FRCPath Part 1 ACICE

First paper

Answer <u>all</u> questions

<u>Question 1</u> (20 marks)

The following questions relate to clinical presentations in immunodeficiency disorders.

a) List **three** of the commonest encapsulated bacteria that cause >85% pulmonary infections in patients with common variable immunodeficiency disorders. (3 marks)
b) List **two** most commonly implicated bacteria and **one** fungus responsible for infections in X-linked chronic granulomatous disease. (3 marks)
c) Mention **two** infections most likely to affect individuals with absolute CD4+T cell count <50/ul. (2 marks)
d) Mention **three** primary immunodeficiency disorders and **one** secondary immunodeficiency condition characterized by severe eczema and low serum immunoglobulins. (4 marks)
e) List **three** critical functions of complement system critical in patients with C7 deficiency making them susceptible to repeated *Neisserial* meningitides. (6 marks)
f) Mention **two sources (cells)** of the serine protease C1-inhibitor, absence of which leads to serious angioedema episodes. (2 marks)

<u>Question 2</u> (20 marks)

Answer questions for both of the following cases:

a) An 18-year-old girl had itching and tingling of her lips and mouth followed by vomiting within minutes after eating tomato-pizza. She has been having regular attacks with both fresh and cooked fruits.
    i. List the most likely diagnosis and **two** possible diagnoses. (3 marks)
    ii. What further clinical information and relevant investigations would help you to support the diagnosis? (4 marks)
    iii. Summarise the main principles of management. (3 marks)

b) A 65-year-old man had three episodes of swollen lips and tongue over the past year. He had a history of perennial rhinoconjunctivitis that did not require regular therapy.
    i. List the most likely diagnosis and **two** possible diagnoses. (3 marks)
    ii. What further clinical information and relevant investigations would help you to support the diagnosis? (4 marks)
    iii. Summarise the main principles of management. (3 marks)

<u>Question 3</u> (20 marks)

a) A 19 year-old woman referred to the clinic after she had three episodes of bacterial meningitis.
Investigations revealed normal complement C3, serum immunoglobulin levels, detectable antibodies to tetanus, pneumococcus and *Haemophilus influenza type B* and normal lymphocyte subsets. CH50 was normal with absent AP50.

i) What is the basis of CH50 and AP50 assays? (3 marks)
ii) Explain the results, and what further tests would confirm diagnosis? (4 marks)
iii) Outline general principles of management. (3 marks)

b) A 3-year-old boy presented with failure to thrive, liver abscess and bacterial adenitis. Investigation revealed he had inflammatory bowel disease.

i) List the most likely diagnosis and **two** other primary immunodeficiency conditions with bacterial infections and inflammatory bowel disease. (3 marks)
ii) What further clinical information would help you to request relevant investigations, what are the investigations and comment on their clinical utility. (4 marks)
iii) Summarise the main principles of management (3 marks)

Question 4 (20 marks)

A junior doctor from the Gastroenterology ward wishes to discuss regarding a 56-year-old female patient with abnormal liver function and positive autoantibody test.

a) List **four** types, including clinical presentation, of autoimmune liver disease and **three** commonly associated autoimmune diseases seen in patients with autoimmune liver disease. (4+3=7 marks)

b) List **three** liver-associated autoantibody tests **with** relevant target antigen **and** the laboratory detection method used. (3 each = 9 marks)

c) The patient underwent liver transplantation but HLA-matched donor was not required. List **four** differences between MHC-Class I and MHC-Class II molecules. (4 marks)

Question 5 (20 marks)

Question 5A (10 marks)

A newly approved therapy prevents progression of type 1 diabetes mellitus by inhibiting auto-reactive T cells destroying the pancreas.

This treatment is an anti-CD3-directed antibody given intravenously once daily over two weeks, with rash and headache noted in 47% of patients.

i. List **three** likely immunological adverse effects in patients receiving this treatment. (6 marks)
ii. List the vaccination strategies you would employ in patients due to receive or receiving this treatment. (4 marks)

Question 5B (10 marks)

i) A recently concluded vertical audit on autoimmune tests in diabetes has identified several inappropriate requests from Rheumatology clinics. As a senior clinical member of the team, suggest five ways (pre-analytical) you could consider improving test utilisation. (5 marks)

ii) The same team wants the laboratory to introduce a new autoantibody test that has a sensitivity of 90% and specificity of 78%. The prevalence of this autoimmune condition is 40%.

What is the positive predictive value of this test? (5 marks)

Sample answers (indicative only)

Question 1

Model answer a	**Marks**
Streptococcus pneumoniae *Hemophilus influenzae* *Moraxella catarrhalis*	1 1 1
Model answer b	**Marks**
Bacteria: *staphylococcus aureus*, gram negative *Enterobacteriaceae, including Salmonella, Klebsiella, Aerobacter & Serratia* *Pseudomonas, Actinomyces and Nocardia* **Fungus** *Aspergillus fumigatus* *Aspergillus nidulans*	1 1 1
Model answer c	**Marks**
Cryptosporidium MAViC CMV (retinitis) Microsporidia *Pneumocystis Carinii* pneumonia / *Pneumocystis Jirovecii* pneumonia Aspergillosis Histoplasmosis (very advanced HIV, SCID)	Accept any 2
Model answer d	**Marks**
PID: Omenn's (SCID, RAG1/2), Wiskott-Aldrich syndrome, Hyper IgE Syndrome, *STAT3/Tyk2*, IPEX **SID:** HIV infection (paediatric HIV can present with hyogamma); *Accept:* severe atopic eczema treated with immunosuppresants causing hypogammaglobulinemia *Accept:* cGVHD causing eczema type rash (with underlying hypogamma) e.g., leaky SCID of *RAG* def	Any 3 1
Model answer e	**Marks**
Opsonisation C3b and Ig = opsonins, bacteria easily phagocytosed when coated with C3b/Ig C5-9 cause pores to form on cell membranes & kill GNB Chemotactic agent production (C5a, C3a, C4a) that attract immune cells B-cell co-stimulation (C3dR = CD21 (CR2) part of BCR complex that allows Ag-specific B cell responses (general function, not for C7 deficient patients).	6 marks (Each 2 marks) Allow 1 mark
Model answer f	**Marks**
C1-INH produced by • Hepatocytes • Fibroblasts • Monocytes (PBMCs) • Placenta • Endothelial cells • Megakaryocytes • Microglial cells	Any 2

Model Answer 2a	Marks
Most likely diagnosis: nsLTP allergy **Differential diagnoses:** Oral Allergy syndrome (Bet v 1) Pollen (grass/tree) & wheat allergy	 1 1 1
Further information and Investigations: Other LTP food reactions & SpIgE pru p 3 (most specific component-resolved diagnostics) Birch pollen allergy & SpIgE Bet v 1 Wheat-related symptoms/WDEIA & SpIgE Wheat or omega-5-gliadin SpIgE nuts Complement C3, C4 levels – exclude C1-INH def especially if any attacks without foods Total IgE level – atopic tendency Skin prick tests to pollens, wheat, tomato, nuts – exclude other allergies	 1 0.5 0.5 0.5 0.25 0.25 1
Management: Discuss nsLTP syndrome, how it differs from OAS; stop offending foods Provide list of related nsLTP foods Keep food diary Emergency management plan (anti-H1, Adrenaline auto-injector)	 1 0.5 0.5 1
Model Answer 1b	
Most likely (common) diagnosis in this age-group : Drug-induced angioedema (ACE-inhibitor, cardiac failure drugs) Two alternative diagnoses: Idiopathic spontaneous angioedema C1-inh def, or acquired C1-inh def angioedema (check for lymph nodes/features of LPD)	 1 1 1
Further information and Investigations: Check medications – if on ACE-I/ARBs – check Complement C3, C4 Check for 'B' symptoms (weight loss, night sweats, lymph nodes) FBC, LDH, USG /CT – for AAE If C4 low, C1-inh antigen & function low – new diagnosis of C1-INH def	 1, 1 1 1 1
Management: Stop offending drug (if any). Start anti-H1 (4 x standard dose, if necessary). Refer to Haematology if any signs of lymphoproliferative disease.	 1 1 1

Answer 3

Model Answer 3a	**Marks**
CH50 and AP50 assays are used to screen deficiency in the complement pathways, CH50 for classical and AP50 for alternative pathways & are based on lysis of Ab-sensitized sheep erythrocytes (CH50) and rabbit erythrocytes (AP50), intact complement results in complement activation and haemolysis of the sensitised RC, results	1 1

are reported at the point of 50% lysis. (Accept ELISA assay test as an answer too). Both assays need to be performed in parallel and are dependent on terminal lytic sequence. To get complexion of the divalent cations calcium and magnesium needed for the activation of the classical pathway, and avoid *in vitro* complement activation, blood collected into EDTA-containing tubes. (Normal CH50 with abnormal AP50 suggests **normal** classical and terminal complement pathways i.e. C1q-C9, Factor H, Factor I (where CH50 and AP50 are both low), suggestive of a defect in the alternative complement pathway. Factor I can also present with normal CH50).	1
Unlikely antibody deficiency disorder, or T-cell immunodeficiency **Normal CH50 activity and undetectable AP50 activity with a normal C3 level suggests a deficiency in one of the alternative pathway components (i.e., FB, FD, or properdin).** Unlikely properdin deficiency as X-linked (unless skewed X-inactivation, and X-linked family history) Possibilities: Factor D deficiency Factor B deficiency • Repeat AP50 on a fresh sample to confirm • Factor D level; Factor B level • If Factor B and D levels are normal then use commercial serum with factor B deficient and factor D deficient to determine loss of function • Confirm with genetic tests	1 1 1 1
Principles of management: Vulnerability to encapsulated organisms, so patients need to be aware of the symptoms of meningococcal infection and seek care immediately if they should develop Conjugate meningococcal B and ACYW and pneumococcal and *Haemophilus influenzae* type B vaccines should be given to all patients, with subsequent monitoring of antibody titres (every 5 years). No contraindication to live vaccines. Prophylactic antibiotics recommended, particularly in patients with recurrent meningococcal infections or those at higher risk of endemic or occupational exposure. The use of prophylactic antibiotics should be balanced against the potential development of resistance. Patients also need education, including an emergency plan in the event of infection and travel. Some patients have emergency antibiotics at home and MedicAlert or similar bracelets.	1 1 1 1
Model Answer 3b	Marks
Most likely diagnosis:	

Chronic Granulomatous disease, commonest is mutation in gp91phox (*CYBB*) X-linked. Possible PIDs with bacterial infections and IBD • Agammaglobulinemia (XLA, CVID, IL-21 deficiency) • LRBA / CTLA4 haploinsufficiency • SCID (ZAP70, IL2RG, ADA, CD3 defects) • Hyper-IgE syndrome (DOCK8 deficiency) • IPEX • Wiskott-Aldrich syndrome • NEMO deficiency	1 1 1
Infections with catalase-positive bacteria (staph aureus, G-ve enterobacteria, salmonella, klebsiella, serratia) and pseudomonas Skin abscesses, perianal abscess, pneumonia, osteomyelitis; BCG-osis Other investigations: NBT - Neutrophils change colourless compound NBT into a compound with a deep blue colour. Absence = defect in NADPH oxidase activity. Very specific, may miss some hypomorphic mutations. DHR → Neutrophil activation by PMA reduces dihydrorhodamine dye to a florescent form which can be detected on flow cytometry, very sensitive. Flow cytometry - gp91 & p22 (cell surface), p47 & p67 (cytosolic). Genetic – confirm with genetic testing, mutations associated with CGD - *CYBB* (X-linked) - *CYBA, NCF1, NCF2*, and *NCF4* (autosomal recessive CGD)	2 liver abscess, IBD features or lymphadenitis (no marks) 1 1
Principles of management: **No BCG vaccine** Genetic testing and counselling of the extended family Daily antibacterial (septrin) and antifungal (itraconazole) prophylaxis Avoid playing with or around compost, hay, wood chips, garden waste, firewood that has dry rot or old fungi *X-linked CGD carrier*: prone to lupus; symptoms of oral ulcers, skin rashes, joint pains, headaches to be taken seriously Steroids for bowel disease BMT as definitive treatment Referral made to Specialist Center	Any 4

Answer 4

Model answer 4a	**7 Marks**
Autoimmune hepatitis (acute, chronic, well-established cirrhosis) Fever, abdominal pains (hepatic tenderness), jaundice Chronic AIH: fatigue, upper abdominal discomfort, mild pruritus, anorexia, myalgia, diarrhea. **Primary biliary cirrhosis**: typically middle-aged females presenting with fatigue, pruritus, jaundice, xanthomas, osteoporosis, dyslipidemia. **Primary sclerosing cholangitis**: fatigue, pruritus, jaundice (relapsing &	Any 4 relevant symptoms (full marks if disease types

remitting)
IgG4-AIH related to AIP (autoimmune pancreatitis).

Associated autoimmune diseases with AIH:
Thyroid disease, Diabetes, Vitiligo, Pernicious anaemia, Sjogren's syndrome.
IgG4-RD (pancreas, biliary tract, lung, kidney and salivary glands).

Muratori et al., Autoimmune hepatitis in Italy: The Bologna experience Journal of Hepatology 50 (2009) 1210–1218. Concomitant autoimmune diseases were present in one fifth of patients, with the following hierarchy: hypothyroidism (13 patients), rheumatoid arthritis (4 patients), ulcerative colitis (4 patients), UCTD (2 patients), SLE (2 patients), multiple sclerosis (2 patients), sicca syndrome (2 patients), hyperthyroidism, (2 patients), alopecia (2 patients), insulin dependent diabetes mellitus (1 patient). Some patients had two coexistent autoimmune disorders in addition to AIH. Occurrence of associated autoimmune diseases was independent of AIH type, sex and age of onset of the liver disease.

mentioned)

Any 3

Model answer 4b — **9 marks**

AutoAntibody	Target Antigen	Lab method	Association
ANA	DNA	HEp-2 IIF, bead-based	Type 1 AIH, PBC
Perinuclear ANCA	MPO (neutrophil granule)	ANCA IIF, ELISA (MPO)	Type 1 AIH, PBC
LKM-1	CYP450 2D6 (microsomal)	Rat liver tissue (IIF), blot, ELISA	Type 2 AIH
AMA	ATP-ase associated antigens of inner mitochondrial membrane	Rat liver tissue (IIF) Blot (AMA-M2)	PBC, AIH
Anti-smooth muscle antibody (anti-F-actin antibody)	Actin, tubulin and intermediate filaments	HEp-2 IIF	Type 1 AIH
Soluble liver and pancreas antigen (SLP)	Glucoronyltransferase repressor tRNA-associated protein	EUROASSAY strip with antigens (blot)	AIH
LC-1 (liver cytosol)	Formiminotransferase cyclodeaminase	EUROASSAY strip with antigens (blot)	Type 2 AIH

3 marks for any autoAbs with correct target antigen (1 mark), lab method (1 mark) & association (1+1+1) x 3 = 9 marks

Model answer 4c — **4 marks**

MHC-Class I proteins	**MHC-Class II proteins**
Expressed by all nucleated cells	Expressed by APCs only
Cells expressing are usually virally-infected or tumour cells	Cells are usually phagocytes, can engulf extracellular antigen
Endogenous antigens undergo proteasome degradation, peptide transported to rER via TAP, peptide-MHC association, peptide presented to CD8+T cells.	Phagocytosed extracellular proteins are processed, peptide-MHC association after dissociation of Ii and peptide presented to CD4+T cells.

Any 4 (0.5 mark for each correct response)

Present peptides that are 8-10 AA in size.	Present peptides that are 13-18 AA in size.	
alpha 1, alpha 2, alpha 3 with TM segment and cytoplasmic tail that associates with β2MG	2 different polypeptide chains; alpha chain (33 kDa) and beta chain (28 kDa); each chain has 2 external domains	
Class I = A,B,C	Class II = DP, DQ, DR	

Answer 5

Model Answer 5A i **Any 3 of the following 4 adverse effects**	**6 marks** **Any 3**
1. Cytokine release syndrome (CRS) Do not start therapy if pre-Rx ALT/AST >3x ULN, bilirubin >1.5x ULN Pre-medicate with anti-pyretics, anti-histamines, anti-emetics before Rx Monitor liver enzymes during Rx; discontinue if ALT/AST >5x ULN, or bilirubin >3x ULN Treat symptoms of CRS (fever, headache, muscle aches, joint pains, nausea); if severe CRS, consider temporarily pausing or discontinue Rx	2 marks (finer details not required)
2. Serious reactions including hypersensitivity reactions Rash, angioedema, urticaria, vomiting, serum sickness, wheezing / bronchospasm / dyspnea, low blood pressure (anaphylaxis); Pulmonary edema (cardiogenic or non-cardiogenic edema, respiratory failure	2 marks (finer details not required)
3. Serious bacterial, viral or fungal infections **Do not start therapy** if ANC <1,500 /uL, laboratory evidence of active infection (EBV, CMV) or any other active serious infection. Expect serious bacterial, viral and fungal infections such as gastroenteritis, pneumonia, cellulites or wound infections (insulin injection sites).	2 marks (finer details not required)
4. Cytopenias (lymphopenia / neutropenia) Do not start therapy if ALC <1,000 /u, or if ANC <1,500 /uL. Monitor counts during Rx; if prolonged severe lymphopenia (<500/uL for >1 week), discontinue treatment.	2 marks (finer details not required)
Model Answer 5A ii	**4 marks**
Vaccination strategies Administer all age-appropriate vaccinations prior to treatment (at least 3-4 weeks?); live vaccines to be administered 8 weeks **prior** to treatment	(2 marks for '*no live vaccines'*

Do NOT administer any live vaccines during treatment, or up to 52 weeks after treatment. Inactivated / mRNA vaccines 2 weeks **before** treatment; no inactivated vaccines during Rx, or up to 6 weeks after Rx; Anti-CD3-Mab treatment may interfere with immune response to vaccination, and decrease vaccine efficacy	in answer)

Model answer 5B i	Marks
Communicate effectively regarding several possible unnecessary requests (via F2F meeting, *or* email) – discuss at Departmental Meeting	1
Present audit of requests at Medical or Rheumatology Grand Rounds – financial perspective – then agree on time frame for using 'gating strategy' for further requests; re-audit as QIP (ensure published internally; newsletter etc)	1
Use NICE guidelines to 'screen out' requests – hold test until clinical details are relevant; is this across Specialty or particular Consultant?	1
Reject test request if no clinical details provided (NICE guidelines)	1
Send comment from lab when rejecting request – asking for specific clinical details why test is required	1

Answer 5B ii

2x2 table

Test	Disease	
	+	-
+	True positive (TP)	False positive (FP)
-	False negative (FN)	True negative (TN)

PPV = TP/(TP+FP) x 100%

TP = Sensitivity x prevalence of disease; **TP** = 90/100 x 40% = **36%**

TN = specificity x % disease-free individuals

= 78/100 x 60% = 46.8%

FP = 60%-46.8% = **13.2%**

Hence, PPV = 36/(36+13.2) x 100% = 73.1%