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Management of Low-cost Drugs and Equipment

Carine Werder

THE DRUG MANAGEMENT CYCLE

This section will describe the key steps for ensuring that drugs, medical devices and other products that are needed to deliver reproductive health services are available. The drug management cycle in general is divided into the following steps:

- Selection
- Quantification
- Procurement
- Storage
- Distribution
- Consumption monitoring.

Selection

The choice of drugs to be available in a health facility will depend on the level of the health facility and the type of care to be provided. In many countries an essential drugs list and standard treatment guidelines have been established, listing the necessary drugs for each health service level and the appropriate treatment for common diseases. Not all drugs in this textbook may be listed or available in all countries. For many conditions several treatment options may be available and a choice may need to be made between these options.

In order to be able to provide the required care, additional medical devices, laboratory materials and equipment will be necessary. For example, drugs purchased as powder for injections may not be packed already together with water for injection or other required diluent nor contain the syringes.

Generic drugs

A question often discussed is if originator products or brand products are more efficacious and safer than generic drugs. The answer is that there is no difference in terms of efficacy and safety between originator products and generic products, if it is a generic product of good quality. The difference is that generic drugs are usually much cheaper than the originator product.

Generic drugs may be developed when the patent protecting the originator product or innovator product has expired. Generic drugs contain the same active pharmaceutical ingredient, in general, in the same dosage as the original product. The manufacturer has to demonstrate that it is equally efficient and safe as the originator product by showing that the pharmacokinetic profile is the same, i.e. that the absorption into the body and concentration in the blood are the same. This is also called bioequivalence.

Quantification

The second step in the supply chain is to establish the quantities needed over a given period of time. There are several methods for forecasting needs. Most commonly used methods are service delivery data, consumption data or morbidity data. The following information is needed to calculate the needs over a given period:

1. Number of cases for a condition expected to be treated in a given period of time: this may be established from past service delivery statistics (number of cases treated in the health facility over a given time period) or from morbidity data or expected incidence of cases.
2. Amount of drugs needed to treat one case: refer to the treatment guidelines and dosing instructions.

Total need = Number of cases × amount of drugs

If a service has been existing for some time, you may also be able to use past data of consumption of drugs, medical devices and laboratory items. It is advisable to add some amount of buffer stock in order to avoid stock-outs, for example if the next order arrives too late or if the number of cases is higher than expected. The size of the buffer stock depends on the situation but in general should be sufficient to last for the time it takes to get new stocks.

For example: you expect 1000 cases every month, one treatment X requires 20 tablets and you want to purchase drugs for 6 months. In general when you place an order, you will get the drugs after 2 months.

Number of tabs needed = 1000 cases/month × 6 months × 20 tablets/case = 120,000 tablets
Buffer stock = 1000 cases/month × 2 months × 20 tablets/case = 40,000 tablets

Therefore the total quantity needed to order would be the number of tablets needed for treatment in 6 months plus the buffer stock – 160,000 tablets.

Procurement and distribution

Procurement and distribution will depend on the specific situation. In the public sector, the government will usually take care of procurement at central level and distribute to the health facilities. In the private sector procurement may need to be managed by the health facility. One of the challenges in procurement is to ensure that the drugs and other products will be of quality and avoid purchasing of spurious items and counterfeits. Therefore, drugs should always be bought from licensed pharmacies or wholesalers.

Storage

Drugs and other pharmaceutical products including diagnostic tests and laboratory reagents as well as medical devices are susceptible to deterioration if exposed to unsuitable storage conditions such as too high temperatures and humidity. Most drugs need to be kept at temperatures below 25–30°C to maintain their efficacy and safety during their entire shelf-life. Some drugs may also be sensitive to low temperatures. Manufacturers perform specific stability studies to determine the storage conditions and the shelf-life of the product. If storage conditions are not adequate, the quality of the products is not guaranteed. Effects of bad storage include, for example, decreased level of active ingredients and therefore lower efficacy. Note that in most cases the deterioration of the product is not visible to the eye.

Therefore, a cool and dry storage place should be assured. It is advised to install thermometers and control the temperature regularly. If there is no possibility of achieving the required storage temperature, then store drugs only for short periods of time in order to limit the negative effects.

Some drugs and laboratory reagents require storage between 2 and 8°C. This is called cold chain. There are special refrigerators for storage of drugs. Household refrigerators are not as exact in maintaining the temperature range and should only be used as an alternative if a special refrigerator is not available. The appropriate working of the refrigerator must be closely monitored. A thermometer should be placed in the refrigerator and temperature recorded regularly, at least twice per day.

Consumption monitoring

For the quantification, assumptions have been made in regard to the number of patients expected over a certain time, which inherently may not always be accurate. Keeping close records on the actual consumption and comparing it with the estimated consumption, will allow early detection of a risk of a stock-outs, but also over-stocks. Comparing the consumption with the actual figures of patients who have been treated for a condition will allow you to monitor appropriate prescribing.

PRESCRIBING AND PATIENT MONITORING

Good prescribing practice

Once the diagnosis is established, the most appropriate therapy will be chosen, which may include prescription of drugs. Some points to consider before prescribing any drugs are:

- A careful drug history is important in order to identify the best possible therapeutic option. The patient should be asked about all drugs: prescription drugs, drugs purchased over the counter or traditional medicines. Ask specifically about certain drugs, for example oral contracep-

tives. The drug history will help to answer some key questions:

- Does the patient currently take any other drugs? This is important in order to identify drugs that may interact with the drugs to be prescribed?
- Did the patient experience adverse drug reactions or allergies with drugs before?
- Does the patient have underlying conditions, for example a renal or a hepatic disease or insufficiency? Pre-existing diseases need to be identified because they may be a contraindication for a drug or may require special attention when prescribing the drug.
- Do the drugs that you want to prescribe require specific monitoring? If yes, is it possible to do this in your health facility?

Important underlying diseases or conditions to consider when prescribing drugs:

- *Hepatic diseases*: This is important as the majority of drugs are eliminated through metabolic pathways in the liver. Whether the disease has an effect on the elimination of drugs will depend on the extent of liver damage. Check for clinical signs of serious liver disease like jaundice, ascites and encephalopathy.
- *Renal disease* may have an effect on the elimination of the drugs that can result in increased toxicity. The glomerular filtration rate (GFR) is used as a measure to determine the severity of renal impairment. Certain drugs may be contraindicated or may require an adaptation of the dosage.
- *Pregnancy and lactation* (see below for further details).

Adverse drug reactions

Drugs in general do not only produce the desired therapeutic effect but may cause other reactions, which mostly, but not always, are adverse. It is therefore important to know the most common adverse reactions possible and pay particular attention to serious adverse reactions. Patients need to be monitored not only for therapeutic effect but also for any other effects. Some adverse reactions may require treatment or prevention. A typical example for this case would be the prophylactic prescription of anti-emetic drugs for chemotherapy.

Adverse drug reactions may be related to dose. Adverse reactions occurring above the normal dosage range are called toxic reactions. These can be avoided by ensuring that the dose remains within the therapeutic range. A typical example for a drug with a narrow therapeutic window and toxic effects at higher doses is digoxin. A typical example of a toxic drug reaction is bleeding occurring at too high doses of warfarin.

Hypersensitivity reactions occur at lower dosages than the therapeutic dose, e.g. penicillin allergy. These can only be avoided by knowing the patient's history. Some adverse reactions may be more likely to occur in specific patient populations or when a patient has a specific precondition. This includes, for example, age, sex, pregnancy and genetic disposition. The time of occurrence of the adverse reactions is relevant and will inform the monitoring needs.

- First-dose reactions occur at the start of the therapy but will not occur later. It is important to know these and give the first dose under adequate monitoring and precautions.
- Early reactions occur early during treatment but the patient will develop tolerance over time. The patient needs to be monitored early during therapy and should be informed about the effect in order to encourage the patient to continue treatment.
- Medium-term reactions are experienced after some time under therapy, but if they do not occur, the risk diminishes over the longer term.
- Long-term reactions: risk for such reactions increases with the time of the therapy. The patient needs to be monitored in the long term.

It is important to discuss potential adverse drug reactions with patients to help them to adhere to treatment, but also to ensure that they will be able to recognize the danger signs requiring them to return to the medical practitioner.

Interactions

Drug–drug interactions are defined as the effects of one drug changing the effects of another drug. In general it is a negative effect but there are cases where the interaction has a desirable effect. Interactions may be pharmaceutical, pharmacokinetic or pharmacodynamic.

Pharmacokinetic and pharmacodynamic interactions

Table 1 provides examples of relevant drug–drug interactions but is not meant to be an exhaustive list.

Table 1 Some drug–drug interactions

Combination of	*With*	*Effect*
Non-steroidal anti-inflammatory drugs (e.g. acetylsalicylic acid, ibuprofen)	Methotrexate	Increased toxicity of methotrexate
	Coumarin derivatives (e.g. warfarin)	Increased anti-coagulation and increased risk of bleeding
	Glucocorticoids, alcohol	Increased risk for gastrointestinal bleeding
Antibiotics: aminoglycoside (e.g. amikacin)	Amphotericin B, ciclosporin, cisplatin, certain diuretics (e.g. furosemide), cephalosporins	Increased oto- and/or nephrotoxicity
	Halothane, neuromuscular blocking drugs	Increased neuromuscular block
Co-trimoxazole (sulfamethoxazole/trimethoprim); sulfadoxine/pyrimethamine	Coumarin derivatives (e.g. warfarin), methotrexate, phenytoin, oral hypoglycemic drugs (sulfonylureas, e.g. glibenclamide, tolbutamide)	Increased effects of the listed drugs
	Indometacin, salicylates	Increased sulfonamide effects
Quinolone antibiotics (e.g. ciprofloxacin)	Antacid preparations, iron, zinc, multivitamins	Decreased absorption of quinolones from gastrointestinal tract. Give drugs at least 2 h apart
	Coumarin derivatives (e.g. warfarin)	Increased anti-coagulation effect and increased risk for bleeding
	Glucocorticoids	Increased risk of developing a tendinopathy
Penicillins	Anti-coagulation drugs, drugs inhibiting thrombocyte aggregation (with high doses of penicillin)	Increased risk for bleeding
Macrolide antibiotics (e.g. erythromycin)	Carbamazepine	Increased blood levels of carbamazepine
	Ciclosporin	Increased nephrotoxicity
	Coumarin derivatives (e.g. warfarin)	Increased anti-coagulation
	Digoxin	Increased digoxin levels (and potential toxicity)
	Valproic acid	Increased valproic acid levels (and potential toxicity)
Tetracyclines (e.g. doxycycline)	Antacid preparations containing aluminum, magnesium or calcium salts, iron preparations, milk	Decreased absorption and decreased efficacy of tetracyclines. If combination necessary, give the products at least 2 h apart
	Oral contraceptives	Decreased contraceptive efficacy
	Methotrexate	Increased methotrexate toxicity
	Ciclosporin	Increased ciclosporin toxicity
	Coumarin derivatives (e.g. warfarin)	Increased anti-coagulation leading to increasing risk for bleeding
Barbiturates (e.g. phenobarbital)	Alcohol and drugs depressing the central nervous system	Increasing depression of central nervous system
	Coumarin derivatives	Decreased anti-coagulation
	Contraceptives	Decreased contraceptive efficacy
	Methotrexate	Increased methotrexate toxicity
Benzodiazepines (e.g. diazepam)	Alcohol and drugs depressing the central nervous system	Increasing depression of central nervous system
	Cimetidine	Increased benzodiazepine effects
	Muscle relaxants	Increased muscle relaxation

Cont.

Table 1 *(cont.)*

Combination of	*With*	*Effect*
Beta-blockers	Anti-arrhythmic drugs, calcium-antagonists like verapamil	Increased cardio-depression
	Cimetidine	Increased beta-blocker serum levels
	Digoxin	Increasing negative chronotrope and dromotrope effects
	Insulin, sulfonylureas	Danger of prolonged hypoglycemia
Carbamazepine	Coumarin derivatives	Decreased anti-coagulation
	Contraceptives	Decreased contraceptive efficacy
	Cimetidine, isoniazid, macrolide antibiotics (e.g. erythromycin)	Increased carbamazepine serum levels leading to increased risk of toxicity
Oral contraceptives	Anti-epileptic drugs, barbiturates, broad-spectrum antibiotics, rifampicin	Decreased contraceptive efficacy
Non-steroidal anti-inflammatory drugs	Coumarin derivatives	Increased anti-coagulation
	Glucocorticoids	Increased risk for gastrointestinal bleeding
	Methotrexate	Increased methotrexate toxicity
	Sulfonylureas	Increased risk of hypoglycemia
	Diuretic drugs (e.g. furosemide)	Decreased diuretic effects
Phenytoin	Antacids (oral combination)	Decreased absorption of phenytoin
	Phenobarbital, carbamazepine	Decreased phenytoin serum levels
	Benzodiazepines, cimetidine, coumarin derivatives, isoniazid, NSAID, methotrexate, rifampicin, sulfonamides, valproic acid, antidepressive drugs	Increased phenytoin serum levels and increased phenytoin toxicity
	Carbamazepine, coumarin derivatives, doxycycline, glucocorticoids, oral contraceptives, valproic acid	Decreased serum levels of the listed drugs
Rifampicin	Oral contraceptives	Reduced contraceptive efficacy
	Coumarin derivatives, anti-convulsants, some anti-retroviral drugs, etc.	Decreased serum levels of listed drugs

Pharmaceutical interactions

Physico-chemical reactions may occur between drugs in solution. These potential interactions are important to keep in mind for parenteral drug therapy. The stability and efficacy of a drug may be altered by the diluent used but also by the combination of two drugs in the same solution. In general drugs should not be mixed with blood, amino acid-containing solutions or fat emulsions.

These incompatibilities are not necessarily visible. To avoid problems, do not combine drugs in intravenous fluids. As an alternative, many drugs can be given through an infusion set with a two-way connector (Y-connector). To administer a second drug without the risk of an interaction, stop the infusion, rinse the connection with normal saline, administer the drug, rinse the connection again and reconnect the initial infusion.

Examples:

- Loss of potency of benzylpenicillin or ampicillin in dextrose solutions after 6–8 h.
- Aminoglycosides are incompatible with penicillins.

DRUGS IN PREGNANCY AND LACTATION

Drugs may have adverse effects on the pregnancy or the fetus. Any drug therapy in pregnancy should be avoided if possible and should be given accordingly only after establishing a strict indication for the therapy. Adverse effects can be caused by a

direct effect on the fetus after crossing the placental barrier or they can occur in relation to physiological changes in the mother's body. The following distinctions are made:

- Genotoxic drugs: these drugs affect embryonic development (e.g. cytotoxic chemotherapy).
- Drugs crossing the placental barrier causing direct pharmacological effects on the fetus (e.g. beta-blockers, opioids).
- Drugs altering cellular pathways: these drugs may have an effect on organogenesis, growth and development (e.g. ace inhibitors).

However there may be effects of pregnancy in regard to the mother's metabolism of drugs, for example an increase in cytochrome P450 activity is observed in the second and third trimester. CYP450 is a group of key enzymes for the elimination of many drugs.

Overview of effects of drugs in pregnancy and lactation

- Drugs affecting the female reproductive system.
- Teratogenic drugs.
- Drugs with potential effects on gestation.
- Drugs affecting labor.
- Drugs causing abortion.
- Drugs affecting lactation itself.
- Drugs affecting newborn metabolism through milk.

Prescribing drugs in pregnancy

- Establish the need for drug therapy: is there an urgent indication for the treatment of the mother? Do the benefits for the mother outweigh a potential risk for the fetus?
- Choose if possible drugs that are well known and for which experience is available.
- Keep dosage as low as possible and limit treatment duration to the shortest effective course.
- Pregnant women requiring continued drug therapy due to a chronic condition, e.g. epilepsy, diabetes etc., are a special case; drug therapy in general should be continued as the underlying condition and a deterioration of the mother's health due to stopped therapy may have adverse effects on the fetus. However, the drug therapy may have to be adapted, for example if possible to switch to safer alternatives.

What to do in cases of suspected exposure to a teratogenic drug

First it is important to confirm the pregnancy. Second establish as clearly as possible the time of exposure in relation to the gestational age and the dose and time duration of therapy. If the woman is pregnant and still taking the drug in question, an immediate stopping of the drug is advised, except when the benefits for the mother outweigh the

Table 2 System for determining risk level of drugs in pregnancy

A	Adequate, well-controlled studies in pregnant women have not shown an increased risk of fetal abnormalities to the fetus in any trimester of pregnancy
B	Animal studies have revealed no evidence of harm to the fetus; however, there are no adequate and well-controlled studies in pregnant women *or* animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester
C	Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women *or* no animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women
D	Adequate well-controlled or observational studies in pregnant women have demonstrated a risk to the fetus; however the benefits of therapy may outweigh the potential risk. For example, the drug may be acceptable if needed in a life-threatening situation or serious disease for which safer alternatives cannot be used or are ineffective
X	Adequate well-controlled or observational studies in animals or pregnant women have demonstrated a positive evidence of fetal abnormalities or risks. The use of the drug is contraindicated in women who are or may become pregnant.

Table 3 Examples of drugs with established embryo- or fetotoxic effects

Non-steroidal anti-inflammatory drugs	Early closure of ductus arteriosus. Do not use in 3rd trimester of pregnancy
Aminoglycoside antibiotics	Fetal toxicity
Chloramphenicol	Grey syndrome
Tetracyclines	Affect bones and teeth
Carbamazepine	Increased risk for spina bifida
Phenytoin	Congenital heart diseases, digital hypoplasia
Valproic acid	Neural tube defects, malformation of extremities
Benzodiazepines, haloperidol	Floppy infant syndrome
Hormones	
Androgens, gestagens	Virilization of female genital system
Anti-androgens	Feminization of male genital system
Coumarin derivatives	Nasal hypoplasia, ocular defects, deafness, cardiac anomalies
Folic acid antagonists (e.g. methotrexate, trimethoprim, phenobarbital, phenytoin)	Malformations of brain and extremities
Cytotoxic drugs	Multiple malformations of organs

NOTE: these drugs may need to be used if no safer therapeutic option is available *and* if the benefit outweighs the risk for the fetus, e.g. in life-threatening situations or serious disease

risks for the fetus, i.e. in a life-threatening situation or serious disease for which safer alternatives cannot be used or are ineffective. Further action will depend on a thorough risk evaluation. The risk level of drugs in pregnancy is commonly indicated using the system shown in Table 2. Examples of drugs with established toxic effects for the embryo or fetus are shown in Table 3 and drugs that can be considered for use in pregnancy are listed in Table 4.

Table 4 Drugs that may be considered for use in pregnancy

Antacid drugs	Aluminum- and magnesium-based products
Analgesics	Paracetamol
Anti-histaminic drugs	Diphenhydramine, dimenhydrinate, clemastine
Antibiotics	Penicillins, cephalosporins, clindamycin, erythromycin
Anti-asthmatic drugs	$Beta_2$-sympathomimetics (e.g. salbutamol)
Anti-malarial drugs	1st trimester: quinine in combination with clindamycin; artemisinin combination therapy (ACT) should only be used if alternatives not available ACT are the drugs of choice in 2nd and 3rd trimester of pregnancy for uncomplicated malaria Note: refer to national treatment guidelines for more detailed recommendations
Anti-coagulation	Heparin
Anti-hypertensive drugs	Methyldopa, $beta_1$-blockers (e.g. atenolol, metoprolol), hydralazine, nifedipine
Treatment of cough	Codeine in low doses, acetylcysteine

Drug therapy during breastfeeding

Drugs may cross into breast milk and cause pharmacological effects in the infant. Therefore any drug therapy for breastfeeding mothers should be clearly indicated and the lowest possible dose used. If using a drug with known adverse effects on the infant is unavoidable, consider interrupting breastfeeding for the period of medication: show the mother how to express breast milk and throw it away. Alternative feeding options should be ensured.

SAFE HANDLING OF CYTOTOXIC DRUGS

This section aims at providing some key elements to ensure safe handling of cytotoxic drugs but cannot replace the need for further guidance. It will focus in particular on measures that can be used in less-resourced settings.

Cytotoxic drugs require special care in handling in order to avoid exposure and adverse effects to the person preparing and administering the drugs. The level of risk and potential exposure depends on the drug preparation to be administered and on the different steps of preparation and administration. The frequency at which personnel is handling such products needs to be taken into account as well. The risk is highest for the preparation and administration of injectable preparations because direct exposure is more likely, e.g. during drug reconstitution and mixing, connecting and disconnecting intravenous tubing and disposal of waste. However, other activities such as dividing or crushing tablets result in high exposure as well. In regard to exposure, keep in mind that patients' excretions may contain unchanged cytotoxic drugs or active metabolites as well.

In specialized hospitals and better-resourced settings, cytotoxic drugs are usually prepared by the hospital pharmacy by experienced personnel using suitable safety cabinets or isolators providing a complete barrier. Personnel should be knowledgeable about the risks and must be trained for the safe handling of these products.

Personnel

- Train all personnel handling or potentially coming in contact with cytotoxic drugs or waste about the risks and appropriate precautions to be respected. Beside medical staff, personnel to be trained may also include, for example, cleaners.
- All procedures should be written down in clear and understandable language. Pictures may be helpful to illustrate the procedures to be followed. All procedures should be displayed in the workspaces.
- Personnel with special risks, in particular pregnant women, should *not* be handling cytotoxic drugs.

Personal protection measures

- Personnel should wear appropriate protective clothing while handling cytotoxic products, including gowns, eye glasses and respiratory protection.
- Gown and head covering: the gown should fully cover the body and be long sleeved. The gowns must be changed when work with the drugs is finished.
- Gloves: wearing gloves is an essential precaution during preparation and administration. In order to achieve suitable protection use of double-gloves is recommended, using powder-free latex gloves where available. Both pairs of gloves must be discarded after use into special containers.
- Eye protection: personnel should wear well-fitting glasses for the preparation of cytotoxic drugs.
- Protection from inhaling particulates from powders and liquids is necessary. Special safety equipment exists but is not widely available in less-resourced settings. In the absence of such equipment, surgical masks can be used as an alternative to achieve a reasonable level of protection. However, surgical masks do not provide complete protection against aerosols.

Preparation

All preparations should be done in a designated room, separate from handling of other drugs and other activities. It is good practice to limit access to this room to trained personnel only. The room should have a sufficiently big working area and a washing facility.

- Personnel should wear protective clothing as described above.
- Before starting the preparation, ensure that all items that are needed for the preparation are available in the working area, i.e. drug, diluent, syringes, infusion fluid, alcohol for disinfection etc.
- Follow the specific instructions for the preparation step by step. A number of devices have been developed to reduce the risk of exposure. For example, spikes with air-filters are recommended for puncturing vials.
- Clearly label the product: product name, dosage and if appropriate patient name. It is good practice to use labels that clearly identify the product as a cytotoxic drug.

Drug administration

Protective clothing should be worn as appropriate. Waste disposal procedures should be in place and followed for all items used during administration.

Parenteral drugs

The usual precautions for administering parenteral preparations apply. All drug containers should be labeled with a cytotoxic drug warning. To connect a cytotoxic drug as a secondary infusion, use of a back-priming technique is helpful. After injections, do not recap needles. Never cut up intravenous infusion sets and bags after use. All materials for the administration of the product should be treated as cytotoxic waste.

Oral drugs

When dispensing tablets or capsules, avoid direct skin contact. Provide the drug for example in a disposable medication cup or something similar and instruct the patient to take the drug directly from the container without using their hands. Do not break or crush cytotoxic drugs outside the designated preparation area.

Topical drugs

To avoid contact with the drug, wear gloves at all times and use, for example, a disposable spatula to apply ointments and lotions to the skin. Cover the area of application as appropriate.

Spills and contact

- If there was contact with skin, it should be washed immediately with soap and water. Eyes should be washed with water or normal saline solution.
- Liquid spills on surfaces and floors should be soaked up first with absorbent material before the area is cleaned with an alkaline detergent.
- For a powder spill, first cover the powder carefully with some absorbent material avoiding creating dust, then pour water on the absorbent material to dissolve the product and soak it up. Then clean the surface with an alkaline detergent.
- Treat all material that was used to clean up the spill as cytotoxic waste.

Waste disposal is an important aspect of the management of cytotoxic drugs. You can read about it in Chapter 31 of this book.

USEFUL REFERENCE WORKS

British National Formulary: free online access from less-resourced countries. Registration required on www.bnf.org

MSF reference books: free for personal use. Available at: http://www.refbooks.msf.org/MSF_Docs/En/MSFdocMenu_en.htm

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FURTHER READING

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