [18].

In addition to doxycycline, other host-modulating drugs have been investigated. A meta-analysis found that non-steroidal anti-inflammatory drugs and bone-sparing agents (such as bisphosphonates) could have potential in the treatment of periodontal disease [19]. Another intriguing possibility is the use of pro-resolving agents drugs that promote the resolution of inflammation, as opposed to merely blocking it [20]. Resolution of inflammation involves host biochemical pathways that restore homeostasis to the periodontal tissue, and some research indicates that periodontitis results from a failure of these resolution pathways [21]. Indeed, the pro-resolving agent resolvin E1, a derivative of the omega-3 fatty acid eicosapentaenoic acid, was shown to regenerate lost tissue and bone [22].

Because of the high costs of slow-release devices and because their application is often exceedingly time consuming or requires several visits, they should only be promoted for routine use if they add substantial adjunctive benefits to mechanical debridement. So far, the clinical benefits of most slow-release devices, even when showing statistical significance, have not been very impressive [23].

Study comparing intravenous and local antibiotic prophylaxis in inguinal hernia mesh repair reported that local intraoperative administration of gentamicin had comparable efficacy in preventing SSI to intravenous gentamicin administration [24].

Controlled trials in cardiac surgery patients after sternotomy have demonstrated a decrease in SSI of up to 80% through the local application of both vancomycin and gentamicin to the cut sternotomy wound edges. However, given the reluctance to widely use vancomycin because of fears of vancomycin resistance developing [15].

Comparative studies showing significant reduction in SSI rates through prophylactic use of topical of local antibiotics: in abdominal surgery, the gentamicin/collagen sponge show a reduction from 18.4% to 5.6% [25] and fusidic acid with reduction from 17.1 to 2.8% [26].

Orthopaedic surgery in hip arthroplasty using antibiotic-impregnated bone cement with reduction from 2.3% to 1.2% in debridement and stabilization of compound limb fractures using gentamicin-impregnated beads obtained reduction from 12% to 3.7% [27,28].

In cardiothoracic surgery on patients undergoing sternotomy using vancomycin obtained reduction from 3.6% to 0.45% [29], gentamicin- collagen sponges obtained reduction from 9% to 4.3% [30] and patients undergoing lung resection with irrigation of the pleural space with fusidic acid obtained reduction in empyema from 6.4% to 1% [31] with intracavitary irrigation with penicillin, gentamicin and bacitracin obtained reduction in empyema from 13% to 0% [32].

In dermatological surgery in patients undergoing clean skin lesion excision using topical chloramphenicol ointment applied to the surgical site obtained reduction from 11% to 6.6% [33], in breast surgery in patients undergoing breast augmentation using irrigation of the implant pocket with cefalotin solution has been shown the reduction from 12.6% to 6.7% [34], and in oculary surgery in post-cataract surgery conjunctival cefasolin application, obtained reduction in endophthalmitis from 0.63% to 0.055% [35].

Conclusion

“On the whole, the position of antimicrobial agents in medical therapy is highly satisfactory. The majority of bacterial infections can be cured simply, effectively, and cheaply. The mortality and morbidity from bacterial diseases has fallen so low that they are no longer among the important unsolved problems of medicine. These accomplishments are widely known and appreciated…” (Jawetz, 1956) [36]. This excerpt from a manuscript published in 1956 by Dr. Ernest Jawetz is ominous that we are 70 years into the antibiotic era. A suitable conclusion for a similar article today might read, “An
increasing number of infections are no longer easily treated, morbidity and mortality are appreciable, and many infectious diseases have become unsolved problems of modern medicine” [37].

References:


