WHO DRUG INFORMATION

WHO Drug Information provides an overview of topics relating to drug development and regulation that are of current relevance and importance, and will include the lists of proposed and recommended International Nonproprietary Names for Pharmaceutical Substances (INN). Its contents reflect, but do not present, WHO policies and activities and they embrace socioeconomic as well as technical matters.

The objective is to bring issues that are of primary concern to drug regulators and pharmaceutical manufacturers to the attention of a wide audience of health professionals and policy-makers concerned with the rational use of drugs. In effect, the journal seeks to relate regulatory activity to therapeutic practice. It also aims to provide an open forum for debate. Invited contributions will portray a variety of viewpoints on matters of general policy with the aim of stimulating discussion not only in these columns but wherever relevant decisions on this subject have to be taken.

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Contents

General Policy Topics
Bioavailability and bioequivalence: moves towards consensus 1

Personal Perspectives
Counterfeits: grappling with the issues 3

Reports on Individual Drugs
Artemether in children with severe malaria 6
IUDs and pelvic inflammatory disease: a reassuring assessment 6
Leprosy: interim appraisal of an M. leprae vaccine 7
Quinine: use of loading doses in falciparum malaria 8
More new experience with oral and parenteral typhoid vaccines 9
Vitamin A supplements and childhood mortality: further encouraging evidence 11

General Information
Tuberculosis chemotherapy: the case for defining national policies 12
Vaccine selection: safety versus immunogenicity 13
Advertising standards reviewed 14

Regulatory Matters
ACE inhibitors and anaphylaxis in patients undergoing haemodialysis 15
Chlorofluorocarbons: restrictions in use 15
Corticosteroids: danger of immunosuppression 15
Didanosine: approved for advanced HIV infection 15
Foscarnet sodium for cytomegalovirus retinitis in advanced HIV infection 16
Metamizole sodium: restrictive rescheduling 16
Nocapine: removed from opium alkaloid preparations 16

Advisory Notices
Beta adrenoreceptor agonists and asthma 17
1% hydrocortisone products available without prescription 17
Nandrolone: do risks outweigh benefits? 18

Essential Drugs
Sexually transmitted diseases 19
Aciclovir 29
Benzylpenicillin 30
Benzathine benzylpenicillin 30
Procaine benzylpenicillin 30
Ceftriaxone 31
Ciprofloxacin 31
Erythromycin 32
Metronidazole 33
Miconazole 33
Nystatin 34
Podophyllum resin 34
Spectinomycin 35
Sulfamethoxazole/trimethoprim 35
Tetracycline 36
Doxycycline 37

Recent Publications
Biological standards: international standards and reference reagents 38
WHO Expert Committee on Biological Standardization 38

Recommended International Nonproprietary Names: List 31
Amendments (Continued) 39
Bioavailability and bioequivalence: moves towards consensus

The economic and political attractions of an open market in pharmaceuticals are incontestable. The competitive pricing that results from the marketing of generic versions of off-patent products significantly reduces drug costs to governments and other purchasers. Manufacture of these products within local industrial facilities can save valuable foreign currency. However, the philosophy is dangerously flawed if the safety and efficacy of these products cannot be adequately assured or if, in creating a more open market, the door is opened to counterfeit and spurious products that escape every modality of control.

Over the past five years WHO has directed much effort into assisting small and less affluent countries to meet this challenge. It has issued Guiding Principles for Small National Drug Regulatory Authorities which emphasize the need to ensure enforcement as well as promulgation of standards. It has revised the WHO Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce in a way that is intended to ensure that the true provenance of an imported product remains on record throughout its peregrinations within international distribution channels. It has updated its Good Practices in the Manufacture and Quality Control of Drugs to embrace recent advancements in pharmaceutical technology and modern concepts of quality assurance. At a more practical level, it has proposed a series of basic chemical tests for verifying the identity of active pharmaceutical substances both in bulk consignments and in finished dosage forms, and it has developed a computer software package to support a simple system of drug registration.

In one particular, however, it has been slow to offer didactic advice. It has not yet issued definitive guidelines on the technical basis for assuring the clinical interchangeability of different versions of a given multisource product. Proof that a product conforms to an agreed pharmacopoeial specification can be inadequate in this regard. Particularly for solid oral dosage forms, it may additionally be necessary to demonstrate bioequivalence in vivo.

Bioequivalence is assessed in terms of the performance of an accredited reference product. "For the present", the consensus statement proposes, "this will usually be a 'clinically proven' market leader product ... in the country or group of countries to which the [marketing] application is made". Missing from the discussion is any consideration of the need or practicability of establishing and maintaining internationally recognized reference standards. Nor is there any examination of ways to detect and rectify potential drift in bioavailability between successive batches of a reference product.

Similarly, the implications that genetically and environmentally determined community variation in drug absorption and metabolism may hold for the
interpretation of bioequivalence studies — or even for their validity within a global context — are acknowledged but not explored.

At a more fundamental level, discussion is not engaged in the working group’s report on impaired bioavailability of readily-absorbed compounds resulting from inappropriate formulation of solid dosage forms. Basic errors in formulation are most likely to occur where technological resources and administrative controls are most severely constrained. Formal bioavailability studies are neither practicable in this context nor, it seems, are they necessary. Although in vitro dissolution tests are unreliable when used in a comparative sense to establish bioequivalence between different products, they do have potential for screening out poor formulations. They are being introduced in leading pharmacopoeias for this purpose, and their application should be rated high on the list of regulatory priorities in both developed and developing countries.

Reference
Personal Perspectives

Counterfeits: grappling with the issues

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With the world confronted by the reality or the prospect of large-scale counterfeit production of almost every conceivable consumer product, it is not surprising that drugs are sometimes manufactured in violation of good manufacturing practices and in total disregard of pharmacopoeial standards and requirements for registration and marketing procedures. The difference between most other counterfeit products and counterfeit drugs is that they create a potential for serious public health hazards. If they are of inferior quality, their use can result in either unanticipated adverse reactions or in therapeutic failure. This not only places patients at risk but undermines the confidence of prescribers and consumers in the genuine product.

Policy options and legislative responses to counterfeiting must be considered in the context of local circumstances and experience. Generalizations as to how national policies and laws should be formulated, revised or updated need to be regarded with caution. One basic requirement, however, is that a coordinated approach among the various interested competent authorities is needed at national level, and that these authorities must remain alert to the methods used in other countries to deal with the problems. On occasion, actions taken by a country that is at the hub of a network of exporters of counterfeit products may relieve “importing” countries of the need for an extensive revision of their laws. None the less, "benevolent" legislative changes adopted in exporting countries are to have impact where they are most needed, they should be founded upon carefully conducted bilateral or multilateral consultations and negotiations. Effective solutions cannot be found overnight; there is no simple formula that can be applied to eliminate the problem immediately from the face of the earth.

Progress towards viable solutions needs to be based on four prerequisites. These are political will, an adequate legislative basis, adequate resources for law enforcement, and effective public education. This implies that wherever counterfeit products are identified, there is a need to review existing policies, procedures, laws, and practices and to identify loopholes that could operate to the advantage of counterfeiters. Where a comprehensive national drugs policy is not already in place, much can be achieved through effective control and rationalization of the drug market.

Counterfeit drugs have been successfully infiltrated into the distribution chain in countries with tightly controlled markets as well as those that remain relatively open. The introduction of counterfeit drugs is, however, much easier where many products are in circulation. When there is no inventory of all available products or when there is no proper system for registration in place, as in some developing countries, the identification of counterfeit drugs is greatly impeded. Developing countries confronted with the problem are well advised to prune out unwanted or unnecessary products from their markets and to introduce a registration system which enables the pedigree of products to be clearly identified. Where domestic manufacturing capability is limited, the need to introduce an import licensing system must be given serious consideration. Such a system, implemented in conjunction with the WHO Certification Scheme, will facilitate monitoring of imported drugs, particularly if these administrative measures are complemented by greater awareness and vigilance among customs officers and import licensing authorities.

Regulatory prerequisites

Over-regulation needs to be avoided at all costs, and any decision to add a plethora of new controls must be carefully weighed against possible administrative overload, excessive costs, bureaucratic delays and inconvenience. However, in all circumstances, it is important that laws and regulations already in place satisfy the following points:

• counterfeit products should be defined without ambiguity;

• the manufacture, import, export, sale, storage, distribution, advertising and use of counterfeit drugs should be explicitly prohibited;
• the enforcement authorities should be empowered to take such action as is necessary to initiate searches, and to carry out tests with a view to identifying counterfeit drugs;

• procedures should be in place which permit the detection and prosecution of offenders. Where possible, the burden of proving that the product is lawful should be "shifted" to the accused or defendant; a certificate of analysis should be made admissible as prima facie proof of the facts stated therein without the need to summon the analyst; powers should be provided to seize suspect consignments; company accounts and financial dealings should be accessible to the courts; mechanisms should be devised for mandatory notification of the existence of counterfeit drugs to the competent authority; and

• courts should be empowered to deal effectively with: convicted persons and counterfeit products (including mandatory gaol sentences for serious offences); compulsory destruction of counterfeit products; publication of the name and identity of convicted persons and counterfeit products; confiscation of assets.

In addition, powers such as those that devolve upon national enforcement authorities from the UN Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances are necessary if effective action is to be taken against large-scale counterfeiters. Countries may even wish to consider whether the powers that now exist to detect illicit drug trafficking in these specific substances should not be extended to the enforcement agencies dealing with pharmaceuticals in general. However, any conferment of such powers must be carried out with caution and in a way that provides appropriate safeguards against excesses.

Wholesale, retail and pharmacy practices also need to be reviewed, since the professionals working within the distribution chain are of key importance in preventing counterfeit products being marketed through legitimate sales outlets. Codes of practice need to establish unequivocally that dealing in counterfeit products is an unethical practice which is subject to disciplinary action. The elimination of informal sales outlets is a far more complex issue. Such systems are frequently culturally-sanctioned and they provide a service which has gained acceptance as a result of default in providing a comprehensive health system.

Developing a “counter-counterfeiting” strategy

An assembly of representatives of the pharmaceutical industry, wholesale and retail trade, health care practitioners, health care institutions, patient groups, and police, customs and other law enforcement agencies needs to be established, by a decision of the highest authority of the land, to develop a coordinated response to the problems associated with counterfeit drug trafficking. The drug regulatory agency must also enlist all the support it can mobilize for the purpose. Unless it enjoys a broad base of support, its efforts may fail to yield the exemplary prosecutions required to create a persuasive deterrent. Drug regulatory authorities need to be more open and frank about the problem. Their officials should not feel inhibited to speak out against laxism in the application of rules which hinder counterfeiters, and they should possess the authority to assign specific tasks that fall within their mandate to appropriate agencies within its network. These agencies should be able to enlist the assistance of WHO, INTERPOL, UNDCP, geo-political groupings such as EEC, IFPMA and any other organization with the mandate and resources to help in dealing with the problem.

For far too long, drug regulatory authorities have attempted to deal with the problem in isolation; counterfeiting is a multi-billion, transnational operation, far too complex in character to be effectively dealt with by drug regulatory authorities alone. The full panoply of controls needs to be instituted in a concerted manner.

Each action that is taken to rationalize the market and prescribing and consumption habits, to augment the powers of enforcement authorities, and to work within an international environment of mutual collaboration and support will make its contribution to an effective strategy. It is through modest advances that a foundation will ultimately be built to deal with the problem, although some countries will be able to achieve tangible results within a shorter time-frame than others.

Infrastructure development is probably the single most important strategy for effective control of drugs available in the market place. There are some countries where a counterfeit is available for almost everything, but products like Coca Cola or Pepsi remain largely exempt. The reason for this
lies in an effective marketing strategy, an extensive distribution network penetrating down to the retail level, and close monitoring of stock movement and products display which hinders any threat of interference with legitimate sales. Feedback is provided through frequent and close contact with wholesalers and retailers.

Because of the complexity and diversity that characterize the pharmaceutical market, it is obviously not possible for manufacturers to maintain a comparable marketing strategy and intelligence system. However, where there are adequate health care institutions, health care personnel, pharmacies and other retail outlets; where there is an effective system to monitor drug requirements and to ensure that supply matches demand; and where there is an effective mechanism to monitor the movement of drugs, counterfeiters will surely find it more difficult to infiltrate the system. The development of a secure infrastructure is no mean attainment, but it is certainly within reach of the vast majority of countries. In this day and age, the people’s ‘right to health’ includes the right of access to a reliable standard of care and, unquestionably, the right to assurance that the drugs they receive are safe, effective and, not least, genuine.
Artether in children with severe malaria

With the rapid incursion of chloroquine-resistant falciparum malaria into the hyperendemic areas of West Africa and ominous indications that the prevalence of strains resistant to quinine is increasing in south-east Asia and South America, there is an urgent need for alternative treatment for severe malaria. Fortunately, clinical experience with artemisinin and its derivatives in China (1, 2), and subsequently in Vietnam (3) and Myanmar (4), has been consistent in confirming their promise as potent antimalarials that seem to reduce parasitaemia more rapidly than other antimalarial drugs.

This experience has now been reinforced by a demonstration that artemether (a water soluble hemisuccinate derivative of artemisinin) is a well tolerated and rapidly effective parenteral treatment for severe malaria in children (5). Forty-three Gambian children aged from 2 to 12 years were studied. All had severe malaria and 19 were in unrousable coma on admission. They were randomized to receive intramuscularly either artemether suspended in groundnut oil using a loading dose of 4 mg/kg followed by 2 mg/kg every 24 hours, or chloroquine sulfate 3.5 mg base/kg every 6 hours. The median duration of parenteral antimalarial treatment was 24 hours in both groups and no patient received more than 3 doses of artemether. Time to parasite clearance and resolution of fever was similar in both groups, and there was no evidence of either systemic or local adverse effects. In all, 8 patients died of whom 6 were receiving chloroquine. The authors emphasize, however, that much larger comparative studies will need to be completed before it can be determined whether or not artemisinin compounds can save more lives than chloroquine or quinine administered in appropriate doses.

Artemether, in particular, has characteristics that favour its use in field conditions. Its slow absorption from the injection site allows once daily dosing; it is well tolerated on intramuscular injection; and it does not degrade readily on storage. Further experience is necessary, however, before its potential as a first-line treatment of severe malaria in rural clinics and health centres can be defined with certainty.

References


IUDs and pelvic inflammatory disease: a reassuring assessment

The possibility that intrauterine devices (IUDs) might be associated with a risk of pelvic inflammatory disease (PID) has been appreciated from the time that they were first introduced some 30 years ago. Assessments conducted on the essentially mechanical devices available during the late 1960s were, in general, reassuring (1, 2). Whereas modest correlations were apparent, many of the infections were regarded as minor insofar that they were treated, apparently effectively, without removing the IUD. During the 1970s, however, increasing use of IUDs in North America and western Europe was concurrent with a marked increase in the incidence of PID. Early controlled studies fuelled speculation that these trends were causally related (3, 4). In the United States, in particular, the use of IUDs decreased by more than two-thirds as a consequence of this concern (5) and two companies decided to withdraw their products from the market.
With hindsight, it seems that the magnitude of the risk was generally overstated (6). Disproportionate attention was focused on the performance of the Dalkon Shield, which was associated with a higher risk of PID than other devices (7), while the contribution of other factors to the rising incidence of PID, notably the prevalence of sexually transmitted diseases, was underestimated (8). Reanalysis of one study has indicated that, among women who are at low risk of sexually transmitted disease, use of an IUD carries virtually no excess risk of PID (9).

Given this history, a need clearly exists to assess the risks associated with currently used devices. Data obtained within a series of prospective efficacy studies coordinated by WHO (10, 11) has created a unique opportunity to accomplish this. In all, information on some 23,000 insertions and more than 50,000 years of use by women largely in the Americas, Asia and Europe was analysed (12). The results confirm that, once the devices have been in place for several weeks, modern copper-releasing IUDs are associated with a rate of PID — as defined on clinical criteria — of only some 1.6 cases per 1000 years of follow-up over periods extending up to 8 years. Indeed, among women at remote risk of sexually transmitted disease, no excess risk of PID was discernible. In contrast, during the 3 week post-insertion period, the incidence of PID peaked transiently by some 6-fold within the cohort as a whole, whereas even higher risks were evident within specific geographical areas, among older recipients, and among women at enhanced risk of sexually transmitted disease.

These results not only underscore the need to ensure careful preliminary assessment of patients and strict asepsis when IUDs are fitted; they reopen the question of whether, in some circumstances, IUDs should be inserted under antibiotic cover (13) and they offer support to the principle that, in the absence of complications, devices should preferably be left in place for the duration of their labelled lifespan (14).

References

Leprosy: interim appraisal of an \textit{M. leprae} vaccine

More than 5 million new cases of leprosy are still identified globally each year and, with the widespread emergence of dapsone resistance, chemotherapy has become both costly and complicated. It is estimated that no more than half the infected patients benefit from full courses of oral multidrug therapy currently recommended by WHO (1). Effective immunization appears to be an attainable goal.
goal since BCG vaccine provides substantial protection in some areas. Elsewhere, however, and for reasons that remain uncertain, its performance has been disappointing (2).

Clinical leprosy is widely presumed to result from an impaired antigen-specific immune response to infection (3). Expectation has consequently been aroused that a vaccine containing killed *Mycobacterium leprae* in addition to BCG might be more effective in stimulating an immune response in patients with preexisting subclinical infections. Indeed, favourable immunological changes and amelioration of symptoms have been reported in a substantial proportion of patients with lepromatous and indeterminate leprosy who have been immunized with the combined vaccine (4, 5). None the less, 5-year follow-up in Venezuela of almost 30,000 contacts who were immunized either with BCG alone or in combination with 6 x 10^8 irradiated, autoclaved *M. leprae* purified from the tissues of infected armadillos has provided no evidence at this stage that the latter offers significantly better protection than BCG alone (6).

Clinical signs of leprosy have thus far developed in 59 patients within the cohort. Of these, 31 had been vaccinated with BCG alone and 28 with the combined vaccine. In most of these cases, however, infection is likely to have antedated vaccination. Surveillance of the group will need to be maintained for a further 10 years before the majority of new cases can be confidently attributed to postvaccination infection. Meanwhile, retrospective analysis of BCG scars on patients who were admitted to the study and those who were excluded because of evidence of leprosy on presentation suggest that BCG alone reduces the risk of infection by some 50% and that the degree of this protection is increased by subsequent booster doses.

References


**Quinine: use of loading doses in falciparum malaria**

The aim in using intravenous quinine to treat patients with falciparum cerebral malaria is to attain effective blood concentrations as rapidly as possible without inducing serious drug toxicity. Use of a rapidly-infused initial loading dose was first advanced on the basis of a study undertaken in south-east Asia over ten years ago (1). However, since there is little margin between the therapeutic and toxic dose of quinine, the practice has remained controversial (2), not least because of concern that dangerously high concentrations might occur in acutely ill young children if the volume of distribution of the drug were reduced (3), and also because it is rarely possible under field conditions to establish whether the patient has taken quinine orally.

None the less, because severe chloroquine-resistant malaria is being encountered with increasing frequency throughout equatorial Africa (4), the need to reappraise both the safety and the efficacy of parenteral quinine therapy within the African context has become urgent. The possibility has been raised that African strains of *Plasmodium falciparum* may be more sensitive to quinine than south-east Asian strains (5). Moreover, because prolonged and repeated intravenous infusions are often impracticable in the rural African setting, the safety of intramuscular administration needs to be established. Two groups have already placed relevant experience on record (5, 6).

The first of these compared the standard regimen used locally in Cameroon — 8 mg base/kg over 8 hours, three times daily for 3 days — with a regimen in which an additional loading infusion of 8 mg base/kg was administered during the first hour of treatment (5). Ten patients in unrousable coma and with *P. falciparum* parasitaemia (> 2000/µl) were allocated at random to each treatment. All patients were discharged fully recovered 3 days after admission, but the length of coma and the
parasite clearance time were significantly reduced among those who received the loading dose.

The second study provides a comparison of the pharmacokinetics and clinical effectiveness of three regimens in a group of 59 children with severe malaria: high dose intravenous or intramuscular quinine — 16 mg base/kg initially, followed by 8 mg/kg every 12 hours — and low dose intravenous quinine — 8 mg base/kg followed by 4 mg/kg every 12 hours. The 12-hour dosing interval was selected as being more practicable under field conditions than the usual 8-hour interval. Blood concentrations of quinine resulting from each of these regimens consistently exceeded the 99% in vitro inhibitory concentration of quinine for 60 locally obtained isolates of *P. falciparum*. None the less, the higher dose regimens resulted in faster rates of parasite clearance and of clinical response.

The application of pharmacokinetic principles to the assessment of antimalarial treatment places the results of small-scale clinical trials on a much sounder basis. However, to assess the safety of therapeutic intervention on trials primarily designed to establish efficacy is far from adequate. Quinine has a narrow therapeutic index. Monitoring of far larger numbers of treated cases will be needed to establish with reasonable confidence whether a loading dose can be administered safely where there is no recourse to tertiary care facilities.

References


More new experience with oral and parenteral typhoid vaccines

It has recently been estimated that, globally, some 30 million cases of typhoid fever occur each year (1) and that the mortality rate in some areas approaches 3% (2). For many years immunization against the disease was dependent upon parenteral administration of inactivated whole-cell preparations. These provide a measure of protection which has been estimated to range in different settings, predominantly in eastern Europe, from about 50% to 90% (3-8). However, because they frequently cause both local and systemic adverse reactions, they have not been used extensively in some areas where the disease is most highly endemic (9, 10).

Over the past decade two other types of vaccine have been developed. One is a parenterally administered capsular polysaccharide vaccine which induces antibodies to the Vi antigen of *Salmonella typhi* (11). The other, known as Ty21a, is a live attenuated non-pathogenic strain of *S. typhi* which can be administered orally (12). This lacks the Vi capsular polysaccharide and, although it induces other antibodies, it is thought to act primarily through induction of protective cell-mediated immunity (13, 14).

The Vi vaccine has been estimated to protect some 60 to 70% of adults and children over periods of observation extending from one to two years (15, 16). Results obtained with Ty21a have been more variable. A liquid formulation protected 88% of adult volunteers in the USA against challenge (17) and, throughout a three-year field study undertaken in Egypt, 3 doses of a similar formulation was 96% efficacious among 6 and 7 year-old children (18). However, lower levels of protection have since been recorded from Chile and Indonesia where the disease has higher prevalence (19-22). It seems that the intensity of many of the infections may have overwhelmed any vaccine-induced protective immunity.

Candidate live oral vaccines that produce Vi antigen are also now under development. These are prepared by recombinant DNA techniques rather than chemical mutagenesis, as is the case with TY21a. The objective is to produce a vaccine
that is more consistently efficient than any of the existing oral and parenteral preparations. At present, the Vi vaccine holds important advantage notwithstanding the need for parenteral administration. It is less expensive and much less costly to deliver since it is extremely stable, it requires no cold chain and is fully effective in a single dose.

References


Vitamin A supplements and childhood mortality: further encouraging evidence

Over the past 10 years evidence has accumulated that vitamin A deficiency places young children at risk not only from xerophthalmia (1) but also from increased vulnerability to respiratory disease, protracted diarrhoea and potentially severe infectious illnesses, including measles (2–5). With one outstanding but unexplained exception (6), community trials in areas where deficiency is endemic have shown that vitamin A supplements administered at daily or weekly intervals reduce early childhood mortality by one-third to one-half (7–9).

A further randomized, double-blind, controlled community trial which involved almost 30 000 children aged from 6 to 72 months living in an area of the Gangetic flood plain in Nepal has recently been reported. The study, which involved administration of gelatin capsules containing either 200 000 IU vitamin A or of placebo as a single dose every 4 months, was concluded prematurely when, at 12 months, 30% fewer deaths had been reported within the treated group (95% confidence interval 0.56–0.88) (10). Most significantly reduced were deaths ascribed to diarrhoea or dysentery, wasting malnutrition and measles. Unexpectedly, no decrease in deaths resulting from respiratory infections was recorded.

The results of this trial are of particular importance in two respects. They largely dispel earlier speculation that the benefits of replacement therapy in vitamin A deficient children may be dependent in some way on other unknown facilitating factors (11–13). They also confirm that, pending efforts to increase the dietary content of vitamin A, periodic administration of high-dose supplements offers a practicable interim expedient. It is estimated that in Nepal alone, where at least 2% of preschool children are xerophthalmic and many more are deficient in vitamin A (14), more than 15 000 lives could be saved each year. Throughout southern Asia as a whole, over a million lives may well be at issue every year (10).

References

General Information

Tuberculosis chemotherapy: the case for defining national policies

In 1990, almost 8 million new cases of tuberculosis were estimated to have occurred in developing countries — predominantly among working adults — and an estimated 2.8 million patients died from the disease, more than from any other infectious condition (1). As yet, there is no indication that the risk of infection is rising. It may even be decreasing slightly although case numbers are rising as a result of population growth. Although there is no clear evidence that the annual risk of infection is rising in countries where HIV infection is widespread, the AIDS epidemic may have an impact on the incidence of tuberculosis. A few African countries have recently reported a doubling of notified cases of tuberculosis. The risk of developing active tuberculosis may be as high as 30–40% during the lifetime of an immunocompromised individual whereas it is less than 10% in immunocompetent individuals (2–5).

Faced with this prospect, all governments need to review the costs and impact of their tuberculosis control programmes and to reevaluate their case-detection strategies. A recently published report of a cost-effectiveness study undertaken in Tanzania, Malawi and Mozambique demonstrates the vital contribution of such information to effective planning and budgeting (6). The study was based upon an analysis of all fixed costs and variable costs — which are a function of the number of patients diagnosed and treated — that are incurred by governments and nongovernmental organizations in providing the tuberculosis programme. The benefits of treatment were estimated by constructing life tables for treated and untreated smear-positive individuals and calculating differences in cure rates, death rates and transmission rates. This excluded the anticipated 25–33% spontaneous cure rate in smear-positive patients (7) as a benefit of treatment.

In terms of extended survival, short-term chemotherapy for smear-positive tuberculosis was confirmed to be at least as cost-effective as immunization against measles and neonatal tetanus. Short-term chemotherapy (2 months of streptomycin, isoniazid, rifampicin, and pyrazinamide followed by 6 months of isoniazid and thiacetazone) was shown to be cheaper and more effective than longer-term regimens. Among patients admitted to hospital, between 86 and 90% of patients who received the short-course regimen were cured at an estimated cost per year of life saved of US$ 1.7–2.1. Standard chemotherapy in both hospitalized and ambulatory patients resulted in cure rates of 60 to 66% at an equivalent cost of US$ 2.4–3.4 (6).

In the longer term, the principal public health benefit of chemotherapy is reduced transmission. The cost of routinely treating smear-negative presumptive cases of pulmonary tuberculosis was estimated to be some 4 to 8-fold more costly. But, on the assumption that 15% of these patients subsequently become sputum positive, and that these account for some 20% of total transmission, this was also perceived to be a highly cost-effective intervention (6).

The same principle was applied to the treatment of patients who are also seropositive for HIV. Because the potential for increased survival in this population is limited, the direct benefits as defined within this study are small (6). However, for as long as there is no evidence to challenge the assumption that all smear-positive patients present the same risk for transmission of the disease, the economic rationale for routinely treating HIV-positive patients was acknowledged to be strong. Prompt treatment of all sputum-positive patients regardless of their potential life-span is an unequivocally sound investment from the public health standpoint.

References


**Vaccine selection: safety versus immunogenicity**

Vaccines against infections of childhood are characteristically among the safest and most effective of medicinal products. Paradoxically, however, their impressive performance portends conflict of interest: as the level of protective immunity rises within a population, the risk of natural infection in an unimmunized individual may sooner or later be outweighed by the risks inherent in vaccination. This dilemma is aggravated when the only possibility of eradicating the target disease within a community is to turn to a more highly immunogenic and possibly more reactogenic vaccine.

Over the past 10 years these concerns have generated much discussion on the relative merits of two mumps vaccine strains (Jeryl Lynn-Moraten and the more immunogenic but somewhat more reactogenic Urabe Am 9-Schwarz strain) (1-5). Conservative estimates of the incidence of severe complications associated with the two vaccines have been cited as 1/1800 000 and 1/400 000 respectively (6). Where there is evidence that mass vaccination coverage has been high enough to block transmission, preference must clearly be accorded to the safer of the two vaccines. However, when infection remains prevalent as a result of inadequate coverage, the enhanced protection against natural infection offered to the community by use of the more immunogenic vaccine may then decisively outweigh the heightened incidence of vaccine-induced complications.

The point at which this inversion of risk occurs depends upon an array of interrelating factors including vaccine efficacy and coverage, the age at which children are immunized, the prevailing rate of transmission of the target disease and the incidence of complications associated with natural and vaccine-induced disease. Vaccination policy is still often determined without an objective analysis of the risks and benefits associated with the selected programme. Mathematical modelling involving adjustment of these factors in accordance with epidemiologically and experimentally derived data may well ultimately provide a more objective secure basis for selecting both vaccines and determining vaccination schedules (6-9). It has already indicated, in relation to mumps, that it may not always be in the interests of the community to use the vaccine associated with the lowest rate of complications (6).

**References**


Advertising standards reviewed

In May 1988, the Forty-first World Health Assembly adopted a series of ethical criteria for medicinal drug promotion (1). In doing so, it urged Member States to develop appropriate measures to ensure that promotional activities support the aim of improving health care through the rational use of drugs, and to monitor and enforce, where appropriate, the implementation of these measures (2). It also appealed to pharmaceutical manufacturers and other interested parties to use the criteria as appropriate to their spheres of competence, activity and responsibility.

This year, the Forty-fifth Assembly reviewed progress made in the implementation of the criteria, particularly by governments and pharmaceutical companies. To provide stimulus and to lend objectivity to this debate, the Swedish National Corporation of Pharmacies has issued a report on an international survey of advertising practices (3). In all, 6710 advertisements drawn from independent medical journals published in 18 countries within a 12-month period during 1988–89 were assessed.

Central to the criteria is the statement that advertisements should usually include:

- the name(s) of the active ingredient(s) using either the international nonproprietary names (INN) or the approved generic name of the drug;
- the brand name;
- content of active ingredient(s) per dosage form or regimen;
- names of other ingredients known to cause problems;
- approved therapeutic uses;
- dosage form or regimen;
- side-effects and major adverse drug reactions;
- precautions contraindications and warnings;
- major interactions;
- name and address of manufacturer or distributor;
- reference to scientific literature as appropriate.

Where advertisements are permitted without claims (reminder advertisements) it is stated that "they ought to include at least the brand name, the international nonproprietary or approved generic name, the name of each active ingredient, and the name and address of the manufacturer or distributor for the purpose of receiving further information".

Not surprisingly, the survey confirms that advertisements are aimed at attracting attention to the brand name. The proportion of advertisements that also cited the generic name ranged from 75–100% within different countries involved. In many instances, however, these were displayed in smaller, thinner typeface.

Most assessors identified relatively few advertisements giving misleading information and it is acknowledged in the report that apparent intercountry differences in this regard may simply reflect different standards among individual reviewers. Of greater consequence is the finding that some 40–50% of advertisements lack clinically important information on contraindications, warnings and adverse effects. Unexpectedly, this deficiency was equally prevalent among advertisements originating from developed and developing countries. The consequences of this deficiency in countries where registered doctors regularly receive compendia of approved drug data sheets and where manufacturers are required to issue approved data sheets on all new drugs as a requirement of registration may be debatable. In countries where prescribers are less likely to have access to collateral information the consequences for patients can only be detrimental. In the last instance, it is the judgement of the practitioner that is crucial to the patient. The question must always be asked: "Do I have sufficient objective information on which to base a decision to prescribe this product?".

References


Regulatory Matters

ACE inhibitors and anaphylaxis in patients undergoing haemodialysis

**United Kingdom** — Reports have been received of patients under treatment with ACE inhibitors who, within minutes of undergoing haemodialysis involving use of high-flux polyacrylonitrile membranes, have developed an anaphylactoid reaction characterized by facial swelling, flushing, hypotension and dyspnoea. The cause of these reactions is, as yet, unclear, but all manufacturers of drugs of this class are required forthwith to incorporate relevant warnings into the officially-approved product information.


Chlorofluorocarbons: restrictions in use

**Switzerland** — The Intercantonal Office for the Control of Medicines has placed manufacturers on notice that, as from 1 January 1993, the use of chlorofluorocarbon propellants will be restricted to the following medicinal products:

- anti-asthmatic preparations containing anticholinergics, beta-adrenoreceptor agonists, corticosteroids, or cromoglicic acid and its analogues;
- nitroglycerine derivatives for relief of angina pectoris;
- new therapeutic or diagnostic agents administered by aerosol that cannot be delivered using other propellants.

Pending the introduction of this restriction the inclusion of chlorofluorocarbons in any medicinal product must be declared in the approved labelling.

**Source:** *Bulletin mensuel de l'Office Intercantonal de Contrôle des Médicaments*, August 1991.

Corticosteroids: danger of immunosuppression

**United States of America** — Because, in recent years, it has received increasing numbers of reports of severe viral infections among children taking immunosuppressant doses of corticosteroids for asthma, allergic rhinitis and juvenile arthritis, the Food and Drug Administration has directed that the warning contained in the approved labelling of these products be strengthened. It emphasizes that all patients receiving these products are at risk of developing serious or even fatal complications of chickenpox and measles and, as far as is practicable, patients and their parents are advised to avoid exposure to these diseases. When exposure is known to have occurred, prophylactic treatment with varicella zoster immune globulin or pooled intravenous immunoglobulin should be considered. If chickenpox develops, treatment with antiviral agents is advised.


Didanosine: approved for advanced HIV infection

**Canada/United States of America** — The antiviral agent, didanosine [dideoxyinosine; DDI; Videx®, Bristol Myers Squibb] has been approved on the basis of a joint review undertaken by the US Food and Drug Administration and the Health Protection Branch, Canada, to treat adults and children with advanced symptomatic HIV infection who are unresponsive to, or cannot tolerate, zidovudine. Controlled studies have shown that didanosine induces a rise in the CD4 cell count, but there are insufficient data, as yet, to indicate whether it prolongs survival or reduces the incidence of opportunistic and other infections. In the absence of specific contraindications, zidovudine consequently remains the first-line treatment for advanced HIV infection.
Didanosine should be taken between meals since the presence of food in the stomach reduces absorption by as much as 50%. About 10% of patients have developed signs of acute pancreatitis during treatment. Onset of abdominal pain, nausea or vomiting during treatment are warning signs. Treatment should be immediately suspended should these signs supervene and didanosine should then be readministered only after pancreatitis has been excluded. Patients should also be monitored for signs of peripheral sensory neuropathy. About 30% of patients enrolled in early clinical trials developed numbness, paraesthesiae or pain in the feet or hands.


**Foscarnet sodium for cytomegalovirus retinitis in advanced HIV infection**

**United States of America** — The Food and Drug Administration has approved the use of the antiviral agent, foscarnet sodium (Foscavir®, Astra) to delay the progression of cytomegalovirus retinitis in patients with advanced HIV infection. Ganciclovir was approved for this indication in 1989. However, many patients receiving zidovudine do not tolerate ganciclovir because both drugs are myelosuppressive.

Foscarnet has an antiviral effect against HIV in vitro and it is possible that, taken in combination with zidovudine, it may further increase the survival of patients with HIV infection. It is intended to be administered by controlled intravenous infusion. Serum creatinine should be monitored throughout treatment, since a degree of renal impairment occurs in most patients. Rises are usually, but not always, reversible following reduction of dosage or discontinuation of treatment. Foscarnet should be withdrawn if creatinine clearance falls below 0.4 ml/min/kg. Transient disturbances in serum calcium and other serum electrolytes may increase the risk of cardiac dysrhythmias and seizures.

A randomized controlled trial of foscarnet and ganciclovir in HIV-infected patients with cytomegalovirus retinitis was terminated prematurely in 1991 because patients treated with foscarnet were estimated to have a survival advantage of about 4-months (2). It is now claimed, however, that this benefit was evident only in patients with a predicted creatinine clearance of more than 1.2 ml/min/kg and that, for patients with lower clearance values, those receiving ganciclovir had the survival advantage (3). It has been estimated that, in the USA, the cost of a 2–3 week induction course of foscarnet is US $1694-2541 and the yearly maintenance cost US $21 900. The comparative costs for ganciclovir are quoted as US $ 4840-1260 and US $ 19 950.

References

**Metamizole sodium: restrictive rescheduling**

**Switzerland** — The Intercantonal Office for Control of Medicines has decided that, as from 1 January 1992, all pharmaceutical products containing the pyrazolone analgesic, metamizole sodium, will be subject to prescription control. This reflects the established association of these preparations with rare cases of agranulocytosis and aplastic anaemia.


**Noscapine: removed from opium alkaloid preparations**

**United Kingdom** — The Committee on Safety of Medicines announced in June 1991 that noscapine, a constituent of the opiate analgesic, papaveretum, had been shown to be genotoxic on testing in vitro. Manufacturers of products containing noscapine were asked to issue warnings that they should not be prescribed for women of child-bearing potential. To avoid this restriction, the major manufacturer of products containing papaveretum in the UK (Omnopon®; Roche) has reformulated them to exclude noscapine. These preparations now contain only three opium alkaloids: papavarine, codeine and morphine, which are retained in the same concentrations as before.


Advisory Notices

Beta adrenoreceptor agonists and asthma

United Kingdom — A working party of the Committee on Safety of Medicines has concluded that the available data do not support a causal link between use of beta adrenoreceptor agonists and death from asthma in England (1). In support of its view the group claims that:

• epidemiological studies carried out in New Zealand and Canada (2-4) fail to establish an association between treatment and death from asthma because the severity of patients' asthma cannot be dissociated satisfactorily from their requirement for increased medication; and

• recent studies interpreted as suggesting that regular administration of beta adrenoreceptor agonists may be associated with deterioration of asthma (5-9) are inconclusive and inconsistent with earlier findings (10-12).

Further clinical studies are needed, it is suggested, to assess the response to beta adrenoreceptor agonists in asthmatic patients in terms of dosage, frequency and regularity of administration, and concurrent use of inhaled anti-inflammatory drugs.

References


1% hydrocortisone products available without prescription

United States of America — After reviewing data on safety and efficacy, the Food and Drug Administration has decided to allow products intended for topical use containing up to a maximum of 1% hydrocortisone to be sold over the counter from pharmacies without a medical prescription. Previously, this exemption applied to products containing no more than 0.5% of the active ingredient.
Products sold in this way must be labelled to warn the user to consult a doctor if, after 7 days' treatment, the skin condition worsens, persists or recurs within a few days.


Nandrolone: do risks outweigh benefits?

Germany — The Advisory Panel for the Evaluation of Medicines of the Federal Health Office has advised that risks associated with the use of the anabolic steroid, nandrolone, may outweigh its therapeutic benefits. Nandrolone is a testosterone derivative, with both androgenic and progestogenic actions, that is currently approved, inter alia, for the palliative management of breast cancer, treatment of osteoporosis and chronic hepatitis, and to assist convalescence after serious illness.

The panel expresses reservation, in particular, about the risk of hepatic toxicity and it concludes that pre-existing hepatic disease should constitute an absolute contraindication for treatment. It also refers to other adverse effects associated with treatment, including virilization in women, inhibition of spermatogenesis and prostatic enlargement in men, and precocious puberty in children, and it notes with concern the use of nandrolone and other anabolic steroids to increase muscle volume and to improve athletic performance.

Essential Drugs

Sexually transmitted diseases

Despite the intensive educational campaigns currently directed to the prevention of HIV infection, and reports from some countries that changes in sexual behaviour have stabilized or even reduced the level of some sexually transmitted diseases, the dramatic rise in their incidence that has occurred globally for several decades has not as yet been decisively stemmed. Since several hundreds of millions of new cases are still treated each year, the economic and social consequences as well as the health implications are considerable. Directly or indirectly, this burden of disease is responsible for much sterility, stillbirth, miscarriage, blindness, brain damage, disfigurement, cancer and even death.

It is vital that treatment is coupled with education of all persons at risk on avoidance of contact and prevention of transmission; that provision is made for tracing, treating and counselling sexual partners; and that screening for sexually transmitted disease is included as a vital component of routine antenatal care.

For reasons that remain uncertain, widespread changes in patterns of infection are also occurring. In many countries chlamydial infections, genital herpes, and warts are now more common than gonorrhoea and syphilis. At the same time, several infections have become unreliably responsive to the more readily-available antimicrobials. Strains of Neisseria gonorrhoeae with either chromosomal or plasmid mediated resistance to penicillin — and latterly to tetracycline — are now widespread. Multiresistant strains of Haemophilus ducreyi are emerging and resistance to metronidazole has been reported in Trichomonas vaginalis.

Other causative agents remain sensitive to most antimicrobial agents, but the treatment of all sexually transmitted diseases becomes more complicated in patients who are infected with the HIV virus or who are otherwise immunocompromised. Where facilities allow, all patients with suspected sexually transmitted disease should be evaluated for HIV, syphilis, gonorrhoea and chlamydia. When there is doubt whether oral treatment arranged on an outpatient basis will be taken reliably, and particularly when sustained effective antimicrobial plasma concentrations are crucial to success, administration of drugs is best supervised by a health professional.

For these reasons, effective treatment is increasingly dependent upon access both to microbiological services and to expensive third-generation cephalosporins and fluoroquinolones. Wherever it is feasible, a laboratory service should be provided for screening and confirmatory testing. As a minimum, this should be equipped to perform light microscopy on wet mounts and Gram's stained slides, darkfield microscopy for Treponema pallidum and, when possible, detection of HIV antibodies.

The reality is that the existence of these facilities remains the exception rather than the rule. Most patients with sexually transmitted diseases are still treated according to prevailing local practices and on the basis of clinical signs alone. However, effective control and containment of the emergence of resistance will never be accomplished without rigorous laboratory control. Consideration of the epidemiology of these diseases over the past 50 years leaves no doubt that investment in the necessary facilities is highly cost-effective. For this reason, emphasis is placed in the following sections upon the importance of microbiological confirmation of the diagnosis and of the antibiotic sensitivity of the causative pathogen, even though this is presently unattainable in many clinical settings.

Gonorrhoea

Gonorrhoea, which results from infection with the Gram-negative bacterium, Neisseria gonorrhoeae, now poses a considerable public health problem. The widespread emergence of strains resistant to penicillin, tetracycline and doxycycline has created a demand for expensive antibiotic therapy which strains health budgets everywhere and which remains unrealized in less developed countries.

Primary infection resulting from sexual contact may involve the mucosal surfaces of the urethra, the cervix, the rectum, the oropharynx or the conjunctivae. Gonococcal conjunctivitis and vulvovaginitis also occur in the newborn, as a result of contact...
with endocervical infection in the mother during delivery.

The inflammatory response to urogenital infection is varied. In men, signs of rapidly progressive purulent urethritis typically occur within a few days. When treatment is inadequate or delayed, acute prostatitis, periurethral abscess and urethral stricture are likely to develop. In women, the initial endocervical infection may be either symptomless or marked by mild vaginal discharge. A substantial number of patients who are not treated early develop inflammatory disease of the pelvis which may result in chronic abdominal pain, menstrual disturbance, infertility or ectopic pregnancy.

Gonococcal conjunctivitis must be treated as a medical emergency. Whereas the inflammatory response can be mild in adults, it is always severe in infants in whom it progresses rapidly to corneal ulceration, perforation and blindness.

Haematogenous dissemination can occur if gonorrhoeal infections are not effectively treated at an early stage. Metastatic complications are varied. Typical and serious lesions include meningitis, endocarditis, and acute destructive monoarthritis with synovial effusion.

Confirming the diagnosis
In men, urethral discharge is the commonest presenting symptom of sexually transmitted disease. Gonococcal and chlamydial infections frequently coexist. Much less commonly, Ureaplasma urealyticum, Trichomonas vaginalis, and Candida albicans are involved in single or mixed infections. Focal intraurethral lesions, including herpes genitalis, warts, or a syphilitic chancre, are also sometimes responsible.

In women, gonorrhoea is a cause of infective vaginal discharge. Examination should be undertaken to exclude a focal lesion and endocervical and vaginal specimens should be examined microbiologically to establish or exclude candidosis, trichomoniiasis and Gardnerella vaginalis infection.

Gonorrhoea can be confirmed in 90% of cases by demonstration of Gram-negative intracellular diplococci on a freshly-prepared slide. Ideally, cultures should be prepared when microscopy is negative. Chlamydia trachomatis cannot be demonstrated by direct microscopy and few clinics have appropriate culture facilities.

Blood samples should be taken for serology in all cases to exclude concurrent infection with syphilis.

Treatment
Since Chlamydia trachomatis — which is now the most prevalent cause of sexually transmitted urethritis — commonly co-exists with gonococcal infection, all patients with gonorrhoea should also be treated concurrently for chlamydial infection unless microbiological facilities exist to exclude it. All pregnant women should be screened for gonorrhoea both during their first antenatal visit and again — if they are considered to be at high risk — during the third trimester.

Antimicrobial therapy can be selected with confidence only when information is maintained on both the in vitro susceptibility of locally-prevalent strains of gonococci and the clinical efficacy of treatment. Specimens should be obtained routinely for culture 4 to 7 days after treatment to detect persistent infections. Resistance, when it is encountered, is of two types:

Chromosomal resistance rapidly rendered sulfonamides obsolete as antigonorrhoeal agents. Strains have latterly emerged that are highly resistant — either singly or multiply — to penicillins, tetracyclines, spectinomycin, erythromycin, thiampenicol and cefalosporins. Cross resistance between penicillin and second and third-generation cefalosporins has seriously compromised the value of cefoxitin and cefuroxime in the treatment of gonorrhoea in many areas. Reduced in vitro susceptibility of some strains to cefotaxime, ceftixone and newer quinolones has been reported more recently, but not as yet to an extent that impairs their clinical efficacy.

Plasmid mediated resistance has been recognized more recently and it spreads more rapidly. It has long compromised the value of penicillins and, more recently, of tetracyclines as antigonorrhoeal agents. Several different penicillinase plasmids have now been identified that code for the same TEM-1 beta lactamase, and at least one of these also confers some resistance against non beta-lactam antibiotics. In some areas strains carrying one of these plasmids have also been found to carry chromosomal resistance. Other strains exhibiting high levels of plasmid mediated resistance to tetracycline were first identified in North America in 1985. They have since been found in northern Europe and Africa but, otherwise, their prevalence remains uncertain. WHO is establishing a network of regional coordinating surveillance centres to collate geographically-specific information on the susceptibility of
gonococci to reference antimicrobials and to promote the standardization of testing methods. The participation of laboratories in both developed and developing countries is encouraged.*

**Uncomplicated genital and anal infections**

Unless there are firm grounds for expecting the infection to be responsive to one of the less expensive antimicrobials, patients should receive a single intramuscular dose of either ceftriaxone, 250 mg, or spectinomycin, 2.0 g. A single oral dose of ciprofloxacin, 500 mg, is comparably effective, but it should not be administered during pregnancy.

In some countries, locally acquired strains of gonococci are also susceptible either to a single intramuscular dose of kanamycin, 2.0 g; or to an oral course of thiamphenicol, 2.5 g daily for 2 days; or trimethoprim (80 mg)/sulfamethoxazole (400 mg), 10 tablets once daily for three days.

In the few areas where gonococci remain fully sensitive, a single dose of an appropriate penicillin taken together with probenecid, 1 g, is effective. Either amoxicillin, 3.0 g, or pivampicillin, 1.4 g, may be given orally; or procaine benzylpenicillin, 4.8 million units may be injected intramuscularly.

**Pharyngeal infection**

Some of the regimens effective in genital gonor­rhoea are unreliable in pharyngeal infections. Those most widely advocated are: a single intramuscular injection of ceftriaxone, 250 mg; or trimethoprim (80 mg)/sulfamethoxazole (400 mg), 10 tablets once daily for 5 days.

**Disseminated infection**

Relatively high and extended parenteral dosage is necessary. For gonococcal arthritis and most other foci of infection, a 7-day course of either ceftriaxone, 1.0 g, given intramuscularly or intravenously; or spectinomycin, 2.0 g twice daily given intramuscularly is usually effective. When strains are known to be fully sensitive to penicillins, benzylpenicillin, 10 million units daily should be given intravenously for 3 days followed by amoxicillin, 500 mg orally for 4 days. When there is evidence of meningeal or endocardial involvement, treatment should be extended to 2 weeks and 4 weeks respectively.

**Gonococcal ophthalmia and conjunctivitis**

Since these conditions threaten sight and are rapidly progressive, adult patients should be admitted to hospital immediately and closely monitored until the infection has resolved. Antimicrobial therapy should be administered without delay and the eyes should be frequently irrigated with saline solution. A single intramuscular dose of either ceftriaxone, 250 mg, or spectinomycin, 2.0 g, is usually effective. When these are not available a single dose of intramuscular kanamycin, 2.0 g, may be substituted, or trimethoprim (80 mg)/sulfamethoxazole (400 mg) may be given orally in a single daily dose of 10 tablets for 3 days.

All infants born to mothers with gonococcal infection should immediately receive a single intramuscular dose of ceftriaxone, 50 mg/kg (to a maximum of 125 mg). If this is not available, kanamycin 25 mg/kg (to a maximum of 75 mg) may be substituted. Infants with signs of conjunctivitis should be isolated immediately and a rigorous system of barrier nursing instituted. Tetracycline ointment, 1%, should additionally be instilled into each eye hourly on the first day and 8-hourly for the next 10 days.

Where facilities for routine screening of pregnant women for gonococcal infection are not available, all infants should receive topical antigonoccal therapy immediately after birth. Tetracycline ointment 1% should be applied after gently cleaning the eyelids. Erythromycin ointment 1% is similarly effective, but more expensive. Silver nitrate eye drops 1% are more toxic.

**Chlamydial infections**

**Lymphogranuloma venereum**

Lymphogranuloma venereum, which is highly prevalent in many tropical countries, was first associated with chlamydiae, a genus of obligate intracellular parasites, in the 1930s. The serotypes involved, L_1, L_2, and L_3, are distinct from those associated with other sexually transmitted chlamydial infections.

Infection results, after a latent period of days or months, in acute, fluctuant inguinal lymphadenopathy. Left untreated, the inflammatory masses, or
buboes, extend into neighbouring tissues and frequently ulcerate to form chronic sinuses and fistulae. Although the disease is seen in its acute phases more frequently in men, the late sequelae are often more severe in women.

Treatment
The disease is usually responsive, in the acute stage, to an oral course of an appropriate antimicrobial, although treatment may need to be extended beyond 14 days. Tetracycline, 500 mg 4 times daily, or doxycycline, 100 mg twice daily, are both effective. When tetracyclines are inappropriate, they may be substituted either by erythromycin, 500 mg 4 times daily, or by a sulfonamide, such as sulfadiazine, 1 gm 4 times daily.

Fluctuant lymph nodes should be aspirated through healthy skin. Incision and drainage or excision of acutely inflamed nodes is contraindicated since it delays healing, but strictures, fistulae and other late sequelae may require surgical intervention.

Other chlamydial infections
Over the past thirty years other serotypes of chlamydiae (D-K) have become highly prevalent everywhere and they are now the most common sexually transmitted pathogens in industrialized countries. They are currently implicated in over half of all cases of nongonococcal urethritis in men. Infection may also result in epididymitis and, in active homosexuals, in chronic proctitis. In women, infection is more often asymptomatic or nonspecific in character, and it is associated more frequently with cervicitis, salpingitis and endometritis than with dysuria and pyuria. Reiter's syndrome, which is characterized by conjunctivitis, arthritis and urethritis, has also been associated with chlamydial infection.

Infection during pregnancy is associated with prematurity, low birth weight, neonatal death and postpartum endometritis. More than half the surviving infants born to women with cervical involvement develop purulent conjunctivitis (or chlamydial ophthalmia); others develop pneumonia; rarely, the vagina, pharynx and rectum may also be infected.

Urethritis, which is confirmed by demonstrating the presence of polymorphonuclear leukocytes in the discharge, is caused by several pathogens other than *C. trachomatis*. The most highly prevalent are *N. gonorrhoeae* and *Ureaplasma urealyticum*. Less commonly, *Candida albicans* and *Herpes simplex* are implicated. However, in one-third of cases seen in centres with fully equipped microbiological facilities no pathogen can be detected. Unless other causes of urethritis can be excluded with confidence by microscopy and culture, patients with presumed chlamydial infections and their recent sexual partners should also be treated concurrently for gonorrhoea.

Treatment
Chlamydial infections involving the urethra, the endocervix, the eye and the rectum usually respond to a 7-day oral course of tetracycline, 500 mg four times daily, or doxycycline, 100 mg twice daily. During pregnancy and in other situations in which tetracyclines are contraindicated, erythromycin, 500 mg four times daily for 7 days, or a sulfonamide in the event of intolerance, should be substituted.

Antimicrobial resistance to recommended regimens has not been reported, but patients should be advised to return for consultation if symptoms persist. Recurrence may result from failure to treat sexual partners or from non-compliance. When symptoms persist or recur after apparently adequate treatment, both patient and partners should be referred for laboratory investigation. Cultures for chlamydia should be taken 6 weeks after completion of treatment.

Where facilities exist, all pregnant women should be screened for chlamydial infection using direct immunofluorescence and rapid-culture techniques, initially during the first antenatal visit and again — for patients considered to be at high risk — during the third trimester. Pregnant women with gonorrhoea should be assumed also to have chlamydial infection and, in every instance, sexual partners should be treated simultaneously. Erythromycin at the above dosages is suitable for use during pregnancy. Tetracyclines are contraindicated because they are potentially toxic both for the fetus and for the mother.

Before neonatal conjunctivitis is treated as a chlamydial infection, gonorrhoea should be excluded microscopically. Erythromycin syrup is usually effective at a dosage of 50 mg/kg administered daily in 4 divided doses for 2 weeks. This regimen can be repeated should inclusion conjunctivitis recur on withdrawal of treatment. Topical therapy is not required. Infantile pneumonia requires more extended antimicrobial therapy.

Vaginitis
Vaginal discharge that occurs only premenstrually or at the time of ovulation, or that is associated with
the use of oral contraceptives or an intrauterine device, is likely to be physiological. Common pathological causes of diffuse vaginitis are candidiasis, chlamydiiasis, trichomoniasis and *Gardnerella vaginalis* infections. Discharge is also associated both with focal infective lesions including syphilitic chancre, herpes and warts, and with non-infective conditions including cervical ectopion, polyps and neoplasms.

Diagnosis is confirmed microbiologically. Because candidosis, trichomoniasis and gonorrhoea may occur concurrently, tests for all three infections should be performed, particularly in high-risk patients. *Candida albicans* can usually be identified as Gram-positive spores and mycelia in smears taken from the vaginal wall. *Trichomonas vaginalis* is most reliably detected by dark-ground microscopy in a wet preparation of an isolate from the posterior fornix. *Neisseria gonorrhoeae* can sometimes be demonstrated as Gram-negative intracellular cocci in isolates taken from the mucous membranes of the endocervix and the urethra but, because many infections are missed on microscopy, cultures should also be prepared. Facilities for isolating *Chlamydia trachomatis* are available only in the most highly equipped laboratories. *Gardnerella vaginalis* can often be seen on light microscopy attached to vaginal epithelial cells. The discharge may have a fish-like odour which is heightened by adding 5-10% potassium hydroxide to a few drops on a glass slide.

**Candidosis**

Most infections are cured by nystatin pessaries, 100 000 units. Two inserted nightly for two weeks are usually effective, but in some areas doses as high as 1 000 000 units nightly are required. More rapid cures can be obtained with more expensive imidazole preparations such as clotrimazole or miconazole, 200 mg daily intravaginally for three days. Vulval irritation may be relieved by local nystatin or clotrimazole cream. A relapse shortly after initial therapy should be treated with a longer course of an imidazole: for example, clotrimazole 100 mg daily for 12 days.

If infection is recurrent, other possible predisposing factors including use of oral contraceptives and tight or insulating clothing should be discussed with the patient.

**Trichomoniasis**

Metronidazole, 2.0 g in a single oral dose, cures the large majority of infections. The cure rate increases to more than 90% when sexual partners, who are usually asymptomatic, are treated simultaneously. Coincident bacterial vaginitis attenuates the effectiveness of the treatment. Patients who do not respond satisfactorily to single doses should receive metronidazole, 800 mg at 12-hour intervals for 5 days. This should also clear any local bacterial infection.

Because metronidazole has been demonstrated to be teratogenic in animals at massive dosage, trichomoniasis is best managed by local therapy during pregnancy and lactation. Pessaries of clotrimazole will at least attenuate symptoms.

Infants with symptomatic trichomoniasis or with asymptomatic infection persisting after the fourth month should receive metronidazole, 5mg/kg orally, three times daily for 3 days.

**Gardnerella infections**

Oral metronidazole, 400 mg twice daily for 5 days is highly effective, but reinfection can occur if partners are not evaluated and treated as appropriate.

**Pelvic inflammatory disease**

Acute pelvic inflammatory disease, primarily involving the endometrium and fallopian tubes, is often a consequence of sexually transmitted disease. The pathological agents most commonly involved are *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. Colonization of the latter is favoured by the use of oral contraceptive preparations. However, bacteria present in the normal vaginal flora, including *Streptococcus* species, *Escherichia coli*, *Haemophilus influenzae* and anaerobes such as *Bacteroides* spp, *Peptostreptococcus* and *Peptococcus*, are also frequently implicated. It is possible that the ascent of these organisms into the endometrial cavity is facilitated by trauma to the endocervical canal from an intrauterine device.

The condition is a frequent cause of pain, dyspareunia, vaginal discharge, dysuria, fever, and sometimes of nausea and vomiting. Untreated, the chronic inflammatory reaction may result in long-term sequelae, including persistent abdominal discomfort, sterility, tubal pregnancy and menstrual disturbances. The diagnosis should be considered in all sexually active women complaining of lower abdominal pain, and — because it can also be asymptomatic — in all women with sexually transmitted disease.

Ideally, all patients in whom the diagnosis is established should be admitted to hospital. Where
this is not feasible, priority should be given to those with severe disease that is unresponsive to ambulatory treatment, adolescents, pregnant women, patients with a suspected pelvic abscess, and those who have signs suggestive of appendicitis or ectopic pregnancy.

**Treatment**

If an intrauterine device is in place it should be removed.

Since mixed infections are common and precise microbiological diagnosis is rarely feasible, a treatment regimen should be chosen that is active against each of the commonly implicated organisms. The objective is to relieve symptoms and, in particular, to arrest progressive tubal damage.

Ambulatory patients have been successfully treated with single dose therapy for uncomplicated gonorrhoea, followed by a ten-day oral course of doxycycline or tetracycline for chlamydial infection taken concurrently with metronidazole, 500 mg three times daily, for anaerobic infections. However, evidence of potential carcinogenicity and teratogenicity has aroused reservations about the routine use of metronidazole for a commonly occurring condition in young women.

Regimens based on cefoxitin (active against *N. gonorrhoeae*, *Enterobacteriaceae* and anaerobes) and doxycycline (active against *C. trachomatis*) are now widely used, while a combination of clindamycin (active against anaerobes and Gram-positive aerobic organisms) and gentamicin (active against Gram-negative aerobic organisms including *N. gonorrhoeae*) is sometimes favoured for treatment of pelvic abscess. Other regimens based on penicillins in combination with beta-lactam inhibitors, quinolones, monolactams and carba-penems are still being evaluated.

Severely ill, hospitalized patients should receive intravenous antimicrobial therapy — either cefoxitin, 2 g four times daily, plus doxycycline 100 mg twice daily; or gentamicin, 1.5 mg/kg 8-hourly together with clindamycin, 900 mg three times daily — for a minimum of 4 days and for at least 48 hours after clinical improvement, followed by oral doxycycline or tetracycline for 10 days.

**Syphilis**

After many years of decline resulting from the success of penicillin therapy, syphilis, which is caused by the spirochaetal organism, *Treponema pallidum*, is again increasing in incidence in many industrialized countries. In less developed countries, where the disease has remained relatively common, the primary illness frequently remains untreated and the late sequelae of the disease are still encountered.

Transmission results almost exclusively from direct contact with infected lesions or, during pregnancy, from congenital infection of the fetus. The primary genital ulcers (or chancre) — which are typically solitary, “punched out”, indurated, painless lesions with a clear exudate — appear between 9 to 90 days after exposure and heal spontaneously within a few weeks. Although the chancre has distinctive morphological characteristics, it should be differentiated microbiologically from other causes of ulceration including herpes genitalis, chancroid, and Behçet’s disease.

Untreated, and within a period of 6 months, the disease enters the secondary phase which is characterized by a transient pleomorphic skin rash and generalized low-grade lymphadenopathy, accompanied occasionally by focal involvement of the eye, the meninges, parotid glands or viscera. Similar episodes, which never persist for more than a few weeks, may recur within the first three years. Infectivity subsides after this time, although women who remain untreated almost invariably infect their progeny for 10 years or more after initial infection.

Infection of the central nervous system may occur in any patient with untreated syphilis of more than two years’ duration. From 5 to 50 years may elapse after the disease becomes quiescent before the tertiary manifestations — benign late syphilis and cardiovascular syphilis — become evident.

Fetal infection may occur at any time throughout pregnancy, and infectivity approaches 100% when the mother has untreated primary or secondary disease. Clinical evidence of infection is often not present at birth and it may readily be missed until the lesions of late syphilis begin to appear during childhood. However, preventive measures adopted in more affluent countries have been highly successful with the result that congenital syphilis has been virtually eliminated where pregnant women are screened routinely for the disease.

**Confirming the diagnosis**

Clinical suspicion of syphilis can be difficult to confirm. During the primary and secondary phases of the disease repeated searches should be made
for spirochaetes in exudates from lesions using
dark-ground microscopy. Serological tests do not
become positive for at least two weeks after the
appearance of the primary lesion. Two of these
tests are specific for treponemal diseases: the
absorbed fluorescent treponemal antibody test and
the treponema pallidum haemaggglutination test.
The first usually becomes positive late in the
primary stage, while the second often takes
somewhat longer to develop. Subsequently, both
tests often remain positive for life even when
prompt, effective treatment is given. For this
reason, quantitative but less specific tests, the
Venereal Disease Research Laboratory Test
(VDRL) and the rapid plasma reagin test (RPR), are
widely used to assess the stage and activity of the
disease. These are flocculation tests that depend
upon the presence and titre of a less specific
antibody (reagin) in the serum.

All pregnant women should be screened for
syphilis, using a non-treponemal test, both during
their first antenatal visit and again — if they are
considered to be at high risk — at least in the third
trimester. Pregnant patients who are positive on
serological testing should be examined clinically for
evidence of infection. If no abnormal signs are
detected two further separate blood specimens
should be submitted for serology within 4 weeks. If
the disease cannot then be excluded with reason­
able certainty the patient should receive
antisyphilitic treatment. If it is certain that a
seropositive patient has been treated adequately in
the past, retreatment is unnecessary unless the
VDRL titre rises 4-fold or more on sequential
testing, or recent sexual contacts are indicative of
recurrence. Following treatment, the VDRL titre
should be estimated at monthly intervals up to the
time of delivery in order to detect reinfection or
relapse.

The risk of congenital syphilis is remote if the
mother has been treated with penicillin during
pregnancy. Passive transfer of antibodies from a
previously infected mother can invalidate postnatal
serological diagnosis of active disease in the child
for as long as 12 weeks. None the less, any
seropositive infant of a seropositive mother should
be treated promptly. It is no longer considered
justifiable to wait for three months to obtain
serological confirmation of the diagnosis. An
infected infant of a mother infected late in preg­
nancy may be both asymptomatic and seronegative
at birth. Such infants should also be treated
immediately, particularly when it is impossible to
monitor their clinical and serological status reliably,
or when it is uncertain whether the mother has
received adequate treatment with penicillin.

Abnormalities in the cerebrospinal fluid may
develop in any patient with syphilis. They occur in
the early stages with sufficient frequency for some
clinicians to require a sample to be examined
routinely one year after treatment before discharg­
ing the patient as cured. This examination is also
vital in the investigation of suspected neurosyphilis.
The disease should be excluded in any patient who
presents with cranial nerve lesions, or optic or
auditory symptoms of uncertain cause. Negative
serological tests virtually exclude neurosyphilis, but
positive tests require careful interpretation. Be­
cause they are persistent, they may provide
evidence of previous as well as current infection.

Radiological assessment, as well as serological
testing, is important in the diagnosis and subse­
quent management of cardiovascular syphilis.

**Treatment**

All patients and their contacts should be additionally
tested and treated, as appropriate, for chlamydial
infection, gonorrhoea and human immunodeficiency
virus.

**Early syphilis**

In cases of not more than 2 years’ duration, two
alternative regimens are widely used: either a
single intramuscular injection of benzathine
benzylpenicillin, 2.4 million units (given, because of
the large volume, as two injections at separate
sites); or a 10-day intramuscular course of procaine
benzylpenicillin, 1.2 million units daily.

However, some authorities recommend that all
patients with either secondary or latent syphilis
should receive more prolonged treatment: either
intramuscular benzathine benzylpenicillin, 2.4
million units once weekly for 3 consecutive weeks;
or intramuscular procaine benzylpenicillin, 1.2
million units daily for 2 weeks.

**Late syphilis (other than neurosyphilis)**

Prolonged courses of penicillin should be adminis­
tered to all patients with benign late syphilis,
cardiovascular syphilis, and latent syphilis that is
likely to be of more than 2 years’ duration. This may
be given either as a 3-week intramuscular course of
procaine benzylpenicillin, 1.2 million units daily, or
as 3 consecutive weekly intramuscular injections of
benzathine benzylpenicillin, each of 2.4 million
units.
Neurosyphilis
Higher dosages are necessary in patients with neurosyphilis to ensure that penicillin levels in the cerebrospinal fluid do not fall below the minimum inhibitory concentration throughout the period of treatment. This is most reliably achieved by administering benzylpenicillin, 4 million units, intravenously every 4 hours for 2 weeks. Alternatively, provided that compliance is assured, single daily intramuscular injections of procaine benzylpenicillin, 1.2 million units, can be given for 2 weeks in combination with oral probenecid, 500 mg 4 times daily.

Syphilis in pregnancy
Syphilis should be treated immediately at all stages of pregnancy in accordance with the foregoing regimens. Treated patients should remain under close supervision throughout pregnancy to ensure that any reinfection is promptly diagnosed and treated.

Congenital syphilis
In children aged up to 2 years, congenital syphilis usually responds well to adequate doses of penicillin, although recovery may be slow in seriously ill patients with extensive involvement of the skin, mucous membranes, bone and viscera. Pneumonia and other intercurrent infections can rapidly supervene, particularly when there are signs of malnutrition.

When the cerebrospinal fluid is abnormal the infant should receive a 10-day course either of benzylpenicillin, 50 000 units/kg daily in 2 divided doses intravenously, or in one daily dose intra-muscularly. When the cerebrospinal fluid is normal, opinion is divided as to whether a 10-day course is required, or whether reliance can be placed in a single intramuscular injection of benzathine benzylpenicillin, 50 000 units/kg.

In children older than 2 years, higher and sustained blood concentrations of penicillin are required. Benzylpenicillin should be given for 2 weeks in a dose of at least 200 000 to 300 000 units/kg daily, rising on a weight adjusted basis to 1.2 million units/kg daily.

Patients allergic to penicillin
Non-pregnant adult patients with early syphilis who are allergic to penicillin should receive a 2-week oral course of either tetracycline, 500 mg four times daily; or doxycycline, 100 mg twice daily. For patients with late syphilis this regimen should be extended for at least one additional week.

Pregnant patients with early syphilis and confirmed allergy to penicillin are seriously disadvantaged because they cannot be given tetracyclines. It is consequently important to assess and, when appropriate, to confirm by skin testing any unsupported report of allergy in such a patient. An attempt at desensitization should be considered. Various alternative treatments have been proposed, but formal proof of efficacy is lacking. These include oral erythromycin, 500 mg, which is sometimes administered 4 times daily for 3 weeks or, alternatively, in women with no history of anaphylaxis, an extended course of a third-generation cefalosporin.

Children with congenital syphilis and confirmed allergy to penicillins should receive erythromycin 7.5 to 12.5 mg/kg daily in 4 divided doses for a period of 30 days. During the first month of life the risk of allergy can safely be discounted.

Post-treatment follow-up
Patients with early syphilis who have been treated with adequate doses of penicillins should be evaluated clinically and serologically after 3 months, 6 months and 12 months to assess the effect of treatment and to detect possible reinfection. Patients treated with other antibiotics should be evaluated more frequently. Nontreponemal tests may remain positive at low titres indefinitely even after adequate treatment.

Patients with cardiovascular syphilis or neurosyphilis should remain under observation for at least 3 years. In addition to clinical and serological evaluations, examination of cerebrospinal fluid and assessment of radiological changes may also be necessary. Retreatment should be considered when:

• clinical signs or symptoms of active syphilis persist or recur;
• a high titre nontreponemal test, such as a VDRL of 1:8, persists for 1 year or, in a pregnant woman, for 3 months;
• a lower titre nontreponemal test increases by 4-fold or more.

The cerebrospinal fluid should be examined before treatment, unless there are conclusive grounds for establishing a diagnosis of early syphilis due to reinfection. In all other circumstances patients should be assumed to have late syphilis and be treated accordingly.
Genital herpes simplex

Genital herpes, which can be caused by the ubiquitous herpes simplex virus, but more frequently by a variant (HSV-2), increased considerably in prevalence among young adults throughout the 1980s, particularly in North America. The disease is painful, recurrent and without cure.

Primary infection is usually signalled within a week by an extremely painful vesicular eruption, on the external genitalia or other foci of sexual contact which subsequently ulcerates and resolves with crusting. This resolves spontaneously and completely within 3 weeks, but the virus remains latent within the involved sensory nerve ganglia. Recurrences, which are usually milder and shorter than the primary attack, are often preceded by local tingling and paraesthesiae. Typically, they occur 3 or 4 times each year and they are liable to recur indefinitely. The incidence of the disease and the frequency and severity of the attacks is greater in patients who are immunodeficient, most commonly as a result of HIV infection.

In the longer term, HSV-2 infection in women may increase the risk of cervical carcinoma. Although the association remains contested, annual cytological examinations are recommended.

The evidence for placental transmission of infection is inconclusive. If it occurs it is likely to result in fetal death and spontaneous abortion. Neonatal infection can occur if the mother’s infection is active at the time of delivery. The risk is low and is greatest during the primary infection. The disease can remain focal in the skin, the eyes, and the oral cavity, but in its disseminated form it can be fatal within a few weeks and cause permanent brain damage in survivors. When active genital lesions are present the possibility of delivery by Caesarian section should be considered. Genital cultures taken late in pregnancy are poor predictors of shedding during delivery.

Confirming the diagnosis

Definitive diagnosis is dependent upon culture and identification of the herpes virus but, in practice, this is often not possible. Treatment is then determined solely on medical history and clinical examination. Syphilis and other causes of genital ulceration should be excluded beforehand.

Treatment

Patients should be warned that they are infectious to their partner when the lesions are present and that they should abstain from sexual activity as soon as they become aware of prodromal symptoms.

Topical treatment has little palliative effect, but pain may be partially relieved by simple analgesics. Bathing the lesions with saline is soothing and may facilitate micturition when this is painful. Urinary retention resulting from uncontrollable pain can necessitate hospital admission.

Although no radical cure is possible, the antiviral agent, aciclovir, inhibits replication of the virus to an extent that markedly reduces viral shedding. Treatment is extremely costly, but systemic therapy, when started early, may inhibit the formation of new lesions and also significantly accelerate healing, particularly during the first attack.

Primary attacks are usually treated with a 7-day oral course of aciclovir, 200 mg five times daily. In subsequent attacks, 5 day courses of treatment may suffice. Severe attacks in immunocompromised patients, which are characterized by widespread mucocutaneous involvement, should be treated in hospital with intravenous aciclovir, 5 mg/kg, every 8 hours until the lesions resolve, and for not less than 5 days.

Continuous suppressive therapy with aciclovir, 200 mg 3 times daily, has been claimed to markedly decrease the rate of recurrences among patients experiencing more than six episodes yearly. At present, there is no indication that this regimen gives rise either to cumulative toxicity or to the development of resistance.

Secondary infections should be treated with an appropriate antibiotic. Trimethoprim/sulfamethoxazole has the advantage, in some situations, that it has no antitreponemal activity and, consequently, does not mask syphilis.

Infants born to women with active genital ulcers or positive herpes virus cultures should be isolated and examined frequently for signs of infection. When possible, cultures for herpes virus should be taken at 24 and 48 hours after birth. In some centres all infants born to a mother with a primary infection are presumptively treated with intravenous aciclovir at the above dosage without awaiting confirmation of infection.
Chancroid

Chancroid, which results from infection by *Haemophilus ducreyi*, is the most common cause of genital ulceration in developing countries and it has been associated with increased rates of HIV infection. It is seen most frequently in men — typically on the prepuce, following a short incubation period of 1–8 days, and it is characterized by extremely painful, soft, destructive lesions, with undermined ragged edges and enlarged inguinal lymph nodes. Clinically, and in the absence of laboratory confirmation, the disease is readily confused with syphilis and genital herpes.

Secondary fusospirochaetal infection of advanced untreated lesions can result in destructive ulceration of the entire external genital region, with stenotic lesions, sinus formation and, in women, rectovaginal fistula.

Treatment

Fluctuant lymph nodes may need to be aspirated through intact skin when the patient is first seen. Effective antimicrobial therapy usually results in rapid healing of the ulcerative lesion and resolution of lymph node enlargement within 14 days, but a high degree of resistance to therapy has been reported in patients with HIV infection.

A single intramuscular dose of ceftriaxone, 250 mg, is highly effective, as is erythromycin given orally at a dose of 500 mg three times daily for 7 days. A single oral dose of ciprofloxacin, 500 mg, has been claimed to be useful in the presence of HIV infection, but the results of confirmatory studies are still awaited. Benzylpenicillin should always be administered at the same time when facilities for darkfield examination and serological diagnosis of syphilis are not available. Resistance of *H. ducreyi* to sulfonamides, tetracylines and penicillins now renders these compounds largely ineffective. None the less, in some countries trimethoprim (80 mg)/sulfamethoxazole (400 mg), 2 tablets twice daily. Intramuscular streptomycin, which is also effective, is no longer recommended because of its ototoxicity and the need to reserve it for the treatment of tuberculosis.

Unresponsive infections have been treated successfully with a variety of regimens. Those most widely used are oral tetracycline, 500 mg four times daily for 2 weeks; chloramphenicol, 500 mg orally four times daily for 3 weeks; or gentamicin 1 mg/kg intramuscularly 3 times daily for 3 weeks.

The treatment of pregnant patients poses difficulties because of the potential toxicity of these antibiotics. Erythromycin alone has proved disappointing. Better results are claimed when it is administered in combination with lincomycin (each at an oral dose of 500 mg four times daily for 2 weeks), but this is associated with a risk of pseudomembranous colitis.

Granuloma inguinale

Granuloma inguinale is a chronic granulomatous infection, usually involving the genitalia and perineum, that is caused by a Gram-negative encapsulated bacterium, *Calymmatobacterium granulomatis* (formerly referred to as *Donovania granulomatis*) that occurs almost exclusively in tropical and subtropical regions. It is believed to be sexually transmitted, but it is not highly contagious.

The primary lesion, which appears after an incubation period ranging from 9–90 days, starts as a papule and slowly develops into a painless, indurated granulomatous ulcer. Lymph nodes become enlarged only when secondary infection supervenes. Secondary fusospirochaetosis results in large, painful and foul-smelling destructive lesions. Untreated, the lesion may involve the whole of the external genitalia, the inguinal region and the anus. Healing then results in intense scarring and stenotic lesions that require surgery. Cancerous change can occur in long-standing lesions.

Treatment

Most infections are cured by a 2-week course of trimethoprim (80 mg)/sulfamethoxazole (400 mg), 2 tablets twice daily. Intramuscular streptomycin, which is also effective, is no longer recommended because of its ototoxicity and the need to reserve it for the treatment of tuberculosis.

Unresponsive infections have been treated successfully with a variety of regimens. Those most widely used are oral tetracycline, 500 mg four times daily for 2 weeks; chloramphenicol, 500 mg orally four times daily for 3 weeks; or gentamicin 1 mg/kg intramuscularly 3 times daily for 3 weeks.

The treatment of pregnant patients poses difficulties because of the potential toxicity of these antibiotics. Erythromycin alone has proved disappointing. Better results are claimed when it is administered in combination with lincomycin (each at an oral dose of 500 mg four times daily for 2 weeks), but this is associated with a risk of pseudomembranous colitis.

Genital warts

Genital warts are caused by a papillomavirus which cannot be cultured. They are nearly always transmitted by sexual contact and are usually asymptomatic. They occur most commonly on the external genitalia, but the perineum, anus, oral cavity and rectum — and in women, the vagina and cervix — may also be involved. They are diagnosed solely on their clinical features and need to be distinguished, in particular, from condylomata lata of secondary syphilis and molluscum contagiosum.

Many patients have other sexually transmitted diseases. They should be examined to exclude gonorrhoea and non-gonococcal urethritis and also, in women, vaginal infection due to chlamydiae, candida, trichomonas or *Gardnerella vaginalis*. 
Serological tests for syphilis should also be undertaken. Women should also be examined by colposcopy for cervical warts. Because of uncertainty regarding risk of malignant change, they should be encouraged to undergo annual cytology testing.

Treatment
Local caustic applications are most frequently used, but treatment failures are frequent. Podophyllum resin, 10–25% in compound tincture of benzoin, should be applied carefully and sparingly to the lesions at weekly intervals, avoiding normal tissue. Where it is available, podophyllotoxin is a less toxic alternative which can be applied by the patient. Trichloroacetic acid applied directly to the wart is less effective and the treated area should be powdered with talc or sodium bicarbonate to remove excess acid. Podophyllum resin applied to vaginal mucosa or to meatal warts should be allowed to dry before it comes into apposition with normal epithelium. External applications should be removed by washing after 1–4 hours. Podophyllin is readily absorbed, locally destructive and teratogenic. Neither podophyllotoxin or podophyllum resin should be applied to large skin surfaces, nor should they be used during pregnancy or lactation.

Surgical removal, electrocautery, cryosurgery and laser treatment may be used when topical applications have failed or when they are contraindicated.

Electrosurgical removal under urethroscopy is preferred for urethral warts, which should be suspected when meatal warts are recurrent. Intraurethral instillation of 5% fluorouracil cream may be effective, but the technique remains to be fully evaluated.

**ACICLOVIR**

*tablet* 200 mg

*powder for injection* 250 mg in vial

Aciclovir, a synthetic pyrimidine analogue derived from guanine is an antiviral agent. It acts against herpes viruses by interfering with DNA synthesis and inhibiting viral replication. Absorption from the gastrointestinal tract is variable and incomplete. It is widely distributed in tissues and body fluids and is excreted in the urine primarily unchanged.

**Uses**
Treatment of primary genital herpes simplex.

**Dosage and administration**

*Adults with normal immune status:* 200 mg five times daily orally for 7 days.

*Immunocompromised patients:* 5 mg/kg every 8 hours for at least 5 days.

**Contraindications**

Aciclovir should not be used in uncomplicated herpes simplex infections in other sites in immunocompetent persons. Known hypersensitivity.

**Precautions**

Aciclovir should be administered by slow infusion over a period of one hour to avoid acute impairment of renal function. Adequate hydration should be maintained.

**Use in pregnancy**

Experimental animal studies have demonstrated mutagenic effects. Aciclovir should not be used during pregnancy.

**Adverse effects**

Headache, nausea and vomiting are the most frequent adverse effects following oral administration. Transient renal impairment may occur during intravenous therapy, possibly as a result of crystallization in the renal tubules. This usually responds rapidly to dosage reduction or withdrawal of the drug. Haemodialysis is necessary in extreme cases of acute renal failure.

**Overdosage**

Since aciclovir is incompletely absorbed from the gastrointestinal tract, oral overdosage is unlikely to have serious effects.

**Storage**

Tablets should be stored in tightly-closed containers below 25 °C. Aciclovir for injection should be stored between 2 and 8 °C.
BENZYL PENICILLIN
powder for injection, 600 mg (= 1 million IU),
3 g (= 5 million IU) (as sodium or potassium
salt) in 5 ml-vial

BENZATHINE BENZYL PENICILLIN
powder for injection, 1.44 g benzylpenicillin (= 2.4 million IU) in 5-ml vial

PROCaine BENZYL PENICILLIN
powder for injection 1 g (= 1 million IU),
3 g (= 3 million IU)

Benzylpenicillin is a beta-lactam derivative of *Penicillium*. It is bactericidal against *Streptococci*, *Neisseriae*, many anaerobes and spirochaetes. It must be administered parenterally because it is degraded in the gastric juice. After intramuscular injection, peak plasma concentrations are reached within 15–30 minutes. It is widely distributed throughout the body, has a plasma half-life of 30 minutes and is excreted mainly in the urine.

Repository formulations of benzylpenicillin are available for parenteral use. They are designed to provide a tissue depot from which the drug is slowly absorbed over a period of 12 hours to several days. Procaine benzylpenicillin produces a peak plasma concentration within 1–3 hours. It is excreted over a period of several days while benzathine benzylpenicillin is detectable in the urine for several weeks.

**Uses**
Primary, secondary and latent syphilis of less than one year’s duration should be treated with either procaine or benzathine benzylpenicillin.
Latent syphilis, neurosyphilis or cardiovascular syphilis require intensive intravenous therapy with benzylpenicillin.

Early congenital syphilis may be treated with either benzylpenicillin or procaine benzylpenicillin but children aged two years or more require intravenous benzylpenicillin.

Value in the treatment of gonorrhoea is limited to the few remaining areas where gonococci remain fully sensitive to penicillins.

**Dosage and Administration**
Benzylpenicillin and its repository formulations must be administered parenterally.

The powder for injection should be diluted in water for injection in accordance with the manufacturer’s directions.

**Primary, secondary and latent syphilis:**
Benzathine benzylpenicillin 2.4 million IU i.m. in a single session, or
Procaine benzylpenicillin 1.2 million IU daily i.m. for 10 consecutive days.

**Latent syphilis, neurosyphilis or cardiovascular syphilis:**
Benzylpenicillin 12–24 million IU i.m. in divided doses for 14 days.

**Early congenital syphilis:**
Benzylpenicillin 50 000 IU/kg i.m. or i.v. in two divided doses for 10 days or
Procaine benzylpenicillin 50 000 IU/kg i.m. daily for 10 days.

**Congenital syphilis of two or more years’ duration:**
Benzylpenicillin 20 000 IU/kg i.m. daily in divided doses for 14 days.

**Gonorrhoea in areas where gonococci remain fully sensitive:**
Procaine benzylpenicillin 4.8 million IU i.m. as a single dose.

**Contraindications**
Known hypersensitivity to penicillins or cephalosporins.

**Precautions**
Facilities should be available for treating anaphylaxis whenever penicillins are used.
Patients should be questioned carefully about previous allergic reactions.
If skin rash develops during treatment, the patient should be transferred to a different class of antibiotic.

Rapid intravenous administration of large doses of benzylpenicillin may cause hyperkalaemia, dysrhythmias and cardiac arrest, particularly in patients with impaired renal function.

**Use in pregnancy**
There is no evidence of teratogenicity with benzylpenicillin or its repository formulations. They can be used during pregnancy.

Desensitization should be attempted of pregnant women with syphilis who are allergic to penicillins.

**Adverse reactions**
Hypersensitivity reactions range in severity from skin rashes to immediate anaphylaxis.
Pain and sterile inflammation can occur at the site of intramuscular injection and phlebitis or thrombophlebitis sometimes occurs after intravenous administration.

Accidental injection into a peripheral nerve causes pain and dysfunction. Unduly high concentrations of benzylpenicillin in the central nervous system can result in confusion, convulsions, coma and fatal encephalopathy.

Interstitial nephritis has been reported and neutropenia and thrombocytopenia have occurred.

**Overdosage**
Overdosage can cause convulsions, paralysis and even death.

Emesis and gastric lavage may be of value if instituted within a few hours of injection. Excessive blood concentrations can be lowered by haemodialysis.

**Storage**
Powder for injection should be stored at temperatures between 2 and 8 °C.

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**CEFTRIAXONE**

* powder for injection 250 mg

Ceftriaxone is a third-generation cefalosporin derived from *Cephalosporium acremonium*. It is highly active against Gram-negative cocci and Gram-negative bacilli. Like benzylpenicillin, it has a beta-lactam ring.

After intramuscular administration, ceftriaxone is distributed widely throughout the body. It has a relatively long plasma half-life of about eight hours and is excreted as unchanged drug both in the urine and bile.

**Uses**
Treatment of penicillin-resistant gonococcal infections.
Treatment of chancroid caused by beta-lactam-resistant *Haemophilus ducreyi*.
Treatment of pelvic inflammatory disease together with tetracycline.

**Dosage and administration**
Ceftriaxone must be administered parenterally.

*Uncomplicated congenital and pharyngeal gonococcal infection:*
250 mg i.m. as a single dose

*Disseminated gonococcal infection:*
1 g daily i.m. or i.v. for 7 days.

*Neonatal gonococcal ophthalmia:*
50 mg/kg i.m. as a single dose.

*Chancroid:*
250 mg i.m. as a single dose.

*Pelvic inflammatory disease:*
250 mg i.m. as a single dose, followed by doxycycline 100 mg twice daily for 10 days.

**Contraindications**
Known hypersensitivity to other beta-lactam antibiotics.

**Precautions**
Blood concentrations of liver enzymes may rise transiently.

**Use in pregnancy**
There is no evidence that ceftriaxone is teratogenic. It may be used during pregnancy.

**Adverse effects**
Hypersensitivity reactions are the most common adverse effects. Skin rashes are relatively frequent, while urticaria, bronchospasm and anaphylaxis are uncommon. Nausea, vomiting and diarrhoea have been reported. Rarely, antibiotic-associated pseudomembranous colitis due to *Clostridium difficile* occurs. When this is suspected, treatment should be immediately discontinued.

Reversible cholestatic jaundice has been reported.

**Storage**
Powder for injection should be stored in tightly closed containers, protected from light.

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**CIPROFLOXACIN**

*tablet 250 mg (as hydrochloride)*

Ciprofloxacin is a synthetic quinolone which acts as a specific inhibitor of bacterial DNA gyrase. It has a broad spectrum of antibacterial efficacy against both Gram-negative and Gram-positive aerobic organisms. Reports of chromosome resistance have been reported but as yet are of little clinical significance.

It is rapidly absorbed from the gastrointestinal tract; it has a plasma half-life of 3–5 hours and is excreted in the urine mainly as unchanged drug.
Uses
Treatment of penicillin-resistant gonorrhoea.
Treatment of chancroid in patients with HIV.

Dosage and administration
Uncomplicated anal and genital gonorrhoea and chancroid infections: 500 mg in a single dose.

Contraindications
Hypersensitivity to any quinolone.
Pregnancy, adolescents and children since arthropathy has been induced in weight-bearing joints of young animals.

Precautions
Reduced dosage should be considered in patients with hepatic or renal impairment.
Ciprofloxacin should be administered cautiously to patients with epilepsy since seizures may be precipitated.
Adequate fluid intake must be assured since crystalluria may occur.

Adverse effects
Ciprofloxacin is generally well tolerated. The most frequently reported adverse effects are nausea, diarrhoea, vomiting, dyspepsia, abdominal pain, headache, restlessness, rash, dizziness and pruritus.

Drug interactions
Plasma concentrations of theophylline may be raised.
Prolonged bleeding time has been reported in patients receiving anticoagulants concurrently.

Overdosage
Gastric lavage is of value if performed promptly. Electrolyte balance must be maintained. Serum concentrations of ciprofloxacin may be lowered by dialysis.

Storage
Tablets should be stored in well-closed containers.

ERYTHROMYCIN
enteric coated tablets 250 mg (as stearate or ethylsuccinate)
oral suspension 125 mg (as stearate or ethylsuccinate)/5 ml

Erythromycin is a macrolide antibiotic produced by Streptomyces erythreus. It has selective bacteriostatic activity against both streptococci and staphylococci and some Gram-positive bacilli.

Because it is inactivated by gastric juices, oral formulations are enteric-coated. It diffuses rapidly into all tissues except the brain and cerebrospinal fluid, and readily crosses the placental barrier. The plasma half-life is approximately 90 minutes. It is partially demethylated in the liver and excreted largely via the bile and faeces.

Uses
• Chlamydia trachomatis infections in patients unable to take tetracycline.
• Confirmed ophthalmia neonatorum.
• Lymphogranuloma venereum as an alternative to tetracycline.
• Syphilis in penicillin-allergic pregnant patients.

Dosage
Chlamydia: 500 mg orally four times daily for 7 days.
Ophthalmia neonatorum: 50 mg/kg of oral suspension daily for 14 days.
Lymphogranuloma venereum: 500 mg four times daily for 14 days.
Syphilis: 500 mg orally four times daily for 30 days.

The effectiveness of erythromycin in syphilis is doubtful and it must be used only as a drug of last resort.

Contraindications
Known hypersensitivity to erythromycin.

Precautions
Hepatic function should be monitored in patients with a previous history of liver disease.

Adverse effects
Nausea, vomiting and diarrhoea can occur. Cholestatic hepatitis, which may present with symptoms suggestive of acute cholecystitis, occasionally complicates prolonged courses of treatment. Symptoms resolve rapidly when the drug is withdrawn. Anaphylaxis and other hypersensitivity reactions are rare.

Drug interactions
Erythromycin, chloramphenicol, and clindamycin which have a similar bacteriostatic action tend to be mutually antagonistic when administered together. Erythromycin decreases the rate of metabolism of carbamazepine and warfarin in the liver to a degree that can warrant readjustment of dosage.
OVERDOSAGE

Symptoms of overdosage include severe nausea, vomiting, diarrhoea and hearing loss. Induction of emesis or gastric lavage may be of value if undertaken within a few hours of ingestion.

STORAGE

Tablets and suspension should be stored in tightly-closed containers.

METRONIDAZOLE

**tablet 200 mg, 250 mg, 400 mg, 500 mg**

**suspension 200 mg/5 ml**

A 5-nitroimidazole derivative with anti-microbial activity against anaerobic bacteria and some protozoa, including *Trichomonas vaginalis*. Metronidazole is almost completely absorbed following oral administration. Its plasma half-life is about 8 hours and it is excreted, largely in the urine, both unchanged and as metabolites.

**Uses**

Treatment of confirmed trichomoniasis. Trichomoniasis in neonates persisting for more than 4 weeks. Treatment of vaginitis due to *Gardnerella vaginalis*.

**Dosage and administration**

Metronidazole should be administered preferably with or immediately after meals.

**Trichomoniasis:**

Adults: 2 g in a single oral dose, or 200 to 250 mg three times daily for 7 days. 
*Infants more than 4 weeks old:* 20 mg/kg daily for 5 days in divided doses.

**Gardnerella infections:**

Adults: 400 mg twice daily for 5 days.

**Contraindications**

- Known hypersensitivity.
- Early pregnancy.
- Chronic alcohol dependence.

**Precautions**

Patients should be warned not to take alcohol during treatment since disulfiram-like reactions can occur.

**Use in pregnancy and lactation**

Metronidazole should not be used to treat trichomoniasis during early pregnancy. For symptomatic relief, clotrimazole 100 mg may be given as a vaginal suppository daily for 7 days. Breastfeeding should be interrupted until 24 hours after cessation of treatment since metronidazole is excreted in milk.

**Adverse effects**

In general, metronidazole is well tolerated, but mild symptoms of headache, gastrointestinal irritation and a persistent metallic taste are common. Less frequently, drowsiness, rashes and darkening of urine occur.

More serious reactions are rare and usually occur only during extended courses of treatment. They include stomatitis and candidiasis, reversible leukopenia, and sensory peripheral neuropathy, which is usually mild and rapidly reversible. Ataxia and epileptiform seizures have been reported among patients receiving dosages considerably higher than those currently recommended.

**Drug interactions**

The action of oral anticoagulants is potentiated. Alcohol may induce abdominal pain, vomiting, flushing and headache. Phenobarbital and corticosteroids lower plasma levels of metronidazole whereas cimetidine raises them.

**Overdosage**

No specific treatment exists. Emesis or gastric lavage may be of value within a few hours of ingestion.

**Storage**

Tablets and suspension should be kept in well-closed containers, protected from light.

MICONAZOLE

**cream, 2% (nitrate)**

A synthetic imidazole antifungal agent active against both dermatophytes and yeasts, and Gram-positive cocci (*Staphylococcus* and *Streptococcus* spp).

**Uses**

A specially formulated cream is used for treatment of vaginal candidosis.

**Dosage**

**Vaginal candidosis:** 10 ml cream should be inserted high into the vagina on 7 consecutive nights.
**PODOPHYLLUM RESIN**  
*solution 10%*

Podophyllum resin is a powdered mixture of resins extracted from the roots of *Podophyllum peltatum*. A solution is prepared by forming a paste with benzoin in alcohol. It is a caustic keratolytic agent for topical application.

**Uses**

Topical treatment of genital warts (condylomata acuminata).

**Dosage and administration**

A 10% solution should be applied to the affected area. Care must be taken to avoid contact with normal tissue. The solution should be thoroughly rinsed off after 1–4 hours.

Therapy may be repeated once or twice weekly for no more than a total of four applications.

The active ingredient podophyllotoxin is available in some countries. It is less corrosive and may be applied without medical supervision.

**Contraindications**

Podophyllum resin should not be applied to large areas of skin, nor should it be used in the treatment of cervical, urethral, anorectal or oral warts.

**Use in pregnancy**

Treatment is contraindicated during pregnancy since podophyllum resin is both teratogenic and fetotoxic.

**Precautions**

Preparations of podophyllum resin should be used only under close medical supervision because of potentially serious local and systemic toxicity that can result from prolonged or excessive applications. Systemic absorption is enhanced when applications are made to friable, bleeding warts.

**Adverse effects**

Systemic effects resulting from excessive cutaneous absorption include nausea, vomiting, abdominal pain and diarrhoea.

Transient leukopenia and thrombocytopenia sometimes provide evidence of bone-marrow depression.

Gross over-application can result in serious neurotoxicity. The signs, which are characteristically delayed in onset are slow to resolve. They include visual and auditory hallucinations, delusions, disorientation, confusion and delirium.
Storage
Topical solution should be kept in tightly closed containers, protected from light and excessive heat. The shelf-life of the resin is variable and some formulations may begin to degrade within a few days.

SPECTINOMYCIN
powder for injection 2 g (as hydrochloride) in vial

Spectinomycin is produced from Streptomyces spectabilis. It is most effective against Neisseria gonorrhoeae in which it selectively inhibits protein synthesis.

It is rapidly absorbed after intramuscular injection and peak plasma concentrations occur after one hour. It is not significantly bound to plasma proteins and is excreted unchanged in the urine.

Uses
Uncomplicated anogenital and disseminated gonorrhoea.
Gonococcal ophthalmia.

Dosage and administration
Uncomplicated anogenital infections: 2 g i.m. as a single dose.
Disseminated gonococcal infections: 2 g i.m. twice daily for 7 days.
Gonococcal ophthalmia: 2 g i.m. as a single dose.

Contraindications
Known hypersensitivity.

Precautions
In patients with renal impairment spectinomycin should be used only when alternative therapies are inappropriate.

Use in pregnancy
Safety in pregnancy has not been established. It should be used in pregnant women only if the need outweighs any possible risk to the fetus.

Adverse reactions
Hypersensitivity reactions occur rarely. Pain at injection site, nausea, fever, dizziness and urticaria have been reported.

Storage
Powder for injection should be stored in vials.

SULFAMETHOXAZOLE/TRIMETHOPRIM

The two components of this combination product have a similar antimicrobial spectrum. They operate synergistically because they independently inhibit different steps in the enzymic synthesis of tetrahydrofolic acid, an essential metabolic process in susceptible organisms.

Trimethoprim is absorbed more rapidly and is more widely distributed in tissues than sulfamethoxazole. Both compounds enter the cerebrospinal fluid; they are extensively bound to plasma proteins, and each is excreted largely unchanged in the urine at a rate that gives a plasma half-life of about 10 hours.

Uses
Treatment of chancroid and gonorrhoea in those areas where strains remain sensitive.
Treatment of granuloma inguinale.

Dosage and administration
Chancroid: sulfamethoxazole 400 mg + trimethoprim 80 mg twice times daily for 7 days.
Gonorrhoea: sulfamethoxazole 4000 mg + trimethoprim 800 mg as a single dose for 3 days.
Granuloma inguinale: sulfamethoxazole 800 mg + trimethoprim 160 mg twice daily for 14 days.

Contraindications
Known hypersensitivity.
Severe hepatic or renal dysfunction.

Precautions
Treatment should be suspended immediately should a rash, or any other manifestation of sulfonamide hypersensitivity occur. The risk of sulfonamide crystalluria is decreased by maintaining a urinary output of at least 1.5 litres daily. Whenever possible, plasma sulfonamide concentrations should be determined periodically. Peak plasma concentrations should be maintained at about 40 micrograms/ml.

Patients must be advised to seek medical advice should they develop a sore throat or fever during treatment. This advice can be of greater value than routine monitoring of the white cell count.
Elderly patients may be more susceptible to severe adverse reactions, especially blood dyscrasias. Treatment should not be unnecessarily prolonged. Supplementary calcium folinate may prevent megaloblastic anaemia.

Use in pregnancy
Because the disease is life-threatening, treatment should in no circumstance be delayed.

Adverse effects
Nausea, vomiting, glossitis and skin rashes are common.
Trimethoprim may induce a megaloblastic anaemia responsive to folic acid.
Sulfonamide-induced hypersensitivity reactions can be severe. They include life-threatening cutaneous reactions such as erythema multiforme (Stevens–Johnson syndrome) and toxic epidermal necrolysis.
Other reactions include granulocytopenia, agranulocytosis, aplastic anaemia, thrombocytopenic purpura and toxic hepatitis. Occasionally, haemolysis may occur in individuals deficient in glucose-6-phosphate dehydrogenase.

Drug interactions
Maintenance requirements for sulfonylureas and coumarin anticoagulants are often reduced as a result of their displacement from plasma proteins by sulfamethoxazole.
Concomitant use of other inhibitors of folate metabolism (such as pyrimethamine, methotrexate and certain anticonvulsants) increases the risk of megaloblastic anaemia.

Overdosage
Symptoms of acute overdosage include vomiting, dizziness and confusion followed by visual disturbances, petechiae, purpura and jaundice.
Crystalluria, haematuria and anuria may also occur. Emesis or gastric lavage may be of value within a few hours of ingestion. Provided urinary output is satisfactory, a high fluid intake should be maintained. Haemodialysis may be of value in eliminating some of the drug. Otherwise, treatment is symptomatic and supportive.

Storage
Tablets should be stored, protected from light, in well-closed containers.

TETRACYCLINE
capsule or tablet, 250 mg (hydrochloride)
eye ointment 1% (hydrochloride)
Tetracycline is a broad-spectrum antibiotic derived from a species of *Streptomyces* that induces bacteriostasis by inhibiting protein synthesis. It is selectively concentrated in susceptible organisms. Absorption from the alkaline contents of the intestine is slow. Peak plasma concentrations occur within 4 hours and decay with a half-life of about 8 hours. Excretion is effected primarily by filtration into the urine. An enterohepatic circulation results in high concentrations accumulating in the liver and bile. Bacteriostatic concentrations are maintained for up to 6 hours after topical administration.

Tetracycline crosses the placenta and is excreted into breast milk.

Uses
Treatment of *Chlamydia trachomatis* infections; lymphogranuloma venereum; syphilis in penicillin-allergic non-pregnant patients; and granuloma inguinale.
Prevention and treatment of conjunctivitis of the newborn due to *N. gonorrhoeae* and *C. trachomatis*.

Dosage
*Chlamydia trachomatis*: 500 mg orally four times daily for 7 days.

*Lymphogranuloma venereum and granuloma inguinale*: 500 mg orally four times daily for 14 days.

*Syphilis*: 500 mg orally four times daily for 15 days. In neurosyphilis and late syphilis, treatment should be continued for a further 15 days.

Prevention of *ophthalmia neonatorum*: A single application of the ointment should be sufficient.

Treatment of *ophthalmia neonatorum*: Ointment should be applied to the conjunctiva 4 times daily for 14 days together with systemic therapy. The treatment may be reduced to 4 days if there is no evidence of conjunctivitis.

Contraindications
Known hypersensitivity.
Severe renal impairment.
Precautions
Troublesome oesophagitis may be averted if the patient is propped up while swallowing capsules, which should be washed down immediately with a glass of water.

Time-expired tetracycline capsules or tablets should be discarded. Degraded tetracycline has been reported to induce renal dysfunction indistinguishable from the Fanconi syndrome and skin lesions similar to those of systemic lupus erythematosus.

Use in pregnancy and early childhood
Tetracycline is generally contraindicated in pregnancy and during early childhood because impaired calcification can result in abnormal osteogenesis, permanent staining of teeth and also, on occasion, hypoplasia of dental enamel.

Adverse effects
Phototoxic reactions occasionally result in porphyria-like skin changes and pigmentation of the nails.

Hypersensitivity reactions are rare. Morbilliform rashes, urticaria, fixed drug eruptions, exfoliative dermatitis, cheilosis, glossitis, pruritus and vaginitis are described. Angioedema, anaphylaxis and pseudotumor cerebri have been reported.

Storage
Tetracycline capsules or tablets should be kept in well-closed containers, protected from light.

DOXYCYCLINE
capsules, 100 mg (as hycylate)

Doxycline is derived from and closely related to oxytetracycline, and shares an identical spectrum of antibiotic activity. It differs from the tetracyclines in that it is more extensively absorbed and more lipid-soluble, and it possesses a longer serum half-life that is independent of the patient's renal status.

Uses
Treatment of Chlamydia trachomatis infections; lymphogranuloma venereum; syphilis in penicillin-allergic non-pregnant patients; granuloma inguinale; pelvic inflammatory disease (together with a third-generation cefalosporin).

Dosage
Chlamydia trachomatis: 100 mg orally twice daily for 7 days.

Lymphogranuloma venereum and granuloma inguinale: 100 mg orally twice daily for 14 days.

Syphilis: 100 mg orally twice daily for 15 days. In neurosyphilis and late syphilis, treatment should be continued for a further 15 days.

Pelvic inflammatory disease: 100 mg twice daily for 10–14 days.

Contraindications
Known hypersensitivity.

[Precautions, use in pregnancy, adverse effects]
Recent publications

Biological standards: international standards and reference reagents

This book provides a catalogue of tabulated information on the availability and specifications of international biological standards and international biological reference reagents. The categories of substances listed include allergens, antibiotics, antibodies, antigens, blood products and related substances, cytokines and endocrinological substances.

International biological standards are intended to be used in laboratory assays to calibrate national or working standards. They provide a means of ensuring uniformity throughout the world in the designation of the potency, activity and specificity of biological substances used in medicine, when these cannot be expressed directly in terms of physical or chemical properties. International biological reference reagents are established to provide materials of high specificity for the identification of biological substances used in the diagnosis of disease, and particularly for identifying microorganisms and their products.

Each substance listed is characterized in terms of its biological activity, expressed as the total number of international units per ampoule; a weight definition of the unit, where necessary; the form in which the substance is provided; the year in which it was established; pertinent references; and the address of the laboratory from which it is available.


WHO Expert Committee on Biological Standardization

The most recent report of this long-standing expert advisory committee demonstrates the rapid pace of innovation in the preparation and development of biological substances that, before the introduction of recombinant DNA techniques, could not be manufactured in commercial quantities.

Since the potency and specificity of each new highly active substance needs to be assured, the challenge to assure their quality, and particularly the interchangeability of equivalent products, is immediate and demanding. This is reflected in several of the topics covered in this report, which include guidelines for the quality assurance of pharmaceutical and biological products made using recombinant DNA technology, and discussions of the need to standardize and improve the reliability of assays for residual DNA; the need for further evaluation of certain substances before an acceptable international standard can be established; and the specific need to establish international reference materials for growth factors and cytokines.

These annual reports also provide the vehicle to establish international requirements to be observed in the manufacture and licensing of potent biological products in order to assure their potency and safety. In this report full and detailed requirements are provided for Haemophilus type b conjugate vaccines and inactivated influenza vaccine.

International Nonproprietary Names for Pharmaceutical Substances

Notice is hereby given that, in accordance with paragraph 7 of the Procedure for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances*, the following names are selected as Recommended International Nonproprietary Names. The inclusion of a name in the lists of Recommended International Nonproprietary Names does not imply any recommendation of the use of the substance in medicine or pharmacy.

Recommended International Nonproprietary Names (Rec. INN): List 31 (Continued)

Lists of proposed (1–58) and recommended (1–27) international nonproprietary names can be found in Cumulative List No. 7, 1988.


Amendments to previous lists


Recommended International Nonproprietary Names (Rec. INN): List 28

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<tr>
<th>p. 3</th>
<th>delete</th>
<th>insert</th>
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<tbody>
<tr>
<td>levdropropizinum</td>
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<tr>
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<th>pemedolacum</th>
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<tbody>
<tr>
<td>pemedolac</td>
<td>(±)-cis-4-benzyl-1-ethyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid</td>
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Recommended International Nonproprietary Names (Rec. INN): List 29

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<th>p. 1</th>
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<tr>
<td>acemannan</td>
<td>Acemannan is a highly acetylated, polydispersed, linear mannan obtained from the mucilage of Aloe barbadensis, Miller (aloe vera).</td>
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<th>beraprostum</th>
<th>replace the chemical name by the following:</th>
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<tr>
<td>beraprost</td>
<td>(±)-(1R,2R,3aS,8bS)-2,3,3a,8b-tetrahydro-2-hydroxy-1-[()E]-(3S,4RS)-3-hydroxy-4-methyl-1-octen-6-ynyl]-1H-cyclopenta[(d)]benzofuran-5-butyric acid</td>
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</tr>
</tbody>
</table>

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Recommended International Nonproprietary Names (Rec. INN): List 30

p. 6  fosquidonum
      fosquidone

replace the chemical name by the following:
benzyl (±)-5,8,13,14-tetrahydro-14-methyl-8,13-dioxobenz[5,6]isoindolo-
[2,1-b]isoquinolin-9-yl hydrogen phosphate

p. 8  moxidectinum
      moxidectin

replace the chemical name by the following:
(6R,25S)-5-O-demethyl-28-deoxy-25-[(E)-1,3-dimethyl-1-butenyl]-6,28-epoxy-
23-oxomilbemycin B 23-(E)-(O-methyloxime)
This book presents and explains the standardized format of a proposed single international summary report to be used by drug manufacturers for the periodic updating of safety data on approved pharmaceutical products. Proposals reflect the consensus reached, following two years of meetings and debate, by a CIOMS Working Group representing 12 pharmaceutical companies and 10 regulatory agencies. The aim of these meetings was to give manufacturing companies a uniform set of procedures for reporting safety information to regulatory bodies. Apart from improving inter-regulatory communications, these uniform procedures should facilitate the work of doctors and scientists responsible for monitoring drug safety in industry.

The proposals, which cover both the scope and content of a periodic drug-safety update, are presented in the form of a nine-point outline of the core information which should be included in any periodic report. Key points agreed on include the frequency of review and reporting, the need for cumulative information on the drug's licensed status for marketing, and the circumstances under which detailed utilization data should be supplied. Other sections of the book explain how the Working Group reached consensus and describe several issues that will need to be resolved in the future. The book concludes with a 21-page example of a periodic safety update for a fictitious drug product.
This book provides model prescribing information for some 33 essential drugs used for the prevention and treatment of protozoal and helminthic infections, including filarial infections, the leishmaniasis, malaria, schistosomiasis and the trypanosomiasis. The book is the product of a consultative process involving internationally accredited experts, WHO's Expert Advisory Panel on Drug Evaluation, selected members of the various WHO expert advisory panels on parasitic diseases, and several non-governmental organizations in official relations with WHO.

The book is organized according to diseases, moving from amoebiasis and giardiasis to intestinal, liver, and lung flukes. Each disease or group of diseases is first introduced with concise information about its causes, mode of transmission, clinical features, and geographical prevalence, followed by general advice on prevention and treatment. Prescribing information is then provided for first-choice and alternative therapeutic and prophylactic drugs. Information includes uses, dosage and administration, contraindications and precautions, use in pregnancy, adverse effects, drug interactions, and advice on storage. Some rarer parasitic diseases, such as Babesia divergens infections and meningocerebralitis due to Acanthamoeba spp, which do not respond to chemotherapy, are nonetheless presented and discussed in order to help prescribers avoid ineffective medications.

"... a great deal of work clearly went into the production of this attractively produced paperback book ... elegant and easy to use ... a mine of admirably concise and accurately compiled data ... will be of enormous value to the health departments of developing countries..."

— Transactions of the Royal Society of Tropical Medicine and Hygiene

"... contains a mine of crystallized data which should prove invaluable to the health departments of developing countries ... The overall project seems to have been well thought out, and can be highly commended..."

— Tropical Diseases Bulletin

"... very valuable ... required reading for all medical practitioners using drugs against parasitic diseases ... candidates taking postgraduate examinations would be well advised to have this information at their fingertips..."

— West Indian Medical Journal
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<tr>
<th>Publication</th>
<th>Price* (Sw. fr.)</th>
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<tr>
<td>The use of essential drugs</td>
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<tr>
<td>Fourth report of the WHO Expert Committee</td>
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<tr>
<td>WHO Technical Report Series, No. 796</td>
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<td>1990 (57 pages)</td>
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<td>WHO model prescribing information: drugs used in anaesthesia</td>
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<tr>
<td>1989 (53 pages)</td>
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<tr>
<td>WHO model prescribing information: drugs used in parasitic diseases</td>
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<tr>
<td>1990 (128 pages)</td>
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<tr>
<td>WHO model prescribing information: drugs used in mycobacterial diseases</td>
<td>9.−</td>
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<tr>
<td>1991 (40 pages)</td>
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<td>Guidelines for developing national drug policies</td>
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<tr>
<td>The International Pharmacopoeia, third edition</td>
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<tr>
<td>Volume 3: quality specifications. 1988 (407 pages)</td>
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<tr>
<td>Basic tests for pharmaceutical substances</td>
<td>14.−</td>
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<td>Basic tests for pharmaceutical dosage forms</td>
<td>24.−</td>
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<td>1991 (v + 129 pages)</td>
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<tr>
<td>International Nonproprietary Names (INN) for pharmaceutical substances, cumulative list no. 7</td>
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<tr>
<td>1988 (xviii + 617 pages)</td>
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Further information on these and other World Health Organization publications can be obtained from Distribution and Sales, World Health Organization, 1211 Geneva 27, Switzerland

*prices in developing countries are 70% of those listed here.