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the SQUARE

healthcare bulletin

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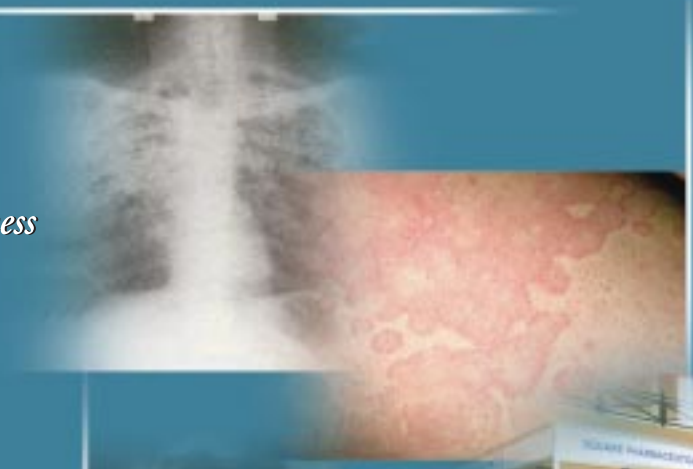

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Editorial

Dear Doctor:

Happy New Year 2007!

Welcome to this edition of "*the SQUARE*" healthcare bulletin!

In this issue we have published a special feature on "Drug Resistant Tuberculosis", which represents a threat to TB control programs. Erratic and inappropriate use of currently available medications, HIV-TB co-infection, and concern about transmission of drug-resistant strains in the general population all contribute to a worrying picture. As this is a very vast topic, we emphasized only the key points. We have an article on "Depression in the Elderly", a widely underrecognized and undertreated medical illness. You will also find an article on "Drug Hypersensitivity Reactions" which is very much important because of its potential morbidity and mortality. Besides, we have our regular feature on "Product Profile", "Medical Breakthrough" and, "*SQUARE* in International Business".

Every effort has been made to make this issue interesting and we are quite sure that you will enjoy this as well.

Wishing you all a safe, healthy and peaceful life throughout the year.

Omar Akramur Rab

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Drug Resistant Tuberculosis

Tuberculosis (TB) was declared a global emergency by the World Health Organization (WHO) in 1993. The global problem of TB has been further complicated by a substantial increase in multidrug resistant tuberculosis (MDR-TB). Multidrug resistant tuberculosis (MDR-TB), which is defined as combined resistance to isoniazid and rifampicin, is a "man-made" disease that is caused by improper treatment, inadequate drug supplies or poor patient supervision. MDR-TB is particularly problematic because it threatens both the individual and the community. For the individual, drug resistant disease often results in treatment failure, progressive disability and death, particularly in resource-poor countries unable to provide the expensive complicated "second-line" treatments. For the community, the patient with chronic MDR-TB disease represents an infectious reservoir of resistant tubercle bacilli.

From a microbiological perspective, resistance is caused by a genetic mutation that makes a drug ineffective against the mutant bacilli. An inadequate or poorly administered treatment regimen allows a drug-resistant strain to become the dominant strain in a patient infected with TB.

The extent and burden of MDR-TB varies significantly from country to country and region to region.

Causes of inadequate antituberculosis treatment

HEALTH-CARE PROVIDERS: INADEQUATE REGIMENTS	DRUGS: INADEQUATE SUPPLY/QUALITY	PATIENTS: INADEQUATE DRUG INTAKE
Inappropriate guidelines	Poor quality	Poor adherence (or poor DOT)
Noncompliance with guidelines	Unavailability of certain drugs (stock-outs or delivery disruptions)	Lack of information
Absence of guideline	Poor storage conditions	Lack of money (no treatment available free of charge)
Poor training	Wrong dose or combination	Lack of transportation
No monitoring of treatment		Adverse effects
Poorly organized or funded TB control programmes		Social barriers
		Malabsorption
		Substance dependency disorders

The magnitude of drug resistance is not yet known in many areas of the world with high burdens of TB, such as most of China, India, Indonesia, Nigeria and countries of the former Soviet Union. Nevertheless, evidence from half the world's nations confirms that drug resistance is a serious problem worldwide.

Drug resistance was strongly associated with previous treatment. In previously treated patients, the probability of any resistance was over 4-fold higher, and of MDR-TB over 10-fold higher, than for untreated patients. The overall prevalence of drug resistance was often related to the number of previously treated cases in the country.

Among countries with a high burden of TB, previously treated cases ranged from 4.4% to 26.9% of all patients registered in DOTS (Directly Observed Therapy Short-course) programs. In the two largest high-TB burden countries (China and India), re-treatment cases accounted for more than 20% of sputum smear-positive cases .

Many identified MDR-TB cases have resistance to drugs other than both isoniazid and rifampicin. In fact, one third of MDR-TB cases had resistance to all four of the first-line drugs tested in the global survey.

Moreover, MDR-TB patients often live for several years before succumbing to the disease. Prevalence of MDR-TB may therefore be three times greater than its incidence, suggesting that the true number of MDR-TB cases in the world today may approach or exceed one million.

Bangladesh Situation

Tuberculosis is a major public health problem in Bangladesh. In 2006, World Health Organization (WHO) ranked Bangladesh sixth among the world's 22 high-burden TB countries. More than 319,000 new cases, including 143,000 sputum smear-positive (SS+) pulmonary TB cases and 70,000 TB-related deaths occur annually. Bangladesh's National TB Control Program (NTP) began implementing Directly Observed Therapy, Short-Course (DOTS) in 1993. By the end of 2004, the NTP estimated DOTS coverage was 99 percent.

While the treatment success rate is fairly high at 85 percent, less than half (44 percent) of the cases are detected, resulting in a larger number of untreated carriers who spread the disease still further. This is primarily due to lack of full

implementation of DOTS by all public health facilities, private sector providers, and nongovernmental organizations (NGOs). Given that private practitioners and NGOs provide a major portion of health services, implementation of DOTS by NGO projects and within the private health care system is paramount.

(Bangladesh situation)	
Country population	139,214532
Global rank out of 22 high-burden TB countries	6
Estimated number of new TB cases	319,252
Estimated TB incidence (fail cases per 100,000 pop.)	229
DOTS population coverage (%)	99
Rate of new sputum smear-positive (55+) cases (per 100,000 pop.)	45
DOTS case detection rate (new SS+) (%)	44
DOTS treatment success rate in 2003 (new SS+) (%)	85
Estimated adult TB cases HIV + (%)	0.1
New multidrug-resistant TB cases (%)	1.6

Treatment strategies for MDR-TB

Different program treatment strategies have different options for treatment. The following are definitions of terms that are often used to describe treatment strategies (Figure-1):

- *Standardized treatment*. Regimens are designed on the basis of representative drug resistance surveillance(DRS) data of specific treatment categories. However, suspected MDR-TB should always be confirmed by drug susceptibility testing (DST) results whenever possible. All patients in a defined group or category receive the same treatment regimen.
- *Empirical treatment*. Each regimen is individually designed on the basis of the previous history of antituberculosis treatment and with the help of representative DRS survey data. Commonly, an empirical treatment is adjusted in each patient when his or her DST results become available.
- *Individualized treatment*. Each regimen is designed on the basis of previous history of antituberculosis treatment and individual DST results.

Classes of antituberculosis drugs

The classes of antituberculosis drugs have traditionally been divided into first-and second-line drugs, with isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin being the primary first-line drugs. These guidelines often refer to this classification but also use a group system based on efficacy, experience of use and drug class.

Regimen design

The following basic principles are involved in any regimen design:

- Regimens should be based on the history of drugs taken by the patient.
- Drugs and regimens commonly used in the country and the prevalence of resistance to first-line and second-line drugs should be taken into consideration when designing a regimen.
- Regimens should consist of at least four drugs with either certain, or almost certain, effectiveness. If the evidence about the effectiveness of a drug is unclear, the drug can be included in the regimen but it should not be depended upon for success.
- Drugs are administered at least six days a week. When possible, pyrazinamide, ethambutol and fluoroquinolones should be given once per day because the high serum levels attained in once-a-day dosing may be more efficacious. Once-a-day dosing is permitted for other second-line drugs, depending on patient tolerance. However, ethionamide/protionamide, cycloserine and PAS have traditionally been given in split doses during the day.
- The drug dosage should be determined by body weight.
- An injectable agent (an aminoglycoside or capreomycin) is used for a minimum of 6 months.
- Treatment is for a minimum duration of 18 months beyond conversion.
- Each dose is given as DOT throughout the treatment. A treatment card is marked for each observed dose.
- DST, when available and from a reliable laboratory, should be used to guide therapy.
- Pyrazinamide can be used for the entire treatment if it is judged to be effective. Many MDR-TB patients have chronically inflamed lungs, which theoretically produce the acidic environment in which pyrazinamide is active.

Figure-1 : Recommended treatment strategies for MDR-TB

Standardized treatment	Representative DRS data in well-defined patient populations are used to design the regimen. All patients in a patient group or category receive the same regimen.
Standardized treatment followed by individualized treatment	Initially, all patients in a certain group receive the same regimen based on DST survey data from representative population. The regimen is adjusted when DST results become available (often DST is only done to a limited number of drugs).
Empirical treatment followed by individualized treatment	Initially, all patients in a certain group receive the same regimen based on DST survey data from representative population. The regimen is adjusted when DST results become available (often DST is only done to a limited number of drugs).

- Early MDR-TB detection and prompt initiation of treatment are important factors in achieving successful outcomes.

Drug selection for the treatment of MDR-TB

Antituberculosis drugs may be placed into five groups (Table-1). The order of the five groups is based on potency, evidence of efficacy, experience of use and drug class.

- Group 1 - *First-line oral antituberculosis drugs*. Group 1 drugs are the most potent and best tolerated antituberculosis drugs. They should be used in patients only where there is laboratory evidence or clinical history to suggest their efficacy. Patients who have strains that test resistant to low levels of isoniazid but are susceptible to higher concentrations may benefit from high doses of the drug. However, since the benefit may be small, isoniazid in this situation should not be included as one of the four core drugs. The newer rifamycins should be considered ineffective if results of DST show resistance to rifampicin.
- Group 2 – *Injectable antituberculosis agents*. A Group 2 injectable agent should be given to all patients in whom susceptibility is documented or suspected, according to a hierarchical order based on efficacy, adverse effects and cost. If the strain is susceptible, streptomycin is the usual injectable agent of choice. Kanamycin or amikacin is the logical second choice given the low cost of these drugs and good experience of their use. Amikacin and kanamycin are considered to be very similar and have close to 100% crossresistance. If an isolate is resistant to both streptomycin and kanamycin, capreomycin should be used. Viomycin is very similar to capreomycin, and these agents also share a high level of cross-resistance.
- Group 3 – *Fluoroquinolones*. A Group 3 drug should be used if the strain is susceptible. Currently, the most potent available fluoroquinolones in descending order based on in vitro activity and animal studies are: moxifloxacin = gatifloxacin > levofloxacin > ofloxacin = ciprofloxacin. However, the long-term safety of the newer-generation fluoroquinolones has not yet been fully evaluated.
- Group 4- *Oral bacteriostatic second-line antituberculosis drugs*. Group 4 drugs are added on the basis of estimated susceptibility, drug history, efficacy, adverse effects profile and cost. If only one of these agents is needed, ethionamide/protionamide is often added because of its proven efficacy and low cost. If cost is not a constraint, PAS may be added first because the enteric-coated formulas are relatively well tolerated. If two agents are needed, cycloserine is commonly used in conjunction with ethionamide/protionamide or PAS. Since the combination of ethionamide/protionamide and PAS has a high incidence of gastrointestinal adverse effects, these two agents are commonly used together only when all three Group 4 agents are needed. Ethionamide/protionamide should be started at a low dose (250 mg) for a few days and then gradually increased every 3–5 days until the full dose is reached. Terizidone contains two molecules of cycloserine and can be used instead of cycloserine because its efficacy is assumed to be similar, although there are no direct studies comparing the two.

Table-1: Alternative method of grouping antituberculosis drugs

GROUPING	DRUGS (ABBREVIATION)
Group 1- First-line oral antituberculosis agents	Isoniazid (H); Rifampicin (R); Ethambutol (E); Pyrazinamide (Z)
Group 2- Injectable antituberculosis agents	Streptomycin (S); Kanamycin (Km); Amikacin (Am); Capremycin (Cm); Viomycin (Vi)
Group 3- Fluoroquinolones	Diprofloxacin (Cfx); Ofloxacin (Ofx); Levofloxacin (Lfx); Moxifloxacin (Mfx)*; Gatifloxacin (Gfx)*
Group 4- Oral bacteriostatic second-line antituberculosis agents	Ethionamide (Eto); Protionamide (Pto); Cycloserine (Cs); Terizidone (Trd)*; *P*-aminosalicylic acid (PAS); Thioacetazone (Lzd)
Group 5- Antituberculosis agents with unclear efficacy (not recommended by WHO for routine use in MDR-TB patients)	Clofazimine (Cfz); Amoxicillin/Clavulanate (Amx/Clv); Clarithromycin (Clr); Linezolid (Lzd)

* The long-term safety and efficacy for MDR-TB treatment have not yet been fully confirmed and therefore use is not yet recommended for treatment of MDR-TB.

* Thioacetazone should be used only in patients documented to be HIV-negative and should usually not be chosen over other drugs listed in Group 4.

The use of thioacetazone is limited by the development of rashes that are more prevalent in HIV-positive individuals and can result in Stevens-Johnson syndrome and death. In addition, thioacetazone has cross-resistance with the thioamides (ethionamide and protionamide) and is considered a relatively weak antituberculosis agent.

- Group 5. The Group 5 drugs are not recommended by WHO for routine use in MDR-TB treatment because their contribution to the efficacy of multidrug regimens is unclear. However, they can be used in cases where adequate regimens are impossible to form with the medicines from Groups 1–4.

Duration of administration of the injectable agent (intensive phase)

The recommended duration of administration of the injectable agent, or the intensive phase, is guided by smear and culture conversion. The minimal recommendation is that the injectable agent should be continued for at least 6 months and at least 4 months after the patient first becomes and remains sputum smear- or culture-negative. The use of an individualized approach that takes account of the results of cultures, smears, X-rays and the patient's

clinical status may also help in deciding whether to continue an injectable agent for longer than the recommended period.

This would apply particularly in the case of patients for whom the susceptibility pattern is unknown, the effectiveness of a drug(s) is uncertain, or extensive or bilateral pulmonary disease is present. Intermittent therapy with the injectable agent (three times weekly after an initial period of 2–3 months of daily therapy) can also be considered for patients in whom the injectable agent has been used for a prolonged period and when the risk of toxicity increases. If the patient has been on an empirical regimen containing five or six drugs, discontinuation of drugs other than the injectable agent can be considered once the DST results are available and provided that the patient continues with at least three of the most potent agents.

Duration of treatment

The recommended duration of treatment is guided by smear and culture conversion. The minimal recommendation is that treatment should last for at least 18 months after culture conversion. Extension to 24 months may be indicated in patients defined as "chronic cases" with extensive pulmonary damage.

Individualized regimen design based on DST for first-line drugs

PATTERN OF DRUG RESISTANCE	SUGGESTED REGIMEN (DAILY UNLESS OTHERWISE STATED)	COMMENTS
H-R	Z-E injectable agent-fluoroquinolone (± one or two Group 4 agents)	One Group 4 agent is sufficient if E and Z susceptibility has been ascertained. Two Group 4 agents should be used in extensive disease, or if the DST result is questionable (i.e. reported susceptibility to E or Z despite a history of these agents being used in a failing regimen).
H-R (± S) and E or Z	Z orE-injectable agent-fluoroquino-lone (+ two or more Group 4 agents)	Only use the first-line agents to which the patient's strain is susceptible. Use alternative injectable agent if S resistance is present. More than two Group-4 agents should be used in extensive disease or if resistance to E and Z is present or suspected. Group 5 agents can be considered if an adequate regimen of four drugs cannot be formed based on DST.

H = isoniazid; R = rifampicin; E = ethambutol; Z = pyrazinamide; S = streptomycin

Extrapulmonary MDR-TB and MDR-TB treatment

The treatment strategy is the same for patients with pulmonary and extrapulmonary MDR-TB. If the patient has symptoms suggestive of central nervous system involvement and is infected with MDR-TB, the regimen should use drugs that have adequate penetration into the central nervous system .

Rifampicin, isoniazid, pyrazinamide, protionamide/ ethionamide and cycloserine have good penetration; kanamycin, amikacin and capreomycin penetrate effectively only in the presence of meningeal inflammation; PAS and ethambutol have poor or no penetration.

Adjunctive therapies in MDR-TB treatment

A number of other measures can be used to lessen adverse effects and morbidity as well as improve MDR-TB treatment outcomes.

Nutritional support

In addition to causing malnutrition, MDR-TB can be exacerbated by poor nutritional status, low body mass index and severe anaemia. Without nutritional support, patients can become enmeshed in a vicious cycle of malnutrition and disease, especially those already suffering from baseline hunger. The second-line drugs may also further decrease the appetite, making adequate nutrition a greater challenge. Nutritional support can take the form of providing free staple foods, and whenever possible should include a source of protein. Vitamin B6 (pyridoxine) should also be given to all patients receiving cycloserine or terizidone to prevent adverse neurological effects. Vitamin (especially vitamin A) and mineral supplements can be given in areas where a high proportion of the patients have deficiencies. If minerals (zinc, iron, calcium, etc.) are given, they should be administered at a different time from the fluoroquinolones, as they can interfere with the absorption of these drugs.

Corticosteroids The use of corticosteroids in MDR-TB patients can be beneficial in cases of severe respiratory insufficiency and central nervous system involvement. Prednisone is commonly used, starting the dose at approximately 1 mg/ kg, with gradual decrease in the daily dose by 10 mg per week when a longer course is indicated. Corticosteroids may also alleviate symptoms in patients with an exacerbation of obstructive pulmonary disease. In these cases, prednisolone may be given in a short tapering course over 1–2 weeks, starting at approximately 1 mg/kg and decreasing the dose by 5–10 mg per day. Injectable corticosteroids are often used initially when a more immediate response is needed.

DOTS-plus

Based upon DOTS, DOTS-Plus is a comprehensive management strategy under development and testing that includes the five elements of the DOTS strategy. DOTS-Plus takes into account specific issues (such as the use of second-line anti-TB drugs) that need to be addressed in areas where there is high prevalence of MDR-TB. Thus, DOTS-Plus works as a supplement to the standard DOTS strategy. By definition, it is impossible to conduct DOTS-Plus in an area without having an effective DOTS-based TB control program in place.

DOTS-Plus is not intended as a universal strategy, and is not required in all settings. DOTS-Plus should be implemented in selected areas with moderate to high levels of MDR-TB in order to combat an emerging epidemic. Via the Green Light Committee (GLC) review process, DOTS-Plus is being implemented in Bolivia, Costa Rica, Estonia, Haiti, Karakalpakstan (Uzbekistan), Latvia, Malawi, Mexico, Peru, Philippines and the Russian Federation (Arkhangelsk, Ivanono, Tomsk and Orel Oblasts). More recently, DOTS-Plus projects have also been approved in Georgia, Honduras, Jordan, Kenya, Kyrgyzstan, Lebanon, Nepal, Nicaragua, Romania and Syria.

Summary of general priciples for designing a regimen

BASIC PRINCIPLES	COMMENTS
1. Use at least 4 drugs certain or highly likely to be effective	Effectiveness is supported by a number of factors (the more present the more likely the drug will be effective in the patients): A. DST results show susceptibility. B. No previous history of treatment failure with the drug. C. No known close contacts with resistance to the drug. D. Drug resistance survey indicates resistance is rare in similar patients. E. The drug is not commonly used in the rare. If at least 4 drugs are not certain to be effective, use 5-7 drugs depending on the specific drugs and level of uncertainty.
2. Do not use drugs for which resistance crosses over	A. All rifamycins (rifampicin, rifabutin, rifapentene, rifalazil) have high levels of cross-resistance. B. Fluoroquinolones are believed to have variable cross-resistance, with in vitro data showing that some higher-generation fluoroquinolones remain susceptible when lower-generation fluoroquinolones are resistant. In these cases, it is unknown whether the higher-generation fluoroquinolones remain clinically effective. C. Not all aminoglycosides and polypeptides cross-resist; in general, only kanamycin and amikacin fully cross-resist.
3. Eliminate drugs that are not safe in the patient	A. Known severe allergy or unmanageable intolerance. B. High risk of severe adverse effects including renal failure, deafness, hepatitis, depression and/or psychosis. C. Quality of the drug is unknown or questionable.
4. Include drugs from Groups 1-5 in a hierarchical order based on potency	A. Use any Group 1 (oral first-line) drugs that are likely to be effective (see section 1 of this table). B. Use an effective aminoglycoside or polypeptide by injection (Group 2 drugs). C. Use a fluoroquinolone (Group 3) D. Use the remaining Group 4 drugs to make a regimen of at least 4 effective drugs. For regimens with ≥ 4 effective drugs, add second-line drugs most likely to be effective, to give up to 5-7 drugs in total, on the basis that at least 4 are highly likely to be effective. The number of drugs will depend on the degree of uncertainty. E. Use Group 5 drugs as needed so that at least 4 drugs are likely to be effective.

Summary of general priciples for designing a regimen

BASIC PRINCIPLES	COMMENTS
5. Be prepared to prevent, monitor and manage adverse effects for each of the drugs selected.	A. Ensure laboratory services for haematology, biochemistry, serology and audiometry are available. B. Establish a clinical and laboratory baseline before starting the regimen. C. Initiate treatment gradually for a difficult-to-tolerate drug, split daily doses of Eto/Pto, Cs and PAS. D. Ensure ancillary drugs are available to manage adverse effects. E. Implement DOT for all doses.

Mono-and poly-resistant strains (drug-resistant tuberculosis other than MDR-TB)

Mono-resistant refers to resistance to a single first-line drug, and poly-resistance refers to resistance to two or more first-line drugs. Treatment of patients infected with mono- or poly-resistant strains using standardized short-course chemotherapy has been associated with increased risk of treatment failure and further acquired resistance, including the development of MDR-TB. While the likelihood of poor outcomes is relatively low with many types of mono- and poly-resistance (i.e. the majority of patients with mono- or poly-resistant strains will be cured with short-course chemotherapy), programmes can use different regimens based on DST patterns (Table-2).

When using this table, it is essential to consider whether resistance has been acquired to any of the drugs that will be used in the recommended regimen.

This table should not be used if further resistance to any of the agents in the suggested regimen is suspected.

Table-2 Suggested regimens for mono-and poly-drug resistance (when further acquire resistance is not a factor and laboratory results are highly reliable)

Pattern of Drug Resisitance	Suggested Regimen	Minimum Duration of Treatment (Months)	Comments
H (± S)	R, Z and E	6-9	A fluoroquinolone may strengthen the regimen for patients with extensive disease.
H and Z	R, E and fluoroquinolones	9-12	A longer duration of treatment should be used for patients with extensive disease.
H and E	R, Z and fluoroquinolones	9-12	A longer duration of treatment should be used for patients with extensive disease.
R	H, Z, Fluoroquinolones, Plus at least 2 months of Z	12-18	An injectable agent may strengthen the regimen for patients with extensive disease.
R and E (± S)	H, Z, Fluoroquinolones, Plus an injectable agent for at least the first 2-3 months	18	A longer course (6 months) of the injectable agent may strengthen the regimen for patients with extensive disease
R and Z (± S)	H, E, Fluoroquinolones, Plus an injectable agent for at least the first 2-3 months	18	A longer course (6 months) of the injectable agent may strengthen the regimen for patients with extensive disease
H, E, Z (± S)	R, Fluoroquinolones, Plus an oral second-line agents, plus an injectable agent for at least the first 2-3 months	18	A longer course (6 months) of the injectable agent may strengthen the regimen for patients with extensive disease

H = isoniazid; R = rifampicin; E = ethambutol; Z = pyrazinamide; S = streptomycin

Management of drug-resistant tuberculosis in special conditions and situations

A. Pregnancy

All female patients of childbearing age should be tested for pregnancy upon initial evaluation. Pregnancy is not a contraindication for treatment of active drug-resistant TB, which poses great risks to the lives of both mother and fetus. However, birth control is strongly recommended for all non-pregnant women receiving therapy for drug-resistant TB because of the potential consequences for both mother and fetus resulting from frequent and severe adverse drug reactions.

Pregnant patients should be carefully evaluated, taking into consideration gestational age and severity of the drug-resistant TB. The risks and benefits of treatment should be carefully considered, with the primary goal of smear conversion to protect the health of the mother and child, both before and after birth. The following are some general guidelines:

- Start treatment of drug resistance in second trimester or sooner if condition of patient is severe. Since the majority of teratogenic effects occur in the first trimester, therapy may be delayed until the second trimester. The decision to postpone the start of treatment should be agreed by both patient and doctor after analysis of the risks and benefits. It is based primarily on the clinical judgment resulting from the analysis of life-threatening signs/symptoms and severity/aggressiveness of the disease (usually reflected in extent of weight loss and lung affection during the previous weeks). When therapy is started, three or four oral drugs with demonstrated efficacy against the infecting strain should be used and then reinforced with an injectable agent and possibly other drugs immediately postpartum.
- Avoid injectable agents. For the most part, aminoglycosides should not be used in the regimens of pregnant patients and can be particularly toxic to the developing fetal ear. Capreomycin may carry the same risk of ototoxicity but is the injectable drug of choice if an injectable agent cannot be avoided.
- Avoid ethionamide. Ethionamide can increase the risk of nausea and vomiting associated with pregnancy, and teratogenic effects have been observed in animal studies. If possible, ethionamide should be avoided in pregnant patients.

B. Breastfeeding

A woman who is breastfeeding and has active drug-resistant TB should receive a full course of antituberculosis treatment. Timely and properly applied chemotherapy is the best way to prevent transmission of tubercle bacilli to her baby.

In lactating mothers on treatment, most antituberculosis drugs will be found in the breast milk in concentrations that would equal only a small fraction of the therapeutic dose used in an infant.

However, any effects on infants of such exposure during the full course of MDR-TB treatment have not been established. Therefore, when resources and training are available, it is recommended to provide infant formula options as an alternative to breastfeeding. The mother and her baby should not be completely separated. However, if the mother is sputum smear-positive, the care of the infant should be left to family members until she becomes sputum smear-negative, if this is feasible.

When the mother and infant are together, this common time should be spent in well-ventilated areas or outdoors. In some settings, the mother may be offered the option of using a surgical mask or a respirator until she becomes sputum smear-negative.

C. Contraception

There is no contraindication to the use of oral contraceptives with the non-rifamycin containing regimens. Patients who vomit directly after taking an oral contraceptive can be at risk of decreased absorption of the drug and therefore of decreased efficacy. These patients should be advised to take their contraceptives apart from times when they may experience vomiting caused by the antituberculosis treatment. Patients who vomit at any time directly after or within the first two hours after taking the contraceptive tablet, should use a barrier method of contraception until a full month of the contraceptive tablets can be tolerated.

For patients with mono- and poly-resistant TB that is susceptible to rifampicin, the use of rifampicin interacts with the contraceptive drugs resulting in decreased efficacy of protection against pregnancy. A woman on oral contraception while receiving rifampicin treatment may choose between two options: following consultation with a physician, use of an oral contraceptive pill containing a higher dose of estrogen; or use of another form of contraception.

D. Children

Children with drug-resistant TB generally have primary resistance transmitted from an index case with drug-resistant TB. When DST is available it should be used to guide therapy, although children with paucibacillary TB are often culture-negative. Nevertheless, every effort should be made to confirm drug-resistant TB bacteriologically by the use of DST and to avoid exposing children unnecessarily to toxic drugs.

The treatment of culture-negative children with clinical evidence of active TB disease and contact with a documented

case of drug-resistant TB should be guided by the results of DST and the history of the contact's exposure to antituberculosis drugs.

There is only limited reported experience with the use of second-line drugs for extended periods in children. The risks and benefits of each drug should be carefully considered in designing a regimen. Frank discussion with family members is critical, especially at the outset of therapy. MDR-TB is lifethreatening, and no antituberculosis drugs are absolutely contraindicated in children.

Children who have received treatment for drug-resistant TB have generally tolerated the second-line drugs well. Although fluoroquinolones have been shown to retard cartilage development in animals, experience with the use of fluoroquinolones has not demonstrated similar effects in humans. It is considered that the benefit of fluoroquinolones in treating MDR-TB in children outweighs any risk. Additionally, ethionamide, PAS and cycloserine have been used effectively in children and are well tolerated.

In general, antituberculosis drugs should be dosed according to body weight (Table -3). Monthly monitoring of body weight is therefore especially important in paediatric cases, with adjustment of doses as children gain weight. All drugs, including the fluoroquinolones, should be dosed at the higher end of the recommended ranges whenever possible, except ethambutol. Ethambutol should be dosed at 15 mg/kg, and not at 25 mg/kg as sometimes used in adults with MDR-TB, as it is more difficult to monitor for optic neuritis in children.

Table-3 Paediatric dosing of second-line antituberculosis drugs

DRUG	DAILY DOSE (MG/KG)	FREQUENCY	MAXIMUM DAILY DOSE
Streptomycin	20-40	Once daily	1 g
Kanamycin	15-30	Once daily	1 g
Amikacin	15-22.5	Once daily	1 g
Capreomycin	15-30	Once daily	1 g
Ciprofloxacin	20-40	Twice daily	2 g
Ofloxacin	15-20	Twice daily	800 mg
Levofloxacinn	7.5-10	Once daily	750 mg
Moxifloxacin	7.5-10	Once daily	400 mg
Gatifloxacin	7.5-10	Once daily	400 mg
Ethionamide	15-20	Twice daily	1 g
Protionamide	15-20	Twice daily	1 g
Cycloserine	10-20	One or Twice daily	1 g
P-aminosalicylic acid	150	Twice or Thrice daily	12 g

In children who are not culture-positive initially, treatment failure is difficult to assess. Persistent abnormalities on chest radiograph do not necessarily signify a lack of improvement. In children, weight loss or, more commonly, failure to gain weight adequately, is of particular concern and often one of the first (or only) signs of treatment failure. This is another key reason to monitor weight carefully in children.

Anecdotal evidence suggests that adolescents are at high risk for poor treatment outcomes. Early diagnosis, strong social support, individual and family counseling and a close relationship with the medical provider may help to improve outcomes in this group.

E. Diabetes mellitus

Diabetic patients with MDR-TB are at risk for poor outcomes. In addition, the presence of diabetes mellitus may potentiate the adverse effects of antituber- culosis drugs, especially renal dysfunction and peripheral neuropathy. Diabetes must be managed closely throughout the treatment of drug-resistant TB.

Oral hypoglycaemic agents are not contraindicated during the treatment of drug-resistant TB but may require the patient to increase the dosage. Use of ethionamide or protionamide may make it more difficult to control insulin levels. Creatinine and potassium levels should be monitored more frequently, often weekly for the first month and then at least monthly thereafter.

F. Renal insufficiency

Renal insufficiency caused by long-standing TB infection itself or previous use of aminoglycosides is not uncommon. Great care should be taken in the administration of second-line drugs in patients with renal insufficiency, and the dose and/or the interval between dosing should be adjusted accordingly.

G. Liver disorders

The first-line drugs isoniazid, rifampicin and pyrazinamide are all associated with hepatotoxicity. Of the three, rifampicin is least likely to cause hepatocellular damage, although it is associated with cholestatic jaundice. Pyrazinamide is the most hepatotoxic of the three first-line drugs. Among the second-line drugs, ethionamide, protionamide and PAS can also be hepatotoxic, although less so than any of the first-line drugs. Hepatitis occurs rarely with the flouroquinolones.

Patients with a history of liver disease can receive the usual drug-resistant TB chemotherapy regimens provided there is no clinical evidence of chronic liver disease, hepatitis virus carriage, past history of acute

hepatitis or excessive alcohol consumption. However, hepatotoxic reactions to antituberculosis drugs may be more common in these patients and should be anticipated.

In general, patients with chronic liver disease should not receive pyrazinamide. All other drugs can be used, but close monitoring of liver enzymes is advised. If significant aggravation of liver inflammation occurs, the drugs responsible may have to be stopped.

Uncommonly, a patient with TB may have concurrent acute hepatitis that is unrelated to TB or antituberculosis treatment. In this case, clinical judgement is necessary. In some cases, it is possible to defer antituberculosis treatment until the acute hepatitis has been resolved. In other cases when it is necessary to treat drug-resistant TB during acute hepatitis, the combination of four non-hepatotoxic drugs is the safest option.

H. Seizure disorders

Some patients requiring treatment for drug-resistant TB will have a previous or current medical history of a seizure disorder. The first step in evaluating such patients is to determine whether the seizure disorder is under control and whether the patient is taking anti-seizure medication. If the seizures are not under control, initiation or adjustment of anti-seizure medication will be needed before the start of drug-resistant TB therapy. In addition, any other underlying conditions or causes of seizures should be corrected.

Cycloserine should be avoided in patients with active seizure disorders that are not well controlled with medication. However, in cases where cycloserine is a crucial component of the treatment regimen, it can be given and the antiseizure medication adjusted as needed to control the seizure disorder. The risks and benefits of using cycloserine should be discussed with the patient and the decision on whether to use cycloserine made together with the patient.

In mono- and poly-resistant cases, the use of isoniazid and rifampicin may interfere with many of the anti-seizure medications. Drug interactions should be checked before their use. Seizures that present for the first time during antituberculosis therapy are likely to be the result of an adverse effect of one of the antituberculosis drugs.

I. Psychiatric disorders

The psychiatric patients should be evaluated before the start of treatment for drug-resistant TB. The initial evaluation documents any existing psychiatric condition and establishes a baseline for comparison if new psychiatric symptoms develop while the patient is on treatment. Any psychiatric illness identified at the start of or during treatment should be fully addressed. There is a high baseline incidence of depression and anxiety in patients with MDR-TB, often connected with the chronicity and socioeconomic stress factors related to the disease. The use of cycloserine is not absolutely contraindicated for the psychiatric patient. Adverse effects from cycloserine may be more prevalent in the psychiatric patient, but the benefits of using this drug may outweigh the potentially higher risk of adverse effects. Close monitoring is recommended if cycloserine is used in patients with psychiatric disorders.

J. Substance dependence

Patients with substance dependence disorders should be offered treatment for their addiction. Complete abstinence from alcohol or other substances should be strongly encouraged, although active consumption is not a contraindication for antituberculosis treatment. If the treatment is repeatedly interrupted because of the patient's dependence, therapy should be suspended until successful treatment or measures to ensure adherence have been established. Good DOT gives the patient contact with and support from health-care providers, which often allows complete treatment even in patients with substance dependence.

Cycloserine will have a higher incidence of adverse effects (as in the psychiatric patient) in patients dependent on alcohol or other substances, including a higher incidence of seizures. However, if cycloserine is considered important to the regimen, it should be used and the patient closely observed for adverse effects, which are then adequately treated.

K. HIV-infected patients

Understanding the regional prevalence of HIV, MDR-TB and MDR/HIV coinfection is the first step in guiding the strategies for MDR-TB/HIV activities. In some areas, MDR-TB is an important potential problem for HIV-infected patients. The patient with drug-resistant TB disease and HIV will require intensive medical care to decrease the high level of mortality. Rigorous infection control measures should be part of the planning. Coordination between the team treating drug-resistant TB and the HIV control programme for training, care and treatment is an essential component. MDR-TB/HIV coinfection has the potential to increase rapidly. All drug-resistant TB and HIV control programmes should coordinate the collaborative activities, which are an integral element of both HIV/AIDS and TB control, aimed at avoiding epidemics of HIV-associated MDR-TB.

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Depression in the Elderly

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Depression is the most prevalent mental health problem of later life, affecting around 10 -15 percent of older people living at home. It is characterized by persistent sadness, discouragement and loss of self-worth. These feelings are accompanied by reduced energy and concentration, insomnia, decreased appetite and weight loss. In the elderly, depression is also frequently characterized by excessive concerns about bodily aches and pains.

Depression worsens the outcome for co-morbid medical conditions and is the main risk factor for suicide in older people. It reduces quality of life for elderly people and is a cause of disability in its own right in this patient group.

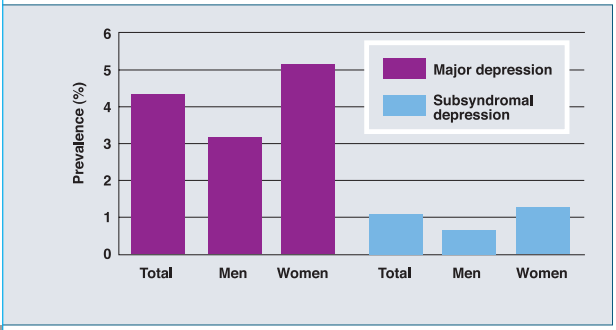

Figure 1. Community prevalence of depression in the elderly.
Adapted from Steffens DC, Skoog I, Norton MC, et al. Prevalence of depression and its treatment in an elderly population: the Cache County study. Arch Gen Psychiatry 2000;57(6):601-7.

In evaluation of a first episode of depression in older patients, numerous medical disorders and other factors associated with age and depression should be considered. Onset of depression may precede a medical disorder (eg, Alzheimer's disease, Parkinson's disease), may be comorbid with a medical disorder (eg, myocardial infarction [MI]), or may follow a medical condition, as often happens after a stroke.

Depression is common in patients with cancer, and 80% of all cancers occur in persons older than 60 years. Depressed mood in patients with a serious medical illness needs to be distinguished from the syndrome of major depression.

What depression is :

The following distinguish major depressive disorder from understandable sadness :

- ❏ Duration (symptoms present for at least two weeks);
- ❏ Lack of fluctuation of symptoms (symptoms occur on most days, most of the time); and
- ❏ Intensity (must be of a degree that is not normal for that individual)

Main features of depression (WHO, 1993)

***Core symptoms* :**

- ❏ Depressed mood for at least two weeks
- ❏ Loss of interest or pleasure in normal activities
- ❏ Decreased energy and increased fatigue

***Additional symptoms* :**

- ❏ Loss of confidence or self-esteem
- ❏ Feeling of helplessness
- ❏ Inappropriate and excessive guilt
- ❏ Recurrent thoughts of death, thoughts of self-harm or suicide
- ❏ Diminished evidence of ability to think or concentrate
- ❏ Agitation or retardation
- ❏ Sleep and appetite disturbance
- ❏ Avoidance of social interaction/going out

For a mild depressive episode there must be two core symptoms and at least four additional symptoms. To make a diagnosis of moderate depression there should be two core symptoms and at least six additional symptoms. For a severe depressive episode all three core symptoms and at least five additional symptoms should be present.

Clinical feature :

The clinical manifestation of later-life depressive disorder may be different to that seen in other age groups. When depressed , older people complain less often of sadness than their younger contemporaries. Hypochondriasis is consistently reported as a common symptom in late-life depression, as is anxiety.

Subjective memory complaint may be a leading symptom in depression and may require exclusion of the diagnosis of dementia. Dementia, however, can initially present as an apparent depressive illness. Cultural factors may modify the presentation of depressive disorder : for example, it has been reported that elderly people from South Asia are more likely to present with physical symptoms rather than with depressed mood.

Types of depressive disorder in later life

Typical major depression accounts for only between one-quarter and a third of older people with significant depressive symptomatology. There is no consensus as to what to call depression that is non-major. Recent evidence suggest that 'minor' and 'major' depression in older people share similar risk factors (such as poor health, isolation & disability) ; both are associated with reduced physical activity, less social contact and increased mortality. So-called 'minor' depression is a risk factor for major depression.

In older people depressive symptoms can be due to the effects of a systemic disorder (such as Parkinson's disease or stroke) or a drug or both. The term 'adjustment disorder' is used when symptoms of low mood and anxiety arise within one month of a major life event such as bereavement or acute illness. A new category of vascular depression has been

Depression in the Elderly

proposed with typical features of reduced insight, apathy and retardation as well as cognitive impairment.

Etiology

There are a number of factors that increase the risk of developing depressive symptoms. There are also factors that are protective, and may counterbalance the risk factors. Life events and chronic stress have been implicated in the development of depression.

Risk and protective factors associated with depression

A. *Risk factors* :

- ❏ Gender : females are at greater risk than males
- ❏ Past history of depression
- ❏ Family history of depression
- ❏ Marital status : widowed and divorced
- ❏ Personality : obsessional traits
- ❏ Co-morbidity : physical illness and disability
- ❏ Being a carer
- ❏ Structural brain changes (such as Parkinson's disease)
- ❏ Vascular

B. *Protective factors* :

- ❏ Good general health : physical fitness, nutrition
- ❏ Coping behaviors
- ❏ Social supports

Persons who develop their first depression in old age are very likely to have very small on head imagery that indicate tiny spots in the brain may not receive adequate blood. Consequent chemical changes in these cells enhance the likelihood of depression, apart from any life stress.

Precipitating factors in depression

***Life events* :**

- ❏ Bereavement
- ❏ Separation
- ❏ Acute physical illness
- ❏ Moving house
- ❏ Financial crisis

***Chronic stress* :**

- ❏ Declining health
- ❏ Sensory loss
- ❏ Housing problems
- ❏ Socioeconomic status
- ❏ Marital difficulties
- ❏ Being a carer (particularly for a person with dementia)
- ❏ Social isolation
- ❏ Alcohol
- ❏ Drugs (such as-blockers, analgesics, anti-Parkinson's drugs, antipsychotics)

Diagnosis

Diagnosis is made as for any other chronic disease, that is :

- ❏ Elicit the history, including core symptoms, onset of low mood, triggers, previous history of depression, current medication, alcohol or benzodiazepine misuse and whether the patient is a carer.

- ❏ Assess the mental state, looking for evidence of cognitive impairment or psychotic symptoms (using the Geriatric Depression Scale)

Geriatric Depression Scale (GDS – 4)

- Are you basically satisfied with your life ? *(score 1 for **no**)*
- Do you feel that your life is empty ? (*score 1 for **yes***)
- Are you afraid that something bad is going to happen to you ? *(score 1 for **yes**)*
- Do you feel happy most of the time ? *(score 1 for **no**)*

A score of two or more is suggestive of depressive disorder

- ❏ Explore patient views – especially their views on the cause of their symptoms and what management plans they would engage with.
- ❏ Assess risk of self – harm.

<u>Assessing risk of self – harm</u>

- ◆ **Demography :** older age, male, socially isolated
- ◆ **History :** previous attempts of self – harm
- ◆ **Physical factors :** including chronic illness or disability, alcohol or benzodiazepine misuse
- ◆ **Mental state :** including threat of self – harm,
- ◆ **Planning :** changing will

- ❏ Carry out a physical examination, including focused neurological examination, looking for signs of vascular disease or Parkinsonism.
- ❏ Investigations

Investigations

- ▼ A physical examination will help determine if there is a medical illness causing the depression.

- Psychological evaluation
- Blood tests : CBC or blood differential, thyroid function tests, liver or kidney function tests
- A variety of other tests may be needed.

Management

The goals of treatment of a depressive episode are to bring about remission of all depressive symptoms and to reduce risk of self-harm neglect. Treatment must aim to help the patient achieve optimal function (physical, psychological and social) and to prevent relapse. Sometimes depression can be alleviated by social interventions to help with isolation or loneliness such as group outings, volunteer work for the healthy elderly, or regular visits from concerned people.

Treatment options are:

- Antidepressant treatment
- Psychological treatment
- Electroconvulsive Therapy (ECT)

Antidepressant Medicines

Selective Serotonin Reuptake Inhibitors (SSRIs) are the first choice for treatment of depression in elderly patients. Compared with tricyclic antidepressants (TCAs) they are much safer in overdose and, for the most part, their side effects are better tolerated. Most antidepressants are effective in the elderly, choice of drug is based on an agent's side effect profile and its potential to interact with other medications.

Psychotherapy

Most depressed people find that support from family and friends, involvement in self-help and support groups, and psychotherapy are very helpful.

Psychotherapy is especially beneficial for those patients who prefer not to take medicine, as well as for those not suitable for treatment with drugs because of side effects, interactions with other medicines, or other medical illnesses. The use of psychotherapy in older adults is beneficial with a broad range of functional and social consequences of depression. Many doctors recommended the use of psychotherapy in combination with antidepressant medicines.

Electroconvulsive Therapy (ECT)

Neuroleptic medications may help treat agitation in some individuals. ECT plays an important role in the treatment of depression in older adults. Because many older patients are unable to take traditional antidepressant medicines due to side effects or interactions with other medications they may taking. ECT is an extremely effective alternative.

Side-effects of antidepressants

Tricyclics :

Anticholinergic : dry mouth, constipation, urinary retention, cardiotoxicity, confusion
Antihistaminic : over-sedation, weight gain
Adrenergic : postural hypotension

SSRIs :

Nausea, Diarrhea, Insomnia, Anxiety, Sexual dysfunction, Headache, Weight loss, Hyponatremia, Discontinuation syndromes.

Some Other Problems may Affect Treatment of Depression in the Elderly

The stigma attached to mental illness and psychiatric treatment is even more powerful among the elderly and is often shared by members of the patient's family, friends, and neighbors. This stigma can keep elderly patients from seeking treatment. In addition, depressed older people may not report their depression because they believe there is no hope for help.

Elderly people may also not be willing to take their medicines because of side effects or cost. In addition, having certain other illnesses at the same time as depression can interfere with the effectiveness of antidepressant medicines.

Alcoholism and abuse of other substances may interfere with effective treatment, and unhappy life events -- including the death of family or friends, poverty, and isolation -- may also affect the patient's motivation to continue with treatment

Prognosis

The outcome of depressive disorder in older people is generally as good as other age group. There may be more susceptibility to relapse in older patients, but the risk of relapse can be reduced by continuing antidepressants.

Complications

Depression may be complicated by Alzheimer's disease or other forms of dementia. It may also complicate other medical conditions in the elderly. Untreated depression in the elderly is associated with a high rate of suicide.

Prevention

Prevention is related to the contributing factors. Social support that help deal with losses, mobility changes and so on can be helpful. In many cases, there is no effective prevention.

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Drug Hypersensitivity Reactions

In the early 1900s, the German scientist Paul Ehrlich described an ideal drug as a "magic bullet". His vision was to invent such a drug that would function precisely at a disease site and would not harm healthy tissues. Although many drugs have been developed since then, none of them could match his criteria precisely. Most drugs produce multiple effects, but only one is considered as therapeutic effect. Other effects may be regarded as unwanted, whether they are harmful or not. These unwanted effects are usually referred as side effects or adverse drug events. However, the term adverse drug reaction is technically more appropriate to describe drug effects which are unwanted, unpleasant, noxious or potentially harmful.

Adverse drug reactions are very unfortunate but common part of modern medical practice. It includes all adverse events related to drug administration, regardless of etiology. The majority of adverse drug reactions is caused by predictable, non-immunologic effects and is mostly due to pharmacologic action of the drug. Drug hypersensitivity reactions or drug allergies are immune mediated side effects and are not predictable. Following data may give us a glimpse of the situation regarding adverse drug reactions. In the American population an estimated 5% to 15% of treated patients suffer from adverse effects. Up to 30% of hospitalized patients experience at least one adverse drug reaction and about 3% of emergency admissions and 0.3% of hospital admissions are attributed to such reactions. Among these adverse effects only 5% to 10% are due to allergic drug reactions.

Drug hypersensitivity or drug allergy results from interactions between a pharmacologic agent and the human immune system. Despite lower incidences, drug allergy is very important because of its potential morbidity and mortality. Therefore, it is important to identify patients who have had an allergic reaction to a particular medication or class of medications. To understand the problem better, classifying adverse drug reactions should be a useful tool.

Types of adverse drug reactions

Certain adverse drug reactions can occur in anyone. One of the most common reactions is *overdoses*, caused either due to excess intake, or due to impaired excretion or metabolism of the drugs, causing toxic effects. Secondly *side effects*, which are undesirable yet potentially unavoidable pharmacologic actions of the medication, such as dry mouth from antihistamines. *Secondary effects* are adverse reactions those have nothing to do with the pharmacologic actions of the drug. As for example, oral candidiasis or thrush may occur following treatment with antibiotics or corticosteroids. Lastly, *drug interactions* involving two or more drugs causing toxicity which otherwise would not be present.

There are other adverse effects however, occur only in susceptible patients. Such as, *drug intolerance*, caused by lower than normal threshold to the pharmacological action of a particular drug unique to the patient. *Drug allergies* are hypersensitivity reactions involving immunologic mechanisms. *Pseudoallergies* are similar to allergic reactions but they lack drug specific IgE. Lastly *idiosyncratic reactions*, usually resulted from genetically determined metabolic or enzyme deficiency particular to the patient.

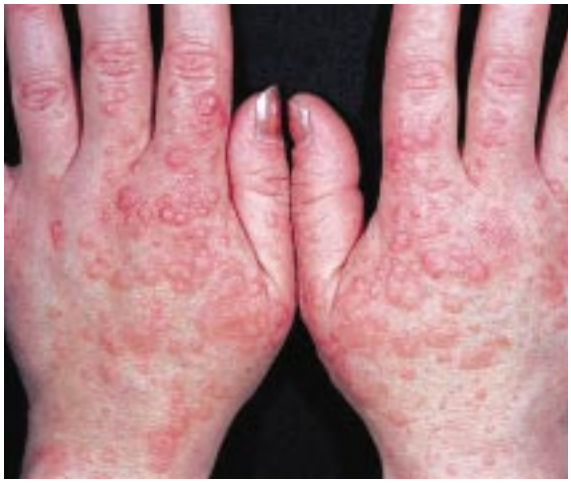

Figure: Erythema multiforme

True hypersensitivity reactions are great imitators of diseases and may present with involvement of any organ system, including systemic reactions such as anaphylaxis. Drug reactions usually manifest with dermatologic symptoms most common of which is morbilliform rashes. Erythematous or maculopapular rashes may appear within one to three weeks after drug exposure, originating on the trunks then spreading to the limbs. Urticaria is typically a manifestation of a truly allergic Type I reaction. Severe non-allergic hypersensitivity cutaneous reactions represent bullous skin diseases. Eczematous rashes are most commonly associated with topical medications and usually represent contact dermatitis. To correlate the clinical symptoms with the underlying immune mechanism, drug hypersensitivity reactions are classified into four categories described by Gell and Coombs (see Table). However there are many other factors that contribute to hypersensitivity reactions.

Factors affecting drug hypersensitivity:

Chemical properties and molecular weight of the drug are the most important drug related risk factors for drug hypersensitivity. Larger drugs with greater structural complexity are more likely to be immunogenic. For a molecule to be regarded as immunogenic it should have a molecular weight greater than 1,000 Daltons and heterologous serum proteins (eg. heterologous antiserum),

Type	Immune reaction	Mechanism	Clinical Manifestations	Timing of reactions
Type I	IgE mediated	Drug IgE complex binding to mast cells with release of histamine, inflammatory mediators	Urticaria, angioedema, bronchospasm, pruritus, vomiting, diarrhea, anaphylaxis	Minutes to hours after drug exposure
Type II	Cytotoxic	Specific IgG or IgM antibodies directed at drug hapten coated cells	Hemolytic anemia, neutropenia, thrombocytopenia	Variable
Type III	Immune complex	Tissue deposition of drug-antibody complexes with complement activation and inflammation	Serum sickness, fever, rashes, arthralgias, lymphadenopathy, urticaria, glomerulonephritis, vasculitis	1 to 3 weeks after drug exposure
Type IV	Delayed, cell mediated	MHC presentation of drug molecules to T cells with cytokine and inflammatory mediator release	Allergic contact dermatitis, maculopapular drug rash	2 to 7 days after cutaneous drug exposure

Table: Gell and Coombs classification of drug hypersensitivity reactions

enzymes (eg. streptokinase) and hormones (eg. insulin) being the common examples. But most of the drugs have a low molecular weight, thus they react as haptens, binding to a carrier protein for induction of a specific immune response.

Further more, not all the drugs, those cause hypersensitivity reactions, are chemically reactive themselves. Initially, these medicines require to be metabolized before they bind to carrier molecules, a process known as bio-activation. The potential role of metabolism is the bio-activation of drugs in generating a chemical signal for activation of the immune system. Thus, a drug which may not be immunogenic itself may produce metabolites which are highly reactive.

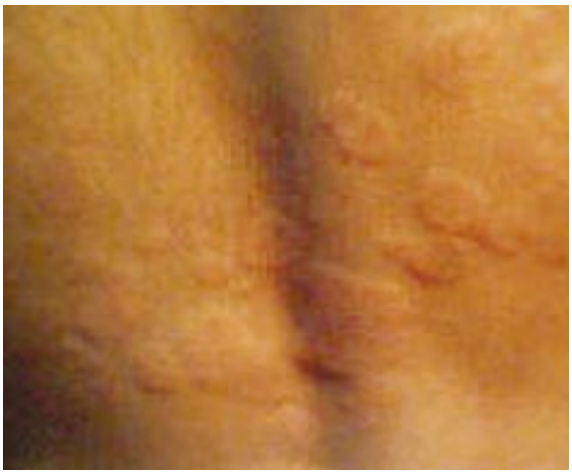

Figure: Urticaria

In fact, almost all drugs associated with a comparatively high incidence of hypersensitivity reactions are known to form reactive metabolites. While liver is quantitatively the primary site of bio-activation for most drugs, the process may also occur in other organs such as skin, kidney or gut.

Another factor affecting the frequency of hypersensitivity reactions is the route of drug administration. Intramuscular and intravenous administrations are more likely to cause drug hypersensitivity and are regarded as most immunogenic route. Allergic contact dermatitis is usually a form of delayed type hypersensitivity reaction following topical administration of medicines. Intermittent and repetitive administration of a certain drug may also contribute to sensitize the immune mechanism of the body. Sensitive patients can then react to minimum doses, especially if given parenterally. However, topical administration of drugs may also result in initiating immune response and consequent allergic reaction.

Cross reactivity is another crucial problem. It is characterized by an immune response to a medication in an individual who has previously sensitized to another similar drug. Reactivity to side chains, as well as to the main structures has been demonstrated. Beta-lactam antibiotics, such as penicillins and cephalosporins, are the most common examples. For a proper diagnosis all of these factors should be taken into consideration.

Diagnosis

Identifying a culprit drug causing reaction is often difficult. Patients frequently take multiple drugs at the same time and the clinical symptoms of drug hypersensitivity reactions may overlap with the symptoms of the underlying disease. The general lack of knowledge of the immunochemistry of drug and its metabolites also greatly hampers the ability to accurately use diagnostic tests to evaluate allergic drug reactions. Another point to be kept in mind is that commercial availability of specific tests is limited. However, determining the causal agent is important for proper management and for guidance in future selection of medications for that patient.

Drug Hypersensitivity Reactions

History of the patient:

Evaluation of a suspected allergic reaction should start with a detailed medical history. All medication taken by the patient, along with doses, indications, date of initiation and duration of therapy should be documented. Details of ongoing medial problems and conditions should be obtained.

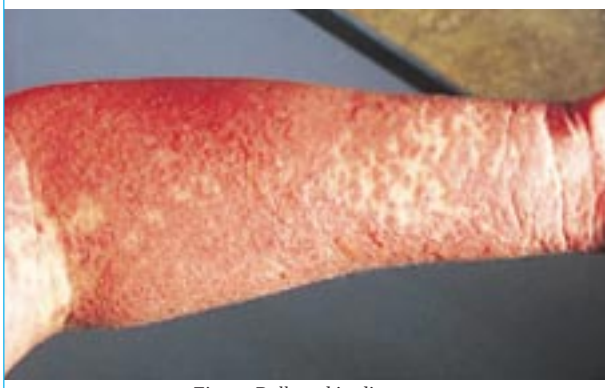

Figure: Bullous skin disease

Clinical manifestations of reaction, associated symptoms are also important. Patients with a history of previous allergic reactions appear to be at increased risk of subsequent attacks even the drugs are chemically dissimilar. Proximity of drug administration to the onset of allergy is important, because agents already used for a long time is less likely the cause than recently introduced agents.

Skin prick test:

Skin testing has an established role in evaluation of IgE-mediated or type I hypersensitivity reactions. But the test is limited to penicillin allergy, muscle relaxants, barbiturates, insulin and biologicals including streptokinase and latex. However, evaluation may be hampered by the relative unavailability of relevant drug metabolites and appropriate multivalent testing reagents. Also, skin testing cannot be done along with antihistamines, tricyclic antidepressants, high doses of sympathomimetics, or any drug that affects the skin test response. Preferably skin testing should be performed 4 to 6 weeks after a reaction. A scratch or puncture test should be done before intradermal test for safety of the patients.

Drug provocation test:

To confirm a suspected drug allergy, rigorous drug provocation test is often required, which is performed in carefully controlled settings possibly in a hospital environment. Either the suspected drug or an alternative, structurally or pharmacologically related drug is given in much lower doses. The dose is increased once every 30 minutes until the daily dose is administered or symptoms of a drug reaction appear. If the symptoms or signs of drug reaction occur within 2 hours of last dose, then the provocation test is considered positive. Positive test results are more suggestive of drug hypersensitivity. Even negative results are important in the sense that the patient may require the medicine which was falsely suspected of causing allergy.

However, drug provocation test can be potentially dangerous and poses certain risks to the patients that should not be taken lightly. Patients often are reluctant to undergo provocative drug challenge when they are convinced that they have had adverse effects from that particular medication. Furthermore, drug provocation test should not be performed on patients with severe comorbid illnesses. Absolute contraindication to this test include patient with severe life threatening reactions such as vasculitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms with organ involvement. Still, provocative drug challenge is considered gold standard of in vivo tests.

In vitro tests:

Among the in vitro tests, radio-allergo-sorbent test (RAST) is a solid phase radioimmunoassay that measures circulating allergen-specific IgE antibodies. RAST and RAST analogues are performed by linking the allergen to a solid phase and incubating with the patient's serum, during which specific antibodies of all immunoglobulin isotypes are bound. A second incubation is done with a radio-labeled, highly specific anti-IgE antibody. The bound radioactivity is then directly related to the drug-specific IgE antibody content in the patient's serum. Results are then compared with a positive reference serum and a negative control serum. Unfortunately, application of RAST for diagnosing a drug allergy is limited because of incomplete knowledge of the structure of most drugs and their metabolites.

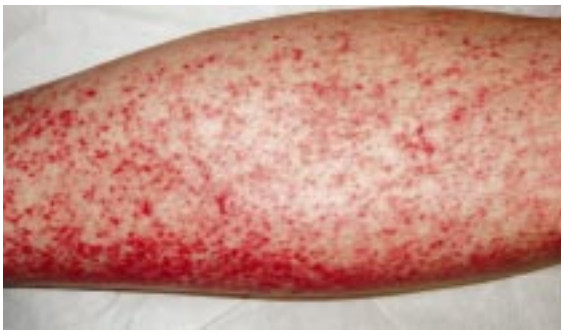

Figure: Drug eruption

Solid phase immunoassays have been developed to detect serum IgE antibodies against the major penicillin determinant. On the other hand, no in vitro RAST is available for minor penicillin determinant antibodies. Immunogenic determinant of many other drugs are undefined, which makes the predictive value of in vitro tests poor.

Other laboratory tests:

Measuring mast cell activation may be helpful if obtained with in four hours of onset of allergic reaction. While, serum histamine levels peak five minutes after anaphylaxis and return to base line within 30 minutes. Serum beta-tryptase levels peak one hour after anaphylaxis and remain elevated for two to four hours after the event. Cytotoxic or Type II reactions result in hemolytic anaemia, thrombocytopenia, or neutropenia and can be diagnosed with a complete blood count.

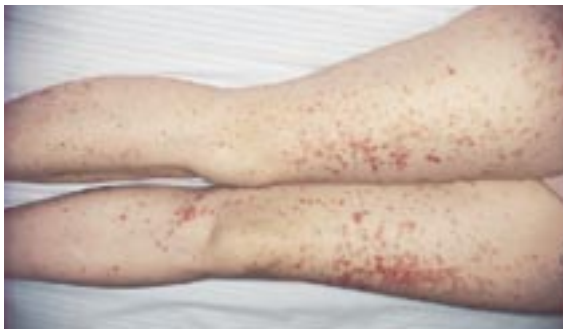

Figure: Maculopapular exanthema

Hemolytic anemia may again be confirmed by positive direct or indirect Coomb's test. In type III or immune complex drug reactions, elevation of nonspecific inflammatory markers such as erythrocyte sedimentation rate and C-reactive protein may occur. More specific laboratory testing for complement levels or circulating immune complexes can be conducted. Patch testing for specific drug agents is an appropriate diagnostic tool for Type IV immune reactions which usually presents with allergic contact dermatitis. Other positive signs for confirmation include erythema, induration and pruritic vesiculo-papular rash developing 48 hours after patch application.

Therapy and management

The most important and effective treatment measure against drug allergy is immediate discontinuation of the offending medication. In the majority of cases, symptoms will resolve within two weeks if the diagnosis is correct. Anaphylactic or anaphylactoid reactions are severe and require emergency treatment. Additional therapy is largely supportive and symptomatic. Intramuscular administration of epinephrine has proven effective in most cases. An intramuscular antihistamine and an intravenous corticosteroid should be added to this treatment. Severe drug reactions such as Steven-Johnson syndrome and toxic epidermal necrolysis require additional intensive therapy.

Pretreatment with corticosteroids or antihistamines is controversial. Substitution with an alternative drug with dissimilar chemical structure may be considered when available. Benefit of discontinuation or substitution should be closely monitored. In some cases, when the offending drug cannot be replaced by a better medicine, desensitization is recommended. Very small incremental doses of the drug are administered every 20-30 minutes. The mechanism appears to be gradual absorption of specific IgE with incremental amounts of drug. Thus sudden release of massive amounts of histamines is avoided. This is a potentially dangerous procedure requiring continuous monitoring settings and should not be used if any suitable alternative exists.

Summary

Drug hypersensitivities are iatrogenic diseases that are unpredictable and embarrassing to the clinician. The cost of allergic reactions for health services is often underestimated since most reactions occur in outpatients. The question of whether it is safe to re-administer a medication is an important clinical judgment, because alternative drugs may be less effective, or may have greater toxicities or costs, or both. Drug hypersensitivities are more diverse and often more complicated than solely IgE mediated reactions. Areas of on going research to improve diagnostic precision for allergic drug reactions include further understanding of the immuno-chemistry of allergenic medications, improvement of in vitro assays, and further validation of computer aided evaluation of adverse drug events. Improving the understanding of drug allergies not only allow to avoid the offending medicine in the future but might also provide hints to understand imitated diseases. At present, the primary diagnostic tool for properly assessing drug hypersensitivity reactions remains a thorough and detailed history obtained by the respective physicians.

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Test Yourself - 22

Correct Answers :

1.	b		2.	a		3.	b		4.	b	d	5.	a	c	6.	c	d

CONGRATULATIONS!

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Test Yourself - 23

1. **All the following regarding "Drug Resistant TB" is correct except:**
   a. MDR-TB is a "man-made" disease.
   b. WHO ranked Bangladesh fifth among the high burden TB countries.
   c. Estimated number of new TB cases in Bangladesh is more than 319000.
   d. Bangladesh implemented DOTS in 1994.
2. **The following points are true for "Depression in the Elderly" except:**
   a. "Agitation or retardation" is one of the core symptoms of depression.
   b. Acute physical illnesses, separation, sensory loss, are among the precipitating factors of depression.
   c. SSRIs are the first choice for treatment of depression in the elderly.
   d. ECT plays an important role in the treatment of depression in young adults.
3. **The below mentioned points are true for "Drug Resistant TB" except:**
   a. "Standardized treatment" is one of the treatment strategies for MDR-TB.
   b. Group -1 antitubercular drugs are the most potent and best tolerated.
   c. Streptomycin, Kenamycin, Terizidone are included in the Group -2 antituberculosis drugs.
   d. The Group -5 drugs are not recommended by WHO for routine use in MDR-TB.
4. **All the following points are true for "Anca" (Cefprozil) except:**
   a. It is contraindicated in patients with impaired renal function.
   b. It is available in "tablet" and "suspension" form.
   c. Cefprozil is in the FDA pregnancy category A.
   d. No dosage adjustment necessary for patients with impaired hepatic function.
5. **The following are correct regarding "Drug Hypersensitivity Reactions" except:**
   a. "Overdose" is not a common type of adverse drug reaction.
   b. Urticaria is typically a manifestation of a truly allergic type 1 reaction.
   c. Drug hypersensitivity reactions are classified into five categories.
   d. Drug hypersensitivities are more complicated than solely IgE mediated reaction.
6. **All the following points are true for "Drug Resistant TB" except:**
   a. Pregnancy is not a contraindication for treatment of active drug resistant TB.
   b. Children with drug- resistant TB do not tolerate the second line drugs well.
   c. Diabetic patients with MDR-TB are at risk for poor outcomes.
   d. Oral hypoglycemic agents are contraindicated during the treatment of drug-resistant TB.

Soon our officials will be visiting you with a token of our appreciation

Maldives's Minister of Economic and Trade Visited SQUARE's Dhaka Plant

The Honorable Minister of Economic Development and Trade of Maldives His Excellency Mr. Mohamed Jaleel visited to *SQUARE* Pharmaceuticals state-of-the-art Dhaka Plant on the 21st April, 2006. Higher officials from the Export Promotion Bureau accompanied the honorable minister during the visit.

The visiting Minister was delighted to see first-hand such world-class pharmaceutical production facility in Bangladesh. He was particularly attracted to the Plant's adoption of the latest technologies in manufacturing and quality assurance. The Plant has been built in conformance with the US FDA and UK MHRA requirements. During the course of the Plant visit, at a discussion, he expressed his willingness to expand relations in pharmaceuticals between Maldives and Bangladesh. *SQUARE* has already completed the necessary regulatory measures for exporting its pharmaceuticals products to Maldives.

Minister from Niger Visited SQUARE's Dhaka Plant

His Excellency Dr. Galadima Ousmane, Honorable Minister of Secondary and Higher Education, Research and Technology of Niger, accompanied by the high officials of Government of Niger, has visited *SQUARE* Pharmaceuticals world class manufacturing facility at Kaliakoir recently.

Mr. Muhammadul Haque, Director, Marketing of *SQUARE* Pharmaceuticals Ltd. welcomed the delegation and briefed on different activities of *SQUARE* group. The Honorable Minister, whose educational background is Pharmacy, has shown keen interest in all the facilities in the sprawling site. The onsite Building Energy Management System and documentations attracted the visitors' special attention.

Incidentally, Niger is *SQUARE*'s 26th export destination and first consignment to the country is in shipment process.

SQUARE's Participation at the 7th SAARC Trade Fair at Karachi, Pakistan

SQUARE Pharmaceuticals Ltd. the leading and the largest pharmaceutical company from Bangladesh participated at the 7th SAARC Trade Fair at Karachi, Pakistan. The Fair was held at the Karachi Expo Centre from the 16th to the 18th of June, 2006. *SQUARE*'s stand situated at a prime location at the Main Hall of the Expo Centre attracted a large number of audiences who were keen to know about the company, its world-class manufacturing facilities and its quality products being presently exported to 28 countries world-wide. On the inaugural day, the 16th of June, 2006, Dr. Saeeda Malik the Minister for Women Development of the Sindh Province in Pakistan who made the official opening of the Trade Fair took a particular interest in the company by visiting its stand with other high-ranking government officials, and inquired about its products and its global activities. She was delighted to know that *SQUARE* being the only local pharmaceutical entity from Bangladesh, which is on the verge of entering the regulatory markets of UK and the European Union. During its participation at the 7th SAARC Trade Fair at Karachi, the company has made contacts with some of the most influential and respected local and global pharmaceutical entities that are operating in Pakistan. They have shown great interest in *SQUARE*'s products, especially its huge range of products in different therapeutic classes to offer to the Pakistan Pharmaceutical Market, and most importantly, its wide range of newer molecules, combination drugs and some of its specialized products like inhalers, suppositories, nasal sprays that have a very unique demand in the Pakistan Pharmaceutical Market. The company has already forged ahead to evaluating these potential prospects for the final selection of partners who would best serve its long-term interest in this highly lucrative market. *SQUARE* plans to launch its operation in Pakistan very soon.

Product Profile-Anca®

Anca®

Composition

Anca® 250 tablet : Each tablet contains Cefprozil USP 250 mg.

Anca® 500 tablet : Each tablet contains Cefprozil USP 500 mg.

Anca® suspensions : After reconstitution each 5 ml suspension contains Cefprozil USP 250 mg.

Pharmacokinetics

Following oral administration of Cefprozil to fasting subjects, approximately 95% of the dose is absorbed. The average plasma half-life in normal subjects is 1.3 hours, while the steady state volume of distribution is 0.23 L/kg. The total body clearance and renal clearance rates are approximately 3 ml/min/kg and 2.3 ml/min/kg, respectively. Plasma protein binding is approximately 36% and is independent of concentration in the range of 2 mcg/ml to 20 mcg/ml.

Indication

Cefprozil is indicated for the treatment of patients with mild to moderate infections listed below:

- Skin and Skin Structure Infections
- Upper Respiratory Tract Infections including -
  - Pharyngitis/Tonsillitis
  - Otitis Media
  - Acute Sinusitis
- Lower Respiratory Tract Infections including -
  - Secondary Bacterial Infection of Acute Bronchitis
  - Acute Bacterial Exacerbation of Chronic Bronchitis
  - Pneumonia
- Acute Uncomplicated Urinary Tract Infections

Dosage & Administration

Cefprozil is administered orally

Population/Infection	Dosage (mg)	Duration (days)
Infants & children (6 months -12 years)		
Upper Respiratory Tract†		
Otitis Media	15 mg/kg q l2 h	10
Acute Sinusitis	7.5 mg/kg q 12 h or	10
(For moderate to severe infections the higher dose should be used)	15 mg/kg q 1 2 h	
Children (2 years 12 years)		
Upper Respiratory Tract†		
Pharyngitis/Tonsillitis	7.5 mg/kg q 12 h	10*
Skin and Skin Structure†		
Uncomplicated Skin and Skin Structure Infections	20 mg/kg q 24 h	10
Adults (13 years and older}		
Upper Respiratory Tract		
Pharyngitis/Tonsillitis	500 q 24 h	10*
Acute Sinusitis	250 q 12 h or	10
(For moderate to severe infections the higher dose should be used)	500 q 1 2 h	
Lower Respiratory Tract		
Secondary Bacterial infection of Acute Bronchitis and Acute Bacterial Exacerbation of Chronic Bronchitis	500 q 12h	10
Skin and Structure		
Uncomplicated Skin and Skin Structure Infections	250 q 12h or 500 q 24 h or 500 q 12h	10

* In the treatment of infections due to Streptococcus pyogenes. cefprozil should be administered for at least 10 days.

† Not to exceed recommended adult doses.

Renal Impairment

Cefprozil may be administered to patients with impaired renal function. The following dosage schedule should be used:

Creatinine Clearance (ml/min)	Dosage (mg)	Dosing Interval
3O-12O	standard	standard
O-29*	50% of standard	standard

* Cefprozil is partly removed by hemodialysis, therefore, Cefprozil should be administered after the completion of hemodialysis.

Hepatic Impairment

No dosage adjustment is necessary for patients with impaired hepatic function.

Contraindication

Cefprozil is contraindicated in patients with known hypersensitivity to the Cephalosporins or to any of the constituents of the preparations.

Side effects

Cefprozil may cause following side effects-

- diarrhea
- vomiting
- stomach pain
- dizziness

Some side effects may be serious but occurs very rarely such as -

- severe skin rash
- itching
- difficulty in breathing or swallowing
- painful sores in the mouth or throat
- yellowing of the skin and eyes
- wheezing
- vaginal discharge and itching
- diaper rash

Drug Interaction

Nephrotoxicity has been reported following concomitant administration of Aminoglycoside antibiotics and Cephalosporin antibiotics. Concomitant administration of Probenecid doubles the AUC for Cefprozil. The bioavailability of the capsule formulation of Cefprozil is not affected when administered 5 minutes following an antacid.

Pregnancy and Lactation

Cefprozil is in the FDA pregnancy category B. This means that it is not expected to be harmful to an unborn baby. Still during pregnancy the drug should be used according to physician's recommendation.

Most Potent Tobacco Carcinogen Found !

Researchers have identified a key compound in cigarettes which appears to be the main culprit causing lung cancers. The chemical acrolein, found in tobacco and also in some cooking oils, is being blamed for the prime cause of lung cancer according to studies conducted with lung cancer cells. It can trigger DNA mutations in cells while reducing the cell's ability to repair the damage.

Cigarettes have a lot of carcinogens, some are more potent and more abundant than others. Previously polycyclic aromatic hydrocarbons (PAHs), a class of carcinogens, were attributed for the cause of lung cancer. But acrolein is found to be 10,000 times more prevalent than PAHs. Alarmingly, cigarettes are not the only source of acrolein. Women, those who cook with oils that are heated to very high temperatures release huge amount of acrolein, can also suffer from lung cancer.

Source: HealthDay, October 2, 2006

Anesthesia Device For Single Tooth

Instead of numbing the entire side of the mouth, now the dentists can sedate a single tooth. Previously dentists used mandibular block, a form of local anesthesia, which used to numb one entire side of the mouth, including the lip, tongue and inside of the cheek. The main disadvantage was that the dentist could block only one side of the mouth at a time. The alternate form of local anesthesia called periodontal ligament (PDL) injection numbs a single tooth that demands repair. Although this avoids affecting surrounding tissues, current techniques for delivering PDL injections were quite painful and difficult to administer. A new Single Tooth Anesthesia (STA) device has recently been developed to make PDL injections easier. The device uses patented computer controlled technology to measure pressure at the tip of the needle, allowing dentists to accurately inject the precise location necessary for an effective anesthesia. This will open up the opportunity for the dentist to work on both side of the mouth during the same visit.

Source: HealthCentersOnline, September 4, 2006

New Hope For Incurable Hepatitis C

Researchers have come up with a new drug combination for Hepatitis C patients who do not respond to existing medications. While 170 million people worldwide are being affected with Hepatitis C, only a little more than half of them can be cured by current medical therapies. The other half, comprising 40 to 50 percent, typically do not respond to most recent drugs such as pegylated interferon and ribavirin therapy, and usually have the most severe liver disease. A new study has tested the combination of ribavirin and infergen – a highly potent form of interferon, on patients having severe liver disease. After six months, about 15 to 20 percent of the patients were tested negative for the Hepatitis C virus. Though the findings are reported as preliminary results of the study, it will provide new hope to the non-responders who face gradual decline of their liver function and ends up in fibrosis, cirrhosis and liver cancer.

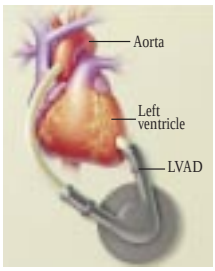
Source: Ivanhoe, October 30, 2006

New 3D MRI Scans Would Cut Diagnosis Time

A new software system has been developed which converts MRI data into a three dimensional picture of the patient's body. Conventional MRIs image dozens of dozens of flat pictures of just slices of patient's anatomy. The process is not only time consuming, taking about an hour, but also patients are required to lie down perfectly still while the machine scans, often needing sedatives. On the other hand 3D scans allow doctors to virtually swim through the patient's body and determine exactly what needs to be done to correct a problem. Also, long before stepping into the operating room surgeons can sit in front of a computer and see exactly what they will encounter when they cut into a patient. The new system is fast, only requiring 5 to 10 minutes to scan and can image very young patients with little or no sedation.

Source: Ivanhoe, October 11, 2006

Implanted Ventricular Device Reverses Severe Heart Failure



Intensive drug therapy administered directly into heart muscle has healed patients with most severe form of heart failure. Medicines were administered through a battery-operated pump implanted in the left ventricle which no longer pumped blood to the body. The left ventricular assist device used a mixture of pharmaceutical drugs which was not just standard therapy. The drugs were delivered in two stages. Initially commonly used drugs such as beta blockers, ACE inhibitors and digoxin were used in treating early stages of heart failure. These drugs help heart to work harder and slow heart failure for a prolonged time. However, in later stages they lower blood pressure or caused renal failure. At this stage clenbuterol, a drug developed in Germany, is used to strengthen the heart. Among the 15 patients who received the treatment, 11 were able to remove the device and four years after 9 were still alive free from heart failure. The new approach not only helps the heart muscle get better but also strengthens and thickens it.

Source: HealthDay, November 1, 2006

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But

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