A Textbook of Clinical Pharmacy

for Pharmacy Students

Lesson 5:

Clinical Pharmacy in Patients with Extreme Body Size

ISBN-13: 979-13-992562-6-0

Porto, Portugal.

Published by CIPF, S.L.

Suggested citation: Fernandez-Llimos F. Lesson 5: Clinical Pharmacy in Patients with Extreme Body Size. In: A Textbook of Clinical Pharmacy for Pharmacy Students. Porto: CIPF; 2026.

Available at http://www.cipf-es.org

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5.1 Body Habitus and Extreme Body Size

In medical terminology, “body habitus” means the overall physical build and constitution of a person, including size, shape, and proportions. It encompasses height, weight, muscle mass, fat distribution, and skeletal frame, often with implications for disease risk or technical aspects of care (for example, imaging, drug dosing, or surgical access).

Traditional radiologic teaching distinguishes four principal habitus types: asthenic, hyposthenic, sthenic, and hypersthenic, which convey information about thoracic dimensions, organ position, and relative body mass but **do not quantify adiposity or lean mass**. In clinical pharmacy practice, such qualitative morphologic categories remain useful for rapid visual assessment and communication, but **they must be integrated with quantitative measures of body size and composition when informing dosing, monitoring, and risk assessment**.

Body size is commonly operationalized using **anthropometric indices**, of which **body mass index (BMI)**, defined as weight in kilograms divided by height in meters squared, is the most widely used for classifying underweight, normal weight, overweight, and obesity severity classes.

$$\mathrm{BMI} = \frac{\mathrm{mass_{kg}}}{\mathrm{height_m}^2}$$

International guidelines and obesity pharmacotherapy reviews typically define overweight as a BMI between 25 and 29.9 kg/m^2, class I obesity as 30.0–34.9 kg/m^2, class II obesity as 35.0–39.9 kg/m^2, and class III or severe obesity as BMI ≥40 kg/m^2, recognizing that these thresholds correlate with progressively higher risks of metabolic and cardiovascular complications. Underweight is generally defined as BMI <18.5 kg/m^2 and signals reduced energy reserves, potential malnutrition, and altered pharmacokinetics, particularly for highly protein-bound or hydrophilic medicines, although BMI alone cannot distinguish between low fat mass and low lean mass.[1]

[1] WHO. Surf report. https://iris.who.int/server/api/core/bitstreams/6c8852f7-9e0c-4252-bb0c-c9724411f878/content

WHO classification of adult underweight, overweight, and obesity according to BMI including additional cut-off points recommended by the WHO Expert Consultation

Classification	BMI (kg/m^2) Principal cut-off points	BMI (kg/m^2) Additional cut-off points
Underweight	<18.50	<18.50
Severe thinness	<16.00	<16.00
Moderate thinness	16.00 – 16.99	16.00 – 16.99
Mild thinness	17.00 – 18.49	17.00 – 18.49
Normal range	18.50 – 24.99	18.50 – 22.99 23.00 – 24.99
Overweight	≥25.00	≥25.00
Pre-obese	25.00 – 29.99	25.00 – 27.49 27.50 – 29.99
Obese	≥30.00	≥30.00
Obese class I	30.00 – 34-99	30.00 – 32.49 32.50 – 34.99
Obese class II	35.00 – 39.99	35.00 – 37.49 37.50 – 39.99
Obese class III	≥40.00	≥40.00

Because **BMI does not capture body fat distribution**, additional anthropometric measures such as waist circumference and waist-to-hip ratio are often used to refine risk stratification, particularly for central or visceral adiposity. Waist circumference categories associated with increased cardiometabolic risk have been incorporated into obesity and cardiology guidelines, underscoring that **two individuals with the same BMI may have very different proportions of visceral fat** and thus different risk profiles and potential pharmacokinetic behavior. From the perspective of clinical pharmacy, these indices extend the concept of body habitus beyond visual appraisal, providing accessible quantitative markers that can be related to disease risk, organ function, and dosing considerations.

Body composition further disaggregates body weight into compartments such as fat mass, lean body mass, and fat-free mass, which are more directly relevant to the distribution and clearance of many medicines. **Lean body mass** typically refers to all non-fat tissues, including muscle, organ tissue, and body water, whereas **fat-free mass** is sometimes used synonymously or with minor technical distinctions depending on the measurement technique and reference standard. Methods to estimate these compartments range from simple anthropometric equations to more advanced techniques such as dual-energy X-ray absorptiometry, bioelectrical impedance analysis, and imaging-based volumetry, each with implications for how accurately the pharmacokinetic “space” available to a medicine is characterized.[5]

The term **extreme body weight** is used variably in the literature, but in the context of pharmacotherapy it usually denotes marked deviations from the normal BMI range, often encompassing both severe obesity (for example, class II–III obesity) and significant underweight, including patients with cachexia or advanced frailty. In such individuals, conventional weight-based or surface area–based dosing algorithms may either overestimate or underestimate the appropriate dose because they assume more typical relationships between total body weight,

adipose tissue, and lean compartments. Clinical pharmacy in this context therefore requires explicit recognition of extreme body size as a spectrum that includes very high and very low body mass, with or without alterations in body composition.

Sarcopenic obesity represents a particularly important phenotype within this spectrum, characterized by the **coexistence of excess adiposity and reduced skeletal muscle mass** or function in the same individual. Consensus statements from nutrition and obesity societies define sarcopenic obesity as the combination of high body fat (often reflected by elevated BMI or waist circumference) with low muscle mass and impaired muscle function, emphasizing that it is a distinct clinical condition rather than a simple sum of obesity and sarcopenia. This phenotype illustrates the limitations of BMI as a solitary descriptor: patients may meet criteria for obesity by BMI yet have severely reduced lean mass, which has direct implications for the distribution volume of hydrophilic medicines, the reliability of creatinine-based renal function estimates, and vulnerability to adverse effects of sedatives, opioids, and other centrally acting agents.[2]

Amputation introduces another dimension to the concept of extreme body size because it alters both absolute body weight and its proportional distribution across compartments. Major limb loss reduces measured body weight but does not proportionally reduce visceral organ mass or, in some cases, adipose tissue distribution, leading to potential misclassification of nutritional status if BMI is calculated without adjustment for the missing limb segments. For clinical pharmacy, this means that standard anthropometric indices must be interpreted cautiously in amputee patients, and, where possible, estimated pre-amputation body weight or adjusted body weight formulas should be considered when these indices are used to guide dosing or to interpret renal function estimates that depend on serum creatinine and body size.

5.1.1 Extreme Body Habitus Modifies Pharmacokinetics and Pharmacodynamics

Marked deviations in body composition and organ size influence every step of pharmacokinetics, so that patients with **extreme body size frequently experience different exposure–response relationships** from those observed in individuals with average body habitus. For clinical pharmacy, the central mechanistic themes are the way altered **proportions of adipose tissue and lean mass modify volume of distribution**, how **obesity, cachexia, and sarcopenia reshape hepatic and renal clearance**, and how these changes interact with pharmacodynamic adaptations at receptor and systems level to affect efficacy and safety of key drug classes.[3],[4]

In obesity, **expansion of adipose tissue and increases in lean mass, plasma volume, and cardiac output enlarge the apparent volume of distribution for many medicines**, particularly those with higher lipophilicity. Hydrophilic agents that distribute predominantly into lean tissues and extracellular water (for example, many aminoglycosides and low-molecular-weight heparins) show more modest volume expansion and often correlate better with ideal or lean body weight than with total body weight, whereas lipophilic drugs (such as certain beta-blockers, benzodiazepines, and some oncology agents) may accumulate in adipose tissue, resulting in a

[2] Donini LM, Busetto L, Bischoff SC, et al. Definition and Diagnostic Criteria for Sarcopenic Obesity: ESPEN and EASO Consensus Statement. Obes Facts. 2022;15(3):321-335.
[3] Bruno CD, Harmatz JS, Duan SX, et al. Effect of lipophilicity on drug distribution and elimination: Influence of obesity. Br J Clin Pharmacol. 2021;87(8):3197-3205.
[4] Trobec K, Kerec Kos M, von Haehling S, et al. Pharmacokinetics of drugs in cachectic patients: a systematic review. PLoS One. 2013;8(11):e79603.

disproportionate increase in volume of distribution and a prolonged elimination half-life. These patterns have direct implications for dose selection: loading doses for lipophilic antibiotics or sedatives in severe obesity may need to be based on total or adjusted body weight to achieve therapeutic concentrations, while maintenance doses must balance larger distribution volumes against sometimes unchanged or only modestly increased clearance to avoid accumulation.

At the level of clearance, **obesity** is associated with complex and pathway-specific changes in hepatic metabolism and renal excretion that cannot be captured by a single adjustment factor. Reviews of obese adults and physiologically based pharmacokinetic modelling show that **obesity increases liver size and hepatic blood flow but differentially affects cytochrome P450–mediated pathways**, with clearance of CYP3A4 substrates tending to be reduced and clearance of drugs primarily eliminated by UGTs or enzymes such as CYP2E1, xanthine oxidase, and N-acetyltransferase often increased.[5],[6] In parallel, glomerular filtration rate and tubular secretory capacity may be elevated in early or uncomplicated obesity, leading to augmented renal clearance of renally eliminated antimicrobials or anticoagulants, whereas longstanding obesity with associated diabetes, hypertension, or heart failure can culminate in chronic kidney disease, reversing the direction of change and increasing the risk of toxicity if doses are not adjusted.

Underweight, frailty, and cachexia represent the opposite end of the spectrum, where loss of both fat and lean tissue typically reduces the volume of distribution for many medicines and is often accompanied by hypoalbuminemia, altered acid–base balance, and microcirculatory changes. Systematic reviews of cachectic patients indicate that reduced lean body mass and intracellular water are associated with smaller distribution volumes for both hydrophilic and lipophilic drugs, causing higher and more fluctuating plasma concentrations for a given dose; at the same time, diminished hepatic metabolic capacity and reduced renal blood flow may lower clearance, further increasing exposure. These combined effects mean that standard weight-normalized doses of cytotoxic oncology agents, renally cleared antivirals, or cardioactive drugs can produce unexpectedly high systemic exposure and toxicity in severely underweight or cachectic patients, supporting the need for cautious dose initiation, close monitoring of organ function, and, where available, therapeutic drug monitoring.[7]

Beyond pharmacokinetics, extreme body size and composition **also modify pharmacodynamic responses through changes in receptor expression, downstream signaling, and physiological reserve**. Obesity-related inflammation and insulin resistance, for example, may alter endothelial function and coagulation pathways, influencing the effect of anticoagulants and antiplatelet agents, while changes in sympathetic activity and cardiac remodeling can modify responsiveness to beta-blockers and other cardiovascular medicines. In cachexia and advanced frailty, reduced muscle mass and impaired neuromuscular function enhance sensitivity to centrally acting medicines such as opioids, sedatives, and neuromuscular blockers, so that

[5] Kosicka-Noworzyń K, Romaniuk-Drapała A, Sheng YH, et al. Obesity-related drug-metabolizing enzyme expression alterations in the human liver. Biomed Pharmacother. 2025;187:118155.
[6] Zhang T, Calvier EAM, Krekels EHJ, et al. Impact of Obesity on Hepatic Drug Clearance: What are the Influential Variables?. AAPS J. 2024;26(3):59.
[7] Trobec K, Kerec Kos M, von Haehling S, et al. Pharmacokinetics of drugs in cachectic patients: a systematic review. PLoS One. 2013;8(11):e79603. Published 2013 Nov 8.

doses derived from population averages can lead to oversedation, respiratory depression, or prolonged neuromuscular blockade unless carefully titrated.

Across therapeutic classes, these mechanisms translate into class-specific challenges and practical adjustments. For **antimicrobials**, increased distribution volume and, in some obese patients, augmented renal clearance may necessitate higher loading doses and altered dosing intervals to maintain pharmacodynamic targets such as time above minimum inhibitory concentration, whereas in cachectic patients the priority is often to reduce doses and extend intervals to avoid toxicity. For **anticoagulants**, body size affects both distribution and clearance, and extreme obesity or underweight can distort the relationship between standard dose, coagulation markers, and clinical effect, prompting the use of adjusted body weight, anti-Xa monitoring, or alternative agents with more predictable pharmacokinetics when evidence is limited. **Cardiovascular agents and oncology drugs** add further complexity because many are highly lipophilic or have narrow therapeutic indices; here, the interaction between altered distribution, pathway-specific metabolic changes, and disease-related organ impairment requires that dose selection and titration be individualized, often favoring gradual escalation from conservative starting doses, careful hemodynamic and toxicity monitoring, and consideration of formulations (for example, extended-release versus immediate-release) that allow more precise control over exposure in patients with extreme body habitus.

The impact of extreme body size on the use of medicines led regulatory agencies to establish specific recommendations for investigating the pharmacokinetics of these patients.[8] Some of these implications in pharmacokinetics may be further explored in Biopharmacy and Pharmacokinetics course (4th year).

5.1.2 Assessing Body Size and Composition

Assessment of body size and composition for pharmacotherapy decisions goes beyond simple weighing of the patient and requires a deliberate choice of which metric best reflects the pharmacokinetic space relevant to a given medicine and clinical question. Actual body weight, ideal and adjusted body weight, body surface area, and lean or fat-free mass are not interchangeable surrogates, and each brings specific strengths and limitations when used to individualize dosing or interpret renal and hepatic function in patients with very high or very low body mass or with amputations.[9] In practice, clinical pharmacists need to select, and sometimes combine, these metrics in a way that is both physiologically plausible and consistent with the evidence available for the drug class under consideration.[10]

Actual body weight (ABW) is the most immediate and intuitive measure and remains the default metric for many weight-based dosing regimens in therapeutic areas such as critical care and infectious diseases. Its advantages are simplicity, universal availability, and direct relevance for dosing of drugs whose distribution closely follows total body mass, such as some lipophilic sedatives or neuromuscular blockers. However, in patients with severe obesity or significant underweight, ABW may misrepresent the size of the pharmacokinetic compartment relevant to the drug, leading to overdosing of hydrophilic medicines when total body weight is used

[8] https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-investigation-pharmacokinetics-obese-population-scientific-guideline_en.pdf
[9] MacDonald JJ, Moore J, Davey V, et al. The weight debate. J Intensive Care Soc. 2015;16(3):234-238.
[10] Gouju J, Legeay S. Pharmacokinetics of obese adults: Not only an increase in weight. Biomed Pharmacother. 2023;166:115281.

uncritically, or underdosing if clinicians are overly cautious; consequently, ABW should be applied with particular care in morbid obesity and in individuals with major limb amputations, where it may substantially underestimate pre-morbid body size.

Ideal body weight (IBW) is a calculated estimate of the weight corresponding to a "normal" body size for a given height and sex, using formulae such as the Devine or Hamwi equations. In obese patients, IBW can serve as a proxy for the lean component that would be expected in someone of that height without excess adiposity, and it has often been used as a dosing scalar for hydrophilic agents whose distribution is driven primarily by lean tissue and extracellular water. The main limitation of IBW is that it assumes a standard body composition that may not hold in sarcopenic obesity, cachexia, or severe underweight, and it is insensitive to interindividual variation in muscle mass; in patients who are markedly underweight, ideal body weight may overshoot the actual lean mass substantially, so that using it to calculate doses or creatinine clearance may result in excessive exposure.[4][5][1]

Devine equation:

$$\mathrm{IBW}_{\mathrm{men}} \approx 0.90 \times \text{height (cm)} - 88$$

$$\mathrm{IBW}_{\mathrm{women}} \approx 0.90 \times \text{height (cm)} - 92$$

Hamwi equation:

$$\text{Men: } \mathrm{IBW} = 48\ \mathrm{kg} + 1.1\ \mathrm{kg} \times (\text{height in cm} - 152.4)$$

$$\text{Women: } \mathrm{IBW} = 45\ \mathrm{kg} + 0.9\ \mathrm{kg} \times (\text{height in cm} - 152.4)$$

Adjusted body weight[11] is designed to bridge the gap between actual and ideal body weight in patients with obesity by adding a fraction of the excess weight above ideal to the ideal body weight. Pharmacokinetic studies and dosing analyses suggest that for some drugs, such as intravenous vancomycin or enoxaparin[12], adjusted body weight better reflects the volume of distribution and clearance than either actual or ideal weight alone and may therefore improve target attainment while reducing the risk of toxicity compared with dosing on actual body weight. Nevertheless, the optimal correction factor varies between studies and drug classes, and adjusted body weight is essentially an empiric construct that must be validated for each medicine; using it without such underpinning may introduce systematic bias, particularly in very extreme obesity or in amputees where the proportion and distribution of adipose and lean tissue depart markedly from those assumed in the original derivations.

Body surface area (BSA) has a long tradition as the primary basis for dosing cytotoxic chemotherapy and some immunosuppressants, reflecting early observations that BSA correlates with basal metabolic rate, cardiac output, and renal function across a wide range of body sizes.[13] Common formula such as the Mosteller or DuBois equations combine height and weight into a single index that approximates body surface area and, by extension, the metabolic and excretory capacity relevant to drugs with narrow therapeutic windows. However, BSA-based

[11] Do not abbreviate as ABW. This abbreviation corresponds to Actual Body Weight.
[12] Roberts GW, De Menezes Caceres V, Damiani A, et al. Determination of the optimal obesity-adjusted dosing weight for enoxaparin. Br J Clin Pharmacol. 2025;91(4):1182-1190
[13] Kaestner SA, Sewell GJ. Chemotherapy dosing part I: scientific basis for current practice and use of body surface area. Clin Oncol (R Coll Radiol). 2007;19(1):23-37.

dosing does not account for interindividual variability in drug metabolism, distribution, and elimination, particularly in obesity or cachexia, and multiple reviews have highlighted its limited ability to predict chemotherapy exposure, leading to calls for alternative strategies based on pharmacokinetic parameters, fixed dosing, or organ function rather than BSA alone.

$$\textbf{BSA (m2)} = \text{Weight (kg)}^{0.425} \times \text{Height (cm)}^{0.725} \times 0.007184$$

Lean body mass and **fat-free mass** are conceptually closer to the compartments into which many drugs distribute and often show stronger correlations with cardiac output, organ size, and glomerular filtration than actual body weight. They can be estimated using anthropometric equations (for example, Hume equation) or directly measured by techniques such as dual-energy X-ray absorptiometry, bioelectrical impedance analysis, or computed tomography–derived muscle area, which are particularly informative in complex phenotypes like sarcopenic obesity or cancer cachexia. The main limitations of these metrics are the need for specific measurements or non-trivial calculations, potential error in the presence of fluid shifts, and **limited availability of drug-specific dosing recommendations based explicitly on lean or fat-free mass**, although the underlying physiological rationale supports their use, especially for agents whose distribution is strongly linked to muscle and organ tissue.[14]

For adult men:

$$\mathrm{LBM}_{\mathrm{men}} = 0.32810 \times W + 0.33929 \times H - 29.5336$$

For adult women:

$$\mathrm{LBM}_{\mathrm{women}} = 0.29569 \times W + 0.41813 \times H - 43.2933$$

Renal and hepatic function estimation are tightly intertwined with body size metrics, and misclassification can have substantial consequences for medicines that rely heavily on these routes of elimination. For creatinine-based estimates of glomerular filtration rate or creatinine clearance, the choice between actual, ideal, or adjusted body weight in equations such as Cockcroft–Gault can meaningfully shift the result, with guidelines and expert sources often recommending actual body weight in individuals with normal body habitus, adjusted weight in obesity, and cautious interpretation in amputees, in whom standard equations may overestimate renal function and predispose to overdosing renally cleared agents. Similarly, hepatic function scores and physiologically based pharmacokinetic models increasingly incorporate indices of body composition and organ size to refine predictions of hepatic clearance in obesity and cachexia, reinforcing that no single measure of body size is universally adequate

[14] Trobec K, Kerec Kos M, von Haehling S, et al. Pharmacokinetics of drugs in cachectic patients: a systematic review. PLoS One. 2013;8(11):e79603. Published 2013 Nov 8.

and that the metric selected should match both the pharmacokinetic profile of the drug and the patient's morphologic context.[15]

Updating the definition of obesity

This Lancet Diabetes & Endocrinology Commission proposes in 2025 a fundamentally revised, clinically oriented definition of obesity that separates excess adiposity as a physical phenotype from obesity as an illness state. The key innovation is the introduction of "**clinical obesity**" and "**preclinical obesity**" as distinct diagnostic categories, analogous to chronic disease and pre-disease states in other specialties and grounded in organ dysfunction and limitations in daily activities rather than BMI alone.

Obesity is first redefined in general terms as a condition characterized by excess adiposity, with or without abnormal distribution or function of adipose tissue, thereby clearly distinguishing it from other adipose tissue disorders such as lipodystrophies. Within this framework, **"clinical obesity" is defined as a chronic, systemic illness directly caused by excess adiposity, characterized by objective alterations in the function of organs, tissues, the whole individual**, or a combination of these, which can lead to life-altering or life-threatening complications such as myocardial infarction, stroke, or renal failure. By contrast, "**preclinical obesity**" denotes excess adiposity with preserved organ and tissue function, associated with an increased but variable risk of developing clinical obesity and other non-communicable diseases, but not constituting illness in itself.

The Commission explicitly challenges the traditional BMI-based definition of obesity as "abnormal or excessive fat accumulation that presents a risk to health", arguing that this risk-factor framing is insufficient to define a disease because it does not characterize an illness phenotype and leads to both under- and over-diagnosis at the individual level. **BMI is relegated to a role as a population-level or screening tool**: the authors recommend that obesity status (excess adiposity) be **confirmed by direct body fat measurement or at least one additional anthropometric criterion (for example, waist circumference, waist-to-hip ratio, or waist-to-height ratio)** with age-, sex-, and ethnicity-specific cut-offs, except in people with very high BMI (over 40 kg/m^2), where excess adiposity can be assumed.

- Rubino F, Cummings DE, Eckel RH, et al. Definition and diagnostic criteria of clinical obesity. Lancet Diabetes Endocrinol. 2025;13(3):221-262.

5.1.3 Pharmacotherapy Optimization in Extreme Body Size

Pharmacotherapy optimization in patients with extreme body size rests on a small number of practice principles that recur across drug classes and clinical settings. In every case, these principles must be applied in a drug-specific and patient-specific way, but they offer a structured

[15] Zhang T, Calvier EAM, Krekels EHJ, Knibbe CAJ. Impact of Obesity on Hepatic Drug Clearance: What are the Influential Variables?. AAPS J. 2024;26(3):59.

approach to dealing with the uncertainty created by marked deviations in body mass and composition.[16]

A first principle is **the deliberate choice of weight descriptor for each dosing decision**, rather than a reflex reliance on actual body weight. For drugs whose distribution predominantly follows lean tissue and extracellular water, ideal or adjusted body weight, or a lean body mass estimate, often provides a more physiologically plausible dosing scalar in patients with severe obesity, whereas actual body weight may be more appropriate for lipophilic agents that distribute extensively into adipose tissue. In contrast, in markedly underweight or cachectic individuals, using ideal body weight or standard body surface area can substantially overshoot the true pharmacokinetic space, so that dose calculation should preferentially use current body weight, sometimes with cautious upward titration if efficacy is suboptimal.

A second principle is **to anticipate when standard doses are likely to under- or over-expose patients**, based on the mechanisms described earlier in the chapter. In severe obesity, drugs with a small volume of distribution and predominantly renal elimination, such as many antimicrobials and low-molecular-weight heparins, may be underdosed if narrow fixed doses or ideal-weight-based regimens are applied without adjustment, whereas highly lipophilic drugs with long half-lives may accumulate if maintenance doses are scaled uncritically to total body weight. At the other extreme, in frailty and cachexia, standard "per-kilogram" doses of cytotoxic chemotherapy, cardioactive drugs, or sedatives can result in unexpectedly high peak concentrations and area under the curve, so that starting doses should often be conservative and escalated only if benefit is insufficient and tolerability allows.

Where evidence is limited or conflicting, a third principle is **to prefer drugs with wider therapeutic indices or more predictable pharmacokinetics whenever clinically acceptable alternatives exist**. Within a class, selecting a medicine with a broader safety margin or greater experience in patients with obesity or underweight reduces the consequences of inevitable exposure variability, even though it does not remove the need for individualization. This strategy is particularly relevant when pharmacokinetic data in extreme body size are sparse or extrapolated from small cohorts, as is the case for many cardiovascular and oncology medicines.

Therapeutic drug monitoring (TDM) is a central tool to manage uncertainty in this population, especially for medicines with narrow therapeutic indices, clear concentration–response relationships, and established target ranges, such as several antimicrobials and immunosuppressants. In patients with extreme body size, interpretation of TDM should explicitly consider the altered volume of distribution and clearance.[17] For example, higher loading doses may be required to reach target concentrations in severe obesity, while subsequent maintenance doses may need adjustment once individual clearance becomes apparent, whereas in cachectic patients standard doses may already produce high levels, prompting pre-emptive dose reduction when troughs approach the upper end of the therapeutic range. TDM is further explored in Biopharmacy and Pharmacokinetics course (4th year).

[16] Barletta JF, Erstad BL. Pitfalls and pearls with drug dosing in the critically ill obese patient: 10 statements to guide ICU practitioners. J Crit Care. 2022;71:154105.
[17] Gorham J, Taccone FS, Hites M. Therapeutic Drug Monitoring of Antimicrobials in Critically Ill Obese Patients. Antibiotics (Basel). 2023;12(7):1099.

Where TDM is not available or not validated, **clinical outcome monitoring**, using structured assessment of efficacy (e.g., resolution of infection, hemodynamic stabilization, anticoagulation status) and early toxicity signals, becomes the primary precaution and should be planned prospectively rather than left to informal observation. Across drug classes, **stepwise dose titration is the practical expression of these principles** and should be used whenever rapid full exposure is not critical for survival: a cautious, staged approach, starting from a dose that errs slightly on the side of under-exposure, allows clinicians to "learn" the patient's pharmacokinetic and pharmacodynamic behavior through repeated assessments and, where possible, intermittent measurement of drug levels or pharmacodynamic markers. In extreme obesity, this may involve larger relative increments when scaling up doses to achieve effect, while in underweight or cachectic patients, much smaller increments and longer intervals between changes may be appropriate to detect and prevent toxicity, always integrating anthropometric data, organ function estimates, and dynamic response to therapy.

5.1.4 Therapeutic Areas where Body Habitus is Particularly Critical

Therapeutic areas in which body habitus is particularly critical are those where small changes in exposure translate rapidly into loss of efficacy or toxicity, and where standard dosing algorithms are tightly linked to body size or organ function estimates. In such settings, extreme obesity, severe underweight, sarcopenic obesity, and amputation can all distort usual relationships between dose, concentration, and response, making individualized clinical pharmacy input indispensable.[18]

Antimicrobials are among the best-studied examples because both under- and over-exposure have immediate clinical consequences. In severe obesity, **hydrophilic agents** such as beta-lactams and aminoglycosides show increased volumes of distribution and, in some patients, augmented renal clearance, so that fixed doses or ideal-weight-based regimens can result in subtherapeutic concentrations. However, in cachectic patients reduced lean mass and low cardiac output may lead to higher peaks and slower clearance at standard doses. These diverging patterns have prompted detailed dosing proposals for some drugs, including extended or continuous infusions of beta-lactams and actual- or adjusted-weight-based loading doses of aminoglycosides in obesity, while evidence remains sparse for many newer agents, reinforcing the need for therapeutic drug monitoring and close outcome surveillance in patients with extreme body size.

In **antithrombotic therapy**, body habitus modifies both pharmacokinetics and pharmacodynamics, and guideline authors highlight extreme obesity and marked underweight as situations in which standard dosing is less reliable. **Low-molecular-weight heparins**, for instance, are often dosed on total body weight, but in patients with very high BMI there is concern about both accumulation and inadequate anticoagulation, leading to recommendations for dose capping, use of adjusted body weight, or anti-Xa monitoring, despite limited trial data at extremes of size. For **direct oral anticoagulants** (DOACs), several observational analyses suggest altered exposure at the extremes of weight, but robust pharmacokinetic and outcomes data are still lacking beyond certain BMI thresholds, so expert reviews recommend individualized decisions, considering use of agents with more data in obesity or, when possible, measurement of drug levels or surrogate coagulation markers in highly atypical body habitus.

[18] Erstad BL, Barletta JF. Drug dosing in the critically ill obese patient: a focus on medications for hemodynamic support and prophylaxis. Crit Care. 2021;25(1):77.

Cardiovascular drugs such as beta-blockers, renin–angiotensin system inhibitors, and antiarrhythmics also exhibit body-size–dependent variability, although with a broader therapeutic margin. In obesity, increased cardiac output, altered autonomic tone, and expanded distribution volumes can shift dose–response relationships so that standard starting doses may be insufficient for heart rate or blood pressure control, whereas in frail, underweight patients the same doses can precipitate hypotension, bradycardia, or conduction disturbances. For drugs with narrow therapeutic indices, such as some class III antiarrhythmics or digoxin, reviews emphasize careful titration, frequent monitoring of ECG and drug levels where available, and cautious interpretation of renal function in sarcopenic or amputee patients, in whom creatinine-based estimates may overstate clearance and predispose to toxicity.

Oncology and biologic therapies represent another area where body habitus is critical because dosing has traditionally relied on body surface area or weight-based algorithms and many agents have narrow therapeutic indices. In cachectic cancer patients, systematic reviews show that loss of lean mass and reduced hepatic and renal function can substantially increase exposure to cytotoxic drugs at standard BSA-based doses, contributing to hematologic and non-hematologic toxicities, whereas obesity can modify both distribution and metabolism in drug-specific ways that are not captured by simple BSA scaling. Guidance documents increasingly advocate using full, uncapped weight- or BSA-based doses in obesity when supported by outcome data, particularly for curative regimens, but recommend dose reductions and intensified toxicity monitoring in severe underweight or sarcopenic states, acknowledging that high-quality pharmacokinetic data in these phenotypes remain limited.

Analgesia and sedation, are especially sensitive to extreme body size, as undersedation carries risks such as agitation and device removal, whereas oversedation can cause respiratory failure and prolonged ICU stay. Reviews of sedatives and opioids in obese critically ill patients note that **highly lipophilic agents** (e.g., propofol, benzodiazepines, and many opioids) exhibit large increases in volume of distribution and context-sensitive half-times, so that dosing on total body weight may be appropriate for initial boluses but leads to accumulation if used for prolonged infusions without adjustment. Conversely, in underweight or cachectic patients, reduced lean mass, hypoalbuminemia, and diminished organ perfusion can cause higher free concentrations and exaggerated clinical effects at standard doses, prompting recommendations for lower starting doses, slower titration, and, where possible, use of agents with shorter half-lives or more predictable pharmacokinetics.

Finally, across intensive-care therapies, (e.g., **vasoactive agents and neuromuscular blockers to anticonvulsants and immunosuppressants**) both obesity and severe underweight magnify the impact of any misestimation of volume of distribution or clearance. Critical care reviews stress that in obese patients, **hydrophilic drugs** such as some catecholamines and neuromuscular blockers often correlate better with adjusted or ideal body weight, while lipophilic drugs more closely track total body weight, yet robust data are lacking for many agents at BMI extremes. In this context, the literature consistently advocates for early and repeated reassessment of effect, adaptation of dosing to dynamic organ function, and use of therapeutic drug monitoring where available, underscoring that extreme body habitus is not an isolated variable but a persistent modifier of pharmacotherapy decisions across therapeutic areas.