• Aromatase inhibitors

  - Oophorectomy – ovary removal surgery not necessary in post

• SERMS
• SERDS

Which of the following is false regarding oestrogen in females?

• Post menopausal women’s main output of oestrogen comes from extra-gonadal fatty tissue

• young breast cancer patients receive some kind of endocrine manipulation – all

• Adrenalectomy is the surgical removal of the source of extra gonadal androgen steroid production and so the removal of oestrogen production.

• Oophorectomy is the surgical or radio therapeutic halting of oestrogen output from the ovaries

Which of the following is false regarding aromatase inhibitors?

• They can be used in pre or post menopausal but is more useful in post menopausal

• Aromatase inhibitors block all oestrogen production – not ovary production only androgen

• The enzyme aromatase is made from nicotinamide adenine dinucleotide phosphate (cytochrome p450 reductase) and P450 arom.

• Type 1 and 2 both block aromatase from converting androstenedione and testosterone into estrone and estradiol

Which of the following is false regarding type 1 aromatase inhibitors?

• Type 1 inhibitors are false substrates for aromatase enzyme which inhibit it irreversibly

• They are highly selective suicide inhibitors

• Inhibitions stops after excretion – permanent inactivation even after metabolic clearance
• Binds primarily through hydrogen bonding and hydrophobic interactions
• Possess some androgenic properties such as weight gain, acne and masculinization
• All end in “ane”

Which of the following is false regarding type 2 aromatase inhibitors?
• Type 2 bind reversibly
• They have a strong but irreversible coordination to heme - reversible
• All end it “zole”
• Better survival than Tamoxifen
• Unlike type 1 they are non steroidal inhibitors

Which of the following is false regarding tamoxifen?
• It is a synthetic, non steroidal, 15 oestrogen antagonist
• It is a substituted alkene formulated as a citrate salt tablet
• It has low side effects and can be given for a long time
• It cures breast cancer – only reduces levels
• Used in treatment of early, advanced, pre or post menopausal women
• Can be used after or before surgery
• It is a prodrug activated by aromatic hydroxylation and N demethylation
• Its inactive metabolite is N desmethyltamoxifen excreted 90% in urine.

Which of the following is false regarding the metabolites of tamoxifen?
• 4-hydroxytamoxifen is <10% of metabolic profile but is 100 fold more potent than tamoxifen itself
• endoxifen (from N desmethyltamoxifen) has similar potency to 4-hydroxytamoxifen but has plasma concentrations ten fold higher. It targets Eralpha for proteasomal degradation causing a decrease in protein levels where tamoxifen merely stabilizes them.
• Norendoxifen I a potent aromatase inhibitor, it is more effective than letrozole - the same effectiveness
Which of the following stages are prevented due to SERM action?

- Messenger crosses membrane
- Binds to receptor
- Receptor dimerization
- Binds to co-activator protein – inhibited by serm as no dimerization) AF1 is active to bind to DNA but AF2 is not active so the cofactor protein cannot bind
- Complex binds to DNA
- Transcription switch on
- Protein synthesis

Outline estradiol binding groups and how it changes in tamoxifen.

- Phenol group positioned in narrow slot orientates the rest of the molecule
- In tamoxifen the phenol binds to Asp instead of the usual Glu. This means the side chain prevents receptor helix 12 folding over and AF2 is not revealed.
- Alcohol binds to histine

Which of the following is false regarding SERDs

- Fulvestrant is a steroidal antioestrogen given as an oily IM injection.
- SERDs bind to, block and accelerate the degradation of the oestrogen receptor
- Gives partial inhibition of oestrogen signaling – complete
- No agonist efficacy unlike tamoxifen which retains partial agonist activity
- Fulvestrant-oestrogen receptor complex is unstable resulting in receptor degradation. It has no effective dimerization but does inactivate both AF1 and AF2

Which of the following is false regarding ErbB?

- Monoclonal antibodies target members of the ErbB family.
• ErbB 2 is a tyrosine kinase associated with HER2 and therefore breast cancer
  • Trastuzumab can be added to a small molecule which is a cytotoxic maytanisinoid which binds at minue end of microtubule preventing division – plus end
• Pertuzumab and trastuzumab both treat HER2 positive breast cancer

Which of the following is false regarding lapatinib?
• Used in metastatic HER2 positive breast cancer.
• Selective dual action kinase inhibitor of EGF and ErbB
  • Potent and irreversible inhibitor of ATP binding – reversible.
• Prevents phosphorylation and subsequent activation of signal transduction
Which of the following is incorrect regarding antibody formulation?

- Protein aggregation is affected to great extent by protein concentration
- Bevacizumab targets VEGF and blocks angiogenesis

\[ \text{Turbidity, aggregate size and viscosity are the only formulation investigations – need structure analysis, chromatographic analysis are also needed.} \]
- Rituximab binds to CD20 causing apoptosis

Which of the following is false regarding monoclonal antibodies?

- They are very efficient with few side effects
- \textbf{They have good perfusion characteristics – poor}
- They are usually in the form of liquids
- They have stability issues which mean they aggregate and precipitate

Which of the following is not an antibody instability in terms of aggregation and particle formation?

- Acid unfolding in low PH
- Reversible dimerization at PH 4-7
- \textbf{Deamidation – covalent instability} 
- Clip mediated aggregation at PH 3-5
- Disulfide linked aggregation at PH 7-9

Which of the following is not an antibody covalent instability

- Deamidation at PH 3-5 and 6-9
- Oxidation due to oxygen species at ph 3-9
- \textbf{Clip mediated aggregation – aggregation and particle formation}
- Acid related hydrolysis ph 3-5
- Proteolysis PH 6-9

Which of the following is not true in terms of liquid concentrates of antibodies

- Increased inter-molecular proximity
Which of the following is not an accepted hypothesis for generation of antibody diversity?

- Somatic recombination where antibody diversity is generated by genetic recombination among relatively few gene segments encoding the variable regions. This occurs via intra chromosomal recombination during B cell differentiation.
- The germline hypothesis says there is a huge number of immunoglobulins and that each one is encoded for by a separate germline gene.
- Somatic hypermutation is the thought that antibody diversity is generated through a very high proportion of immunoglobulin gene mutation during B cell differentiation.

Which of the following is false regarding mAB?

- A mAB recognizes and binds to just one epitope.
- mAB are generated from a single clonal lymphocyte.
- We can produce them by simply cloning a single lymphocyte. Lymphocytes do not grow continuously in culture.
- mAB are produced using special mice.

Put the following procedure in the right order:

1. inject a mouse with an antigen of interest
2. isolate the lymphocytes from the mouse spleen
3. fuse the lymphocyte with mice myeloma cells to allow culture
4. culture the fused cells in HAT media (hypoxanthine, amethopterin and thymine) unfused cells die
5. the growing hybridomas are then isolated and grown in separate wells to generate clones
6. the clones are screened for the antibody
7. the gene of interest can be isolated and re clones.
Which of the following is not part of transgenic technologies for cloning antibodies?

- Transgenic means an animal with a deliberate modification of the genome
- Must be done through germ line
- Microinjection of DNA into fertilized embryos
- Collection of unfertilized embryos from super ovulated female – fertilized

Match the therapeutic to the corresponding fragment

- Fab 1) antigen fragment can be two fragments and therefore bi specific
- Domain antibodies 2) single domain antibody fragments
- scFv 3) single chain variable fragment
- Fc-fusions 4) fusion between an immunoglobulin Fc domain and another peptide

Which of the following is false regarding Ig molecules

- IgG is more hydrophobic than many other proteins and so precipitates more readily in ammonium sulphate
- IgG is very soluble in aqueous buffer
- **Unstable at room temperature – stable**
- Often stable of a wide pH range

Outline how Chromotography purifies antibodies (4.5 marks)

Two main affinity resins are used for the primary step capture chromatography (0.5 marks) protein A is derived from staph aureus and contains five regions than bind to the Fc region of IgG (0.5 marks) one molecule of protein A can bind to at least two IgG (0.5 marks) protein G is a cell surface protein from group G streptococci and is a type 3 Fc receptor (0.5 marks) protein G binds through a non immune mechanism (0.5 marks) protein G binds to all human, mouse and rat (A doesn’t bind to rat) (0.5 marks) there are three parts to chromatography, primary removes main impurities (0.5 marks) intermediate removes minor impurities (0.5 marks) polishing chromatography separates product related impurities (0.5 marks)
Which of the following is not a screening tool for colorectal cancer?

- Faecal occult blood test
- **Endoscopy**
- Flexible sigmoidoscopy
- Colonoscopy
- Histology and biopsy
- Imaging such as CT

Match the staging to the description

- **T1** 1) tumor only in the inner layer of bowel
- **T2** 2) tumor has grown into muscle layer of bowel
- **T3** 3) tumor reaches outer layer of bowel
- **T4** 4) covered outside of bowel or grown into another structure

Which of the following is not required for preparation for bowel resection surgery?

- Macrogol 3350
- Picolax
- **Folinic acid**
- Antibiotic prophylaxis
- Thromboembolism prophylaxis

When is cetuximab added to colorectal therapy?

- When the patient cannot tolerate FOLFOX
- When the patient is palliative
- **When the patient is palliative and have inoperable liver mets or KRAS wild type**
- When XELOX is not tolerated
A patient has gastric cancer how would you treat and why? (3 marks)
Surgery is the only curative therapy for gastric cancer (0.5 marks) depending on the extent of the cancer the surgery can be complete or subtotal (0.5 marks) the patient should also have a radical lymphadenectomy (0.5 marks) Adjunctive chemotherapy should also be given to improve survival (0.5 marks) an example regime would be ECX (0.5 marks) This is epirubicin, cisplatin and capecitabine (0.5 marks).

Outline the differences between treatment in oesophageal and gastric cancers (8 marks)
Surgery is mainstay cure for oesophageal disease with a two phase oesophagectomy and two field lymphadenectomy. (1 mark) Pre op chemo should be given if the patient is T3 and/or node positive. (1 mark) The chemo regime for this is ECX which is Epirubicin, cisplatin and capecitabine. (1 mark) For gastric cancer surgery is the only curative option. (1 mark) Total or subtotal gastrectomy should occur with radical lymphadenectomy and adjunctive chemotherapy. (1 mark) The regime here would be 5FU and capecitabine. (1 mark) Both cancers are treated with palliative radiotherapy. In oesophageal cancer this is to relieve chest pain and dysphagia and is helpful in 70% of patients. Both cancers are also treated with palliative chemotherapy. (1 mark) Only oesophageal is treated with radical chemo radiotherapy if the patient is inoperable or unfit for surgery. (1 mark)

Outline how you might expect someone with colorectal cancer to present and how this might differ from someone with an upper GI cancer (6 marks)
Patients with colorectal cancer present with symptoms which we reference as ALARM symptoms. They will experience anorexia and weight loss due to an impaired ability to absorb nutrients (1 mark). They can experience anaemia due to either bleeding internally into the GI tract or due to lack of iron uptake (1 mark) the patient will see a change in bowel habit this may lead to alternating diarrhoea and constipation, this can attribute to weight loss (1 mark) the patient may see blood and mucous in the stool due to the tumour causing bleeding, they may experience abdominal pain and a palpable mass along with this (1 mark)
Outline the folfox regime for colorectal cancer you should include side effects and dose adjustments (10 marks)

Folfox consists of oxaliplatin, 5fu and folinic acid (0.5 marks). Oxaliplatin is a platinum derivative which forms both inter and intra strand cross links in DNA (0.5 marks). It can cause nephrotoxicity, ototoxicity and alopecia (0.5 marks). It can also cause atypical adverse effects such as bone marrow suppression and paraesthesias and dysaethesias (0.5 marks). If neurological symptoms occur for longer than 7 days then the next dose should be reduced from 85 to 75mg/m2 (0.5 marks). If paraesthesia without functional impairment happens until next cycle then the dose should be reduced to 65mg/m2 (0.5 marks). If pharyngolaryngeal dysaethesias occur then the infusion should be given over 6 hours instead of 2 (0.5 marks). If hematological toxicity occurs then suspend next dose until it returns to normal (0.5 marks). If mucositis occurs then don’t give next dose until it recovers to at least grade 1 (0.5 marks). 5FU or capecitabine is a antimetabolite which prevents thylidimate synthase from turning uracil into thymine (0.5 marks). It has similar side effects to oxaliplatin but it does not have the neurological disorders (0.5 marks). It does however cause hand foot palmar plantar erythema (0.5 marks). It is important to check if the patient is DPD deficient if they are they cannot break down the drug as quick (0.5 marks). Therefore there is a lower chances of neutropenia, anaemia and thrombocytopenia as well as diarrhea, mucositis and nausea and vomiting (0.5 marks). Folinic acid is given to work synergistically with 5FU (0.5 marks). It increases the drugs half life (0.5 marks). Although it doesn’t have many side effects of its own it can increase the side effects of 5FU (0.5 marks). Throughout treatment we should monitor: FBC (0.5 marks). Symptoms such as mucositis, neurological disorders and hand foot syndrome (0.5 marks). And renal and liver function (0.5 marks).

A palliative patient with inoperable liver mets has had cetuximab added to her regime. How does this drug work and what test do we need to do before we initiate? (4 marks)

Some cancer cells have the receptor epidermal growth factor receptors on their surface (0.5 marks). The endogenous ligands for these receptors are epidermal
with urine. (1 mark) Because we know acrolein reacts with thiol and this is where our problems come from therefore we need to block the thiol binding. (1 mark) Glutathione in the body is protective in this way but there is not enough in the body to help with the acrolein produced by a cancer patient. (1 mark) Therefore we can treat with N acetyl cysteine but more commonly we use MESNA. (1 mark) MESNA is used because it is hydrophilic and therefore has low volume of distribution and stays in the circulatory system. (1 mark)
Outline the different ways we can modify a liposome (3 marks)

If we add PEG to the terminal amine of phosphatidyethanolamine to provide a surface hydration layer around the liposome (0.5 marks). This avoids recognition by macrophages and RES to create a stealth liposome (0.5 marks). We can also create Thermosensitive liposomes (0.5 marks). They are designed to leak above 40 degrees which is the temperature of the interior of a tumor (0.5 marks). We can conjugate liposomes with monoclonal antibodies (0.5 marks). Meaning that the drug contents will be released in target cells (0.5 marks).

Outline how you entrap a drug in a liposome (3 marks)

A lipophilic drug is mixed together with the lipids and dissolved in the organic solvent (0.5 marks). After rehydration of the film the lipid drug molecules are formed inside the lipid bilayer (0.5 marks). If the drug substance has some hydrophilic groups some of the drug molecules will also be found in the aqueous inner cavity of the vesicles (0.5 marks). The amount depends on the partition coefficient (0.5 marks). Hydrophilic drugs can be directly encapsulated by dissolving them in the buffer used for the rehydration of the dried lipid film however the method shows poor entrapment (0.5 marks).

Outline the stability issues with liposomes and how we can overcome this (6 marks)

Liposomes containing hydrophilic drug are unstable in aqueous medium (0.5 marks). As the drug diffuses out from the inner cavity into the outer phase (0.5 marks). Lipids are also prone to oxidation (0.5 marks). Therefore we should include an antioxidant such as alpha tocopherol (0.5 marks). Hydrolysis of the ester bonds in the lipids can occur (0.5 marks). This is prevented by keeping the solution at pH 6.5 (0.5 marks). On storage small liposomes fuse to form larger more stable liposomes, (0.5 marks). To prevent this from occurring we can freeze dry them then reconstitute (0.5 marks). This is not appropriate for hydrophilic drugs (0.5 marks) as the liposomes temporarily become porous and the drug leaks out (0.5 marks). If the drug is lipid soluble (0.5 marks) it can be incorporated into the lipid part of the vesicle (0.5 marks).
Outline why post translational modification is superior to an increase in p53 transcription (2 marks)

It is rapid and sensitive to the magnitude of stress (0.5 marks) it is reversible if needed and is stress dependent (0.5 marks) so it is not causing unnecessary cell damage (0.5 marks) it requires less energy to complete (0.5 marks)

Outline how p53 regulates apoptosis

P53 can work by two pathways, the intrinsic or extrinsic (0.5 marks) I the intrinsic pathway p53 stimulates two proteins BAD and BAX (0.5 marks) these cause cytochrome C to be released from the mitochondria (0.5 marks) this pairs with APAF1 to stimulate CASP 3 protein which triggers apoptosis (0.5 marks) this all happens in the cytoplasm (0.5 marks) the extrinsic pathway works by p53 stimulating a cell surface protein which forms a disc complex FADD and CASP8 (0.5 marks) this then activates CASP3 to cause apoptosis (0.5 marks)

Which of the following statements is true?

- Only a mouse with p53 is viable
- Only a mouse with MDM2 is viable
- A mouse must have both MDM2 and P53 to be viable
- A mouse can either lack both MDM2 and p53 or neither of them and still be viable

Outline how MDM2 and p53 keep balanced

P53 is a tumor suppressor gene and MDM2 is a oncogene (0.5 marks) they balance each other out by one causing cell division and one halting cell division (0.5 marks) once p53 is activated it binds to mRNA which codes for the translation of MDM2 (0.5 marks) this means that p53 is switched off through degradation once it has completed its job (0.5 marks)

How is p53 mutation linked to cancer? (2 marks)

The p53 gene is tumor suppressor gene (0.5 marks) when it mutates it usually causes cancer (0.5 marks) typically the mutation is a missense mutation in one allele which results in high levels of a non functional protein (0.5 marks) p53 is mutated in 50% of cancers and is linked to a poor response in therapy (0.5 marks)
which of the following is false regarding SCLC treatment?

- Limited stage disease with good performance status gets combination chemo and thoracic radio
- Surgery is well established – not really used
- Extensive stage is mainly chemotherapy
- Prophylactic cranial irradiation reduces risk of brain metastases by 54%
- First line chemo is carboplatin and etoposide for 4-6 cycles
- Second line is topotecan and CAV

Outline the extensive signs and symptoms that a person with lung cancer might present with (3 marks)

More than 90% of patients are symptomatic (0.5 marks) respiratory symptoms include cough, dyspnea, chest pain, haemoptysis and wheezing (0.5 marks) other symptoms include nerve compression, superior vena cava obstruction, pleural effusion, dysphagia and bone pain (0.5 marks), they could present as clubbing, cachexia or anaemia but these symptoms are not specific (0.5 marks) patients may have a unilateral wheeze (0.5 marks) or reduced breath sounds (0.5 marks)
Which of the following is not part of the mode of action for enzalutamide?

- Inhibits AR testosterone binding with higher affinity
- Blocks activational change of receptor induced by binding
- Partial AR agonist – full partial occurs in bicalutamide resistance
- Inhibits AR-test nuclear translocation and transcription

True or false PSA is the diagnostic marker for prostate cancer?

True however PSA can also be raised in many other circumstances such as BPH and prostatitis therefore a raised level does not necessarily indicate cancer. However a raised level would lead to an invasive ultrasound and biopsy which would be unpleasant for the patient especially if not required. 4ng/ml is the upper limit. Furthermore 20% of patients with prostate cancer will have normal PSA and so would be missed by this test.

What is prostatitis? (5 marks)

Prostatitis means inflammation of the prostate (0.5 marks) there are four categories of this, category 1 is acute bacterial prostatitis (0.5 marks) usually E.Coli infection is the cause of this and it leads to neutrophil infiltration (0.5 marks) category 2 is chronic bacterial prostatitis (0.5 marks) symptoms and causes similar to category 1 (0.5 marks) category 3 is chronic pelvic pain syndrome (0.5 marks) this will cause pain on urination, ejaculation, although bacterial DNA can be detected there is no bacterial cause (0.5 marks) category 4 is asymptomatic inflammatory prostatitis (0.5 marks) no symptoms but bacteria and leucocytes are present (0.5 marks) any of these can be treated with antibiotics, alpha blockers and NSAIDs (0.5 marks)

What is benign prostate hyperplasia?

This is the hyperplasia of prostatic stromal and epithelial cells (0.5 marks) it leads to the formation of large, discrete nodules in the periurethral region of the prostate (0.5 marks) it compresses and narrows the urethral canal to cause partial or sometimes complete obstruction (0.5 marks) it is caused by androgen stimulation (0.5 marks) there is no gene mutation and when the hormonal stimulation is removed the hyperplasia regresses (0.5 marks)
prostate cancer upon death (0.5 marks) if this is the case then no treatment is needed as there is no benefit to outweigh the side effects of chemo and unpleasantry of surgery (0.5 marks) however if the cancer is fast growing or has risk of spreading then surgery may be undertaken to remove the prostate (0.5 marks) this can be done by key hole surgery or using the da vinci robot (0.5 marks) using the da vinci robot we see less infection, (0.5 marks) less blood loss, fast healing and less time in hospital (0.5 marks) we can also give medication such as LHRH which is also known as chemical castration (0.5 marks) this lowers the amount of androgen produced by the testicles. (0.5 marks) the medication is called goserelin (zoladex) it acts as an inhibitor of the pituitary gonadotropin secretion and is given as a subcut injection ever 4 or 12 weeks (0.5 marks) it is possible to see a testosterone flare at first but this settles down (0.5 marks) we can also give AR inhibitors like casodex (bicalutamide) (0.5 marks) these bind to the androgen receptor directly and prevent activation, therefore it works for both androgen over expression or androgen independent activation (0.5 marks)

How can castration resistant prostate cancer occur and how can we treat it? (6 marks)
This occurs when cells overcome the need for androgen binding to activate AR in (0.5 marks) it can occur through many pathways (0.5 marks) for example hypersensitive, cells can become more sensitive to the low levels of androgen this can happen by producing more receptors (0.5 marks) promiscuous pathway involves AR being activated by ligands and not the normal DHT (0.5 marks) outlaw is when other pathways activate AR (0.5 marks) bypass is when other mechanisms activate the same genes without AR involvement (0.5 marks) lurker is when independent cells are present and treatment only kills dependent cells leaving these behind (0.5 marks) there is currently no cure for this (0.5 marks) however we can treat with a new drug called enzalutamide which prevents AR binding to DNA (0.5 marks) it gives a survival advantage of around 4 months (0.5 marks) we can also treat with abiraterone (0.5 marks) which blocks cyp17 to stop cells making androgens (0.5 marks)
Lymphoma

What is the difference between hodgkins and non hodgkins lymphoma?

• Hodgkins is curable
• Non hodgkins is curable
• Reed sternberg cells are present in hodgkins
• Blasts care present in hodgkins

Which of the following is not a low grade NHL?

• Follicular
• Lymphocytic
• Mantle cell
• Marginal zone

Which of the following is not a high grade NHL?

• Diffuse large cell
• Burkitts
• Lymphoplasmacytoid
• Mantle cell

Which of the following is not a mechanism of evading apoptosis for hodgkins lymphoma?

• Chromosomal translocations
• Genetic muttions
• Incoeration of Epstein barr virus
• Deactivation of transcription factors - Activation of transcription factor NFkB
• Interactions with components of microenviroments

Which of the following in not a biomarker for HL?

• Mild anaemia
• Raised ESR and CRP
Leukaemia

Which of the following is not a characteristic of acute leukemias?

- Young immature blast cells in the bone marrow
- Fulminant presentation
- **Mature cells**
- Very aggressive treatment course

Which of the following is not a characteristic of chronic leukemia?

- Mature differentiated cells
- Often subclinical or incidental at presentation
- **Fast course of chemo – slow indolent course**
- Frequent splenomegaly

Which of the following is false regarding doubling time?

- Doubling time can be a minimum of two weeks
- Doubling can be a minimum of four days and max two weeks
- 30 doublings is the limit of standard detection
- 40 doublings is lethal tumor burden

Which of the following is an incorrect leukemia staging?

- **Stage 1 is symptomatic – stage one is normal 2 is symptoms**
- Stage 3 is diagnosis
- Stage 4 is worsening
- Stage 5a is anaemia
- Stage 5b is infection

Which of the following is not a presentation of leukemia associated with bone marrow failure?

- Anaemia
- Thrombocytopenia
- Acquired gene encoding for enzymes that destroy antibacterial agents (beta lactamases) (0.5 marks)
- Acquired efflux pumps this is common in quinolone resistance (0.5 marks)
- Acquired target genes such as altered cell wall preventing antibiotic binding (0.5 marks)
- Acquired mutation to the porin gene which reduces access into cells. (0.5 marks)

Clinical resistance is the failure to achieve and antimicrobial concentration that inhibits the growth of an organism. (0.5 marks)

Outline why is it important to identify bacterial types and the challenges we face. (8 marks)

Overuse or incorrect use of antibiotic agents has contributed to development of resistance. (0.5 marks) Typing bacteria means we use the right agent the first time. (0.5 marks) It means we are not giving empirical treatment. (0.5 marks) We can identify already resistance bacteria and change treatment accordingly. (0.5 marks)

It is hard to be accurate and confident with results of typing. (0.5 marks) Methods must be very sensitive to detect extremely virulent bacteria as there may be as low as 100 cells. (0.5 marks) Results may take up to 48 hours, this is not ideal when wanting to treat infection. (0.5 marks) Susceptibility is not widely available at the same time. This is expensive. (0.5 marks)

What methods can we use to identify bacteria? (7 marks)

Gene probes and mass spectrometry are very fast methods of screening bacteria (0.5 marks) however they are too expensive (0.5 marks) even though they are suitable for primary care. (0.5 marks) Mass spec can “over diagnose” or “under diagnose” certain species because it struggles to distinguish between some species of bacteria. (0.5 marks) DNA probes uses polymerase chain reaction to identify
• It is a broad spec antibiotic with intracellular action
• It binds to mRNA inhibiting protein synthesis
  **Fine for pregnant women - contraindicated**
• Used in combination with artesemin or quinine for falciparum malaria
• No children under 12
• Causes photo toxicity

How can we counsel to prevent malaria? (4 marks)
We use the ABCD method. Awareness about the risk of malaria (0.5 marks) this would include being aware of areas of travel and temperature effecting virulence (0.5 marks) bites of mosquitoes should be avoided (0.5 marks) prevention includes taking nigh time measures (0.5 marks), stay indoors if possible, use a mosquitos screen, air conditioning and long clothing and repellent (0.5 marks) DEET repellent is the most appropriate and is suitable for over 2. (0.5 marks) chemoprophylaxis and compliance is key (0.5 marks) diagnosis of febrile illness should occur without delay. (0.5 marks)

outline what chemoprophylactic options there are and why it effects our choice (4 marks)
casual prophylaxis is directed against malaria parasite in the liver stage. This takes about 7 days (0.5 marks) to develop and can prevent the parasite from progressing and infective red blood cells. (0.5 marks) Suppressive prophylaxis is directed against RBC malaria (0.5 marks) and is required for several weeks to prevent infection. (0.5 marks) Prophylaxis against hypnozoites (0.5 marks) stops the parasite in the dormant state and may remain dormant for months. This is needed with p ovale and p vivax. (0.5 marks) Choice depends on the patient, are they a long term traveller? (0.5 marks) Are they Immunocompromised? Are they epileptic, elderly or pregnant? (0.5 marks)

Endocarditis
has no traditional symptoms of a UTI (0.5 marks) I would want a FBC to indicate raised inflammatory markers (0.5 marks)

What risk factors does the patient have for C difficile (3 marks)
The patient has diabetes especially poorly controlled, which puts them at higher risk (0.5 marks) they are taking omeprazole and PPI put a patient at higher risk (0.5 marks) she has had multiple short courses of antibiotics (0.5 marks) which kill the natural gut flora allowing C difficile to take over (0.5 marks) she is over 65 (0.5 marks) and lives in a sheltered accommodation (0.5 marks) furthermore she has now been prescribed cephaalexin which puts a patient at high risk for developing C difficile (0.5 marks)

How should C difficile be managed? (5 marks)
The patient should be isolated as they are incredibly infectious (0.5 marks) they should have fluid replacement to fix the dehydration caused by diarrhea (0.5 marks) the patient should be assessed for severity including a Mini Mental State Examination (MMSE) (0.5 marks) for mild to moderate c difficile the patient should be prescribed metronidazole by mouth (0.5 marks) 400mg every 8 hours for 10-14 days (0.5 marks) for severe vancomycin oral should be added to this (0.5 marks) 125 mg 4 times a day for 10-14 days (0.5 marks) if the patient cannot swallow this can be given by NG tube (0.5 marks) stop her omeprazole as this can worsen C diff (0.5 marks) stop Lisinopril as ACE inhibitors when acutely unwell can cause renal decline (0.5 marks) stop statin as when acutely unwell this can increase risk of myopathy (0.5 marks) possibly stop or reduce dose of anti-diabetic medication if patient is not eating (0.5 marks)

How would you prevent future UTI?
Counsel patient to maintain good hygiene (0.5 marks) maintain adequate fluid intake (0.5 marks) do what we can to get diabetes under control (0.5 marks) so that there is not excess sugar in the urine (0.5 marks) reduce PPI dose to 15mg which is prophylactic dose (0.5 marks) or switch to something like ranitidine which has lower C diff risk (0.5 marks) the atorvastatin 40mg should be 80mg because she has diabetes (0.5 marks)
load more effectively (0.5 marks) and helps to reduce the development of resistance (0.5 marks) it maintains the health of a HIV patient over longer periods of time before AIDS is observed (0.5 marks) treatment is usually initiated with: 2 NRTIs and NNRTI, boosted protease inhibitor or integrase inhibitor (0.5 marks) tenofovir, emtricitabine and efavirenz (0.5 marks) we use 2 NRTIs because some are more easily activated than others (0.5 marks) emtricitabine requires 3 phosphorylations to be activated where tenofovir only requires 2 as it is a nucleotide (0.5 marks) the first step is very slow and is the rate determining step (0.5 marks) also tenofovir is a purine and emtricitabine is a pyrimidine (0.5 marks) therefore using these together there are more opportunities to inhibit RT (0.5 marks) this is the best step to work at, best to inhibit formation of DNA in the first place (0.5 marks) overall RT and integrase are key enzymes in HIV early life (0.5 marks) inhibiting both means permanent infection is prevented which reduces likelihood of transmission (0.5 marks) NRTIs were the first agents identified as active against HIV and many years research shows they are good (0.5 marks) newer NRTIs have better side effect profiles and lower doses (0.5 marks) the drugs also work synergistically with an additive effect (0.5 marks) this reduces the concentration and therefore side effects of each (0.5 marks).

**Explain what the term post-exposure prophylaxis means and circumstances when its use may be appropriate.**

PEP is the initiation of medication without the conformation of the disease (0.5 marks) if a patient believes they have been exposed to the virus (0.5 marks) by means such as condom failure with a HIV positive person (0.5 marks) this is used to reduce the risk of the infection taking hold (0.5 marks)

**Boosted protease inhibitors are commonly used in preference to non-boosted regimens. What does boosted mean and what advantages does this offer the patient?**

A boosted regime is when two protease inhibitors are given together to reduce the metabolism of concordantly administered inhibitors (0.5 marks) ritonavir for example inhibits cyp450 leading to improved bioavailability of the other drug
give phenoxymethylpenicillin 500mg QDS for 5 days (0.5 marks) if a person is systemically unwell then give xo amoxiclav 500/125 tds for 5 days (0.5 marks) if allergic doxycycline (0.5 marks)

Discuss a marker we can use to look for infection including the advantages and drawbacks of its use (4 marks)
C reactive protein is something which increases in response to an inflammatory event (0.5 marks) its usual levels are 5010mg/L (0.5 marks) but can rise within 2 hours of an event reaching up to 50,000 times normal within 48 hours (0.5 marks) levels are usually raised to around 40-200 in bacterial infections (0.5 marks) but only increased to 10-40 in viral infections (0.5 marks) therefore the test allows us to see if the symptoms are bacterial or viral and therefore need antibiotics (0.5 marks) however they can overlap in the early stages of bacterial infection so it is possible it can be missed (0.5 marks) it can also raise in response to a non related inflammatory event such as a co-morbidity like IBS (0.5 marks)

What mantra do we use when prescribing antibiotics?
We start smart then focus (0.5 marks) this means that we should only start antibiotic therapy when there are clear signs of infection (0.5 marks) we should take a thorough drug allergy history to find out if they are penicillin allergic (0.5 marks) and if so to what extent (0.5 marks) we should avoid any use of broad spectrum antibiotics is we can avoid it (0.5 marks) to try and avoid resistance development (0.5 marks) it is important to document all start and stop dates to ensure patient is not left of medication long term (0.5 marks) if possible obtain cultures prior to initiating therapy (0.5 marks) however if severe sepsis is suspected then initiate medication within one hour of diagnosis (0.5 marks) then we focus after around 48-72 hours (0.5 marks) documenting differences needed for cultures (0.5 marks) and continuing need for antibiotics (0.5 marks) we should 1) stop antibiotics if there is no evidence of infection (0.5 marks) switch antibiotics from intravenous to oral wherever possible (0.5 marks) change antibiotics to narrower spectrum (0.5 marks) continue and document next review date (0.5 marks)
Meningitis

What causes meningitis (6 marks)

Neisseria meningitides is a gram negative bacterium (0.5 marks) known as diplococci (0.5 marks) there are thirteen subgroups five of which are the majority causes in humans (0.5 marks) A, B, C, Y and W135 (0.5 marks) there are other bacteria which can cause it such as step pneumonia which is gram positive (0.5 marks) H influenza which is gram negative (0.5 marks) it can also be caused by a virus which lives in the intestines called enterovirus (0.5 marks) this however is less severe and usually resolves on its own (0.5 marks) it is caused usually by poor hygiene (0.5 marks) it can also be a fungal cause which is rare but life threatening (0.5 marks) this is common in patients with some kind of impaired immune function (0.5 marks) it is difficult to diagnose and treat and is usually candida (0.5 marks) it can also be non-infective and caused by head injury or some cancers (0.5 marks)

which of the following does not increase your risk of developing meningitis?

• Asplenia
remainder of the course (0.5 marks) under 15 it should be halved from the start (0.5 marks) anyone who has experienced a blood dyscrasia should not take this drug (0.5 marks) due to the antifolate affect (0.5 marks) it interacts with a large number of medications (0.5 marks) such as MTX, AZA, phenytoin, digoxin etc (0.5 marks) it can also cause GI affects and blood disorders (0.5 marks)

How does trimethoprim work?
Trimethoprim binds to dihydrofolate reductase (0.5 marks) and inhibits the reduction of dihydrofolic acid (DHF) to tetrahydrofolic acid (THF). (0.5 marks) THF is an essential precursor in the thymidine synthesis pathway (0.5 marks) and interference with this pathway inhibits bacterial DNA synthesis (0.5 marks) meaning DNA replication cannot occur and the bacterial cell undergoes apoptosis (0.5 marks)

Which of the following cannot cause pyelonephritis?
- E coli
- Kleb pneumonia
- Staph aureus
- Enterococcus
- Pseudomonas
- Proteus

Pyelonephritis can develop into sepsis. What warning signs would you be looking for to spot this? (4 marks)
The patients temperature, is it above 38 (0.5 marks) or below 36 (0.5 marks) are they tachycardic (0.5 marks) are they hypotensive (0.5 marks) are they short of breath (0.5 marks) do they have impaired consciousness (0.5 marks) are they dehydrated, can they tolerate fluids? (0.5 marks) extra caution should always be taken in pregnant, elderly, Immunocompromised, renal compromised or diabetic patients (0.5 marks)
What goals are set out for evaluating patients with sepsis?
Within three hours you should measure serum lactate (0.5 marks) to identify acidosis (0.5 marks) take blood cultures before antibiotics (0.5 marks) administer broad spectrum antibiotics (0.5 marks) then administer 30ml/kg crystalloid for hypotension or lactate >4mmol (0.5 marks) within 6 hours you should apply vasopressors (0.5 marks) to maintain MAP over 65 mmHg (0.5 marks) In the event of septic shock measure venous pressure, venous oxygen and lactate (0.5 marks) targets include CVP over 9 mmHg and normalization of lactate (0.5 marks)

What is the sepsis six? (10 marks)
Number 1 is oxygen (5 marks) inflammation disrupts the ability of oxygen to reach the tissues (0.5 marks) so give high flow oxygen 15L per min (0.5 marks) and aim for sats or 98% (0.5 marks) the second is cultures (0.5 marks) to determine sensitivity and resistance (0.5 marks) immediately after that give iv antibiotics (0.5 marks) within 1 hour of A&E admission (0.5 marks) they should be broad spectrum and bacterioidal (0.5 marks) review antibiotics after culture results and every 24 hours (0.5 marks) switch to oral agents as soon as possible (0.5 marks) number 4 is fluids (0.5 marks) to improve cardiac output and correct hypovolaemia (0.5 marks) 500ml hartmans in 15 minutes or less (0.5 marks) 250ml if patient has heart failure or CKD (0.5 marks) reassess response with urine output (0.5 marks) pulse and MAP (0.5 marks) five is lactate (0.5 marks) to assess acidosis (0.5 marks) >4 there is a 50% mortality rate (0.5 marks) finally urine output (0.5 marks)