


8. Calculation of Doses: Patient Parameters



Objectives

Upon successful completion of this chapter, the student will be able to:

- Describe factors to consider in determining doses for pediatric and elderly patients
- Calculate doses based on factors of age, body weight, and body surface area.
- Utilize dosing tables and nomograms in calculations.
- Calculate doses for single and combination chemotherapy regimens.



Introduction

- n The **usual dose** of a drug is the amount that ordinarily produces the desired therapeutic response in the majority of patients in a general, or otherwise defined, population group.
- n The **drug's usual dosage range** is the range of dosage determined to be safe and effective in that same population group.
 - ∴ provides the prescriber with dosing guidelines in initially selecting a drug dose for a particular patient and the flexibility to change that dose as the patient's clinical response warrants.
- n **Usual doses and dosage regimens** are based on the results of **clinical studies** conducted during the **drug development process** as well as on **clinical information** gathered following the initial approval and marketing of the drug.



- n For certain drugs and for certain patients, drug dosage is determined on the basis of **specific patient parameters**.
 - ∴ include the patient's age, weight, body surface area, and nutritional and functional status.
- n Patients requiring individualized dosage are
 - ∴ neonates and other pediatric patients, elderly patients with diminished biologic functions,
 - ∴ individuals of all age groups with compromised liver and/or kidney function (and thus reduced ability to metabolize and eliminate drug substances),
 - ∴ critically ill patients, and patients being treated with highly toxic chemotherapeutic agents.
- n Certain drugs with a **narrow therapeutic window** often require individualized dosing based on blood level determinations and therapeutic monitoring.
 - ∴ Digoxin at a blood level of 0.9 to 2 ng/mL is considered therapeutic, but above 2 ng/mL it is toxic.'



Pediatric Patients

- n Pediatrics is the branch of medicine that deals with disease in children from birth through adolescence (青少年時期).
- .. **neonate** (newborn): from birth to 1 month;
 - n **Premature**: born at less than 37 weeks' gestation.
- .. **Infant**: 1 month to 1 year;
- .. **early childhood**: 1 year through 5 years;
- .. **late childhood**: 6 years through 12 years;
- .. **Adolescence**: 13 years through 17 years of age.



Pediatric Patients

- n Proper drug dosing of the pediatric patient depends on a number of factors:
 - .. the patient's age and weight,
 - .. overall health status,
 - .. the condition of such biologic functions as respiration and circulation,
 - .. the stage of development of body systems for drug metabolism (e.g., liver enzymes) and drug elimination (e.g., renal system).



n In the neonate:

- Biological functions and systems are underdeveloped.
 - n Renal function develops over the span of the first 2 years of life.
- the most commonly used drugs in neonates, infants, and young children are **antimicrobial agents**, which are eliminated primarily through the **kidney**.
- If the rate of drug elimination is not properly considered, **drug accumulation** in the body could occur, leading to drug overdosage and toxicity.
- Thus, the use of **pharmacokinetic data** (i.e., the rates and extent of drug absorption, distribution, metabolism, and elimination; see Chapter 22), together with individual patient drug handling characteristics and therapeutic response, provides a rational approach to pediatric drug dosage calculations.



- n Doses of drugs used in pediatrics, including neonatology, may be found in **individual drug product literature** as well as in **references**.
- n Calculations associated with pediatric dosing by intravenous infusion are discussed in Chapter 13, and those related to pediatric parenteral and enteral nutrition appear in Chapter 14.

Case in Point 8.1: A hospital pharmacist is asked to determine the dose of clindamycin for a 3-day-old neonate weighing 3 lb. 7 oz. In checking the literature, the pharmacist determines that the dose is listed as follows:⁴

- <1200 g: 10 mg/kg/day divided q12h.
- <2000 g and 0–7 days old: 10 mg/kg/day divided q12h
- <2000 g and >7 days old: 15 mg/kg/day divided q8h
- >2000 g and 0–7 days old: 15 mg/kg/day divided q8h
- >2000 g and >7 days old: 20 mg/kg/day divided q6h

Each divided dose is to be added to an intravenous infusion at the scheduled hour and infused over a period of 20 minutes.

Clindamycin is available in an IV bag containing 600 mg/50 mL of injectable solution. How many milliliters of this solution should be given for each divided dose?

$$\text{Body weight} = 3 \text{ lb } 7 \text{ oz} = 3 \times 454 + 7 \times 28.35 = 1560.45$$

$$10 \text{ mg/kg} \times 1560.45 / 1000 = 15.6 \text{ mg}$$

$$\text{Each divided dose} = 15.6 \text{ mg} / 2 = 7.8 \text{ mg}$$

$$\text{Volume of the injectable solution: } 600 \text{ mg} / 50 \text{ mL} = 7.8 \text{ mg/x}$$

$$X = 0.65 \text{ mL}$$

Case in Point 8.2: A pediatric patient is being administered enalaprilat (VASOTEC IV) every 12 hours by intravenous injection to manage hypertension and possible heart failure.⁴ Based on a dose of 5 mcg/kg, the patient is receiving 55 mcg of enalaprilat per dose. The physician wishes to convert the patient to oral enalapril at a dosage of 100 mcg/kg as a single daily dose. The standard procedure is to crush a 2.5-mg tablet of enalapril, mix with sterile water to make 12.5 mL, and administer the appropriate dose using a calibrated oral dispenser. Calculate the dose, in milliliters, to be administered to this patient.

$$5 \text{ mcg/kg} \times x \text{ kg} = 55 \text{ mcg}$$

$$X = 55 / 5 = 11 \text{ kg}$$

$$100 \text{ mcg/kg} \times 11 \text{ kg} = 1100 \text{ mcg}$$

$$2500 \text{ mcg} / 12.5 \text{ mL} = 200 \text{ mcg/mL}$$

$$1100 / 200 = 5.5 \text{ mL} \dots \dots \dots (\text{Ans})$$



Geriatric Patients

- n The term "elderly" is subject to varying definitions with regard to chronologic age,
- n The functional capacities of most organ systems decline throughout adulthood and important changes in drug response occur with advancing age.
- n Geriatric medicine or geriatrics is the field that encompasses the management of illness disability in the **elderly**.



n Pharmacotherapy:

- .. the use of pharmacologically active substances in the treatment of disease and illness
- .. is of disproportionate use in the elderly compared with other age groups.
- n Some conditions are particularly common in the elderly, including:
 - .. degenerative osteoarthritis,
 - .. congestive heart failure,
 - .. venous and arterial insufficiency,
 - .. stroke,
 - .. urinary incontinence,
 - .. prostatic carcinoma,
 - .. parkinsonism,
 - .. Alzheimer disease.



- n Many elderly patients have coexisting pathologies that require multiple-drug therapies.
- n Medications in the elderly are prescribed not only to relieve symptoms and manage diseases but also to improve bodily function, enhance the quality of life, and prolong survival.



- n Most age-related physiologic functions peak before age 30 years, with subsequent gradual linear decline.
- n Reductions in physiologic capacity and function are cumulative, becoming more profound with age.
- n Kidney function is a major consideration in drug dosing in the elderly because reduced function results in reduced drug elimination.
- n Renal blood flow diminishes nearly 1% per year after age 30, making the cumulative decline in most persons 60 to 70 years of age, about 30% to 40%, a value that is even greater in older persons.'



- n Because reduced kidney function increases the possibility of toxic drug levels in the body and adverse drug effects, initial drug dosing in the elderly patient often reflects a downward variance from the usual adult dose.
- n There is a frequent need for dosage adjustment or medication change due to adverse effects or otherwise unsatisfactory therapeutic outcomes.
- n Pharmacokinetic parameters are important in the dosing of certain drugs in the elderly patient.



- n There are a number of other common features of medication use in the elderly, including:
 - the long-term use of maintenance drugs;
 - the need for multi-drug therapy,
 - with the attendant increased possibility of drug interactions and adverse drug effects;
 - difficulties in patient compliance.
 - n due to impaired cognition, confusion over the various dosing schedules of multiple medications, depression or apathy, and economic reasons.



Special Considerations in Dose Determinations for Elderly Patients

- n Therapy is initiated with a lower-than-usual adult dose.
- n Dose adjustment may be based on the therapeutic response.
- n The patient's physical condition may determine the drug dose and the route of administration employed.
- n The dose may be determined, in part, on the patient's weight, body surface area, health and disease status, and pharmacokinetic factors.
- n Concomitant drug therapy may affect drug/dose effectiveness.
- n A drug's dose may produce undesired adverse effects and may affect patient compliance.
- n Complex dosage regimens of multiple drug therapy may affect patient compliance.



Dosage Forms Applicable to Pediatric and Geriatric Patients

- n solid dosage forms, such as tablets and capsules:
 - .. are preferred for the oral administration of drugs because of their convenience, ease of administration, ready identification, transportation, and lower cost per dose.
 - .. are difficult or impossible for the pediatric, geriatric, or infirm patient to swallow.
- n Liquid forms are preferred, such as oral solutions, syrups, suspensions, and drops.
 - .. An **advantage** of liquid forms is that the dose can easily be adjusted by changing the volume of liquid administered.
 - .. When necessary, liquid forms of medication may be administered by oral feeding tube.
- n **Chewable tablets** and **solid gel forms** (medicated "gummy bears") that disintegrate or dissolve in the mouth are also often used for pediatric and geriatric patients.



DRUG DOSAGE BASED ON AGE

- n The **age** of the patient being treated is frequently a consideration in the determination of drug dosage, especially in the young or elderly.
- n **newborns** are abnormally sensitive to certain drugs because of the **immature** state of their **hepatic and renal function**.
- n **Elderly individuals** may also respond abnormally to the usual adult dose of a drug because of **impaired ability to metabolize or eliminate** the drug or because of other concurrent **pathologic conditions**.



- n Various rules of dosage in which the **pediatric dose** was a **fraction of the adult dose**, based on relative age, were created for youngsters (e.g., **Young's rule**).
- n Today these rules are **not in general use** because age alone is no longer considered a singularly valid criterion in the determination of children's dosage, especially when calculated from the usual adult dose, which itself provides wide clinical variations in response.
- n Some of these rules are presented in the footnote for perspective and historical purposes."

TABLE 8.1 CALCULATION OF PEDIATRIC DOSAGES OF DIGOXIN BASED ON AGE AND WEIGHT

AGE	DIGOXIN DOSE ($\mu\text{g}/\text{kg}$)
Premature	15 to 25
Full term	20 to 30
1 to 24 months	30 to 50
2 to 5 years	25 to 35
5 to 10 years	15 to 30
Over 10 years	8 to 12

From the data in Table 8.1, calculate the dosage range for digoxin for a 20-month-old infant weighing 6.8 kg.

From the data in Table 8.1, calculate the dosage range for digoxin for a 20-month-old infant weighing 6.8 kg.

$$\frac{30 \text{ ug}}{x} = \frac{1 \text{ kg}}{6.8 \text{ kg}}, \quad x = 204 \text{ ug}$$

$$\frac{50 \text{ ug}}{y \text{ ug}} = \frac{1 \text{ kg}}{6.8 \text{ kg}}, \quad y = 340 \text{ ug}$$

Dose range, 204 to 340 μg , answer.



- n **over-the-counter medications** purchased for self-medication include labeling instructions that provide guidelines for safe and effective dosing.
- n For pediatric use, doses generally are based on **age groupings**, e.g., 2 to 6 years old; 6 to 12 years old; and, over 12 years of age.
- n For children 2 years of age or younger, the label recommendation generally states "**consult your physician.**"



Dose for child or infant

^a Young's rule, based on age:

$$\frac{\text{Age}}{\text{Age} + 12} \times \text{Adult dose} = \text{Dose for child}$$

Cowling's rule:

$$\frac{\text{Age at next birthday (in years)} \times \text{Adult dose}}{24} = \text{Dose for child}$$

Fried's rule for infants:

$$\frac{\text{Age (in months)} \times \text{Adult dose}}{150} = \text{Dose for infant}$$

Clark's rule, based on weight:

$$\frac{\text{Weight (in lb)} \times \text{Adult dose}}{150 \text{ (average weight of adult in lb.)}} = \text{Dose for child}$$

Note: The value of 150 in Fried's rule was an estimate of the age (12.5 years or 150 months) of an individual who would normally receive an adult dose, and the number 150 in Clark's rule was an estimate of the weight of an individual who likewise would receive an adult dose.



DRUG DOSAGE BASED ON BODY WEIGHT

- n The usual doses for drugs are considered generally suitable for **70-kg (154-lb)** individuals.
- n The **ratio** between the **amount of drug** administered and the **size of the body** influences the **drug concentration** at its site of action.
 - ∴ drug dosage may require adjustment from the usual adult dose for **abnormally lean or obese patients**.



CALCULATIONS CAPSULE

Dose Based on Body Weight

A useful equation for the calculation of dose based on body weight is:

$$\text{Patient's dose (mg)} = \text{Patient's weight (kg)} \times \frac{\text{Drug dose (mg)}}{1 \text{ (kg)}}$$

This equation is based on a drug dose in mg/kg and the patient's weight in kilograms. When different units are given or desired, other units may be substituted in the equation as long as the terms used are consistently applied.



DRUG DOSAGE BASED ON BODY WEIGHT

- n The determination of drug dosage for young patients on the basis of **body weight** is considered more dependable than that based strictly on age.
- n The dosage of a number of drug substances is frequently expressed on a **milligram (drug) per kilogram** (body weight) or **milligram per pound** basis.



Examples: The usual initial dose of chlorambucil is 150 ug/kg of body weight once a day. How many milligrams should be administered to a person weighing 154 lb?

$$\begin{array}{rcl}
 \text{n } 150 \text{ ug} & = & 0.15 \text{ mg} \\
 \text{n } 1 \text{ kg} & = & 2.2 \text{ lb}
 \end{array}
 \quad
 \frac{2.2 \text{ (lb)}}{154 \text{ (lb)}} = \frac{0.15 \text{ (mg)}}{x \text{ (mg)}}$$

$$x = 10.5 \text{ mg, answer.}$$

Or, solving by dimensional analysis

$$\frac{1 \text{ mg}}{1000 \text{ } \mu\text{g}} \times \frac{150 \text{ } \mu\text{g}}{1 \text{ kg}} \times \frac{1 \text{ kg}}{2.2 \text{ lb}} \times \frac{154 \text{ lb}}{1} = 10.5 \text{ mg, answer.}$$



The usual dose of sulfisoxazole for infants over 2 months of age and children is 60 to 75 mg/kg of body weight. What would be the usual range for a child weighing 44 lb?

$$n \ 1 \text{ kg} \qquad \qquad = 2.2 \text{ lb}$$

$$n \ 20 \text{ kg} \qquad \qquad = 44 \text{ lb}$$

$$n \ 60 \text{ mg/kg} \times 20 \text{ kg} \qquad = 1200 \text{ mg}$$

$$n \ 75 \text{ mg/kg} \times 20 \text{ kg} \qquad = 1500 \text{ mg}$$

Thus, the dosage range would be 1200 to 1500 mg, answer.

CASE IN POINT 8.3: A hospital pharmacist is called to a pediatric nursing station to calculate the quantity of an injection to administer to a pediatric patient. The daily dose of the injection for the child's weight is stated as 15 mg/kg/day, divided into three equal portions. The child weighs 10 kg. The injection contains 5 mg/mL of the prescribed drug.

How many milliliters of injection should be administered?

$$15 \text{ mg/kg} \times 10 = 150 \text{ mg}$$

$$150/3 = 50 \text{ mg}$$

$$50 \text{ mg} / 5 \text{ mg/mL} = 10 \text{ mL} \dots\dots(\text{Ans})$$



Use of Dosing Tables Based on Body Weight

- n For some drugs dosed according to body weight or body surface area, dosing tables appear in **product literature** to assist the physician and pharmacist.
- n An example is presented in **Table 8.2**.



TABLE 8.2 DOSING BY BODY WEIGHT FOR A HYPOTHETICAL DRUG

BODY WEIGHT		TOTAL mg/DAY		
kilograms	pounds	0.5 mg/kg	1 mg/kg	2 mg/kg
40	88	20	40	80
50	110	25	50	100
60	132	30	60	120
70	154	35	70	140
80	176	40	80	160
90	198	45	90	180
100	220	50	100	200



Example: Using Table 8.2 and a daily dose of 0.5 mg/kg, how many 20-mg capsules of the drug product should be dispensed to a patient weighing 176 lb if the dosage regimen calls for 15 weeks of therapy?

n $176 \text{ lb} = 176 / 2.2 = 80 \text{ kg}$

n Daily dose = 40 mg/day

n 1 cap. = 20 mg

n Daily dose = $40 / 20 = 2 \text{ cap./day}$

n $2 \text{ capsules/day} \times 7 \text{ days/week} \times 15 \text{ weeks}$
= 210 capsules, answer.



DRUG DOSAGE BASED ON BODY SURFACE AREA (BSA)

n widely used in two types of patient groups:

- 1) **cancer patients** receiving chemotherapy,
- 2) **pediatric patients** of all **childhood ages**,

n Exception: premature and full-term newborns, whose immature renal and liver functions require additional assessment in dosing.



TABLE 8.3 APPROXIMATE RELATION OF SURFACE AREA AND WEIGHTS OF INDIVIDUALS OF AVERAGE BODY DIMENSION

KILOGRAMS	POUNDS	SURFACE AREA IN SQUARE METERS	PERCENTAGE OF ADULT DOSE*
2	4.4	0.15	9
3	6.6	0.20	11.5
4	8.8	0.25	14
5	11.0	0.29	16.5
6	13.2	0.33	19
7	15.4	0.37	21
8	17.6	0.40	23
9	19.8	0.43	25
10	22.0	0.46	27
15	33.0	0.63	36
20	44.0	0.83	48
25	55.0	0.95	55
30	66.0	1.08	62
35	77.0	1.20	69
40	88.0	1.30	75
45	99.0	1.40	81
50	110.0	1.51	87
55	121.0	1.58	91

* Based on average adult surface area of 1.73 square meters.
Adapted from Martin EW et al., *Techniques of Medication*, J. B. Lippincott, 1969:31, who adapted it from *Modell's Drugs of Choice* (Mosby).



Body Surface Area Dosage with Relation to Weight in Children.

- n **Table 8.3** shows the approximate relation between **body weight** and **surface area** of average body dimensions.
 - may be used in the calculation of pediatric doses based on BSA as related to weight.
 - The pediatric dose is expressed as a **percentage of the adult dose**, based on the relationship of the square meter area of a given weight and the average adult surface area of 1.73 m².
- n **Approximate doses for children** may be calculated by multiplying the adult dose by this percentage.



n *Example: If the usual adult dose of a drug is 100 mg, determine the approximate dose for a child with a BSA of 0.83 m² or 48% of the average adult BSA (from **Table 8.3**).*

n 100 mg X 0.48 = 48 mg, answer.



TABLE 8.4 PEDIATRIC DOSING GUIDELINE FOR A HYPOTHETICAL DRUG BASED ON BSA

PATIENT'S BSA (m ²)	DOSE LEVEL			
	250 mg/m ² DOSE	300 mg/m ² DOSE	350 mg/m ² DOSE	400 mg/m ² DOSE
0.25	62.5 mg	75 mg	87.5 mg	100 mg
0.50	125 mg	150 mg	175 mg	200 mg
1.00	250 mg	300 mg	350 mg	400 mg
1.25	312.5 mg	375 mg	437.5 mg	500 mg
1.50	375 mg	450 mg	525 mg	600 mg



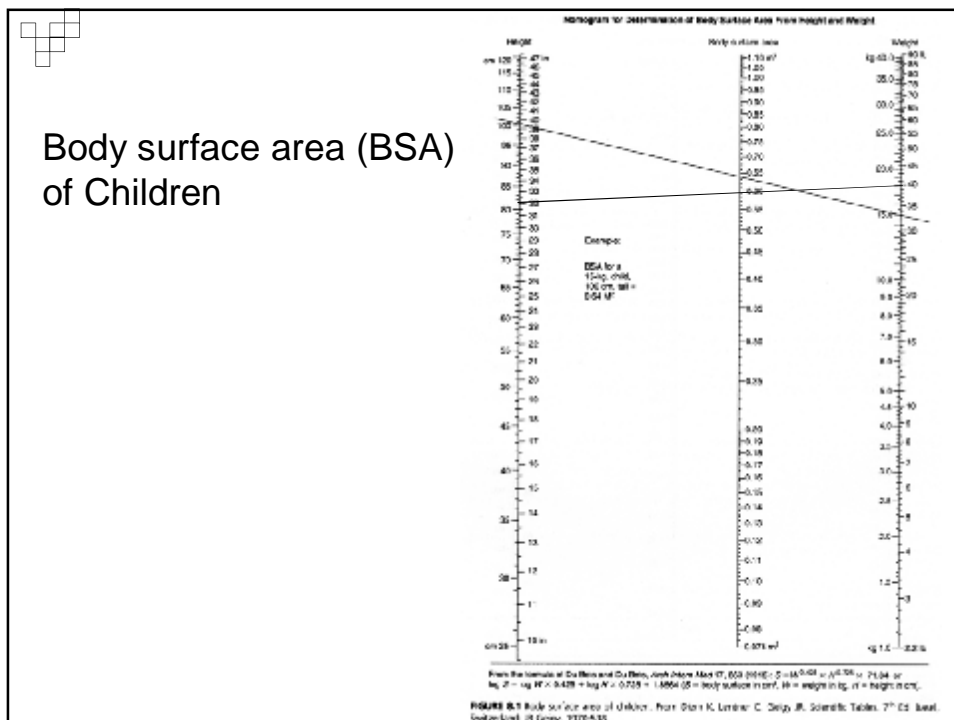
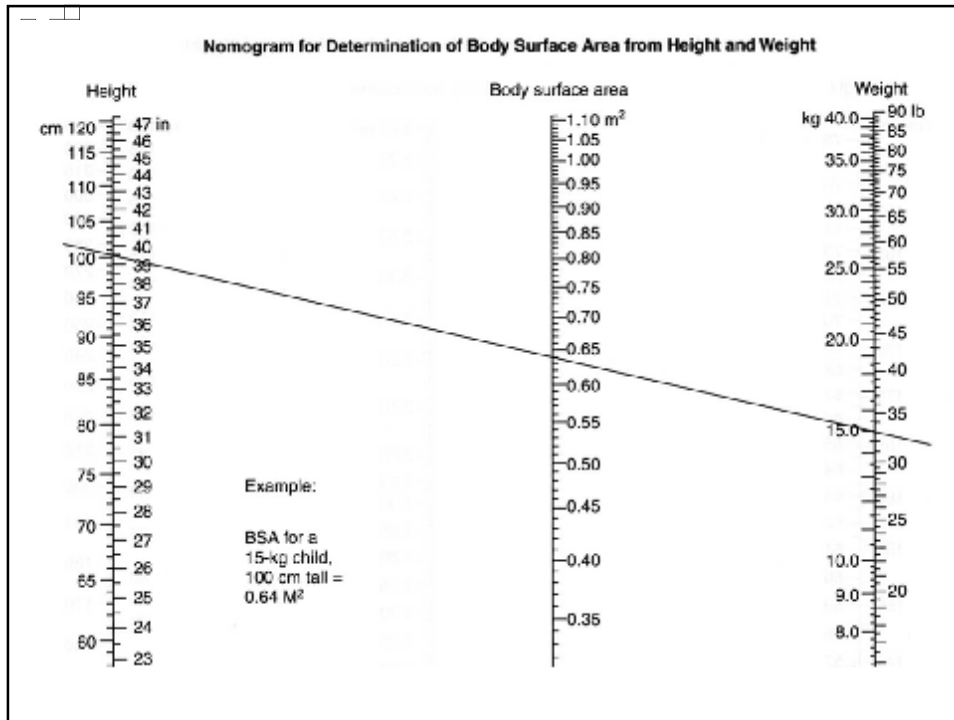
Use of Dosing Tables Based on Body Surface Area

- n For certain drugs, **dosing tables** may be provided to determine the approximate dose based on a patient's body surface area.
- n **Table 8.4** presents an example for a hypothetical drug.



Nomograms: Body Surface Area Dosage with Relation to Weight and Height in Children or Adults

- n For more precise calculation of doses based on BSA, one should refer to a **standard nomogram**, which includes both **weight and height** as factors influencing **BSA**.
- n The nomograms in **Figures 8.1 and 8.2** may be used for determining BSA from weight and height.
- n The BSA in square meters (m^2) is indicated where a straight line drawn to connect the height and weight of the child intersects the surface area column.
 - In the example shown in Figure 8.1, a child weighing 15 kg and measuring 100 cm in height has a BSA of $0.64 m^2$.



Body surface area (BSA)
of Children



n The dose is then calculated as follows:

· If the adult dose is given,

$$\frac{\text{BSA of child (in m}^2\text{)}}{1.73 \text{ m}^2 \text{ (average adult BSA)}} \times \text{Adult dose} = \text{Approximate dose for child}$$

· *Examples: If the adult dose of a drug is 75 mg, what would be the dose for a child weighing 40 lb and measuring 32 in. in height? (Use the body surface area method.)*

n From the nomogram, the BSA = 0.60 m²

n 0.60 (m²)/1.73 (m²) X 75 mg=26 mg, answer.



· If the dose per square meter is given,

$$\text{BSA of child (in m}^2\text{)} \times \text{Dose per m}^2 = \text{Approximate dose for child}$$

· *Example: The usual pediatric dose of ephedrine sulfate is stated as 25 mg/m². Using the nomogram, calculate the dose for a child weighing 18 kg and measuring 82 cm in height,*

n From the nomogram, the BSA = 0.60 m²

n 25 mg/m² X 0.60 m² =15 mg, answer.



n The nomogram in **Figure 8.2** designed specifically for determining the BSA of adults may be used in the same manner as the one previously described.

n The adult dose is then calculated as follows:

$$\frac{\text{BSA of adult (m}^2\text{)}}{1.73 \text{ m}^2} \times \text{Usual adult dose} = \text{Dose for adult}$$



Examples: If the usual adult dose of a drug is 120 mg, what would be the dose based on BSA for a person measuring 6 ft tall and weighing 200 lb?

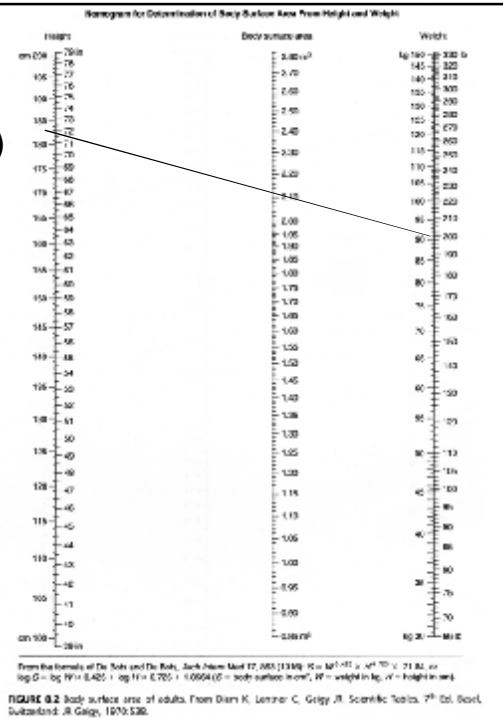
n BSA (from the nomogram) = 2.13 m²

(2.13 m²/1.73 m²) X 120 mg=147.75 mg or 148 mg,
answer.

If the dose of a drug is 5 mg/m², what would be the dose for a patient with a BSA of 1.9 m²?

∴ 5 mg/m² X 1.9 m² = 9.5 mg, answer.

Body surface area (BSA) of Adult



n BSA Equation:

$$BSA, m^2 = \sqrt{\frac{Ht (cm) \times Wt (kg)}{3600}}$$

Example: Calculate the BSA for a patient measuring 165 cm in height and weighing 65 kg.

$$BSA, m^2 = \sqrt{\frac{165 (cm) \times 65 (kg)}{3600}}$$

$$BSA = 1.73 m^2, \text{ answer.}$$



CALCULATIONS CAPSULE

Dose Based on Body Surface Area

A useful equation for the calculation of dose based on body surface area is:

$$\text{Patient's dose} = \frac{\text{Patient's BSA (m}^2\text{)}}{1.73 \text{ m}^2} \times \text{Drug dose (mg)}$$

If there is need to determine a patient's BSA, a nomogram, or the following equation may be used:

$$\text{Patient's BSA (m}^2\text{)} = \sqrt{\frac{\text{Patient's height (cm)} \times \text{Patient's weight (kg)}}{3600}}$$



Dosage based on the Medical condition to be treated

TABLE 8.5 PARENTERAL DOSAGE SCHEDULE FOR A HYPOTHETICAL DRUG BASED ON PATIENT AGE AND CONDITION BEING TREATED

	DOSE	ROUTE	FREQUENCY
Adults			
Urinary tract infection	250 mg	IV or IM	q12h
Bone and joint infections	2 g	IV	q12h
Pneumonia	500 mg–1 g	IV or IM	q8h
Mild skin infections	500 mg–1 g	IV or IM	q8h
Life-threatening infections	2 g	IV	q8h
Lung infections (normal kidney function)	30–50 mg/kg (NMT 6 g/day)	IV	q8h
Neonates (up to 1 month)	30 mg/kg	IV	q12h
Infants and Children (1 month to 12 years)	30–50 mg/kg (NMT 6g/day)	IV	q8h



SPECIAL DOSING CONSIDERATIONS IN CANCER CHEMOTHERAPY

- n Chemotherapy:
 - .. applies to the treatment of disease with chemicals (drugs).
 - .. often is associated with the treatment of cancer with chemotherapeutic agents.
- n In treating cancer:
 - .. chemotherapy,
 - .. surgery,
 - .. radiation therapy,
 - .. hormone therapy,
 - .. immunotherapy.
 - .. alternative treatments
 - .. complementary therapy.
- n **Combination therapy** is included in a **patient's treatment plan** (e.g., **radiation and chemotherapy**).



- n **Chemotherapy** is considered the **mainstay** of cancer treatment in that it is effective in widespread or metastatic cancer,
- n **Surgery or radiation therapy** are limited to specific body sites.
- n Almost all chemotherapeutic agents presently available act by **destroying cancer cells** through their effect on **DNA synthesis or function**.
- n The **major categories** of chemotherapeutic agents :
 - .. **alkylating agents**,
 - .. **antimetabolites**,
 - .. **plant alkaloids**,
 - .. **antitumor antibiotics**,
 - .. **steroid hormones**.



n Chemotherapeutic agents:

- most often are administered **orally** or by **intravenous injection** or **infusion**;
- other routes of administration may be used as required, including **intramuscular injection** or administration to a **specific site**, such as the **lung (intrapleural)**, the **abdomen (intraperitoneal)**, the **skin (topical)**, or others.

n By using combinations of drugs having **different mechanisms of action** against the target cancer cells, the effectiveness of treatment may be **enhanced**, **lower doses used**, and **side effects reduced**.



Cancer chemotherapy is unique in following ways

- n may involve **single or multiple drugs** of well-established drug therapy regimens or protocols,
- n may involve the use of **investigational drugs** as a part of a clinical trial.
- n Combinations of drugs may be given by the **same** or by **different routes of administration**.
- n The drugs may be administered concomitantly or alternately on the **same or different days** during a prescribed treatment cycle (e.g., 28 days).



Cancer chemotherapy is unique in following ways

- n The **days** of treatment generally follow a prescribed format of written instructions
 - "D" for day, followed by the day(s) of treatment during a cycle,
 - n a dash (-) meaning "to"
 - n a comma (,) meaning "and."
 - Thus "D 1-4" means days 1 to 4, and "D1,4" means days 1 and 4.



n The **drugs** used in combination chemotherapy often fit into a standard drug/dosage regimen identified by **abbreviations** or **acronyms**. For example,

- **bladder cancer**: "MVAC" consists of **methotrexate** + **vinblasrine** + **doxorubicin** (or **acrinomycin**) + **cisplatin**;
- **colorectal cancer** : "FU/LU" is **fluorouracil** + **leucovorin**;
- **lung cancer**: "PC" is **paclitaxel** + **carboplatin**;
- **ovarian cancer**: "CHAD" for **cyclophosphamide** + **hexamethylmelamine** + **adriamycin** + **diamminedichloroplatinum** (cisplatin).



n The drugs themselves are commonly **abbreviated in medication orders:**

- "MTX" for methotrexate,
- "DOX" for doxorubicin,
- "VLB" for vinblastine,
- "CDDP" for cisplatin.



n For systemic action, chemotherapeutic agents are usually dosed based either on body weight or on body surface area.

n The drug doses stated in standard regimens must be **reduced**, based on a particular patient's **diminished kidney or liver function**.

n For each patient, a pharmacist must be capable of:

- correctly interpreting a medication order for chemotherapeutic agents,
- following the individualized dosing regimen,
- calculating each dose of medication prescribed,
- dispensing the appropriate dosage forms and quantities/strengths required.

Example Calculations of Chemotherapy Dosage Regimens

Regimen: VC¹²

Cycle: 28 d; repeat for 2–8 cycles

Vinorelbine, 25 mg/m², IV, D 1,8,15,22

Cisplatin, 100 mg/m², IV, D 1.

For each of vinorelbine and cisplatin, calculate the total intravenous dose per cycle for a patient measuring 5 ft. 11 in. in height and weighing 175 lb.

From the nomogram for determining BSA (a) find the patient's BSA and (b) calculate the quantity of each drug in the regimen.

(a) BSA = 2.00 m², answer.

(b) Vinorelbine: 25 mg × 2.00 (BSA) × 4 (days of treatment) = 200 mg.

Cisplatin: 100 mg × 2.00 (BSA) × 1 = 200 mg, answers.

Regimen: CMF¹⁰

Cycle: 28 d

Cyclophosphamide, 100 mg/m²/d po, D 1–14.

Methotrexate, 40 mg/m², IV, D 2,8.

Fluorouracil, 600 mg/m², IV, D 1,8.

Calculate the total cycle dose for cyclophosphamide, methotrexate, and fluorouracil for a patient having a BSA of 1.5 m².

Cyclophosphamide: 100 mg × 1.5 (BSA) × 14 (days) = 2100 mg = 2.1 g.

Methotrexate: 40 mg × 1.5 × 2 = 120 mg.

Fluorouracil: 600 mg × 1.5 × 2 = 1800 mg = 1.8 g, answers.

Case in Point 8.4¹⁴: In treating a 54-year-old female patient, an oncologist selects the drug temozolomide, an antitumor agent used in the treatment of refractory astrocytoma (brain tumor). The drug is used as part of a 28-day regimen, during which the first five days of treatment include temozolomide at a once-daily dose of 150 mg/m²/day. The patient's medical chart indicates that she measures 5 ft. in height and weighs 117 lb. The physician asks the pharmacist to determine the proper combination of available capsules to use in dosing the patient. The drug is available in capsules containing 5, 20, 100, and 250 mg of temozolomide. What combination of capsules would provide the daily dose of this drug?

$$BSA (m^2) = \sqrt{\frac{152.4 \times 53.2}{3600}} = 1.5 m^2$$

Daily dose = 150 mg/m² X 1.5 m² = 225 mg

To obtain 225 mg, the patient may take two 100-mg capsules, one 20-mg capsule, and one 5-mg capsule daily, answer.



TABLE 10.1 CREATININE CLEARANCE DOSING GUIDELINES FOR CEFTAZIDIME (IV OR IM)^a

RENAL FUNCTION	CREATININE CLEARANCE (mL/min/1.73m ²)	DOSE	FREQUENCY
Normal to mild impairment	100–51	1 g	q8–12h
Moderate impairment	50–31	1 g	q12h
Severe impairment	30–16	1 g	q24h
Very severe impairment	15–6	500 mg	q24h
Essentially none	<5	500 mg	q48h

^a Table modified from product literature for FORTAZ (ceftazidime), GlaxoSmithKline, Research Triangle Park, NC, 2007.

**CALCULATIONS CAPSULE****Creatinine Clearance Equations⁶⁻⁹****Jelliffe equation**

For males:

$$\text{CrCl} = \frac{98 - 0.8 \times (\text{Patient's age in years} - 20)}{\text{Serum creatinine in mg/dL}}$$

For females:

$$\text{CrCl} = 0.9 \times \text{CrCl determined by equation for males}$$

Cockcroft-Gault equation

For males:

$$\text{CrCl} = \frac{(140 - \text{Patient's age in years}) \times \text{pt. wt., kg}}{72 \times \text{Serum creatinine in mg/dL}}$$

For females:

$$\text{CrCl} = 0.85 \times \text{CrCl determined using formula for males}$$

**CALCULATIONS CAPSULE****Creatinine Clearance Equations⁶⁻⁹****Adjusting CrCl for body surface area**

$$\frac{\text{BSA}}{1.73} \times \text{CrCl} = \text{Adjusted CrCl}$$

Schwartz equation

For pediatric and adolescent patients:

$$\text{CrCl} = \frac{k \times \text{Patient's height (cm)}}{\text{Serum creatinine (mg/dL)}}$$

CASE IN POINT 10.2⁵: A 35-year-old male patient weighing 180 lb. and standing 5 ft. 8 in. tall has been diagnosed with AIDS. His physician prescribes lamivudine (EPIVIR) as a component of his treatment program and knows that the dose of the drug must be adjusted based on the patient's renal function. Laboratory tests indicate that the patient's serum creatinine is 2.6 mg/dL and has held at the same level for 5 days.

(a) Calculate the patient's ideal body weight (IBW) and use in subsequent calculations if the IBW is lower than the patient's actual weight.

(b) Calculate the patient's CrCl by the Cockcroft-Gault equation.

(c) Select the appropriate dose of lamivudine from the dosing schedule:

Creatinine Clearance	Initial Dose	Maintenance Dose
<5 mL/min	50 mg	25 mg once daily
5–14 mL/min	150 mg	50 mg once daily
15–29 mL/min	150 mg	100 mg once daily
30–49 mL/min	150 mg	150 mg once daily



CLINICAL LABORATORY TEST VALUES AND DOSAGE

n Determining Dosage Using Equations Specific to Clinical Conditions and Drug Products.

• The following is used in determining the amount of *iron required (mg)* to bring hemoglobin values to normal levels:

$$\text{body wt (lb)} \times 0.3 \times \left[100 - \frac{\text{Hb (g / dL)} \times 100}{14.8 \text{ g / dL}} \right]$$

In the equation, 14.8 g/dL is the normal value of hemoglobin (Hb) in adults and the factor 0.3 (%) is its iron content.



TABLE 10.2 EXAMPLES OF NORMAL RANGES OF SERUM CHEMISTRY VALUES^a

LABORATORY TEST	NORMAL VALUES (RANGE, IN US UNITS)	CONVERSION FACTOR (MULTIPLY)	INTERNATIONAL SYSTEM ^b
Albumin	3.6–5.1 g/dL	10	= 36–51 g/L
Calcium	8.6–10.3 mg/dL	0.25	= 2.2–2.6 mmol/L
Cholesterol, total	125–200 mg/dL	0.026	= 3.25–5.2 mmol/L
HDL cholesterol	> or = 40 mg/dL	0.026	= > or = 1.04 mmol/L
LDL cholesterol	<130 mg/dL	0.026	= <3.38 mmol/L
Glucose	65–99 mg/dL	0.055	= 3.58–5.45 mmol/L
Triglycerides	<150 mg/dL	0.011	= <1.65 mmol/L
Creatinine	0.5–1.4 mg/dL	88.4	= 44.2–123.8 μmol/L
Urea Nitrogen (BUN)	7–25 mg/dL	0.357	= 2.50–8.93 mmol/L

^a Normal values shown may vary between test laboratories and may be referred to as “reference,” “healthy,” or “goal” values.

^b The international system is generally expressed in mmol (or other units) per liter.

Example Calculations Involving Clinical Laboratory Tests

If a patient is determined to have a serum cholesterol level of 200 mg/dL, (a) what is the equivalent value expressed in terms of milligrams percent, and (b) how many milligrams of cholesterol would be present in a 10-mL sample of the patient’s serum?

$$(a) 200 \text{ mg/dL} = 200 \text{ mg}/100 \text{ mL} = 200 \text{ mg}\%, \text{ answer.}$$

$$(b) \frac{200 \text{ (mg)}}{x \text{ (mg)}} = \frac{100 \text{ (mL)}}{10 \text{ (mL)}}$$

$$x = 20 \text{ mg, answer.}$$

If a patient is determined to have a serum cholesterol level of 200 mg/dL, what is the equivalent value expressed in terms of millimoles (mmol) per liter?

$$\begin{aligned} \text{Molecular Weight (m.w. of cholesterol)} &= 387 \\ 1 \text{ mmol cholesterol} &= 387 \text{ mg} \\ 200 \text{ mg/dL} &= 2000 \text{ mg/L} \\ \frac{387 \text{ (mg)}}{2000 \text{ (mg)}} &= \frac{1 \text{ (millimole)}}{x \text{ (millimoles)}} \\ x &= 5.17 \text{ mmol/L, answer.} \end{aligned}$$

Using the equation for determining iron deficiency, calculate, the number of milliliters of an iron dextran solution containing 50 mg/mL of iron to be administered to a 150-lb patient with a hemoglobin value of 10 g/dL.

$$\begin{aligned} \text{Iron required (mg)} &= 150 \times 0.3 \times \left[100 - \frac{10 \times 100}{14.8} \right] \\ &= 150 \times 0.3 \times 32.4 \\ &= 1458 \text{ mg} \end{aligned}$$

By proportion,

$$\begin{aligned} \frac{50 \text{ mg}}{1458 \text{ mg}} &= \frac{1 \text{ mL}}{x \text{ mL}} \\ x &= 29 \text{ mL, answer.} \end{aligned}$$

n Calculating Approximate Drug Serum Concentrations from Literature Data and Loading Dose Information.

.. Experience in dosing has shown that for certain drugs, a correlation exists between dose and serum drug concentrations.

n Example: *In dosing the drug gentamicin in pediatric patients, for every 1 mg/kg of gentamicin administered, serum drug concentrations are expected to increase by 2.5 ug/mL. What would be the expected serum drug concentration after administration of a 2.5-mg/kg dose of gentamicin?*

n 1 mg/kg = 2.5 ug/mL serum drug concentration

n 2.5 mg/kg = 6.25 ug/mL serum drug concentration, answer.