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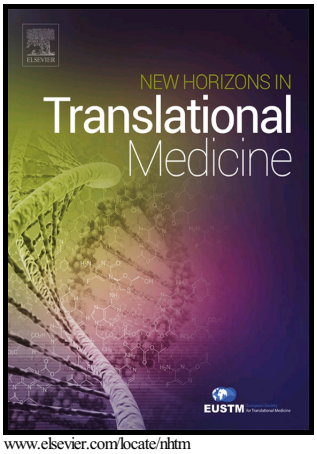

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Pros, Cons and Future of Antibiotics

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ABSTRACT

The advantages of antibiotics have been most clearly seen in those acute bacterial infections which had a high mortality before the introduction of antibiotics. The reality of the potential harmful effects of antibiotics, both short term in individual patients and long term in favoring emergent resistance and opportunistic pathogens are discussed. Bacterial resistance makes the standard treatments ineffective, and increases the risk of infection spreading. The shortage of novel antibiotics has strengthened the efforts of genome sequencing to control bacterial resistance. The future would include novel approaches, based on a re-conceptualization of the nature of resistance, disease and prevention.

Keywords: antibiotics; bacterial resistance; opportunistic pathogens; novel approaches

Introduction

Penicillin was the first scientifically noted antibiotic, i.e. chemotherapeutic agent elaborated by a micro-organism. Antibiotics have the toxic effects on bacteria by either impairing cell wall synthesis (bactericidal), impairing cytoplasmic membrane synthesis and function, or impair nucleic acid and protein synthesis (bacteriostatic). Bacteria have a tenacious hold on life and

naturally develop resistance to antibiotics. This is seen with the rising tide of strains resistant to last-resort antibiotics. Infections caused by resistant organisms have higher death rates, last longer and are more expensive to treat. Apart from improving measures to prevent infections the future would include discovering new ways of attacking bacteria without driving resistance [1].

1. The Pros

The advantages of antibiotics are seen in the treatment of life-threatening acute bacterial infections, surgical infections and the effective use as prophylaxis.

1.1. Acute bacterial infections

The advantages of antibiotics have been most clearly seen in those acute bacterial infections which had a high mortality before the introduction of antibiotics. In endocarditis, the mortality was almost 100% before 1990 and is approximately 20% overall in 2010, though death usually is due to cardiac failure or embolic complications rather than unsuccessful antibiotic treatment [2]. In bacterial meningitis, the 90% mortality in 1990 has been reduced to 8-20% in 2010 and mortality from acute osteomyelitis has reduced from 50% to less than 1% [3, 4]. The prompt use of effective antibiotics in cystic fibrosis has been a major reason for the decreased respiratory morbidity and increased longevity seen over the last several decades [5]. Successful eradication can be achieved in approximately 80% of cases of new Pseudonomas aeruginosa infection by various combinations of oral, inhaled and intravenous antibiotics [6]. Inhaled antibiotics with twice daily colistin or tobramycin solution are used to control chronic P.aeruginosa infection and will preserve lung function and decrease the need for additional intravenous treatments [7]. Acute respiratory exacerbations are usually treated early with two intravenous antibiotics that have different mechanisms of action, to reduce the potential for encouraging bacterial resistance from frequent therapy and to benefit from any potential antibiotic synergy [8]. There is significant benefit associated with antibiotic therapy in exacerbations of chronic obstructive pulmonary disease [9, 10]. Therapeutic antibiotics may be

required in endodontics as an adjunct to operative treatment when there is pyrexia and/or gross local pulp swelling [11]. Most patients with recurrent uncomplicated urinary tract infection (UTI) caused by the usual uropathogens Escherichia coli, Staphylococcus saprophyticus, Klebsiella pneumoniae and Proteus mirabilis may be treated successfully by family physicians [12]. Specialist referral for recurrent uncomplicated UTI is indicated when risk factors for complicated UTI are present [13, 14]. The early initiation of broad spectrum antibiotics have been shown to be critical during the systemic inflammatory response (SIR) phase of infection in preventing the evolving process of sepsis. Mortality is significantly lowered when appropriate antibiotics are prescribed early in surgical sepsis [15].

1.2. Antibiotic prophylaxis

There are many other infections in which morbidity and the serious consequences of spread, both systemically in individual patients and to others within the community, have been considerably diminished. This included the use of antibiotic prophylaxis for bacterial meningitis in high risk patients [3]. Continuous low-dose antibiotic prophylaxis is effective at preventing UTIs [16]. It is generally agreed that viral induced respiratory tract damage may facilitate secondary bacterial infection. Prophylactic treatment with daily oral flucloxacillin is used to reduce the prevalence of Staphylococcus aureus infection in cystic fibrosis patients and to prevent secondary bacterial infection when the patient has a presumed acute viral respiratory infection [17].The use of oral antibiotics at the start of mild “viral” respiratory exacerbations should cover the possibility of secondary infection with common respiratory pathogens e.g. Haemophilus inflenzae or Streptococcus pneumonia [18]. If the patient has chronic P.aeruginosa infection ciprofloxacin may be prescribed to try and prevent a Pseudomonas-associated deterioration [19, 20].

1.2.1. Surgical site infection

Although it is still inferior to good surgical and aseptic technique, antibiotic prophylaxis in high risk surgical patients such as operations lasting more than 2 hours, abdominal procedures, endogenous or exogenous contamination and co-morbidity reduces the risks of surgical site infection substantially [21-24]. The choice of antibiotic depends on the most likely organisms

to be encountered; the type of operation; the likelihood of the development of resistance, and financial costs involved (Table 1) [25, 26]. Broad spectrum cephalosporins are widely used in general and orthopaedic surgery especially when prosthetic material is being implanted, and given at the time of induction to counter the expected organisms at time of contamination (Table 2) [26].

1.2.2. Transplant recipients or the immunosuppressed

Prophylactic peri-operative antibiotic therapy (for example while central line or drains are in situ) reduces the incidence of infection, particularly for cardiac and pulmonary transplant patients. Partial gut decontamination using oral non-absorbable antibiotic regimens can be effective in reducing the rate of endogenous Gram -negative infection in transplant recipients, but total decontamination using agents active against anaerobes are avoided as they may encourage colonization by Gram- negative aerobic opportunists which are multiply antibiotic-resistant. Transplant recipients with a past history of tuberculosis would receive prophylactic isoniazid although the dose of the immunosuppressive cyclosporine A should be adjusted appropriately as anti- tuberculous drugs may reduce plasma cyclosporine concentration from liver enzyme induction [27]. Long-term prophylaxis is useful in patients on immunosuppressive therapy and in post splenectomy patients. The small risk (1%) but > 50% mortality from overwhelming post splenectomy infection by blood-borne encapsulated organisms is prevented [28].

2. **The Cons**

The disadvantages are manifested in the side-effects, the development of resistance and opportunistic pathogens.

2.1. Side-effects

A reason for limiting the use of antibiotic agents for genuine therapeutic indications is their ability sometimes to induce severe or fatal adverse reactions.

2.1.1. Hypersensitivity

Penicillins, have harmful consequences in 1% of patients including death from type I anaphylactic shock in the sensitized allergic patient. Serum sickness (type III reaction), penicillin- induced thrombocytopenia and haemolytic anaemia due to cytotoxic antibodies (type II allergy) may occur after high doses of penicillin [29, 30]. There is 10% cross-sensitivity between penicillin-derivatives, cephalosporin and carbapenems due to similarity of the side chain rather than the beta- lactam structure that they share, and therefore a history of previous drug sensitivity must be sought to avoid the same or closely-allied drug [31]. Certain drugs are more liable to be toxic when used in particular disease states. Ampicillin and amoxicillin skin eruptions are more common when lymphoid tissue is exuberant, as in lymphomas or glandular fever [32].

2.1.2. Drug interactions and toxicity

Some drug combinations increase the risk of reactions, such as nephrotoxicity associated with the combination of an aminoglycoside or frusemide with certain cephalosporins. Interference with the anticoagulant action of warfarin can be a dangerous side-effect of various antibiotics. The low oestrogen pill may lose its contraceptive effect if taken with rifampicin or other drugs that induce liver enzymes. Some antibiotics have other potential side-effects, particularly if the patient's capacity to excrete them is transiently or permanently impaired. This includes the aminoglycosides e.g. gentamicin with renal and ototoxicity; the anti-tuberculosis drugs-rifampicin, isoniazid with hepatic and neurological impairment [32-34]. Aminoglycosides, lincosamides and amphotericin may potentiate renal impairment when prescribed in conjunction with cyclosporine A but reducing the immunosuppression may cause allograft rejection [27].

2.1.3. Effect on commensal flora

Antibiotics, particularly those with a wide spectrum of activity, alter the normal flora of the body, allowing colonization by and multiplication of resistant and opportunistic pathogens. These may then cause secondary infection such as candidal vaginitis in a healthy woman, or fungal and systemic infection in a highly susceptible patient such as a transplant recipient on immunosuppressive therapy [1, 27, 35]. The serious complication of pseudomembranous colitis, is caused by the anaerobic bacterium, Clostridium difficile, which can multiply when the normal colonic flora is suppressed and is relatively insusceptible to many commonly used antibiotics but metronidazole or vancomycin [36, 37]. The increased mortality from Clostridium difficile infection by 400% between 2000 and 2007 is partly due to the emergence of a fluoroquinolone resistant C. difficile strain [38]. If transplant patients develop pseudomembranous colitis, absorption of the immunosuppressive drugs is impaired, thus increasing susceptibility to allograft rejection [27].

2.2. Antibacterial resistance

The known mechanisms of bacterial resistance are genetic alterations, the metabolism of the antibiotic by bacteria e.g. beta -lactamases, altered affinity of receptor site, alterations in cell wall permeability (antibiotic efflux pump) and the influence of environmental factors at sites of infection [39-41] . In pus, most bacteria are in the dormant phase and relatively resistant. Intracellular organisms such as the tubercle bacillus, Brucella abortus, and Salmonella typhi are not affected by humoral immune mechanisms but by the slow cellular immune mechanisms. This partly explains the slowness with which these infections respond to antibiotics [27]. Infections at sites where the concentrations of polymorphs and macrophages is low, such as on heart valves and the meninges, are more resistant to antibiotics than infections elsewhere [24]. The spread of resistance is facilitated by inappropriate antibiotic therapy (Table 3) [39, 43, 44].

2.2.1. Methicillin-resistant staphylococcus aureus (MRSA)

Following the random oral antibiotic treatment of localized soft tissue infections (boils, carbuncles, etc.) bacterial resistance tend to emerge as methicillin - resistant staphylococcus

aureus (MRSA) [45]. MRSA have a thick capsule that impair diffusion of antibiotics to their site of action in the cell wall. The organism may then be introduced into a hospital following admission of a patient so treated and usually associated with high morbidity and mortality [1, 46, 47]. Vancomycin has been the 'gold standard' treatment for MRSA for many years but for its adverse reactions (allergic rash, drug fever) and nephro/ototoxicity [34]. Teicoplanin is another glycopeptide antibiotic with better activity in MRSA bacteraemia and a much longer half-life with less serious side effects [48]. Recent novel second-generation semisynthetic lipoglycopeptide antibiotics, dalbavancin, oritavancin of the same class as vancomycin, were shown to treat serious and life-threatening infections caused by Gram- positive bacteria including MRSA [49]. Linezolid and tedizolid are members of the novel class of synthetic oxazolidinones and are also effective protein synthesis inhibitors. Although restricted by their adverse effects of bone marrow depression and mitochondrial toxicity it is of great value in cases of multi-drug resistance such as in vancomycin -resistant enterococci, MRSA, hospital-acquired pneumonia and potentially intractable Gram- positive infections (Table 3 [50].

2.2.2. Opportunistic pathogens

- 'Opportunist' organisms are usually of low pathogenicity but cause serious infections mainly when the host's defense mechanisms against infection are impaired. These micro-organisms were little encountered in the pre-antibiotic era but now prosper because they are already resistant or can easily acquire resistance to commonly used antibiotics [1, 51]. In addition, some of these organisms survive well in the external environment and episodes of nosocomial infection caused by them are increasing [52]. In patients made highly susceptible by underlying diseases, major surgery, instrumentation, cytotoxic or immune-suppressive therapy, and the acquired immune deficiency syndrome, infection remains a major problem. 'Infections by Gram- negative organisms such as Klebsiella, Pseudomonas, Enterobacter, Serratia associated with instrumentation of urinary or gastrointestinal tract and would easily give rise to septicaemia and death in the more susceptible immunocompromised patient [1, 27, 35]. In surgical practice, prolonged prophylaxis is detrimental as super infection by fungi, antibiotic-resistant pseudomonas, enterococci and staphylococci ensues. These

infections are difficult to treat and carry a high mortality [34]. Enteric streptococci account for 10-20% of severe infections related to the abdomen and are not sensitive to all common prophylactic antibiotics [35]. These resistant opportunistic pathogens are a threat to advanced surgical procedures. [1, 53].

3. The Future

Whole- genome sequencing (WGS) has become an essential tool for drug development by enabling the rapid identification of resistance mechanisms, particularly in the context of tuberculosis (TB), which remains a global public health problem [54]. TB is always treated with multiple antibiotics to minimise the chance of treatment failure as a result of the emergence of resistance during treatment. The early elucidation of resistance mechanisms also has implications for the design of clinical trials. For example, a simple mutational upregulation of an efflux pump may confer cross-resistance between antibiotics [55]. Thus WGS can influence the choice of antibiotics that are included in novel regimens. However, with the shortage of novel antibiotics and the evolution of the resistance mechanisms of the pathogen new interventions are needed [56].

3.1. Quorum Quenching

One such promising strategy is the recently demonstrated quorum-quenching approach, also known as antipathogenic or signal interference, which abolishes bacterial infection by interfering with microbial cell-to-cell communication, also known as quorum sensing. Most of the bacteria seem to use quorum-sensing signaling molecules ranging from fatty acid derivatives to oligopeptides and furanones systems in modulating the target gene expression among family members. Research on synthetic derivatives that target the plasmid R factors and their interactions with the signaling molecules have progressed in recent years [57].

3.2. Phage therapy

Western scientists mostly lost interest in further use and study of phage therapy for some time when antibiotics were discovered in 1941 [58]. Bacteriophages or viral phage therapy are much more specific than antibiotics, as they are indirectly harmless not only to the host organism , but also to gut flora, reducing the chances of opportunistic infections They would have a high therapeutic index and because phages replicate in vivo, a smaller effective dose can be used [59, 60]. Phages are currently being used particularly in Russia and Georgia to treat bacterial infections that do not respond to conventional antibiotics, [61]. They tend to be more successful than antibiotics where there is a biofilm covered by a polysaccharide layer, which antibiotics typically cannot penetrate. In the West, no therapies are currently authorized for use on humans probably for fear of viral transmission, although phages for killing food poisoning bacteria (Listeria) are now in use [62].

Phage tail-like particles (PTLPs) are typically produced by bacteria as a defense mechanism against other bacteria of the same species and exhibit specific and potent bactericidal activity. Phage tail-like particles kill Clostridium difficile and represent an alternative to conventional antibiotics [63]. If demonstrated to consistently and specifically eradicate C difficile, it would represent a novel antibacterial therapy that is inexpensive, naturally occurring, and sparing of the beneficial bacteria of the gut.

3.3. Monoclonal antibodies

With major rapid advancements in genetic sequencing humanized monoclonal antibodies are the fastest growing group of biotechnology-derived molecules in clinical trials. Since 1986 about 30 monoclonal antibodies against plant/bacterial toxins, enzymes, radionuclides, with cytotoxic drugs etc, are currently approved for clinical use [64]. The infusion of monoclonal antibodies (a modern advance on serum therapy, which is more than a century old) or white blood cells that attack microbes holds promise for treating infections although expensive [65]. Their advantage is their specificity and flexibility. The short-coming in sepsis is that using monoclonal antibodies or antagonists to endotoxin, tumour necrosis factor (TNF) and interleukin(IL)-1 as adjuvant to the established basic principles of management have not reduced mortality. It is now recognized that the redundancy in the inflammatory response is

such that if one component is removed, another mediator will continue the response. Moreover, if the pool of endogenous antagonists (e.g. IL-1 receptor antagonist or soluble TNF receptors) is replete, addition of exogenous antagonists is unlikely to be efficacious [35, 66]. Research is now focused in developing new targets and optimizing their effects with the addition of beneficial modifiers.

3.4. Host targets

An option is to treat infections by attacking host targets rather than bacterial targets. Recent preclinical research have successfully deployed therapies that either moderate the inflammatory response to infection or limit bacterial growth by blocking access to host resources without attempting to kill the bacteria [67]. For example, an antibiotic of a novel class (Lpx C inhibitors), which blocks synthesis of the antigenic gram-negative lipopolysaccharide, could not kill Acinetobacter baumannii but prevented the microbe from causing disease in vivo [68]. Other examples include anti-inflammatory monoclonal antibodies, probiotics to compete with microbial growth, and sequestration of host nutrients (e.g. iron) to create a resource-limited environment in which microbes cannot reproduce [69]. Probiotic therapies using lactobacillus spp, Bifido-bacterium spp., and Propionibacterium spp have been utilized against S. aureus and P.aeruginosa. The proposed mechanism for the inhibitory effect lies in the production of organic acids and the subsequent lowering of pH of the bacterial cytoplasm [70]. Such strategies have the potential to reduce resistance when pursued in concert with standard antibiotic therapy.

3.5. Potential of old-generation antibiotics

The global problem of advancing antimicrobial resistance has led to a renewed interest in the use of old antibiotic compounds, such as polymyxins, fosfomycin, fusidic acid, cotrimoxazole, aminoglycosides and chloramphenicol, as valuable alternatives for the treatment of difficult-to-treat infections. Due to the low-level use of many of the old antibiotic compounds, these have

remained active against a large number of currently prevalent bacterial isolates [71, 72]. Nebulised colistin sulphate (polymyxin) is effective in reducing the incidence of allograft infection in cystic fibrosis lung transplant recipients [27, 72]. The use of a combination of antibiotics with different sites of action are used to reduce bacterial resistance, for example in the triple therapy of tuberculosis (rifampicin, ethambutol, isoniazid) until the sensitivity of the tubercle bacilli is known [73]. The synergy between a sulphonamide antibiotic (sulphamethaxole) and a dihydrofolate reductase inhibitor (trimethoprim) in co-trimoxazole takes advantage of the bacterial cell wall impermeability to dietary folate necessary for nucleic acid synthesis and together cause bactericidal action [39] . This is used effectively in treating the opportunistic pneumocystis jiroveci pneumonia in AIDS and in transplant recipients. Patients allergic to high dose oral co-trimoxazole may receive intravenous pentamidine isethionate or combination treatment with primaquine and clindamycin may be used [27, 71]. The availability of novel genetic and molecular modification methods prodxvides hope that the toxicity and efficacy drawbacks presented by some of these agents can be surpassed in the future [1, 71].

3.6. Plant antimicrobials

The rich chemical diversity in plants promises to be a potential source of antibiotic resistance modifying components and has yet to be adequately explored. Plant antimicrobials are agents with weak or narrow- spectrum activities. By primarily affecting bacterial efflux of antibiotics they can work in synergy with antibiotics through increasing the sensitivity of bacterial cells to antibiotics. This can be useful against antibiotic resistant strains of pathogenic bacteria such as Salmonella typhii [74]. The aqueous extracts of tea (Camella sinensis) have been shown to reverse methicillin resistance in MRSA and also to some extent penicillin resistance in beta-lactamase producing Staphylococcus aureus [75]. Disruption of bacterial adhesion is another mechanism of plant antimicrobial activity which could be explored [76].

3.7. Broadening the spectrum of research and informed advice

Infection prevention eliminates the need to use antibiotics, but would require new technologies that can more effectively disinfect environmental surfaces, people, and food. Medical technology that enables biodesignable or antibiotic impregnated implants is rapidly evolving [77, 78]. Improving resistance to infection by improving the standard of life of the human population and thus reduce the flourish of micro-organisms will remain a severe challenge to Public health [79]. Routine immunization against the common infectious diseases and immunization for travellers may be of avail during outbreaks or epidemics and prevent the spread of the disease. New vaccines against endotoxins hold great promise for preventing antibiotic-resistant infections [80].

4. CONCLUSIONS

Despite preventive efforts, infections will always occur, and we will always need safe and effective antibacterial therapy for them. Antibiotic resistance already exists and widely disseminated in nature to drugs not yet invented. A greater innovation is the development of therapies that do not drive resistance.

Authors contribution

EPW substantially contributed to the conception, design and literature search, JCA contributed to the pharmacological and toxicological issues, DSN contributed to the public health and epidemiological issues in Cameroon.

Consent

None required.

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TABLES

TABLE. 1 Examples of antibiotic prophylaxis

Operation	Infection site	Likely organisms	Prophylactic antibiotics
Colectomy	wound	E.coli, Anaerobes. Bacteroides	Cefuroxime, Metronidazole
Hip replacement	prosthesis	Staph. aureus	Cefuroxime
Bladder instrumentation	Urinary tract	E.coli, Klebsiella spp	Gentamicin
ERCP	Biliary tract	E.coli	Ciprofloxacin
Vascular graft	graft	Staph. aureus, staph.albus	cefuroxime

ERCP, endoscopic retrograde cholangiopancreatography (Check with the local hospital's local policy)

Table 2. Common antibiotics and their uses.

Antibiotic Infection	Common uses First choice	Alternatives
Chest infection	Penicillin + erythromycin	Co-amoxiclav (Amoxycillin and Clavulinic acid- a β-lactamase inhibitor)
Wound infection (cellulitis)	Penicillin + flucloxacillin (penicillinase resistant)	Co-amoxiclav
Intra-abdominal infection (endogenous organisms	Cefuroxime (β -lactamase stable) + metronidazole	Cefotaxime (β- lactamase stable).

likely)		Gentamicin (aminoglycoside)
Cholecystitis-cholangitis	Cefuroxime + metronidazole	Piperacillin (very active against pseudomonas spp)
Urinary tract infections	Trimethoprim	Gentamicin Co-amoxiclav
Pelvic inflammatory disease	Tetracyclines + cefuroxime + metronidazole	
Severe sepsis	Gentamicin + metronidazole + penicillin	Imipenem (β- lactam antibiotic)
MRSA	Vancomycin	dalbavancin, oritavancin tedizolid, , Linezolid
Pseudomembranous colitis	Metronidazole, Vancomycin	dalbavancin, oritavancin tedizolid, Linezolid
Gas gangrene	Penicillin + metronidazole	Ticarcillin (β- lactamase sensitive),Teocoplanin

TABLE. 3 Reasons for inappropriate antibiotic therapy .

1. **Desire to benefit the patient**
2. **Fear of missing a treatable condition**
3. **Misconception that antibiotics may do good but can do no harm**
4. **Fear of litigation**
5. **Insufficient knowledge of antibiotics**
6. **Insufficient knowledge or rationalization of the possible aetiological agents**
7. **Confusion due to multiplicity of similar antibiotics**
8. **Expert guidance not readily available or sought**