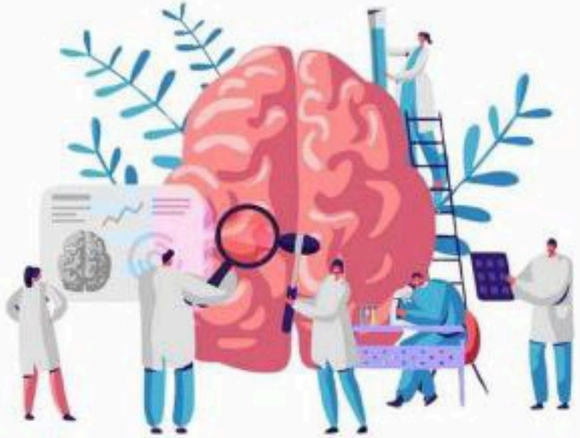


تفريغ لحاينتك

محاضرة: DOSAGE ADJUSTMENT

الصيدلاني\ة: Alaa Otoum

لجان الدُّفعات

Soul Academy

DOSAGE ADJUSTMENT

Renal and Hepatic Diseases

MEASURING RENAL FUNCTION

Glomerular filtration rate (GFR)

1. determined from excretion rate of a freely filtered substance* (e.g., inulin) and its concentration in plasma:

$GFR = (C_{ur})\ (Q_{ur})\ / Cp$

where C_{ur} is concentration in urine, Q_{ur} is urine flow rate, and Cp is concentration in plasma.

* must be a substance not actively secreted or reabsorbed.

TABLE 41–4. Sensitivity and Clinical Utility of Renal Function Tests

	Accuracy	Clinical Utility	Cost
Inulin clearance	++++	+	$$$$
Radiolabeled markers	+++	+	$$$
Nonisotopic contrast agents	+++	++	$$$
Creatinine clearance	++	+++	$$
Serum creatinine	+	++++	$

+, least acceptable; ++, adequate; +++, better; ++++, best.

الاعتماد الحالي في الـ Hospitals

إله دخل بس بجزئية الـ "filtration"

هيا إذا كانت قيمته كتير عالية هاد بعني ما عم بصير الـ filtration، بالتالي أمور الكلى مش منيحة.

أما إذا كانت قيمته قليلة معناها صار الـ filtration بالتالي أمور الـ kidneys بيدة.

MEASURING RENAL FUNCTION

- 2. we usually use creatinine clearance (Clcr) as an index of GFR
  a. creatinine is an easily measured endogenous substance
  b. creatinine rises in proportion to decreases in GFR

Fig. 16–4. The mean plasma concentration-time profiles of cefepime, a cephalosporin antibiotic, are different in patients with varying degrees of renal function after i.v. infusion of a 1000-mg dose over 30-min. The subjects were grouped according to their measured creatinine clearance values (in mL/min). (Adapted from Barbhaiya, R.H., Knupp, C.A., Fargue, S.T., Matzke, G.R., Guay, D.R.P., and Pittman, F.A.: Pharmacokinetics of cefepime in subjects with renal insufficiency. Clin. Pharmacol. Ther., *48*:268–276, 1990.)

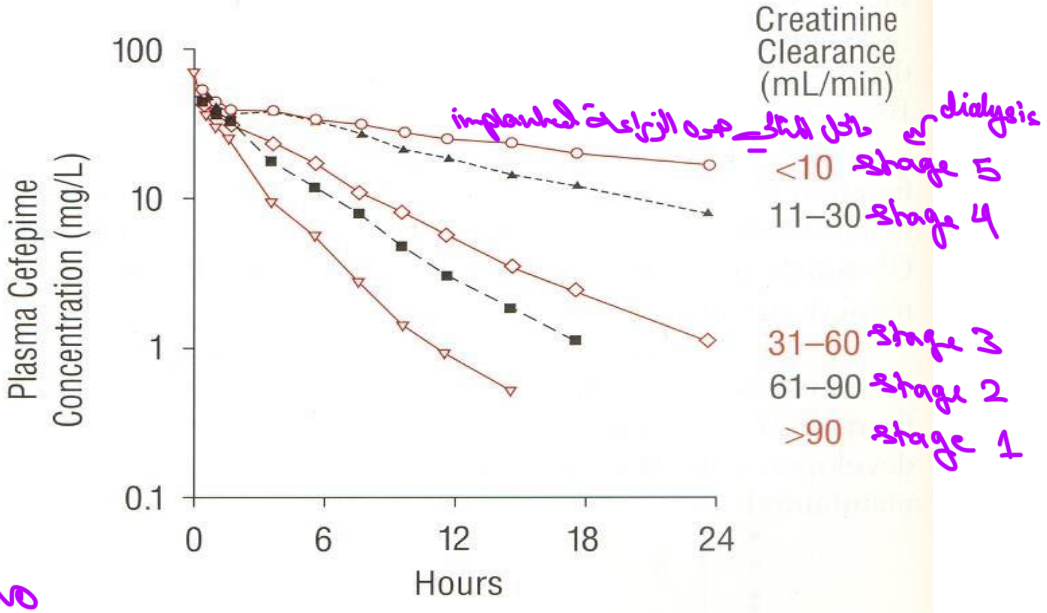
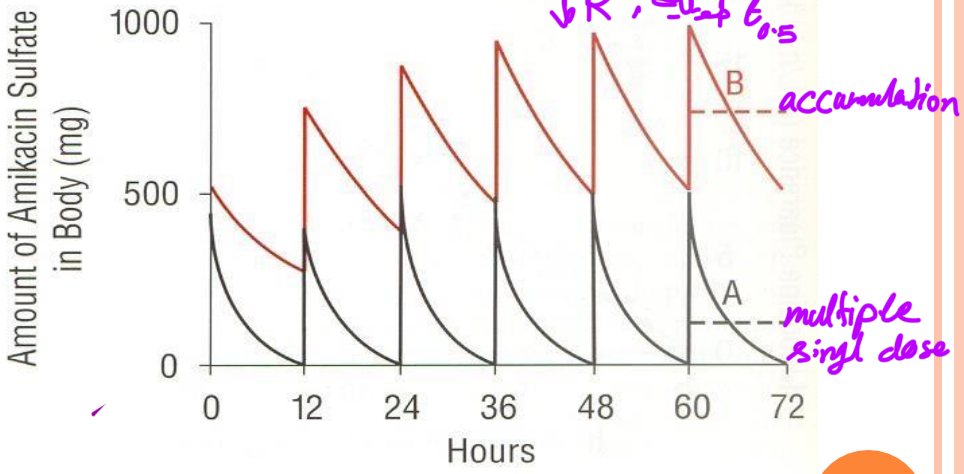


Fig. 16–5. Sketch of the amount of amikacin sulfate in the body with time following a regimen of 500 mg every 12 hr in a patient whose renal function is normal, curve *A*, and in a patient whose age and weight are the same but whose renal function is 17% of normal, colored curve *B*. Intravenous bolus administration is simulated. The normal half-life is assumed to be 2 hr. The dashed lines are the average plateau values.



where age and weight are in years and kilograms, respectively. Now, under any condition,

$$CLu(d) = CLu_R(d) + CLu_{NR}(d) \qquad 6$$

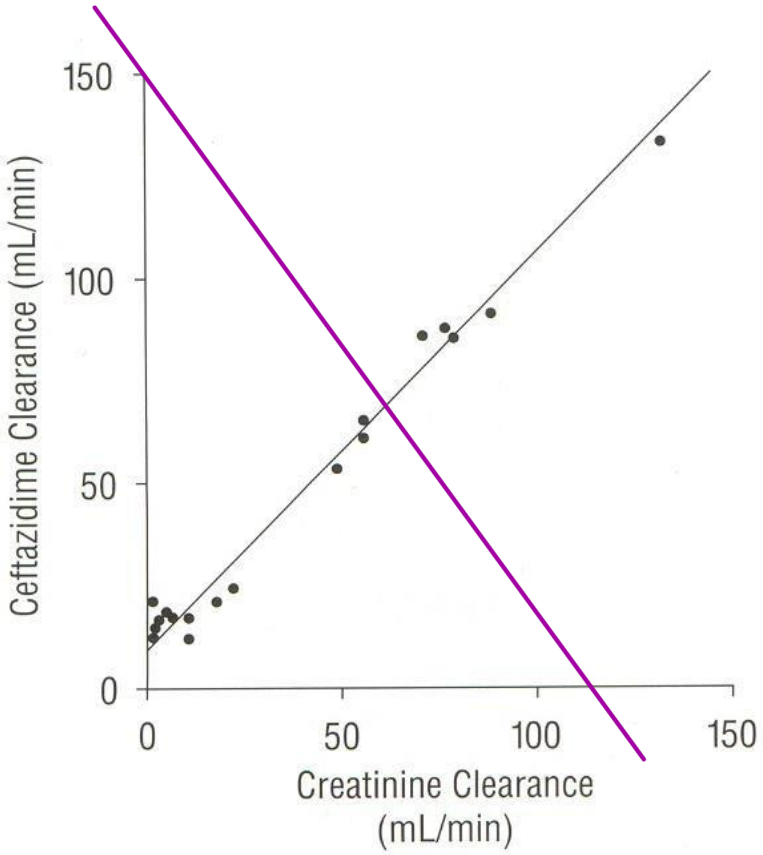


Fig. 16–6. The total clearance of the cephalosporin, ceftazidime, varies linearly with creatinine clearance in a group of 19 patients with varying degrees of renal function. Note that some clearance remains (y-intercept) when there is no renal function. (Drawn from the data of van Dalen, R., Vree, T.B., Baars, A.M., and Termond, E.: Dosage adjustment for ceftazidime in patients with impaired renal function. Europ. J. Clin. Pharmacol., *30*:597–605, 1986.)

Normal creatinine clearance values

Healthy young male:

125 ml/min/1.73m^2

Healthy young female: * 85%

110 ml/min/1.73m^2

By 60 years of age, reduced to about 70% of young adult

* شرط عشان اعمل dose adjsment :

١. مش شرط دايما ارتفاع الـ creatinine يعني عنده مشاكل بالـ Kidney ممكن يكون المريض عنده muscle lysis عادي بكون مستوى الـ createnine عالي ف عشان أقدر احكم سبب ارتفاعه أنه عنده مشكلة بالـ Kidney بده يكون مرتفع عنده uria برضه .

٢. إنه يكون الدواء 30% يصير الـ excreted عن طريق الـ Kidney على الأقل .

٣. لازم يكون GFR نازل بنسبة 30% ولكن كيف ؟؟

مثال مريض طبيعي عنده الـ GFR ٩٠ والطبيعي لازم 120 ف بالتالي في داعي أعمل dose adjsment ولكن لو إجاني مريض كبير بالسن وبرضه الـ GFR كان عنده ٩٠ بعادي الحالة بعتبرها قيمة NORMAL لأنه هون أصلا بما إنه كبير بالعمر بالتالي الـ ٩٠ هي عبارة عن الـ 70% من 120 ف بعتبرها normal .

* طب في حال إجاني شب عمره 28 سنة الـ GFR عنده طلعت 90 مافي داعي احسب الـ dose adjsment الها طب ليش ؟؟
لأنه أنا بحكم مباشرة من أول مره لازم أعمل فحص على شهرين ثلاث أشوف هل هو كان طول الوقت الـ GFR عنده ٩٠ وهاد الاشي بسميه (Basline / Basic)
يعني ممكن يكون هذا المريض الطبيعي عنده أصلا 100 مش 120 بالتالي لما يكون عنده ٩٠ مقارنة بـ ١٠٠ ما بقدر اعتبره كثير نازل فمافي داعي احسب dose adjusment

Estimation of Creatinine Clearance

- Several investigators have developed mathematical relationships to estimate CLcr when urine is unavailable.
- These factors include age, gender, weight, and serum creatinine concentration.
- Perhaps the most widely used of these estimators is the one developed by Cockcroft and Gault, which identified age and body mass as factors that significantly improved the estimate of CLcr.

Estimation of Creatinine Clearance

- Cockcroft and Gault

Normal GFR 120 ml/min/1.7 m²

Age ← بتعتمد على
Serum creatinine ←
ideal body weight ←

$$CL_{CR}(ml/\min)[male) = \frac{(140 - Age) * BW}{72 * SrCr_{ss}}$$

بما إنها بالمقام معناها كل ما زادت هنا بيعني انه GFR خفت.

$$CL_{CR}(ml/\min)[female) = \frac{(140 - Age) * BW}{85 * SrCr_{ss}}$$

كـ نفس تبعت الـ male بس بضرب 85٪

$$CL_{CR}(ml/\min)[female) = 0.85 * CL_{CR}male$$

- Age:years, Weight:Kg, SrCr:mg/dl ← لازم تكون هاي الوحده
- **Creatinine** Unit **Conversion** between mg/dL and µmol/l---
  → **1 mg/dL is equivalent to 88.4µmol/L**

كـ لازم أحولها لازم تكون بس mg/dl

Estimation of Creatinine Clearance

- The Cockcroft-Gault method should only be used in patients
  1) ≥18 years old,
  2) actual weight within (20-30)% of their ideal body weight (IBW) and
  3) stable serum creatinine concentrations.

Case 1: ideal باخذ الـ ideal < actual
Case 2: actual باخذ الـ ideal > actual
بشرط انه يكون أقل من 30% من الـ actual

هو دائما دنا باخذ الـ IBW الـ ideal من الـ actual
يعني لو واحد كان الـ IBW = 80 و الـ ideal هي = 70 بالتالي باخذ الـ 70

$$IBW(males) = 50 + 0.9(ht - 150)\,(height > 150cm)$$

$$IBW(females) = 45 + 0.9(ht - 150)\,(height > 150cm)$$

ولكن لو كان مريض وزنه 60 ولكن الـ ideal هو 70 يعني هو underweight يعني وزنه أقل من الـ ideal بهاي الحالة باخذ الـ actual لانه الـ creatinine بتنكس في muscle mass مش fat.

EXAMPLE 1

- A 40-years old female 70Kg 170 cm has a serum creatinine of 176.8 µmol/l. Calculate her creatinine clearance.

$$IBW(females) = 45 + 0.9(ht - 150)\,(height > 150cm) = 63Kg$$

- Thus we can use Cockcroft-Gault equation since the actual weight is within 20-30%of IBW

- Serum creatinine =2 mg/dl (176.8/88.4)

$$CL_{CR}(ml/\min)[female) = \frac{0.85*(140 - Age)*BW}{72*SrCr_{ss}}$$

- =41.3 ml/min

stage 3

Dosage adjustment

- When to adjust
- 1) More than 30 % of the drug is excreted in urine

AND

- 2) The decrease in renal function is more than 30 %

Dosage adjustment in uremic patients-Assumptions

- The assumptions on how these dosage regimens are calculated include the following:
- The renal elimination rate constant (*k*) decreases proportionately as renal function decreases.
- The non-renal routes of elimination (primarily, the rate constant for metabolism) remain unchanged.
- The apparent volume of distribution is not changed (but remember that this is not always the case! See next slide)
- Changes in the renal clearance of the drug are reflected by changes in the creatinine clearance.

Dosage adjustment in uremic patients

- The overall uremic elimination rate constant, *k*u, is the sum of renal and non-renal elimination.

$$K_u = K_u^r + Knr \rightarrow\rightarrow K_u = K_N^r * \left(\frac{CL_{Cr}^U}{CL_{Cr}^N}\right) + Knr$$

- Divide by K(normal)

$$\frac{K_u}{K_N} = \frac{K_N^r}{K_N} * \left(\frac{CL_{Cr}^u}{CL_{Cr}^N}\right) + \frac{Knr}{K_N}$$

u : uremic; r:renal; nr: non-renal; N: normal; CL_{Cr}: creatinine clearance; f_e: fraction eliminated renally

$$\frac{K_u}{K_N} = fe * \left(\frac{CL_{Cr}^u}{CL_{Cr}^N}\right) + (1 - fe)$$

$$\frac{\tau_u}{\tau_N} = \frac{K_N}{K_u}$$

المقلوب

Example 2

- The maintenance dose of an antibiotic is 80 mg every 6 hours for a patient with normal renal function. Calculate the maintenance dose for a uremic patient with creatinine clearance of 20 mL/min. Assume a normal creatinine clearance of 100 mL/min. The antibiotic is reported to be 100% excreted by the kidney

$x_0 = 80\ mg$

$cl\ cr\ (U) = 20\ ml/min$

$cl\ Cr\ (N) = 100$

$fe = 1$

$$\frac{K_u}{K_N} = fe * \left(\frac{CL^u_{Cr}}{CL^N_{Cr}}\right) + (1 - fe)$$

$$\frac{Ku}{K_N} = 1 * \frac{20}{100} + (1-1)$$

$$\frac{Ku}{K_N} = 0.2$$

$$\frac{Ku}{KN} \begin{cases} \text{dose} = \frac{x_u}{x_N} = \frac{x_u}{80} = 0.2 \Rightarrow x_u = 16\ mg \text{ every } 6\ hr \\ \text{frequency} = \frac{Ku}{Kr} = \frac{\tau_N}{\tau_u} = \frac{6}{0.2} \Rightarrow \tau_u = 30\ hr \end{cases}$$

80 mg every 30 hr

Solution

- K=Kr

$$\frac{K_u}{K_N} = 1*0.2 + (1-1)$$

$$K_u = K_N^r * \left(\frac{20}{100}\right) + 0$$

$$\frac{K_u}{K_N} = 0.2$$

- Remember for this drug fe=1, if the same dose is to be maintained
- $$\frac{\tau_u}{\tau_N} = \frac{K_N}{K_u}$$ ➔
- $$\tau_u = \frac{K_N}{K_u} * \tau_N = 6 * \frac{1}{0.2} = 30\,h$$

Solution

- If the same dosing interval is to be maintained

$$\frac{K_u}{K_N} = \frac{X_u}{X_N}$$

- Xu=80*0.2= 16 mg four times daily

EXAMPLE 3

- Ranitidine is an H2-receptor antagonist used in the treatment of peptic ulcer. After administration of the average dose of ranitidine in patients with normal kidney function (150 mg q 12 hr), 70% of the dose is excreted unchanged in urine. What will be the ranitidine dose required in a patient with only 30% of normal kidney function ?

  30 mg q 12 hr

  45 mg q 12 hr

  100 mg q 12 hr

  75 mg q 12 hr (150*.51)

$fe = 0.7$

$$\frac{K_u}{K_N} = fe * \left(\frac{CL^u_{Cr}}{CL^N_{Cr}}\right) + (1 - fe)$$

$= 0.7 * 0.3 + 1 - 0.7$

$= 0.21 + 0.3 = 0.51$

$\frac{Ku}{KN} = 0.51$

$\frac{Ku}{KN}$ → dose $= \frac{x_u}{x_N} = 150 * 0.51 = 76$ mg Q every 12 hr

→ frequency $= \tau_u = 12 * 0.51 = 25$ hr

EXAMPLE 4

- Lincomycin is given in a dose of 600 mg every 6 hours to a 75-kg male patient. What doses would be used (Renal clearance for licomycin = 60 % and the normal half-life is 4.6 hours)

  ما الها دخل على السؤال

  ↳ fraction excreted.

1. In complete renal FAILURE?

   ↳ CLCr = 0

2. When Clcr is 10 ml/min?
   Assume normal Crcl=120 ml/min

$X_m = 0.4 * 600$

$= 240\ mg$

$$\frac{K_u}{K_N} = fe * \left(\frac{CL^u_{Cr}}{CL^N_{Cr}}\right) + (1 - fe)$$

$$= 0.6 * \left(\frac{10}{120}\right) + 1 - 0.6$$

$$= 0.45$$

ماني داعي احسب τ هون فقط حسب dose.

$$0.45 = \frac{\chi_u}{\chi_N}$$

$$\chi_U = 0.45 * 600$$

$$= 270 \text{ mg}$$

Solution

- When CrCl =10mL/min

$$\frac{K_u}{K_N} = 0.6*(10/120) + (1-0.6) = 0.45$$

- New dose=600*.45=270 mg.

Solution

- When CrCl =0mL/min

$$\frac{K_u}{K_N} = 0.6*(0/120) + (1-0.6) = 0.4$$

- New dose=600*.4=240 mg.

شرط الدواء يتكون hepatic eliminated

DOSE ADAPTATION FOR PATIENTS WITH LIVER DISEASE

ما عليه أسئلة حل.

INTRODUCTION

- The liver is involved in the clearance of many drugs through a variety of metabolic pathways and/or biliary excretion of unchanged drugs or metabolites. → Biotransformation.
- Alterations of these metabolic and/or excretory functions in patients with liver disease can lead to drug accumulation or, less often, to failure to form an active metabolite. → toxicity

narrow therapuhic index oral خصوصًا إذا كانت الدواء
- Liver is the principal site of drug metabolism: For orally administered compounds, there is the:"First Pass Effect"

INTRODUCTION

Dose adaptation for patients with liver disease is more difficult than for patients with impaired renal function. unlike the creatinine clearance for the kidney, for the liver there is no *in vivo* surrogate to predict drug clearance.

Due to the lack of such *in vivo* markers, predictions concerning dose adaptation in patients with liver disease can only be made based on the **kinetic properties of the drugs in patients with liver disease**.

Clients at risk for impaired liver function

- Primary **liver disease** (eg, hepatitis, cirrhosis, cholestasis)
- Diseases that impair **blood flow** to the liver (heart failure, shock, major surgery, or trauma).
- **Hepatotoxic** drugs (acetaminophen, INH, statins, methotrexate, phenytoin, aspirin and alcohol)
  - Malnourished people or those on **low- protein** diets
- Patients with **Clinical signs** for hepatotoxicity (nausea, vomiting, jaundice, hepatomegaly).
  - Serum bilirubin levels above 4 to 5 mg/dl
  - Prothrombin time greater than 1.5 times control
  - Serum albumin below 2.0 g/dl
  - Elevated alanine and aspartate aminotransferases (ALT & AST).

EFFECT OF HEPATIC DISEASE ON PHARMACOKINETICS

- Drugs are often metabolized by one or more enzymes located in cellular membranes in different parts of the liver. Drugs and metabolites may also be excreted by biliary secretion.
- Hepatic disease will influence the pharmacokinetics of drug with high hepatic **extraction ratio**
- Hepatic disease may lead to:
  - Failure to form an active or inactive metabolite

وهاد الاشي موجود بال liver ومش موجود بال renal وهو عبارة عن ال fraction اللي راح بال metabolism، ال fraction اللي راح

  - Increased bioavailability and drug accumulation after oral administration due to decreased metabolic activity
  - Alteration in drug **protein binding** (alters Vd), and kidney function.

EFFECT OF HEPATIC DISEASE ON PHARMACOKINETICS

- Most liver function tests indicate only that the liver has been damaged; they do not assess the function of the cytochrome P-450 enzymes or intrinsic clearance by the liver.

- The influence of hepatic disorder on the drug bioavailability & disposition is unpredictable because of the multiple effects that liver produces.

Adjustment of Dosage in Hepatic Impairment

The altered response to drugs in liver disease could be due to decreased metabolizing capacity of the hepatocytes, impaired biliary elimination, due to biliary obstruction (e.g. **Rifampicin accumulates in obstruction jaundice**)

Impaired Hepatic blood flow leading to an increase in bioavailability caused by a reduction in first pass metabolism (e.g. Bioavailability of Morphine and **Labetalol** have been reported to double in patients with Cirrhosis)

Hepatic clearance

Cl_{hep} can be expressed for a given drug as the product of the **blood flow** across the liver **(Q)** and the **extraction of this drug** (E) during its first passage across the liver:

← ما ح يكون عليه اسئلة حل

$$Cl_{hep} = Q \times E = Q \times (C_{in} - C_{out})$$

Cin is the concentration of a drug in the portal and Cout hepatic outflow concentration

Factors affecting Hepatic clearance

Hepatic drug clearance depends therefore on 3 majors determinants:

- The extent of drug binding to the blood components
- Hepatic blood flow
- Hepatic metabolic activity.

Conclusion

The most dangerous drugs in patients with liver cirrhosis are those with a low bioavailability and a narrow therapeutic range when administered orally.

For these drugs, both initial and maintenance doses have to be reduced by 50% or more of the normal dose, depending on the severity of liver disease, hepatic extraction and metabolism, and toxicity of the drug.

مش مطلوب

Chronic Liver Disease Assessment - Child-Pugh Score

Parameters		Score		
		1	2	3
	Albumin	> 35 g/L	28 – 35 g/L	< 28 g/L
	Ascites	Absent	Slight	Moderate
	Bilirubin	< 34.2 µmol/L	34.2 – 51.3 µmol/L	> 51.3 µmol/L
	Encephalopathy	None	Grade 1 – 2	Grade 3 – 4
PTT	Seconds over control	< 4	4 – 6	> 6
	INR	< 1.7	1.7 – 2.3	> 2.3

Score	Class	Description	1-Year Survival (%)	2-Year Survival (%)
5 – 6	A	Well-compensated disease	100	85
7 – 9	B	Significant functional compromise	80	60
10 – 15	C	Decompensated disease	45	35

Reference:

1. Pugh RN, Murray-Lyon IM, Dawson JL, et al. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973; 60:646.
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3. Trey C, Burns DG, Saunders SJ. Treatment of hepatic coma by exchange blood transfusion. NEJM 1966; 274:473.