Current Trends in Malaria and Tuberculosis Chemotherapy

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ABSTRACT

Over the past few decades, research on chemotherapy has developed several agents and treatment approaches/protocols for the treatment of microbial infections, including Plasmodium and Mycobacterium infections. However, failure in the successful treatment of both infections (i.e., malaria and tuberculosis) has posed great challenges to humans. This is majorly due to the development of resistance to available drugs. In addition, malaria is endemic in the sub Sahara and the incidence of tuberculosis (TB) is also very high and worsens rapidly due to the high prevalence of human immunodeficiency virus (HIV) infection, making the treatment of both conditions even more difficult in such regions. Effective management of these diseases is very important, due to their adverse socio-economic impacts globally and especially in the sub Sahara. This article briefly discusses the history and general principles of antimicrobial chemotherapy. The paper also summarizes the current status and some new advances in the chemotherapy of malaria and tuberculosis.

Key words: Antimicrobial, chemotherapy, drug resistance, Plasmodium, Mycobacterium, nanotechnology.

Historical perspective of chemotherapy:

The term chemotherapy was introduced in 1907 by the German biochemist, Paul Ehrlich to refer to antiparasitic therapy in describing his important early studies on Trypanosoma brucei, the tsetse fly-borne parasite that causes African trypanosomiasis commonly called sleeping sickness. Chemotherapy now refers more broadly to the use of any chemical compound that selectively acts on microbes (bacteria, fungi, parasites, virus etc) or cancer. One of the early chemicals developed by Ehrlich which was both remarkably nontoxic to humans and remarkably toxic against a number of treponemal diseases (including syphilis and yaws) was the arsenical compound, Salvarsan arsphenamine, which was also called the “magic bullet”.

Selective toxicity of chemicals has been exploited and widely employed as a technique for defense among animals and plants since the ancient days. Many fungi and bacteria make toxic substances that kill or suppress the growth of competing microorganisms or facilitate infection of a host. Some plants make a vast array of toxins for their self-defense. Humans first discovered this process in 1929 with Alexander Fleming’s chance observation of the antibacterial effect of a substance (penicillin) secreted by Penicillium notatum mould (now called Penicillium chrisogenum) mould [12,33]. Penicillin was subsequently purified and produced in large quantities and introduced for clinical use by Howard Florey in 1940. Following the successful synthesis of penicillin by scientists, many other potential natural antibacterial compounds were discovered and synthesized, including tetracycline, streptomycin and the cephalosporins, which were collectively called “antibiotics” to refer to antibacterial substances produced by various species of microorganisms (bacteria, fungi, and actinomycetes) that suppress the growth of other microorganisms. Following chemical analysis and other studies resulting in the elucidation of the structures of these natural antibiotics, semisynthetic derivatives of the natural products were developed by chemists. These semisynthetic drugs and other classes of related drugs were safer and more effective than the naturally produced drugs, as the new semisynthetic or wholly synthetic drugs had improved pharmacokinetic properties, greater stability and extended spectrums of action. The meaning of the term “antibiotics” has now been extended to also include synthetic antimicrobial agents, such as sulfonamides and quinolones.

Furthermore, rational development of several compounds that can interfere with microbial biological process/replication has also been greatly facilitated with increasing knowledge of molecular mechanisms of microbial biology/replication. Currently, antimicrobial agents are readily available and are among the most commonly used and misused of all drugs. The emergence of microbial drug
resistance is one major consequence of the widespread, indiscriminate and irrational use of antibiotics in humans [31,18,44]. This often results from exposure to very low concentrations of antimicrobials, which may provide a path whereby human pathogens could eventually evolve high-level antimicrobial drug resistance [34,18]. Thus, inappropriate use of antibiotics accelerates the development of resistance in pathogens [56,18,44].

Principles of antimicrobial chemotherapy:

There are principles that guide the use of antimicrobial agents in order to minimize potentially toxic and the promotion of selection of resistant microorganisms.

Selection of an antimicrobial agent:

The practice of choosing a particular antimicrobial therapy without proper evaluation of the disease is irrational and potentially dangerous. Optimal and judicious selection of antimicrobial agents for the therapy of infectious diseases requires good clinical judgment and knowledge of microbiological factors and the pharmacology of the antimicrobial agent to be used [26].

Microbiological factors:

Good knowledge of the most likely microorganism to cause a specific infection in a given host and the clinical presentations of the infection may suggest the identity of the infecting microorganism(s) [16,26]. Such knowledge is required in initiating an initial empirical therapy for microbial infections in some class of patients, especially in the critically ill or hospitalized patients, who require broad-spectrum antimicrobial agents [26,41,32]. After initiation of empirical therapy, identification of the infecting pathogen is required to be done using a microscope in the laboratory in order to make definitive diagnosis. Furthermore, because sensitivity of microorganisms to antimicrobial drugs varies widely among different bacterial strains and even within a particular specie, microorganisms sensitivity tests is very essential in antimicrobial therapy.

Sensitivity of a microorganism to specific antimicrobial agents (antimicrobial susceptibility testing) is done by in vitro laboratory tests, and is used to predict efficacy in vivo and make appropriate drug selection [51,26]. The most commonly used are the agar- or broth-dilution tests which provide quantitative information and disk-diffusion tests, which provide qualitative information. The dilution tests are used to measure the minimum inhibitory concentration (MIC) or minimum bactericidal concentration (MBC), which represents the lowest concentration of the agent at which bacteriostatic or bactericidal activity occurs respectively. The static versus cidal designation may also depend on both the pharmacological properties of the drug and such clinical factors as immune system function, inoculum size, drug concentration in tissue and duration of therapy. A cidal drug may prove to be merely static if an inappropriately low dose or short treatment course is prescribed. A static drug may be cidal if given in high doses for prolonged courses to exquisitely sensitive pathogens.

Once pathogen identity and antimicrobial susceptibility data are available, antimicrobial agents with a narrower spectrum are used to replace initial broad spectrum agents, in order to reduce toxicity and prevent the emergence of antimicrobial resistance.

Pharmacological factors:

Evaluation of the pharmacology of the drug is another important principle of antimicrobial chemotherapy. This includes its pharmacokinetics, pharmacodynamics, selective drug toxicity, resistance and possible drug interactions. Consideration of these factors is needed to make a proper selection, dosage and route of administration of antimicrobial drug [26].

Current status and new developments of malaria chemotherapy:

Malaria results from infection with Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale or Plasmodium malariae, but a large majority of the clinical cases and mortalities is caused by Plasmodium falciparum [7,13,37]. Recently, a fifth human parasite has been identified to be P. knowlesi, which has the long-tailed and pig-tailed macaque monkeys as the natural hosts [57,68].

P. falciparum is the leading cause of disease in most parts of the world, producing about 250 million new infections, with a mortality estimate of about 1 million deaths each year; and approximately 85% of these deaths are among children, and most occur in Africa [74]. Half of the world's population is at risk from malaria, however, the disease is endemic in sub-Saharan Africa and children below the age of five suffer the greatest burden of the disease [3,60,73]. In Nigeria, nearly 110 million of clinical cases of malaria are diagnosed per year, about 50% of the adult population experiencing at least one malaria episode per year and young children having 2-4 attacks of malaria annually [17]. Despite efforts to control the disease, malaria is among the top three deadly communicable diseases and the most deadly tropical disease [53]. The consequences of the disease are further compounded by extremely low living conditions in poor nations.

The current line of malaria therapy recommended by the World Health Organization is
diagnostic testing in all cases of suspected malaria and treatment based on clinical symptoms alone is only reserved for settings where diagnostic tests are not available [74].

**Diagnosis:**

Early diagnosis and prompt treatment are fundamental components of the WHO global strategy for malaria control [71,74]. Current confirmatory qualitative methods include parasitological confirmation by microscopy or rapid diagnostic test (RDTs). In most malaria endemic countries of sub-Saharan Africa, the standard for laboratory confirmation of a clinical malaria diagnosis is a peripheral blood film, examined microscopically. However, some limitations of the microscopic-based diagnosis of malaria including low sensitivity, labour-intensiveness, requirement for trained personnel (expertise) and quality equipment, is now making RDT to become preferable, especially because of its higher sensitivity both in clinical and research settings [36,39,4,74].

**Microscopy:**

Thick and thin smears of sample blood are usually prepared on separate frosted slides and stained using standard staining method ("Field's stain" or "Giemsa stain"). The Field's stain method is more often used because the method provides a readable film within few minutes compared to the "Giemsa stain". Blood slides are then read under a microscope, each film graded as positive (asexual malaria parasites seen) or negative (no malaria parasites seen) based on the inspection of 200 fields of the thick smear. The parasite density is estimated assuming 8,000 white blood cells/μl [69]. The thin smear is useful in species identification.

**Rapid diagnostic test:**

RDTs are handheld cassettes detecting *Plasmodium* parasites by an antibody-antigen reaction. They are available in several formats and designed to detect one or more antigens including *Plasmodium falciparum* specific histidine rich protein 2 (PfHRP-2), *P. falciparum* specific parasite lactate dehydrogenase (Pf-pLDH), *Plasmodium vivax* specific parasite lactate dehydrogenase (Pv-pLDH) or antigen common to the four *Plasmodium* species: pan-pLDH or aldolase [5,39]. RDT generally involves blotting a small volume of blood (2-20μl) on a nitrocellulose strip containing monoclonal antibodies, which react with parasite specific antigens available in the blood of infected patients to give visible, diagnostic and control bands [36]. Test is considered positive when the antigen and control lines are visible in their respective windows and negative when only the control band is visible.

RDTs have high sensitivity and specificity (>90%) at a parasitaemia >100 asexual parasites/μl [39,4]. The accuracy (sensitivity and specificity) of RDTs is mostly dependent on the parasite species, transmission intensity, parasite density, amount of circulating antigens, local polymorphisms of target antigen and persistence of antigens after treatment. RDTs can also serve as a source of parasite DNA, as sufficient DNA could be successfully extracted from malaria rapid diagnostic tests (RDTs), used and collected as part of routine case management services in health facilities, and thus forming the basis for molecular analyses, surveillance and quality control (QC) testing of RDTs [27].

**Current drug treatment:**

Correct use of an effective antimalarial drug will not only shorten the duration of malaria illness but also reduce the incidence of complications and the risk of death. Antimalarial drug resistance has spread and intensified over the last 15–20 years, leading to a dramatic decline in the efficacy of most antimalarial drugs including aminoquinolines, halofantrine, sulfadoxine-pyrimethamine etc [6,10,76,50,55].

Currently, the drugs with significant effects on the parasite are the artemisinin and its derivatives. Artemisinin and its derivatives are the most rapidly acting of all the current antimalarial drugs and they are highly efficacious against multi-drug resistant *P. falciparum* [25,42]. Development of resistance to artemisinin monotherapy [35], has prompted the use of artemisinin-based combination treatments (ACTs), involving the use of an artemisinin compound with other antimalarial agents [66,42,74]. ACTs have been demonstrated to have better parasite clearance and efficacy than single artemisinin therapies and combination therapy offers hope for preserving the efficacy of antimalarial drugs [1,11,42]. The World Health Organization has recommended these regimens/combinations as: artesunate-sulfadoxine-pyrimethamine (artesunate-SP), artesunate-amodiaquine, artemether-lumefantrine and artesunate-mefloquine. A fifth combination has recently been added- dihydroartemisinin-piperaquine [74]. The ACTs are presently recommended and used as the first line antimalarial agents in malaria chemotherapy [42,74]. In order to reduce the drug resistance, the WHO has also recommended the removal of oral artemisinin monotherapy formulations from the circulation because their use is thought to hasten the development of parasite resistance.

**Artemisinins:**

Artemisinin (*qinghaosu*) was discovered in 1972 by Chinese scientists as the active principle of the leaves of a Chinese medicinal plant known as...
Artemisia annua L. [29]. It is a sesquiterpene trioxane lactone with a peroxide bridge linkage. It acts against the asexual stages and gametocytes thereby having potent schizontocidal activity and able to reduce the rate of malaria transmissibility in places of high malaria incidence.

Modification of artemisinin has yielded artemether and arteether (oil soluble derivatives) and dihydroartemisinin (DHA), sodium artesunate and artelinic acid (water soluble derivatives). Artemisinin and its derivatives (except DHA) are all metabolized to DHA, which is the biological active metabolite of the drugs at variable rates [40,22,21].

The artemisinin derivatives have more potent blood schizontocidal activities than the parent compound and are the most rapidly effective antimalarial drugs known [35]. Artemisinins have also been shown to have anti-inflammatory [64,77] and antiproliferative effects against a wide range of cancer cell lines [28,65,30].

Mechanism of action:

Artemisinins are selectively distributed into P. falciparum infected erythrocytes, where they cause malaria parasite’s death through generation of free radicals [63]. The peroxide bond (endoperoxide bridge) of artemisinin is activated by iron (II)-heme produced during hemoglobin degradation in erythrocytes. This results in the generation of toxic reactive oxygen species (ROS) responsible for parasites death [49,75]. However, some studies have also reported that artemisinins endoperoxide cleavage do not require activation by heme iron [46,30].

Adverse effects:

Artemisinins have been reported to be relatively safe, however there are concerns on some recently reported adverse effects. Apart from the reported minor cardiovascular effects observed during clinical trials, artemisinin compounds have been demonstrated to cause neurotoxicity, especially in the vestibular, motor and auditory brain stem nuclei in animal studies [20]. Furthermore, artemisinins have been recently shown to affect testicular function [43,2] and female reproductive function [67,47] in animal models. These effects appear to be due to sustainable high levels of the drugs and their metabolites and calls for caution in prolonged or repetitive treatment with artemisinin and its derivatives, which may occur in areas of high transmission.

New drugs for malaria treatment:

Antiretrovirals:

Recent studies have indicated that antiretroviral protease inhibitors may affect outcome in malarial disease. The human immunodeficiency virus (HIV)-1 protease inhibitors saquinavir, ritonavir and indinavir directly inhibit the growth of Plasmodium falciparum in vitro at clinically relevant concentrations [58]. By these findings, drug-drug interactions that occur between antiretrovirals and some antimalarials in malaria and HIV coinfection can be avoided. Concurrent administration of SP and nevirapine and zidovudine have been shown to cause serious adverse drug reactions and diagnostically challenging drug toxicities [8]. These findings are particularly important due to the existing high rate of malaria and HIV-1 coinfection in sub-Saharan Africa and the effort to employ highly active antiretroviral therapy for effective management and prevention of HIV/AIDS in this region.

NITD609:

NITD609, is an experimental drug which has been shown to be effective against the two most common parasites responsible for malaria (P. falciparum and P. vivax) and also against a range of drug-resistant strains in mice with malaria [52]. NITD609, observed to be a potential drug candidate among 12,000 chemicals that were screened using an ultra-high throughput robotic screening technique, has been identified to be structurally and chemically different from all other currently used antimalarials and belongs to a class of drugs called spiroindolones [78]. The compound has been reported to target malaria parasite protein different from proteins attacked by the conventional malaria drugs and also to have unique pharmacokinetic profile [52,78]. NITD609 is currently undergoing clinical trials and if the results obtained in the mice are reproducible after the clinical trials, then NITD609 has the promise to be a breakthrough in malaria treatment.

Current status and new developments of tuberculosis chemotherapy:

Tuberculosis (TB) is a pervasive disease of the respiratory system, caused by Mycobacterium tuberculosis. It is a leading chronic bacterial infection and constitutes a major public health challenge [19]. The spread of multidrug resistance TB (MDR-TB) and the appearance of extensively drug-resistant TB (XDR-TB) pose new challenges for its prevention, treatment and control [48]. Approximately, two billion people are currently infected with Mycobacterium tuberculosis representing about 30% of the global population. The infection is endemic in developing countries, where higher mortality has been reported [45,14]. The most effective pharmacotherapy is a multidrug combination of active anti-tuberculosis agents.
Current drug treatment:

Anti-tuberculosis drugs are grouped into first-line, second-line or third-line drugs, according to their potencies and efficacies.

First-line drugs:

The first-line drugs used in treating TB are: isoniazid (INH), rifampin (RMP), pyrazinamide (PZA), ethambutol (EMB) and streptomycin (SM). These drugs are administered orally and are shown to have excellent potency against M. tuberculosis [23].

Second-line drugs:

The second-line drugs used for the treatment of TB are: aminoglycosides (e.g., amikacin and kanamycin); polypeptides (e.g., capreomycin, viomycin and enniomycin; fluoroquinolones (e.g., ciprofloxacin, levofloxacin and moxifloxacin); thioamides (e.g., ethionamide and prothioamide) and cycloserine [23,45].

Third-line drugs:

The third-line drugs for treating TB include rifabutin, linezolid, thioidazine, arginine, Vitamin D, macrolides (e.g., clarithromycin) and thioacetazone [23,45].

Anti-TB drug regimens:

Combination of the above drugs for effective tuberculosis treatment is dependent on the form of tuberculosis.

Latent and active TB:

There are two forms of TB: latent TB and active TB. In latent TB, the bacteria are dormant in body and this phase can last for up to decades and can also develop into active TB. The usual treatment of latent TB is one anti-tuberculosis drug (usually isoniazid) giving daily for 6-12 months in HIV-negative people. This has greatly reduced the subsequent risk of developing active TB [59].

In active TB, the bacteria multiply and spread in the body, thereby causing tissue damage. The most effective pharmacotherapy is a multidrug combination of INH, RMP, PZA and EMB for an initial 2-month intensive treatment (initial intensive phase). This is followed by a continuation phase, usually 4-month treatment with RMP and INH exclusively [70,45]. During the initial intensive phase of treatment, the agents destroy almost all bacilli in the three physiological categories, while any residual dormant bacilli or replicating rifampin-resistant mutants are eliminated during the continuation phase.

Drug-resistant TB:

There are different forms of drug-resistant TB and each regimen requires different drug combination for their effective treatment:

Multidrug-resistant (MDR-TB):

Multidrug-resistant TB is a form of TB in which the bacteria become resistant to INH and RMP, but may or may not be resistant to other agents. Less patient compliance and poor adherence to administration schedules due to the prolonged pharmacotherapy and associated pill burden remain the main reasons for therapeutic failure and development of MDR strains [9]. Treatment takes longer usually with any of the first-line drugs and mostly second-line drugs, which are more expensive and have more side-effects [38,72].

Extensively drug-resistant (XDR-TB):

XDR-TB is a more aggressive form of MDR-TB in which the bacteria are resistant to the first-line drugs (INH and RMP) and any fluoroquinolone, and at least one of three injectable second-line drugs: capreomycin, kanamycin and amikacin [9,72]. As with MDR-TB, XDR-TB can be either transmitted or developed, for example, if MDR-TB drugs are misused or mismanaged. Treatment options for XDR-TB are fewer, more expensive and less effective with many unpleasant side effects. Treatment requires the use of two or more new drugs in addition to initial regimen containing INH and RMP.

Novel technologies applied to the treatment of TB:

Despite potentially curative pharmacotherapies being available for over 50 years, the therapeutic outcome has not been satisfactory because of length of drug treatment and the pill burden, which affect patient lifestyle. Furthermore, the oral route, through which most anti-TB drugs are administered, represents many pharmacokinetic problems, including bioavailability [14]. Current concern is therefore to design novel antibiotics that will overcome drug resistance, shorten the treatment course and reduce drug interactions with the aim of improving patient healthcare.

New technologies such as the design of carrier-based drug delivery systems (nanotechnology) are under investigation for treating TB. Nanotechnology appears as one of the promising approaches for the development of more effective chemotherapeutic agents for TB treatment and other conditions [24,54,61]. This technology involves the development of novel microparticulate, encapsulation and various other carrier-based drug delivery systems for incorporating the principal anti-
TB agents. Biodegradable polymers and liposomes are used as carriers to trap specific amounts of the drugs and administered either intravenously or subcutaneously [56]. The drugs are then released gradually over time as they diffuse out into the body in sufficient amounts that are lethal to the *M. tuberculosis* parasite, which ultimately reduces the dose and duration of treatment.

**Conclusion:**

Microbial infections are known to cause diseases that have high mortality rates, including malaria, tuberculosis and HIV/AIDS. Every human is exposed to these unfriendly microbes, while over 40% of the global population is infected with one pathogenic microorganism or the other, which poses great concerns in public health. Effective treatment of these diseases has not been very successful due to the development of resistance by microorganisms to the available chemotherapeutic drugs. This impacts severe adverse socio-economic effects on the society, because of the debilitating health consequences from such diseases. Misuse and irrational use of chemotherapeutic agents is a major cause of development of drug resistance by *P. falciparum* and *M. tuberculosis* and other microorganisms. As pharmacologists and other scientists discover and design novel drugs and treatment approaches for *P. falciparum* and *M. tuberculosis* infections, there is hope that they will be more effectively eradicated in the future, if the drugs are used properly.

**References**


