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Alternatives to conventional antimicrobial drugs: a review of future prospects

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Background – Growing antimicrobial resistance poses the threat that before long no suitable drugs will be available for treatment of common infections. This review examines promising new strategies for treatment and control of microbial diseases, with an emphasis on staphylococcal infection.

New drugs and targets – Advances in microbial genomics have provided tools identifying many new targets for antimicrobial drugs. Of particular interest amongst these are inhibition of microbial efflux pump activity, interruption or diversion of riboswitches controlling bacterial metabolism, and metagenomics, which allows analysis of genes from unculturable organisms.

Biological approaches – Advances are also being made in biological systems for disease control, with the exploitation of antimicrobial peptides to attack micro-organisms and modulate immune responses, and the use of bacteriophages or their lysins to eliminate bacteria. There are new approaches in the development and targeting of vaccines and immunoglobulin preparations based on advanced knowledge of microbial physiology and immunoregulation.

Working with the biome – With increasing recognition of the value of the normal microbiota in modulating immunity and the establishment of pathogens, there is growing interest in understanding the mammalian microbiome. Strategies are being developed to promote or maintain the normal microbiota, including the use of probiotics, and there is re-evaluation of the potential of bacterial interference.

Looking ahead – Whilst these approaches are likely to generate new methods of disease control, few will yield usable products within the near future. There will be a continuing need for careful use of existing drugs based on firm diagnosis, rigorous hygiene and prudent antimicrobial stewardship.

Introduction

The closing years of the 20th century and the first decade of the 21st century have been notable for the emergence of multiresistant bacteria.[1,2] Not least amongst these have been the pathogenic staphylococci, particularly meticillin-resistant *Staphylococcus aureus* (MRSA) and, more recently, meticillin-resistant *Staphylococcus pseudintermedius* (MRSP), a species with even broader resistance.[3] At the same time, the risks posed by less virulent organisms, such as the coagulase-negative staphylococci, have been increasingly recognized; these bacteria have been reported as the fastest-growing cause of bloodstream infections in the UK[4] and are particularly threatening because of their ability to form highly resistant biofilms on implants and central lines.

The growing extent of antimicrobial resistance poses the threat that no suitable antimicrobials will be available for systemic treatment of common diseases. Indeed, this situation has already been reached with common clones of MRSP for which no registered veterinary drugs to which they are sensitive may be available.[3] The development of multiresistance has been met by increasing efforts to develop new antimicrobials, and drug discovery has been spurred on by the arrival of the genomic era and the ability to sequence complete bacterial genomes rapidly. However, the expectation that new antimicrobial drug targets would be identified that could be treated with newly developed drugs has not yet been realized.[5]

It is increasingly recognized that bacteria can develop a wide range of resistance mechanisms, which they can use to resist or evade the antimicrobial agents. Indeed, a recent report on metagenomic analysis of DNA from 30,000-year-old Beringian permafrost sediments identified genes encoding resistance to β-lactam, tetracycline and glycopeptide antibiotics, demonstrating that resistance is a natural phenomenon predating the modern selective pressure of clinical antimicrobial use.[6] Another study demonstrates fluoroquinolone resistance in aquatic bacteria in the absence of exposure to these drugs.[7] The implication is that resistance mechanisms can be developed by bacteria against a very wide range of agents, many of which they will have encountered in the past in natural interaction with other competing micro-organisms. There is now renewed interest in the search for drugs which have activity against the whole cell, rather than individual genes, with a focus on modes of therapy against mechanisms that are less likely to promote resistance.

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This review examines some of the promising areas of interest and development for new antimicrobial strategies. These include the potential for identification of new drugs and target systems, biological approaches to infection, and methods of harnessing the protective effect of the mammalian biome.

New antibacterial drugs and bacterial targets

The remarkable advances in microbial genomics since the first bacterial genome was sequenced in 1995[8] have provided the tools to reveal a great variety of potential targets for antibacterial drugs. Amongst these, efflux pumps, riboswitches and, on a broader level, metagenomics are of particular interest.

Efflux pumps have been identified as a principal contributor to antimicrobial resistance in bacteria. They enable bacteria to move toxic substances actively from cells into the external environment; multiple efflux pumps may be present, and individual efflux pumps can confer resistance to several antimicrobials. Although they are believed to play a more significant role in Gram-negative bacteria, they have been shown to be important in enterococci, streptococci and staphylococci. In *S. aureus*, efflux pumps define the basal level of resistance to ciprofloxacin. Recent work shows that a variety of different efflux pump genes may be overexpressed, including *norA*, *norB*, *norC*, *mdeA* and *mepA*, either singly or in combination, and that this is related to the particular strains of *S. aureus* that are tested;[9] clinical isolates may be primed to eliminate antimicrobial compounds, emphasizing the significance of efflux mechanisms in clinical settings. Efflux pumps also appear to be involved in protecting bacteria from stress responses, in the excretion of toxic bacterial metabolites and the secretion of virulence factors. Thus, efflux pump inhibitors show considerable promise both in the battle against antimicrobial resistance and as agents that can compromise bacterial survival and reduce their pathogenic potential. Much research is focused in this area, but as yet no agents are available for clinical use.[10]

Riboswitches are components of an mRNA molecule that regulate its activity in a concentration-dependent way when bound to a specific small target molecule. In most cases, metabolite binding to the receptor represses expression of the gene or genes encoded by the mRNA. Different classes of riboswitches regulate genes responsible for synthesizing or transporting essential coenzyme intermediates or coenzymes, for regulating synthesis or transport of key metabolites, and for sensing metabolite second messengers for regulation of key adaptive pathways, such as motility and biofilm formation.[11] This offers the potential for designing metabolite analogues that bind to the receptors with lethal consequences for the bacteria or effects on their virulence.[12] Indeed, there is now evidence that the long-recognized antimicrobial activity of pyrithiamine is in fact mediated by its inhibition of bacterial growth by targeting thiamine pyrophosphate riboswitches and leading to repression of thiamine biosynthesis.[13] A wide range of riboswitches has already been identified in bacteria, and there is scope for discovery of many more. Although these offer exciting possibilities, much work remains to be done to identify nontoxic riboswitch-targeting compounds with sufficient bioavailability to be used as antimicrobial drugs.

In the past, identification of targets for antimicrobial activity depended on isolation of organisms in culture. However, the development in 1985 of direct analysis of 5S and 16S RNA gene sequences to describe the diversity of micro-organisms in environmental samples without culturing them,[14] together with the development of PCR and sequencing technology, have led to the discovery that the great majority of microbes are unculturable. It is now possible to isolate microbial genomic DNA directly from environments and to clone it into cultured organisms for preservation and study. Metagenomics is the study of libraries of such DNA derived from particular environments, and it was this technology that was used by D'Costa *et al.*[6] to demonstrate resistance genes in the Permian deposits of Alaska mentioned in the Introduction. Such techniques are now being used to investigate aspects of bacterial metabolism and interaction and have already identified new antibiotics,[15–19] although the frequency of clones expressing such activity is low. A major challenge in this discipline is the development of new methods to permit more sophisticated analysis of the wealth of material that is being generated.[20]

Biological approaches to microbial infection

Protective biological systems exist in all organisms to enable them to survive and interact with other life forms in their environments. Medicine has always taken advantage of such systems, and our increasing knowledge of both animal and microbial physiology is providing new opportunities for biological approaches to disease control. In this section, I will consider the potential offered by antimicrobial peptides and bacteriophages to attack and protect against pathogenic bacteria, and new approaches to the use of vaccines and immunoglobulin preparations.

Host defence peptides

Antimicrobial peptides are produced by a wide variety of organisms, from single-celled microbes to vertebrates. Whilst originally studied for their antibacterial activity, they are now recognized to have a wider range of functions. In mammals, at physiologically relevant salt concentrations and normally available peptide concentrations they can have reduced microbicidal activity and may be more important for their immunomodulatory and cell-protective activity; hence, the broader term, 'host defence peptides' (HDPs) is increasingly used.[21,22]

There have been limited studies of HDPs in veterinary species. Cathelicidins are found in epithelial cells and leucocytes and are important in early innate defence against infection. Cloning, tissue expression and biological activity of the canine cathelicidin, K9CATH, was reported in 2007,[23] and it was shown to have broad and potent activity against Gram-positive bacteria, including *S. aureus*, as well as Gram-negative bacteria. β-Defensins are amongst the best-characterized HDPs. They are often expressed by epithelial cells, including those in the skin

and respiratory tract[24] and have antimicrobial activity against both Gram-negative and Gram-positive bacteria. β-Defensins have been studied in the tissues of healthy dogs; cBD1, cBD103 and cBD107 were extensively expressed and five others were demonstrated. cBD1 showed 12-fold increased expression in the lesional skin of atopic dogs when compared with nonlesional skin, whilst cBD103 was downregulated in the atopic skin.[25] In a study using human β-defensin 3, which is recognized as a defensive molecule for the skin, against 22 *S. pseudintermedius* isolates from healthy and both lesional and nonlesional skin, growth inhibition was demonstrated *in vitro* for all of them.[26]

Amongst the antimicrobial peptides which are now being evaluated for therapeutic use are prokaryotic bacteriocins. These molecules are attracting renewed interest because of resistance to conventional drugs and because they are a feature of probiotic bacteria (considered in more detail below in the section on Working with the biome).[27] Bacteriocins generally have a narrower spectrum of activity than the eukaryotic HDPs, although those from *Bacillus* spp. can inhibit a wider range of microbes, including both Gram-positive and Gram-negative bacteria, and some fungi.[28] Prokaryotic bacteriocins include the lipopeptides, colistin (polymyxin E) and daptomycin, which are already used in clinical medicine, and other peptides that are currently in clinical trials.[22,23]

The HDPs are of special interest as antimicrobial drugs because of their range of activities and because, despite wide exposure to micro-organisms in nature, there is little evidence of resistance. Nevertheless, resistance resulting from repeated exposure to these agents has been demonstrated experimentally, and this may also occur as a consequence of therapeutic use. Indeed, it may be that the wide variety of these agents in nature is a consequence of the need for organisms to protect against development of resistance and an indication that they have evolved in response to bacterial co-evolution.[29,30]

Bacteriophages

Another form of antimicrobial therapy which offers great promise, but is by no means new, is the use of bacteriophages. Bacteriophages were discovered at the Pasteur Institute in Paris during the First World War, and phage therapy began to be used quite widely in the 1920s. Some remarkable recoveries were described in human patients, but these reports were often difficult to substantiate and, with the arrival of antibiotics, phage therapy declined.[31] It continued to be used, however, at institutions in Georgia and in Poland, where it is currently used as a rescue therapy for patients after failure of standard antimicrobial treatment, with impressive success rates.[32] A recent report from Poland describes eradication of MRSA carrier status in a healthcare worker consequent on bacteriophage therapy.[33]

Staphylococcus aureus should be a good candidate for phage therapy. Isolates have been shown to be susceptible to a closely related group of virulent myophages which tend to exhibit a broad host range amongst *S. aureus* strains and often possess the ability to infect coagulase-negative staphylococci as well.[31] The great majority of research into the therapeutic potential of bacteriophages has been carried out in experimental animals, and the relevance of these studies to clinical disease remains uncertain. However, phages have been used to prevent and treat neonatal *Escherichia coli* infections in calves, lambs and pigs.[34] In dermatology, a recent report described an open study of topical treatment of chronic, nonresponsive *Pseudomonas aeruginosa* otitis in 10 dogs on a single occasion with a mixture of six bacteriophage strains. Efficacy was evaluated 48 h later and showed a fall in mean clinical score of 30% and in mean bacterial count of 67%, whilst the bacteriophage counts rose approximately 100-fold; there was no evidence of toxicity.[35] Phage therapy has also been tested against subclinical *S. aureus* bovine mastitis in a placebo-controlled multisite trial involving Holstein cattle. Intramammary infusions of phage suspension or saline were administered daily for 5 days, but there was no significant effect.[36]

There are concerns that bacteriophages may carry and transmit virulence or resistance genes and thus increase the hazards posed by bacteria that they target.[37] For this reason, lytic phages are chosen for therapeutic purposes rather than temperate phages which incorporate themselves into the bacterial genome. Concerns that resistance will develop are also an issue, and a variety of different resistance mechanisms has been recognized. However, in the battle between the target bacteria and the bacteriophages, the phages are able to develop and proliferate much more rapidly and, provided that they are selected to be suitable for the environment in which they are used, are likely to maintain their antibacterial efficacy.[31] A strategy which avoids the risks posed by phage transmission of virulence genes is the production and use of lytic enzymes or other bactericidal components derived from bacteriophages. Animal models have shown encouraging results with the use of lytic enzymes, and much work is in progress aimed at developing products which can be used clinically, particularly for the treatment of Gram-positive pathogens, including the staphylococci.[31]

Vaccines and immunoglobulins

In the preantibiotic era, there was an emphasis on the development of methods for promoting host resistance both in preventing and in treating microbial disease. The advent of vaccines and the use of hyperimmune serum were major advances. The crisis caused by multiresistant bacteria has stimulated increased research into these areas and led to the development of increasingly sophisticated products. Vaccines which were previously prepared from attenuated whole cells or lysates are now being replaced by safer products made with polysaccharide capsule components with protein carriers, toxoids and proteins. There has been a special emphasis in the human field on vaccines aimed at *S. aureus* and particularly the community-associated MRSA, which causes severe, life-threatening infections in otherwise healthy people. Even so, no *S. aureus* vaccine has yet been licensed for human use despite reaching, in one case, phase III clinical trials.[38] Interestingly, the *S. aureus* surface protein IsdA, which decreases bacterial cellular hydrophobicity, rendering them resistant to bactericidal human skin fatty acids and antimicrobial peptides,[39] has been used as a target with other surface protein antigens

(IsdB, SdrD and SdrE) in a vaccine giving maximal protection in a mouse *S. aureus* immunization model, and this may prove to be more successful in clinical use.

In the veterinary field, *S. aureus* vaccines have been developed for bovine mastitis, and a systematic review published in 2010 evaluated 24 papers describing studies *in vivo*.[40] The vaccine compositions were mainly bacterin–toxoid, DNA–recombinant protein, and recombinant protein alone. The authors concluded that both new-technology vaccines employing DNA and/or recombinant protein and some long-standing bacterins had yielded beneficial results, supporting their use in the prevention and control of bovine *S. aureus* mastitis. In the small animal field, there is now an urgent need to prevent or control canine pyoderma and other infections caused by multiresistant *S. pseudintermedius*. Although good responses can be achieved in some animals using unregistered vaccines made from lysed cells of *S. aureus*[41] and from autogenous *S. pseudintermedius* vaccines,[42] there is a need for high-performance registered products. The recent description of the *S. pseudintermedius* genome and related proteomic studies have identified candidate therapeutic targets, which offer prospects for the development of vaccines and other products for the control of canine pyoderma,[43] but it is likely to be some years before these become available.

Passive immunization with polyclonal hyperimmune IgG or with monoclonal antibodies is also being developed for the prevention of staphylococcal disease and for its treatment in combination with antimicrobial drugs during active infections in humans. A recent phase II monoclonal antibody study in human low-birth-weight/premature infants prevented staphylococcal sepsis when used at a dose rate of 90 mg/kg and looks promising.[44] Premature infants are deficient in functional opsonins and prone to catheter infections, and this antibody is able to opsonize both coagulase-negative and *S. aureus* strains. Indeed, there may be greater potential for the use of passive immunization against coagulase-negative staphylococci, which are likely to be more susceptible to this approach. However, such products are costly, and economies of scale will need to be achieved before these are likely to be useful in the veterinary field.

Working with the microbiome

The bacterial communities that occupy the different regions of the body form the microbiota. This varies in different individuals and between body regions, and is affected by climate, stress, exposure to antimicrobials and other influences. The great majority of these communities occupy the skin and mucosal surfaces, including the gut, and it is increasingly recognized that they can be beneficial, particularly in relation to immune regulation and protection from establishment of pathogens.[45] The microbiome is a much broader term, which describes the genetic content of the entire community of cells associated with a particular host, including those of the host. This is important because it enables the collective genome to be viewed as a functional 'super-organism', to which the principles of metagenomics can be applied.[46] This discipline is still in its infancy, but it allows the influence of genes in unculturable organisms to be taken into account. These can include virulence and resistance genes, which may be maintained in commensal organisms, leading to increased hazard if these organisms become pathogenic or transfer genes to pathogens. This is of particular relevance to staphylococcal disease. The staphylococcal cassette chromosome, *mec*, which confers meticillin resistance and is associated with multiresistance, is believed to have been acquired by pathogenic staphylococci from coagulase-negative species.[47]

When antibacterial therapy is applied, it can affect microbial species in addition to the target pathogens both by direct antimicrobial effects and by disturbance of the natural balance of bacterial populations. A variety of natural mechanisms may contribute to restoration of the microbiota following such disturbance,[48] and the use of probiotics to aid this process has been advocated. Probiotics are micro-organisms (bacteria or yeasts) which exhibit health-promoting effects, typically produce bacteriocins, and include bacterial species belonging to the genera *Lactobacillus* and *Bifidobacterium*, amongst others. However, there is a need for a more precise definition and greater rigour in the execution and reporting of studies of their beneficial effects.[48,49] Nevertheless, there is evidence that they may have immunomodulatory activity on the gastrointestinal tract, and beneficial effects have been reported following their use in pregnant women with a family history of allergic diseases; evidence of eczema over their first 12 months was reduced in infants of mothers given the probiotic.[50] In dogs, administration of probiotic to beagles and their puppies genetically predisposed to atopy and sensitized to *Dermatophagoides farinae* appeared to reduce immunological indicators of atopic dermatitis but did not ameliorate clinical signs.[51] Topical administration of a bacterial lysate cream in humans significantly reduced clinical signs and pruritus and was associated with reduced *S. aureus* colonization of the skin, but these effects were thought to be related to a direct immunomodulatory effect on skin-associated immune responses.[52]

The skin microbiota in mammals is acquired by first contact of neonatal individuals with micro-organisms in the external environment. Staphylococci become established at this time, and in dogs, as in man, dominant strains become established and persist throughout life.[53,54] Although established staphylococci are believed to protect their host from the establishment of other potentially pathogenic strains from the environment, it is well recognized that carriers of *S. aureus* are predisposed to infection by their endogenous strains.[55] During the 1960s, bacterial interference was used to control outbreaks of staphylococcal skin disease in babies by decolonization and implantation of a less virulent *S. aureus* strain,[56] but availability of more effective anti-staphylococcal antibiotics led to the abandonment of this approach. Bacterial interference has also been used to control staphylococcosis of turkeys,[57] and was shown experimentally to prevent fatal exudative epidermitis caused by *Staphylococcus hyicus* in neonatal pigs.[58] The mechanisms involved in preventing staphylococcal disease in these different disease-control procedures are not understood. However, in the exudative epidermitis

study, establishment of the interfering *Staphylococcus* was associated with suppression of skin populations of the pathogenic *S. hyicus*, and it is possible that its population densities did not reach levels required for quorum sensing and initiation of toxin production. Studies are continuing to investigate the possibilities of suppressing quorum-sensing mechanisms in the control of human staphylococcal disease.[59] Bacteria interference and interruption of quorum sensing[60] could be of special interest in controlling *S. pseudintermedius* infection in dogs.

Looking ahead

It is clear that there is great potential for the development of novel and adapted antimicrobial strategies, both those which attack and destroy pathogenic micro-organisms and those which inhibit or subvert their activity. Currently, few of these are likely to provide forms of therapy which can be applied in the human field without considerable refinement, and it is likely that the human market will be developed in most cases before veterinary products are made available. Thus, there will be a continuing need during the coming years to make the best use of existing antimicrobial agents.

With the rapid and widespread emergence of the meticillin-resistant staphylococci, there is already a move towards increased use of topical therapy. Staphylococci which show resistance to antimicrobials when delivered at concentrations used for systemic therapy are generally still sensitive to the higher levels that can be achieved topically.[61] For extensive disease, antimicrobial shampoos, conditioners, sprays and rinses can be used, whilst more localized lesions can be treated with creams, gels and lotions containing antibiotics and other antimicrobial agents. Evidence of the efficacy of the topical approach is provided in a report of the first European clinical outbreak of canine multiresistant *S. intermedius* (subsequently shown to be *S. pseudintermedius*) pyoderma and otitis published in 2007; six of the 12 affected dogs were treated successfully with topical antimicrobial therapy (fusidic acid, chlorhexidine, chlorhexidine and miconazole or ethyl lactate) alone and four of them responded to combinations of topical and systemic therapy;[62] one dog with otitis media was euthanased, and the other dog which had improved was lost to follow up. It should be noted, however, that these treatments were applied in the dermatology referral practice, where underlying problems were also attended to.

Whatever new drugs are produced, it is unlikely that we shall see another period of continual development of new and potent antimicrobials such as we have experienced during the past 60 years. Whilst highly effective antimicrobial strategies will undoubtedly be developed, we should not expect any 'magic bullets'. There will continue to be a need for careful diagnosis and rigorous hygiene to prevent transmission of resistant pathogens, and prudent antimicrobial use.

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Résumé

Contexte – Le développement des résistances antimicrobiennes constitue la menace qu'avant longtemps aucun médicament approprié ne sera disponible pour le traitement des infections courantes. Cet article examine de nouvelles stratégies prometteuses pour le traitement et le contrôle des maladies microbiennes en mettant l'accent sur les infections à staphylocoques.

Nouvelles molécules et cibles – Les avancées dans la génomique microbienne ont fourni des outils d'identification de plusieurs nouvelles cibles pour les antimicrobiens. Parmi elles, sont d'un intérêt particulier : l'inhibition de l'activité de la pompe à efflux microbienne, l'interruption ou le détournement de riborégulateurs contrôlant le métabolisme bactérien et les métagénomiques qui permettent l'analyse de gènes d'organismes non cultivables.

Approches biologiques – Des progrès sont également réalisés dans les systèmes biologiques pour le contrôle des maladies avec l'exploitation de peptides antimicrobiens pour l'attaque de micro-organismes et la modulation des réponses immunitaires et l'utilisation de bactériophages ou leurs lysines pour éliminer les bactéries. Ce sont de nouvelles approches dans le développement et le ciblage de vaccins et de préparations d'immunoglobulines basées sur l'avancée des connaissances de la physiologie microbienne et l'immunorégulation.

Travailler avec l'écosystème – Avec la reconnaissance croissante de la valeur du microbiote normal dans la modulation de l'immunité et l'établissement des pathogènes, il y a un intérêt croissant dans la compréhension du microbiome des mammifères. Des stratégies sont développées qui développent ou maintiennent le microbiote normal incluant l'utilisation de probiotiques et il y a une ré-évaluation du potentiel d'interférence bactérien.

Vision de l'avenir – Alors que ces approches permettent de gérer de nouvelles méthodes de contrôle des maladies, peu seront utilisables dans un futur proche. Il y aura un besoin continu d'utiliser avec précaution les médicaments existants reposant sur un diagnostic précis, une hygiène rigoureuse et une gestion antimicrobienne.

Resumen

Introducción – La creciente resistencia antimicrobiana provoca la amenaza de que en poco tiempo no haya fármacos disponibles para el tratamiento de infecciones comunes. Esta revisión examina nuevas estrategias prometedoras en el tratamiento y el control de enfermedades microbianas, con un énfasis en la infección por estafilococos.

Nuevos fármacos y dianas – Los avances en las estrategias genómicas microbianas han proporcionado herramientas que identifican muchas nuevas dianas para los fármacos antimicrobianos. Entre estos tienen particular interés la inhibición de la actividad de la bomba de eflujo microbiana, la interrupción o la desviación de los iniciadores ribosómicos que controlan el metabolismo bacteriano, y el estudio metagenómico, que permite el análisis de genes de organismos no cultivables.

Estrategias biológicas – También se están produciendo avances en los sistemas biológicos para el control de enfermedades con la utilización de péptidos antimicrobianos para atacar microorganismos y para modular inmunorespuestas, y el uso de bacteriófagos o de sus lisinas para eliminar bacterias. Hay nuevas estrategias en el desarrollo y la búsqueda de dianas de vacunas y de preparaciones de inmunoglobulinas basados en el conocimiento avanzado de la fisiología microbiana y de la inmunoregulación.

El trabajo con el bioma – Con el creciente reconocimiento del valor de la microfauna normal en la modulación de la inmunidad y el establecimiento de patógenos, hay mayor interés en entender el microbioma de mamíferos. Se están desarrollando estrategias que promueven o mantienen la microfauna normal, incluyendo el uso del probióticos y hay una nueva evaluación del potencial de intervenir en las interferencias bacterianas.

Mirando al futuro – Mientras que estos acercamientos tienen muchas posibilidades de generar nuevos métodos de control de enfermedades, pocos aportarán productos utilizables en un futuro cercano. Seguirá habiendo una necesidad de continuar utilizando los fármacos actuales con cuidado basados en diagnósticos certeros, higiene rigurosa y en la administración prudente de antimicrobianos.

Zusammenfassung

Hintergrund – Die zunehmende antimikrobielle Resistenz stellt insofern eine Bedrohung dar, indem es auf kurz oder lang keine geeigneten Medikamente für gewöhnliche Infektionen mehr geben wird. In dieser Review werden viel versprechende Strategien für die Behandlung und die Kontrolle mikrobieller Krankheiten, mit der Betonung auf Staphylokokken-Infektion, untersucht.

Neue Wirkstoffe und Ziele – Die Fortschritte in der mikrobiellen Genomforschung stellen die Grundlage für viele neue Angriffspunkte für Antimikrobiotika dar. Darunter sind die Inhibition der mikrobiellen Effluxpumpen, die Unterbrechung oder Ableitung von Riboswitches, die den bakteriellen Metabolismus und die Metagenomik kontrollieren und die Analyse der Gene nicht kultivierbarer Organismen ermöglichen, von speziellem Interesse.

Biologischer Ansatz – Es werden auch Fortschritte mit biologischen Systemen gemacht, wie die Verwendung antimikrobieller Peptide zur Krankheitskontrolle, wobei Mikroorganismen angegriffen werden und die Immunantwort moduliert wird, sowie die Verwendung von Bakteriophagen oder ihrer Lysine um

Bakterien zu eliminieren. Es gibt neue Möglichkeiten bei der Entwicklung der Zielgruppe der Vakzine und Immunglobulin-Aufbereitungen, welche auf dem fortgeschrittenen Wissen der mikrobiellen Physiologie und Immunregulation basieren.

Arbeiten mit dem Biom – Mit zunehmender Erkenntnis des Wertes der normalen Mikrobiotika bei der Modulation der Immunität und der Etablierung der Pathogene, kommt es auch zu einem zunehmenden Interesse die Mikrobiome der Säugetiere zu verstehen. Es werden Strategien entwickelt, welche die normale Biozönose fördern oder erhalten, wie zum Beispiel die Verwendung von Probiotika. Es wird auch die Möglichkeit einer bakteriellen Interferenz reevaluiert.

Zukunft – Während diese neuen Möglichkeiten wahrscheinlich neue Methoden zur Krankheitskontrolle schaffen werden, werden sie jedoch in der nahen Zukunft nur wenige verwendbare Produkte liefern. Die Notwendigkeit, vorhandene Wirkstoffe vorsichtig und basierend auf einer genauen Diagnose einzusetzen, strenge Hygienemaßnahmen einzuhalten und Antimikrobiotika verantwortungsvoll einzusetzen, wird weiterhin bestehen bleiben.

要約

背景 – 抗生物質に対する耐性が増加したため，近年，一般的な感染症の治療に使用可能な適切な薬剤がなくなってしまうという脅威がある。この総説は微生物による疾患のコントロールと治療、特にブドウ球菌の感染症に注目して、有望な新しい戦略を検証する。

新規薬剤と標的 – 微生物ゲノム学の発展により，抗生物質にとっての，多くの新しい標的を特定する方法が得られてきた。微生物の排出ポンプ活性の抑制、細菌の代謝を調節するリボスイッチの障害や転換ならびに培養不可能な有機体からの遺伝子解析を行うメタゲノムなどは特に興味深い。

生物学的なアプローチ – 微生物を攻撃し、免疫反応を調節する抗菌ペプチドの開発による疾患コントロールのための生物学的なシステムも進歩し、バクテリオファージやそれらのリシンが細菌の排除のために利用されている。新しい微生物生理学や免疫調節の知識に基づいて，ワクチンの標的や免疫グロブリンの調製に対する新しいアプローチが行われている。

生物群での作用 – 免疫調節における正常微生物叢の意義と病原性の意義に対する認識が高まるにつれ、ほ乳類の微生物叢に対する理解に興味が増している。プロバイオティクスの使用を含む、正常な微生物叢の促進あるいは維持する方法が発達し、細菌の干渉能の再評価が行われている。

今後の展望 – これらのアプローチが新しい疾患制御の方法として生み出されようとしているが、近い将来利用可能な新製品が生まれる余地はほとんどない。しっかりした診断、厳密な衛生環境、用心深い抗生物質の管理に基いて，現存する薬剤を注意深く使用することが要求される。

摘要

背景 – 由于抗菌药物耐药性的增长，在不久的将来，将会造成普通感染治疗时无药可用的风险。本文调查了用于治疗及控制细菌性疾病的有前景的新策略,着重于葡萄球菌感染。

新药和目标 – 改进的微生物基因组学为抗菌药物提供了识别许多新目标的工具。在微生物流出泵活性的抑制中，特别的兴趣点是干扰或转移核糖开关用以控制细菌代谢，以及基因组分析未培养的生物体基因。

生物学探讨方法 – 改进同样发生在生物系统，可以探索利用抗菌肽攻击微生物和调节免疫反应控制疾病，以及利用噬菌体或细胞溶解酶清除细菌。基于微生物生理和免疫调节的先进知识，用新方法开发疫苗和免疫球蛋白制剂。

生物群系工作 – 随着对正常微生物群的免疫调节和确立病原菌的认识不断提高，人们对了解哺乳动物的微生物群更有兴趣了。目前正在开展促进或维持正常微生物群的方法,包括益生菌的用途和重新评估细菌的干预能力。

前瞻 – 当这些策略能产生新方法控制疾病时，在不久的将来就会开发出少数可用的产品。在确诊、严格卫生管理和慎用抗菌药的基础上，我们还将继续谨慎使用现有药品。