



ANTIVIRULENCE STRATEGIES TO COMBAT THE MENACE OF ANTIBIOTIC RESISTANCE

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ABSTRACT

Antibiotic therapy is often quite problematic for the clinician as well as the microbiologist due to emergence of resistance in most of the medically important bacteria. Antivirulence strategies are fast coming up and should therefore be the topic of future medical research to mitigate this problem.

KEYWORDS: virulence, antibiotic, new strategies.

INTRODUCTION

Antibiotic resistance is one of the main problems that healthcare professionals across the world are facing currently, in both community as well as in the hospital.^[1] Overall, most of the medically important bacteria, which have been described as antibiotic resistant or “nightmare bacteria” now “pose a catastrophic threat” to people across the globe.^[2]

Bacteria like *Staphylococcus aureus* and *Escherichia coli*, to name a few, are acquiring antibiotic resistance at an alarmingly fast rate and challenging timely therapy and recovery of the patients.^[3] Needless to say, this necessitates newer strategies, like anti-virulence strategies and interfering mechanisms with cell-to cell signalling, so that even if bacteria are not killed, their virulence is mitigated.^[4]

The problem

Nowadays most healthcare associated bacterial infections like pneumonia and urinary tract infection, are caused by the famed “ESKAPE” pathogens or bacteria, which is a collective abbreviation comprising *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* spp.^[5] Nowadays most clinical isolates of *Escherichia coli* and *Klebsiella pneumoniae* are highly resistant to third generation cephalosporin antibiotics, making treatment options very very difficult and limited.^[1] Also, refractoriness of *Shigella* spp. and *Salmonella* spp. to ciprofloxacin and other fluoroquinolones is really a big problem.^[1] Biofilm formation and beta-lactamases is also a prominent mechanism of resistance in bacteria.^[6] Adding to the problem is the misuse of antibiotics in about 50% cases,

and widespread use in livestock to promote growth, which increases consumption anyhow and adds to the problem of antibiotic resistance.^[2]

Newer strategies

Antibody against virulence factors

This is a new alternative to antibiotics. Antibiotics to virulence factors has been found to be successful in case of *Bordetella pertussis* infection.^[7] In certain subjects high level of antibodies to *S. mutans* in serum and saliva definitely protect from dental caries.^[8]

Antitoxins

Antibody to toxins, neutralise the toxins and leave bacteria untouched, and may offer a simple solution to antibiotic resistance; this has been tried with great success in *Clostridium difficile* diarrhea.^[9] Antitoxin antibodies have also been found to be very successful against *Anthrax bacillus* in animal models and is in process of drug development.^[10] One more elegant example of toxin inhibition is the use of cholesterol biosynthesis inhibitor to block the virulence of *Staphylococcus* spp.^[10] Similarly, Type III secretion system inhibitors have been found to be quite successful in inhibiting Type III secretion system of *Y. pestis* and *Salmonella enterica* serotype Typhimurium.^[10]

Antibodies

Antibodies against structural components or antigens of bacteria are also a new weapon in this armoury. Anthim, Raxibacumab and Valortim are anthrax-specific antibodies currently undergoing clinical trials.^[10] Antibody-based drugs are also currently being developed against LPS, alginate capsule and flagellin in

Pseudomonas aeruginosa to tackle this dangerous pathogen.^[10]

Natural molecules

Newer, natural, non-toxic compounds and molecules are the need of the hour to treat bacterial infections. They can also be source of future antibiotics. Pyocyanin, the blue-green diffusible pigment present in *Pseudomonas aeruginosa*, has been found to inhibit appreciably, the growth of *Staphylococcus aureus*, *S.epidermidis* and *Micrococcus* spp.^[11] Also, extract of Ajwain (*Trachyspermum ammi*) seed, a common kitchen spice, can effectively inhibit growth of *Staphylococcus aureus*, and at the same time impair expression of protease enzyme by the bacterium, an important virulence factor.^[12]

Inhibition of quorum sensing

Inhibition of quorum sensing can be a vital weapon to target the ever-increasing problem of antibiotic resistance in medically important bacteria, and has been experimentally tried in *Vibrio cholerae* and *Staphylococcus aureus*; this is all the more important since quorum sensing is key to biofilm formation by the bacteria of medical importance.^[13] Quorum sensing is also important for bacterial sporulation and swarming motility and can hence be important targets.^[14]

Pilicides

Pilicides are agents that destroy the pili or fimbriae in bacteria, especially Gram negative bacteria, and consequently minimise adhesion to biological surfaces.^[14] They are being tried experimentally at the moment.^[13] Pilicides usually target periplasmic chaperones, that are proteins required for the assembly of pili, that allow the pathogenic Gram negative bacteria to adhere to host tissue.^[15] Mono or oligosaccharides that can block the carbohydrate specific binding site of pili or fimbriae, are also a very good candidate in this context.^[14] To inhibit adhesion mechanism in yeasts, probiotic bacteria such as *Lactobacillus reuteri*, *Bifidobacterium infantis*, *Bifidobacterium lactis*, *Lactobacillus acidophilus* and *Lactobacillus casei* have been tried for inhibition of *Candida* colonization, and at least 26 patents have been filed and are being assessed in this regard.^[16]

Inhibition of secretory systems in bacteria

During pathogenesis, bacteria use secretory systems to transport and inject their toxins (effector molecules) into target cells of the host.^[14] Certain compounds, like acylated hydrazones of salicylaldehydes have been found to very effectively inhibit secretion system in *Chlamydia* spp. and attenuate virulence; small molecules have similarly been effective in inhibiting secretion system in *Francisella* spp. and *Pseudomonas aeruginosa*.^[14]

Targeting virulence gene expression

In case of *Vibrio cholerae*, targeting the virulence genes by a new molecule called virstatin (4-[N-1,8-naphthalimide]-n butyric acid) has been found to

minimise production and liberation of the Cholera Toxin from the gene of the bacterium and attenuate virulence.^[14] Gene regulators, like accessory gene regulators have been devised to tackle Methicillin resistant *Staphylococcus aureus* (MRSA), a dangerous community as well as nosocomial pathogen, and numerous patents have been claimed in this regard.^[17]

Inhibitors of drug efflux pumps

Efflux pumps in bacteria tend to flush out the antibiotics that enter bacterial cells, and inhibiting them can be a very good treatment option as well as antivirulence strategy. For example, compounds like 1-(1-naphthylmethyl)-piperazine and phenyl-arginine- β -naphthylamide act as inhibitors of RND efflux pumps and also virulence traits in *Vibrio cholerae*, and are being tried for this purpose.^[16]

CONCLUSION

Antivirulence strategies are very important and fast coming up, and are slated to replace antibiotics in the near future. Further research is urgently needed in this direction.

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