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Certain Important Issues Relevant to the Medical and Health Sciences

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Short Commentary

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These are very happening days for the medical and health sciences. Considerable progress has been made by the mankind in its fight against various infections and diseases. However this is a never-ending battle, with new challenges appearing constantly. Through this article I am sharing my views on some issues which in my opinion are important to the field of medical and health sciences.

ANTI-VIRULENCE STRATEGY TO DEAL WITH ANTIMICROBIAL DRUG RESISTANCE

Spread of antibiotic-resistance among pathogenic microbes has been well recognized as a global problem. Drug-resistant infections already kill hundreds of thousands every year globally, and by the year 2050, that figure is estimated to be more than 10 million. If no appropriate actions are taken, then it may lead to huge economic losses amounting up to $100 trillion by 2050 [1]. The widespread problem of antibiotic-resistance among pathogenic microorganisms has persuaded researchers to design novel strategies to deal with virulent microbes. One of such promising approaches is to target virulence, rather than only aiming at killing the pathogen. Among the many virulence traits which can be the possible target of the anti-infective agents, the most attractive seems to be the Quorum Sensing (QS). QS is a means of intercellular communication among bacteria that regulates expression of many genes including those involved in production of virulence factors, biofilm formation, efflux pump activity, toxin production, pigment production, etc. Consequently, QS is increasingly being viewed as an attractive target for the development of novel anti-infective measures that do not rely on the use of antibiotics [2]. Anti-QS seem to be a promising strategy to combat bacterial infections as it is less likely to allow bacteria to develop resistance, since it does not impose that strong selection pressure. A number of anti-QS approaches have been documented and natural as well as synthetic products are being studied in this context. Screening the natural products and/or large combinatorial chemistry libraries for potential anti-QS property may pave the way for development of novel anti-virulence leads, and can help in dealing with the problem of antibiotic-resistance among bacterial pathogens.

Besides QS, few more attractive targets in the pathogenic microbial populations include siderophore production, riboswitches (areas of bacterial RNA that are used to control translation of mRNA), beta-lactamases, efflux pumps, etc. Finding new effective inhibitors of the bacterial efflux-pumps and drug-degrading enzymes (e.g. penicillinases, cephalosporinases) will help increasing the utility-span of existing antibiotics. Targeting siderophore production can be a strategy effective against a wide range of pathogens, as siderophores are used for iron-scavenging purpose by many pathogenic (as well as non-pathogenic) bacteria in their respective habitats. Iron being an essential element for microbial growth, siderophore-inhibitors can control them by inducing iron-deprivation. This seems especially attractive against bacteria like Staphylococcus aureus, which strip the red blood cells of its iron and use it for their own purposes [3].

DECLINED INTEREST OF CORPORATE SECTOR IN ANTIMICROBIAL RESEARCH

The pace at which pathogenic microbial populations develop antibiotic-resistance, ideally we need to keep introducing novel antimicrobial agents at the same pace. However that has not been possible for various reasons. The whole process of

drug-discovery starting from identification of lead compound(s), through efficacy testing, clinical trials, regulatory approvals, and finally putting it into market is a long tedious process. This takes more than a decade of time along with a fat budget demand. However, effective life-span of any antimicrobial drug is always being challenged by the rapidly evolving pathogens. In addition to this antibiotic-consuming patients will purchase a particular antibiotic only till the time they get rid of the infection. Thus any pharmaceutical firm will not find a long-term customer in them. In contrast to this, these firms find it more lucrative to invest in development of drugs which target life-style diseases (e.g. diabetes, high blood pressure, hypercholesterolemia, etc.), where the patient becomes a life-long customer of the drug-manufacturers. This has resulted in a declined interest on the part of big pharmaceutical companies (who have the huge budget required for research and development) in discovery and development of novel antimicrobial agents. An antimicrobial may be rendered useless owing to drug-resistance among its target microorganism(s), even before its patent expires. It seems that large scale research programmes for development of novel antibiotics and anti-virulence products will have to be sustained to a significant extent by public funding.

RISE IN FUNGAL INFECTIONS

Most fungi primarily are not human pathogens. In fact, majority of them basically are saprophytes. However, few of them can act as opportunistic pathogens when they find an easy target in some immunocompromised person. Till recently bacteria and viruses have remained the pathogens of biggest concern to humans. But now with increase in hospital facilities and advancement in the medical and health sciences, immunocompromised people (e.g. those with HIV infection or organ transplant) can survive longer than before. It means that fungi have their target population available in more number than before. This situation demands for development of effective antifungal agents. Fungi being eukaryotic organisms (as their human host), it becomes difficult for most potent antifungal agents to satisfy the criteria of selective toxicity, because many of the cellular targets are common in the fungal pathogen and their human host [3]. With antibacterial agents, this problem is much lesser because bacterial pathogens have many targets altogether absent from their human host (e.g. 70S ribosome, cell wall, etc.).

Further with increased use of different types of medical devices (e.g. catheters, stents, pacemaker, artificial hip joints, etc.) there has been an increased probability of biofilm-associated infections, as all these devices installed in/on human body provide additional sites of attachment for the pathogenic bacteria. Microbes inside a biofilm can be much more resistant to antimicrobials than their planktonic counterparts [3]. Thus there is a pressing need for development of anti-biofilm agents too, suitable for therapeutic use.

NON-THERAPEUTIC USES OF ANTIMICROBIALS

We need to reconsider the wide-spread practice of use of antimicrobial substances for non-therapeutic purposes, for example in cosmetics, hand-washes, etc. A number of soaps claimed to be antimicrobial are available in market, and an increasing number of consumers are purchasing them for a perceived better hygiene. Here we must ponder on certain common-sense issues. Efficacy of any hand-washing exercise is primarily dependent on the mechanical removal of dirt particles and microbial cells, which is achieved by rubbing hands together. In addition to this, any particulate matter (whether of microbial origin or not) is likely to be trapped inside the foam, which further can be removed along with flowing water. This mechanical removal and foam-trapping of the dirt in no way gets affected by presence or absence of any antimicrobial agent in the soap. Now, if any antimicrobial agent used as an ingredient in the soap is to exert its effect, it must be provided sufficient contact time with its target microbial flora on the hand. Most of us finish our hand-washing in few seconds. Is that much time sufficient to achieve any notable microbial killing on the skin? In most cases not. Further, all these antimicrobial agents incorporated in the soaps gets diluted when they pass down the drainage, and this results in unnecessary exposure of the microbial populations (including those, which are not pathogenic) in the environment to the sub-MIC concentrations of these antimicrobial agents, which only contributes to increased level of drug-resistance. Resistance thus acquired can rapidly pass-on through horizontal gene transfer to the originally sensitive microbial populations. It seems to be logical to restrict the use of antimicrobial hand-washes within clinical-setting / hospitals only. Routine domestic hand-wash does not seem to be anyway gaining from inclusion of antimicrobial agents in soap formulations.

Another developing tendency in some part of the human society is use of hand-sanitizers in place of the ordinary soap. It must be noted here, that sanitizers may kill the microbes present on hand, but they cannot remove those dead cells and any other dirt, as washing can do. Thus use of hand-sanitizers is more appropriate when disinfection is the primary aim, but they cannot be a replacement for soaps.

ISSUES SPECIFIC TO DEVELOPING COUNTRIES

Research for developing new therapeutic agents against infectious diseases is a costly affair. Most of such research, demanding huge funds, is being carried out in developed countries. However certain infectious diseases like malaria and tuberculosis are prevalent largely in the developing / underdeveloped countries of Africa and Asia. Developed world of Europe and US may focus more on infections like HIV / AIDS, as that is an issue more pressing for them. This is not to say that HIV is not a matter of worry in Asia/Africa, but the point is that developing countries should divert major portion of their research funds on battling against problems (e.g. malaria and tuberculosis) specifically relevant to them, and may not be among the priorities of the funding agencies of the west.

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There is also a need for educating the people in developing/underdeveloped world and make them aware regarding the importance of maintaining high levels of hygiene and sanitation. This may help in controlling the infections transmitted through fecal-oral route (e.g. cholera, typhoid, etc.). Governments of the developing countries need to take the issue of supplying safe drinking water to masses, aggressively, and to divert enough funds on priority basis to work in this area. Programmes on mosquito control can also have considerable impact in reducing the disease burden, with respect to the vector-borne infections such as dengue, malaria, yellow fever, etc. Malnutrition is another area of big concern for the not-so-developed world, as the malnourished populations, owing to their somewhat immune-compromised state, bear an inherent increased risk of certain infections including those caused by opportunistic pathogens.

NEGLECT OF TRADITIONAL WISDOM

Most ancient civilizations had developed some sort of indigenous system of medicine relying largely on natural products (e.g. crude plant extracts). For example Ayurved in India, Unani in Arabian countries, etc. However till now development of modern chemotherapeutic agents have largely focused on isolation of a single active ingredient, and then using it as the lead compound. Though this approach has met considerable success, this approach cannot accommodate the traditional wisdom of employing polyherbal formulations for therapeutic purposes. Now it is well-known that synergy is not an uncommon phenomenon while working with natural products. That means standardized crude natural extracts can work against a particular disease, but fractions derived from it may not. The modern protocols designed to evaluate the efficacy of any preparation against a disease or infectious agent may not always be suitable for evaluating efficacy of crude natural products, which are a mixture of many known or unknown phytochemicals. Failure of the conventional efficacy protocols to validate the traditional medicine use can be an obstacle in getting appropriate regulatory approvals required for widespread use of traditional medicine. It calls for development of new guidelines and protocols for evaluating in vitro and in vivo efficacy of the natural product formulations. Though WHO has already issued certain guidelines, still much remains to be done [4].

If specific thematic groups with international participation can be formed on above mentioned issues, followed by making appropriate recommendations to competent authorities, and necessary measures taken in right direction, it will help enhancing the overall health status of mankind across the globe.

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