UNIVERSITI SAINS MALAYSIA

First Semester Examination
Academic Session of 1994/95

October/November 1994

FCP 556 : Biostatistics, Study Design and Clinical Pharmacokinetics

(2 hours)

This examination consists of two sections.

Section A consists of 50 multiple choice questions.

Section B consists of two (2) long questions.

Answer ALL questions.

Answers to Section A must be entered into the scripts provided.

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Section A

Mark (/) on the opposite space corresponding to a correct or most appropriate answer for each question. Each question has only one correct or most appropriate answer or statement.

1. Which of the following statements is true?

..... (a) Therapeutic drug monitoring (TDM) service can increase the cost of patient-care.

..... (b) TDM can prevent the occurrence of gentamicin toxicity.

..... (c) TDM is suitable for all drugs.

..... (d) None of the above statements is true.

2. Which of the following statements is true?

..... (a) A suitable method for the determination of serum digoxin is by using HPLC.

..... (b) Gentamicin is inactivated by piperacillin in-vitro.

..... (c) Plasma phenytoin concentration is best monitored using the spectrophotometer.

..... (d) Gentamicin concentration is usually measured in whole blood.

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3. Which of the following information is least useful in interpreting plasma drug concentration?

..... (a) Name of patient.

..... (b) Age of patient.

..... (c) Disease state of patient.

..... (d) Time blood is taken from patient.

4. Which of the following statements is true?

..... (a) Penicillin can be destroyed by gentamicin if they are mixed together.

..... (b) The penicillin-gentamicin interaction occurs only in-vitro.

..... (c) The minimum volume of blood required to assay for gentamicin concentration is 5.0 ml.

..... (d) Plasma penicillin concentration does not need to be monitored because of its high therapeutic index.

5. The decline of plasma drug concentration in a patient given 320 mg of the drug was found to fit with the following equation:

$$C = 4.7\ \mu g/ml\ e^{-(2.07/hr)t} + (8.18\ \mu g/ml)e^{-(0.18/hr)t}.$$

What is the terminal half-life of the drug?

..... (a) 2.07 hr.

..... (b) 8.18 hr.

..... (c) 3.05 hr.

..... (d) 4.7 hr.

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6. Which of the following statements regarding the use of folinic acid rescue is true?

..... (a) Rescue should be started 1 hour prior to the dose of methotrexate.

..... (b) A dose of 15 mg/m^2 is recommended in all cases.

..... (c) Rescue could be terminated once the methotrexate level falls below 0.2×10^{-7} M.

..... (d) Rescue should be terminated after 48 hours of methotrexate infusion.

7. Which of the following statements regarding the pharmacokinetics of methotrexate is true?

..... (a) The half-life is dependent on liver function.

..... (b) The absorption from gastrointestinal tract is relatively poor and erratic.

..... (c) Leucovorine rescue is used to accelerate its elimination.

..... (d) Approximately 50% of the methotrexate in the blood is bound to albumin.

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The next three questions are about the following case:

MA is a 12-year old boy admitted to HUSM for the 3rd course of high dose methotrexate therapy. A dose of 13 mg intravenous methotrexate (calculated based on body surface area) was given. The blood level of methotrexate obtained after the dose were:

Time post-infusion	Methotrexate (Molar)
12 hr.	5×10^{-3}
24 hr.	2×10^{-5}
36 hr.	4×10^{-6}
48 hr.	5×10^{-7}
72 hr.	1×10^{-8}

8. Which of the following doses of folinic acid is the most appropriate for the initial rescue?

..... (a) 10 mg/m^2 Q 6 hr.

..... (b) 100 mg/m^2 Q 6 hr.

..... (c) 1000 mg/m^2 Q 6 hr.

..... (d) 15 mg/m^2 Q 6 hr.

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9. When is the appropriate time to discontinue the leucovorine rescue?

..... (a) At 48-hour post-infusion.

..... (b) At 60-hour post-infusion.

..... (c) At 72-hour post-infusion.

..... (d) At 84-hour post-infusion.

10. When should folinic acid rescue therapy be initiated?

..... (a) Immediately after discontinuation of infusion.

..... (b) At 12-hour post-infusion.

..... (c) At 24-hour post-infusion.

..... (d) At 36-hour post-infusion.

11. The out-patient pharmacist conducted a study to examine the types of prescribing error among the doctors at both the general out-patient and specialist clinics. Which of the following would be the most appropriate statistical test for the above study?

..... (a) Student's t-test.

..... (b) Chi-square.

..... (c) ANOVA.

..... (d) Sign test.

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12. Which of the following statistical tests is appropriate for a continuous data?

..... (a) Student's t-test.

..... (b) Chi-square.

..... (c) ANOVA.

..... (d) Sign test.

13. Which of the following tests is appropriate for analyzing data on a nominal scale?

..... (a) z-test.

..... (b) Fisher's exact test.

..... (c) Student's t-test.

..... (d) F-test.

14. Which of the following statements is true?

..... (a) The student's t-test is performed to determine associations between two variables.

..... (b) The possibility of type-1 error can be reduced by increasing the sample size.

..... (c) The choice of an appropriate statistical test is not dependent on the study design.

..... (d) The Fisher's exact test is more sensitive than the Chi-square in determining differences between two pairs of variables.

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15. Which of the following disease states can affect theophylline clearance?

..... (a) Acute pulmonary infections.

..... (b) Cor pulmonale.

..... (c) Diabetes mellitus.

..... (d) Chronic arthritis.

16. What is the most appropriate dosing interval for chronic oral theophylline therapy in children between the ages of 1-9 years?

..... (a) 8-12 hourly.

..... (b) 4-6 hourly.

..... (c) 12-24 hourly.

..... (d) 6-8 hourly.

17. What is the most appropriate aminophylline loading dose for a 56-year old patient who weighs 78 kg. and has a baseline theophylline concentration of 3.2 mg/L for a targeted theophylline concentration of 15 mg/L?

..... (a) 400 mg.

..... (b) 600 mg.

..... (c) 800 mg.

..... (d) 1000 mg.

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18. A patient (45 year old, 68 kg) given IV infusion of aminophylline of 30 mg/hr for 72 hours was to be discharged. What would be the most appropriate dosage regimen for conversion to oral theophylline?

..... (a) 200 mg BD.

..... (b) 250 mg BD.

..... (c) 300 mg BD.

..... (d) 350 mg BD.

19. Which of the following drugs can significantly delay theophylline clearance?

..... (a) Rifampicin.

..... (b) Phenytoin.

..... (c) Ethynilestradiol.

..... (d) Isoniazid.

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20. Which of the following statements regarding study designs is not true?

(i) Quasi-experimental designs involve the production of 'time-series'.

(ii) Time-series designs involve the repeated observations of subjects before and after treatment.

(iii) A quasi-experimental design permits the investigator to control the time at which a treatment is introduced or withdrawn.

(iv) A quasi-experimental design affords greater control over extraneous variables than an experiment.

..... (a) (i) and (iii) only.

..... (b) (ii) and (iv) only.

..... (c) (i), (ii) and (iii) only.

..... (d) (iv) only.

21. Representative sample.....

..... (a) is defined as the inverse of the square root of the sample size.

..... (b) reflects precisely the crucial dimension of a population.

..... (c) must be a random sample.

..... (d) consists of at least 700 cases.

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22. Which of the following statements is/are true?

(i) If a research produces statistically significant results, then its design is adequate.

(ii) The application of scientific method ensures the validity of a researcher's conclusion.

(iii) Random assignment of subjects to treatment groups ensures that the investigation uncovers causal effect.

(iv) Without adequate control the size of an effect may be difficult to estimate.

..... (a) (i) and (iii) only.

..... (b) (ii) and (iv) only.

..... (c) (i), (ii) and (iii) only.

..... (d) (iv) only.

23. The expectation of the experimenter when conveyed to the experimental subjects is termed .....

..... (a) Rosenthal effect.

..... (b) Placebo effect.

..... (c) Hawthorn effect.

..... (d) Murphy effect.

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24. Which of the following statements regarding the results of scientific research is true?

..... (a) The outcome must conform to public expectations.

..... (b) It must be obtained only in controlled laboratory situations.

..... (c) It should not be used to support existing theories.

..... (d) It should be made available for critiques and replication.

25. Which of the following statements regarding placebo effect is true?

..... (a) It is another name for relaxing subjects.

..... (b) It occurs only if there is no double-blinding.

..... (c) It only happens in drug studies.

..... (d) It can occur in both experimental and control groups.

26. An appropriate study design will be one which .....

..... (a) requires sophisticated instrumentation.

..... (b) would give the expected answer.

..... (c) minimizes all possible errors.

..... (d) is experimental in nature.

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27. A study is said to be externally valid if .....

..... (a) it has been an experimental study.

..... (b) quota-sampling has been used.

..... (c) its results can be generalized to other equivalent settings.

..... (d) all the subjects in the sample have been equivalent.

28. Which of the following statements regarding sample size is true?

..... (a) As the size increases the sample becomes more bias.

..... (b) The ecological validity of the study increases with an increase sample size.

..... (c) The sampling error decreases with an increase in sample size.

..... (d) As the sample size increases, the population becomes more accessible.

29. If the internal validity of a study is adequate then ....

..... (a) the results could be generalized to other situations.

..... (b) the result may demonstrate causal effect.

..... (c) the results will be statistically significant.

..... (d) the results will be clinically useful.

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30. If a pilot study shows that the effect is small in relation to sampling error then the researcher should .....

..... (a) use a relatively small sample.

..... (b) use a relatively large sample.

..... (c) use incidental method of sampling.

..... (d) abandon the research project.

31. Which of the following statements concerning a 'literature review' is true?

..... (a) It is a list of research publication relevant to an investigation.

..... (b) It should discredit research findings that are inconsistent with the hypothesis under study.

..... (c) It should include only findings that directly support the hypothesis being investigated.

..... (d) It should be a critical review of findings relevant to an investigation.

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32. Which of the following is/are (an) aim(s) of critical analysis of a publication?

(i) To identify the relevance of the results for clinical practice.

(ii) To identify the planning of the study.

(iii) To identify the internal and external validity of the study.

(iv) To identify and attack incompetent researchers in one's area of interest.

..... (a) (i) and (iii) only.

..... (b) (ii) and (iv) only.

..... (c) (i), (ii) and (iii) only.

..... (d) (iv) only.

33. Which of the following statements is true?

..... (a) The use of correct research methods does not constitute an ethical necessity.

..... (b) A research protocol is a summary of the data obtained in an investigation.

..... (c) The population being studied is defined after the sample has been selected.

..... (d) A hypothesis is a proposition about the relationship existing between variables or predictions of differences between groups.

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34. A researcher is interested to determine the effect of dietary sodium on blood pressure of newborn infants. Which of the following would be the best study design for the study?

..... (a) The Solomon four-group design.

..... (b) The post-test, control group design.

..... (c) The pre-test, post-test control group design.

..... (d) The one-group, pre-test, post-test design.

35. Which of the following will avoid bias in a randomized controlled trials?

..... (a) Blinding the patients and the clinicians.

..... (b) Randomizing the study sample.

..... (c) Having a control.

..... (d) All of the above.

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36. Which of the following describes the features of a Cohort study?

(i) It comprises a study on a group of people exposed to the drug and another not exposed that are followed over time.

(ii) The incidence of the unintended drug effect is assessed in both groups.

(iii) It is generally prospective in design.

(iv) The level of drug exposure should be established before the study starts.

..... (a) (i) and (iii) only.

..... (b) (ii) and (iv) only.

..... (c) (i), (ii) and (iii) only.

..... (d) (I), (ii), (iii) and(iv).

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37. Which of the following questions are relevant to determine the validity of the results of a clinical trial?

(i) Was the assignment of patients to treatments really randomized?

(ii) Were all clinically relevant outcomes reported?

(iii) Were all patients who entered the study accounted for at its conclusion?

(iv) Is the therapeutic maneuver feasible in your practice?

..... (a) (i) and (iii) only.

..... (b) (ii) and (iv) only.

..... (c) (i), (ii) and (iii) only.

..... (d) (i), (ii), (iii) and(iv).

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38. Which of the following questions deal(s) with the applicability of the results of a clinical trial?

(i) Were all clinically relevant outcomes reported?

(ii) Were the study patients recognizably similar to your own?

(iii) Is the therapeutic maneuver feasible in your practice?

(iv) Were all patients who entered the study accounted for at its conclusion?

..... (a) (i) and (iii) only.

..... (b) (ii) and (iv) only.

..... (c) (i), (ii) and (iii) only.

..... (d) (i), (ii), (iii) and(iv).

39. Which of the following question deals with both validity and applicability of the results of a clinical trial?

..... (a) Was the assignment of patients to treatments really randomized?

..... (b) Were the study patients recognizably similar to your own?

..... (c) Were both statistical and clinical significance considered?

..... (d) Were all clinically relevant outcomes reported?

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40. Which of the following is not a true description of pharmacoepidemiology?

..... (a) It is defined as the application of epidemiological knowledge, methods, and reasoning to the study of the effects and uses of drugs in human population.

..... (b) It is also known as post-marketing surveillance.

..... (c) It offers a methodology both to increase the health benefits of drugs and to reduce their risks.

..... (d) None of the above.

41. Which of the following is true about observational studies?

..... (a) The investigator has partial control over random allocations of treatments.

..... (b) Observational studies do not include descriptions of studies of drug utilization.

..... (c) It is usually carried out in the Phase III clinical trials.

..... (d) Case-control studies are usually conducted after marketing.

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42. Which of the following is/are (a) limitation(s) of pre-marketing studies?

..... (a) They involve relatively small numbers of patients.

..... (b) They involve short durations of therapy.

..... (c) They involve highly screened volunteers.

..... (d) All of the above.

43. Observational study design used in epidemiological research comprises of all of the followings except...

..... (a) cross-sectional study.

..... (b) randomized trial.

..... (c) cohort study.

..... (d) case-control study.

44. A study in which drug exposure and disease status or symptoms determined at the same point in time is a ...

..... (a) case-control study.

..... (b) cohort study.

..... (c) cross-sectional study.

..... (d) clinical trial.

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45. Phenytoin 300 mg was initiated in a 15 year old boy with tonic-clonic seizures 3 days earlier and the blood level measured was 5.3 mg/L. Your action would be...

..... (a) to increase the maintenance dose by 50%.

..... (b) to increase the maintenance dose to 330 mg.

..... (c) do nothing as the blood level is not at steady-state yet!

..... (d) to add carbamazepine

46. Carbamazepine was to be initiated in a patient with tonic-clonic seizures. Your dosing recommendation would be.....

..... (a) to give a loading dose, followed by the full maintenance dose.

..... (b) not to give a loading dose and to start with the maintenance dose.

..... (c) to give a loading dose, followed by 1/4 of the full maintenance dose at week 1, and increase by 1/4 each week until full maintenance dose is achieved.

..... (d) not to give loading dose. Start with 1/4 of the full maintenance dose at week 1, and increase by 1/4 each week until the full maintenance dose achieved.

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47. The steady state blood level data of an antiepileptic drug from 2 different dosing regimens in a patient were 10 mg/L at 300 mg/day and 16 mg/L at 330 mg/day. This data is consistent with.....

..... (a) first-order kinetics.

..... (b) Michaelis-Menten kinetics.

..... (c) auto-induction.

..... (d) None of the above.

48. A 45 year old man with severe head injury was given 300 mg/day phenytoin injection. 7 days later, phenytoin level was found to be 7.8 mg/L. If the desired blood level is 14 mg/L, which method can be used to determine the new dosing regimen?

..... (a) Bayesian method.

..... (b) Ludden's method.

..... (c) Mullen's method.

..... (d) Sawchuk-Zaske's method.

49. When dosing a patient with antiepileptic drugs, loading doses may be given for all except.....

..... (a) phenytoin.

..... (b) carbamazepine.

..... (c) phenobarbitone.

..... (d) diazepam.

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50. If an adverse effect is suspected to occur in one out of 40,000 subjects, how many subjects need to be observed in order to be 95% likely to detect it?

..... (a) 80,000.

..... (b) 120,000.

..... (c) 160,000.

..... (d) 200,000.

(50 marks)

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Section B

QUESTION 1

A. A study was performed to determine the effects of an exercise program on patients with occlusion of some of the major arteries in the legs.

Method: A group of 50 patients was selected by a vascular surgeon to participate in the study. A dependent variable for the group, that is the distance walked by the patients to the limit of pain tolerance were taken (pretest).

The exercise program plus daily walks with encouragement to increase daily walking distance was then administered to the group.

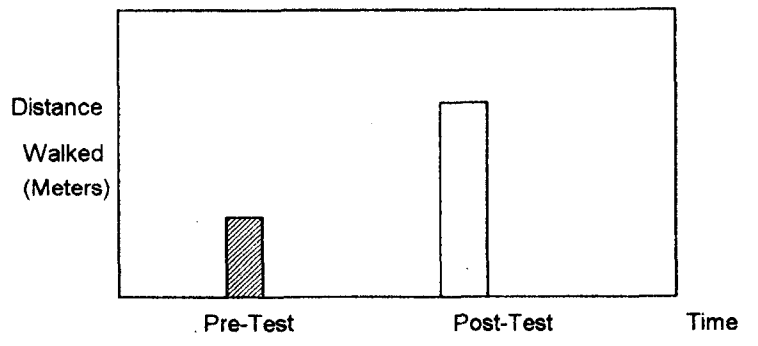
Since more than 50% of the patients were smokers, advice to stop smoking was also given. Apart from this, the patients were also put on diet that were low in animal fats.

After six weeks, the group dependent variables (post test) were taken.

Results: (a) Smoking declined markedly.

(b) The results were not evaluated statistically but it appeared to indicate an increase in walking distance (Figure).

Fig. 1. Relationship Between Distance Walked And Time



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i) Comment on whether this change in the walking distance was caused by the exercise program.

(6 Marks)

ii) Considering your comments in A, discuss how this study could be redesigned to improve internal validity.

(7 Marks)

B. CC, a 10-year old, 30 kg male presented to the Outpatient Clinic with a complaint of recurring cough and wheezing for a few weeks. These symptoms worsen after she had a bout of upper respiratory tract infections. A diagnosis of asthma was made and the doctor intended to start her with an oral theophylline therapy.

i) How should Miss CC's oral theophylline therapy be initiated?

(5 Marks)

ii) Is the trough theophylline concentration appropriate to monitor CCs therapy? Give your reasons.

(5 Marks)

Would a non-sustained release tablet of theophylline be appropriate for CC?

(2 Marks)

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QUESTION 2

The following serum concentrations were obtained for ticarcillin after a 5G dose was given to a volunteer:

Time After Dose (hr)	Plasma Concentration (mg/L)
0.25	320.0
0.50	270.0
1.00	200.0
2.00	106.0
3.00	60.0
4.00	32.0
5.00	17.0
6.00	9.3

i) Fit the above data to a suitable equation and determine the values for the constants in the equation.

(5 Marks)

A 3.0 G dose of ticarcillin was administered to another volunteer after a 1.0 G dose of probenecid was administered. The plasma concentrations of ticarcillin obtained were as follows:

Time After Dose (hr)	Plasma Concentration (mg/L)
0.25	216.0
0.50	171.0
0.75	142.0
1.00	122.0
2.00	78.4
3.00	53.2
4.00	36.4
5.00	24.9
6.00	17.0

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ii) Fit the above data to a suitable equation and determine the values for the constants in the equation.

(10 Marks)

iii) Explain the differences you observed in your answers to (i) and (ii).

(5 Marks)

iv) Discuss how you would use the information you obtain from studies such as in (i) and (ii) to plan strategies for individualizing drug therapies.

(5 Marks)

...29/-

Appendix

Normal Laboratory Values

1.	Ammonia	80-110 mcg/dl or	47-65 umol/L
2.	Amylase	4-25 IU/ml	
3.	Billirubin		
	- Direct	0-0.2 mg/gl	0-3 umol/L
	- Indirect	0.2-0.8 mg/dl	30-14 umol/L
	- Total	0.2-1 mg/dl	30-17 umol/L
4.	CO_2	20-30 mEq/L	24-30 mMol/L
5.	pCO_2	35-45 mmHg	
6.	CI	100-106 mEq/L	100-106 mMol/L
7.	Cpk	50-170 U/L	
8.	Creatinine (SCr)	0.6-1.5 mg/dl	60-130 umol/L
9.	Random blood sugar	70-110 mg/dl	3-10 umol/L
10.	Iron	50-150 mcg/dl	9.0-26.9 umol/L
11.	Lactic dehydrogenase	70-210 IU/L	
12.	Magnessium	1.5-2.0 mEq/L	0.8-1.3 mMol/L
13.	pO_2	75-100 mmHg	
14.	pH	7.35-7.45	
15.	Acid phosphatase		
	Male	0.13-0.63 IU/ml	36-176 nmol s^{-1}/L
	Female	0.101-0.65 IU/ml	2.8-156 nmol s^{-1}/L
16.	Alkaline phosphatase	39-117 IU/L	
17.	Phosphorous	3.0-4.5 mg/dl	1.0-1.5 mMol/L
18.	Potassium (K+)	3.5-5.0 mEq/L	3.5-5.0 mMol/L
19.	Calcium (Ca^{2+})	8.5-10.5 mg/dl	2.1-2.6 mMol/L
20.	Sodium (Na+)	135-145 mEq/L	135-145 mMol/L
21.	Bicarbonate (HCO_3-)	24-38 mEq/L	24-28 mMol/L

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22.	Protein		
	- Total	6.0-8.5 g/dl	60-85 g/L
	- Albumin	3.5-5.0 g/dl	35-50 g/L
	- Globulin	2.3-3.5 g/dl	23-35 g/L
	- Transferrin	200-400 mg/dl	2.0-9.0 g/L
23.	Transaminase (SGOT)	0-40 IU/L	0-0.32 umol s^{-1}/L
24.	BUN	8-25 mg/dl	2.9-8.9 mMol/L
25.	Uric Acid	3-7 mg/dl	0.18-0.42 mMol/L
26.	Blood Pictures		
	Red blood cell (RBC)		
	Male	4.8-6.4 x $10^6/mm^3$	
	Female	4.2-5.4 x $10^6/mm^3$	
	White blood cell(WBC)	4.0-11.0 x $10^3/mm^3$	
	P	60-75%	
	L	20-40%	
	M	4-8%	
	B	0-1%	
	E	1-3%	
	Platelate (Plt)	200-400 x $10^3/mm^3$	
27.	ESR Male	0-10 mm/jam (Wintrobe)	
	Female	0-15 mm/jam (Wintrobe)	
28.	Hematocrit		
	Male	45-52%	
	Female	37-48%	
29.	Hemoglobine (Hgb)		
	Male	13-18 g/dl	
	Female	12-16 g/dl	
30.	Prothrombin time (PT)	75-100% baseline	
31.	APTT	25-37 sec.	
32.	Creatinine Clearance (CrCl)	105-150 ml/min/1.73 m^2	
33.	TT_4	3.0-7.5 mcg/dl	
34.	RT_3U	25-35%	
35.	FTI	1.3-4.2	

...31/-

NORMAL HEMODYNAMIC VALUES AND DERIVED INDICES

Normal Value	Units		
BP S/D/M	Blood Pressure Systolic/Diastolic/Mean	120/80/93	mm Hg
CO	Cardiac Output	4-6	Liters/min.
RAP	Right Atrial Pressure (Mean)	2-6	mm Hg
PAP S/D/M	Pulmonary Artery Pressure Systolic/Diastolic/Mean	25/12/16	mm Hg
PCWP	Pulmonary Capillary Wedge Pressure (mean)	5-12	mm Hg
CI	Cardiac Index $CI = \frac{CO}{\text{Body Surface Area}}$	2.5-3.5	Liters/min/m^2
SV	Stroke Volume $SV = \frac{CO}{\text{Heat Rate}}$	60 - 80	ml/beat
SVI	Stroke Volume Index $SVI = \frac{SVI}{\text{Body Surface Area}}$	30 - 50	ml/beat/m^2
PVR	Pulmonary Vascular Resistance $PVR = \frac{MPAP - PCWP}{CO} \times 80$	< 200	dynes.sec.cm^{-5}
TPVR	Total Peripheral Vascular Resistance $TPVR = \frac{MBP - RAP}{CO} \times 80$	900-1400	dynes.sec.cm^{-5}
LVSWI	Left Ventricular Stroke Work Index $LVSWI = (MBP-PCWP)(SVI)(.0136)$	35-80	gm-m/m^2/beat

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