Test Taking Strategies for BPS Exams

Sub-Specialty Topics: Oncology & Toxicology

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Agenda

- Oncology:
  - Dose-Limiting Toxicities
  - Core Knowledge – mABs
  - Core Knowledge – TKIs
  - Chemotherapy Associated Side Effects and Supportive Care
  - Live Q&A
- Toxicology
  - Core Antidotes for the BPS Exams
  - Live Q&A
- A Special Coupon Code

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Oncology

Dose-Limiting Toxicities

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DOSE-LIMITING TOXICITIES OF CHEMOTHERAPY

- **Alkylating Agents:**
  - Mucositis → melphan
  - Irritant with vesicant-like properties (bendamustine)
  - _____ → *bleomycin & busulfan*
  - Skin hyperpigmentation → bleomycin
  - *Hemorrhagic cystitis (cyclophosphamide & ifosfamide)*

- **Immunomodulatory (imids)**:
  - *Teratogenicity* → thalidomide > lenalidomide
  - Peripheral neuropathy → thalidomide > lenalidomide
  - Bone Marrow Suppression (BMS)
  - *Bradycardia*
  - Skin reactions (including SJS and TEN)
  - _____

DOSE-LIMITING TOXICITIES OF CHEMOTHERAPY

- **Anthracyclines**:
  - *Cardiac toxicity* (especially if cumulative doses > _____) → daunorubicin & doxorubicin
  - *Extravasation risk*
  - BMS

- **Folate Antagonists:**
  - *Mucositis*
  - *Liver* and *kidney toxicity* or *fibrosis* → methotrexate
  - Mild to severe dermatologic toxicity → pemetrexed

DOSE-LIMITING TOXICITIES OF CHEMOTHERAPY

- **Platinum analogs:**
  - _____ → cisplatin
  - CNS and ototoxicity → cisplatin
  - Carboplatin → most likely to cause thrombocytopenia
  - *Cisplatin* → most emetogenic agent

- **Pyrimidine Antagonists:**
  - *Severe diarrhea* (5-FU)
  - BMS

DOSE-LIMITING TOXICITIES OF CHEMOTHERAPY

- **Taxanes:**
  - *Peripheral neuropathy* → mainly paclitaxel
  - Edema → especially docetaxel
  - BMS
  - Hypersensitivity reactions

- **Topoisomerase Inhibitors**:
  - *Severe acute and delayed diarrhea*
  - Pulmonary fibrosis
  - BMS & severe diarrhea → _____
  - *Genetics?*

DOSE-LIMITING TOXICITIES OF CHEMOTHERAPY

- **Vinca Alkaloids:**
  - *Peripheral neuropathy* (vincristine >> vinblastine=vinorelbine)
  - Extravasation risk
  - BMS (except vincristine)
  - IV admin only → never give intrathecally

Oncology

mABs

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Monoclonal Antibodies

- Monoclonal Antibodies:
  - Referred to as “mAbs”
  - Very specific targets or binding sites
  - Biologic agents:
    - Large proteins
    - Cannot tolerate gastric acidity
    - Must be administered parenterally
    - Naming of mAbs is specific and structured
    - based on source of antibody per the International Nonproprietary Names (INN) by the WHO

Monoclonal Antibody Naming

- Naming set by the International Nonproprietary Names (INN) by the World Health Organization (WHO):
  - Drug Name organization:
    - Prefix-substem A-substem B-suffix
    - Prefix per manufacturer
    - Substem A = target class
    - Substem B = species mAb derived
    - Suffix (or stem) = -mab

Monoclonal Antibodies – Substem B

Name Ending	Type of Antibody
-umab	100% human antibody
-zumab	Humanized (only 5-10% mouse make up the complementarity-determining-regions (CDR)
-ximab	Chimeric (67% human Fc or constant regions + 33% mouse make up the variable regions)
-omab	Murine (100% mouse)
-xizumab	Combined humanized & chimeric chains
-axomab	Rat/Mouse Chimer
-emab	Hamster
-amab	Rat
-imab	Primate

Monoclonal Antibodies – Substem A

Name Ending	Target Class	Example
-b(a)--mab	Bacterial	-bixumab; -bumab
-c(i)--mab	Cardiovascular	- cixumab; -cumab
-f(u)--mab	Fungal	-fuzumab; -fumab
-k(i)--mab	Interleukin	-kiximab; -kumab
-l(i)--mab	Immunomodulating	-liximab; -lumab; -lixizumab
-n(e)--mab	Neural	-nezumab; -numab
-s(o)--mab	Bone	-somab; -sumab
-tox(a)--mab	Toxin	-toxazumab; -toxumab
-t(u)--mab	Tumor	-tuzumab; -tumab; -tomab
-v(i)--mab	Viral	-vizumab; -vumab

Note: If Substem B starts with an "x" or "z", a 2nd vowel (noted in parenthesis) is added to avoid problems with pronunciation.

Common mAb Targets

Target Abbreviation	Description
Anti-PD-1	Programmed Cell Death Protein 1
Anti-PD-L1	Programmed Cell Death Protein 1 Ligand 1
CD19/CD3	Cluster Designation 19/Cluster Designation 3
CD20	Cluster Designation 20
CD30	Cluster Designation 30
CD38	Cluster Designation 38
CD52	Cluster Designation 52
CLTA-4	Cytotoxic T-Lymphocyte Associated Antigen
EGFR	Epidermal Growth Factor Receptor
HER-2	Human Epidermal Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor

mAbs - EGFRIs: Mechanism of Action

- Epidermal Growth Factor Receptor (EGFR)
- Selectively block ErbB1 (EGFR), ErbB2 (HER2), and ErbB4 (HER4):
  - Tumor growth inhibition
  - Tumor regression
- Clinical Connection:
  - Epidermal cell lines are affected which contribute to the side effect profile of the skin, GI tract, & lung

mAb - VEGFRIs: Mechanism of Action

- Vascular Endothelial Growth Factor Receptor (VEGFR)
- Primary mechanism is to reduce angiogenesis that supplies blood and nutrients to cancer
- Clinical Connection:
  - As such endothelial cell lines are affected which contribute to the side effect profile of bleeding, proteinuria, and affects of BP

mAbs – VEGFR: Notes

- Side Effects:
  - GI (perforation risk)
  - Bleeding/hemorrhage
  - Wound dehiscence or impaired healing
  - HTN
  - Proteinuria
  - Thrombotic events
  - Posterior reversible encephalopathy syndrome
  - Infusion-related reactions
- Other:
  - ONJ with bevacizumab (especially if on bisophosphonate)

High-Yield CORE CONCEPTS

- mABs in General:
  - mAbs come from different sources and have different targets
  - All are given parenterally and have long half-lives
  - All generally need pre-medication with antihistamine at minimum due to infusion reaction
  - SE & toxicities involve multiple organs

Oncology

TKIs

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Common TK Targets

Target Abbreviation	Description
ANLKI	Anaplastic Lymphoma Kinase
BCR-ABL	Fusion Protein
BTK	Bruton Tyrosine Kinase
BRAF	BRAF Kinase
FLT3	FMS-Like Tyrosine Kinase 3
EGFR	Epidermal Growth Factor Receptor
VEGFR	Vascular Endothelial Growth Factor Receptor
JAK	Janus Associated Kinase
Other Targets	C-KIT, PDGFR, RAF

High-Yield CORE CONCEPTS

- Tyrosine Kinase Inhibitors:
  - They all share name ending "-nib"
  - Are all administered orally
  - All cause diarrhea
  - Most are CYP3A4 substrates and risk of DDI
  - All prolong the QT interval
  - All VEGFR inhibitors → HTN, hemorrhage, proteinuria
  - All EGFR inhibitors → skin rash, diarrhea, ILD
  - All PDGFR inhibitors → edema (dasatinib worse)
  - Bosutinib, dasatinib, erlotinib, and +/- gefitinib all require gastric acidity for absorption

Oncology

Chemotherapy Associated Side Effects & Supportive Therapy

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CHEMOTHERAPY-INDUCED NAUSEA & VOMITING

- **PATHO:**
  - Complex physiology involving numerous CNS sites including the CTZ, emetic center, cerebral cortex and peripheral sites.
- **CLASSIC PRESENTATION:**
  - Can be one or mixture of acute, delayed, anticipatory, breakthrough, or refractory.
- **CLASSIC FINDINGS:**
  - No specific lab abnormalities, but dehydration, hyponatremia, hypokalemia may occur due to vomiting.
- **TREATMENT:**
  - Antiemetics targeted to specific type of nausea (antihistamines, benzamides, benzodiazepines, butyrophenones, cannabinoids, phenothiazines, serotonin antagonists, NK1 RA)

CHEMOTHERAPY INDUCED DIARRHEA

- **PATHO:**
  - Commonly associated with irinotecan, tyrosine kinase inhibitors (EGFR inhibitors), 5-FU, and HER-2 inhibitors.
- **CLASSIC PRESENTATION:**
  - Increased stool frequency, dizziness, abdominal pain, weakness.
- **CLASSIC FINDINGS:**
  - Diarrhea graded as uncomplicated (grade 1 or 2), or complicated (grade 3 or 4).
- **TREATMENT:**
  - Uncomplicated diarrhea treated primarily with loperamide
  - Complicated diarrhea treatment includes
    - Loperamide
    - IV fluid and electrolyte replacement
    - Antibiotics
    - Octreotide

FEBRILE NEUTROPENIA

- **PATHO:**
  - Decreased neutrophil concentration resulting in impaired immunity and increased susceptibility to bacterial, viral, fungal and other infections.
- **CLASSIC PRESENTATION:**
  - Fever, usually weakness or malaise, cough or shortness of breath if the infection involves the lungs
- **CLASSIC FINDINGS:**
  - > 38.3 °C or 101 °F for a single episode or 100.4 for > 1 hour + an absolute neutrophil count < 500 cells/mm3 (or ANC expected to fall < 500 over the next 48 hours)
- **TREATMENT:**
  - IV empiric antibiotic therapy to include monotherapy with an antipseudomonal beta-lactam agent.
    - No antifungal agents unless indicated

HYPERURICEMIA / TUMOR LYSIS SYNDROME

- **PATHO:**
  - Rapid and massive cellular breakdown with the subsequent release of cell contents and cytokines into the bloodstream leading to systemic complications including hyperuricemia hyperkalemia, hyperphosphatemia with subsequent hypocalcemia.
- **CLASSIC PRESENTATION:**
  - Nausea vomiting, cardiac dysrhythmias, renal failure
- **CLASSIC FINDINGS:**
  - Presence of 2 or more abnormal labs occurring within 3 days before her up to 7 days after use of cytotoxic chemotherapy for malignancy: Hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia
- **TREATMENT:**
  - Prophylaxis (allopurinol, hydration, rasburicase)
  - Treatment (IV hydration, allopurinol, rasburicase, HD)

EXTRAVASATION

- **PATHO:**
  - Accidental complication of chemotherapy administration where the drug deposits outside of the blood vessel and into the tissue at the location of IV insertion thereby damaging the tissue in the surrounding area.
- **CLASSIC PRESENTATION:**
  - Can range from redness with or without pain to blistering and tissue necrosis depending on the timeframe from extravasation and agent used
- **CLASSIC AGENTS:**
  - Bendamustine (Alkylating Agent), Dactinomycin, Daunorubicin, Doxorubicin, & Idarubicin (Anthracyclines), Oxaliplatin (Platinum analog), Paclitaxel (Taxane), Vinblastine, Vincristine, Vinorelbine (Vinca Alkaloids)
- **TREATMENT:**
  - Stop infusion immediately, gently aspirate extravasated solution, elevate extremity, apply dry, cold compress for 20 minutes 4 times daily x 1-2 days followed by drug (extravasate) specific treatments.

Live Q&A

Toxicology

Core Antidotes for BPS Exams

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Activated Charcoal

- It is a non-absorbable absorbent
- Only used now if presents within 1 hour of ingestion AND:
  - Airway can be protected AND
  - Patient is not actively vomiting or nauseous AND
  - No evidence of GI obstruction or risk for perforation
- Historically advocated to be given at a 10:1 (charcoal:poison) ratio.
  - Most of the time dose of agent ingested is not known
  - Can be difficult to give this much
  - Don't give with the cathartic sorbitol (increases risk of vomiting and does not improve outcomes)
  - Dilute each 1 g of charcoal with 8 cc water (so 25 g is mixed with about 4 ounces of water and 50 g is mixed with 8 ounces)

Whole Bowel Irrigation

- Not recommended unless ingestion of _____ product (verapamil, diltiazem, glyburide XL, theophylline) because no RCTs have assessed outcome.
  - If used follow with activated charcoal as WBI can decreased efficacy if sued together
  - Avoid if any presence of ileus, bowel obstruction or toxic megacolon or hemodynamic instability
- GoLYTELY (original agent) but now replaced with other formulations (e.g., NuLYTELY) which has 52% less salt and no added Na sulfate which improves taste and fluid- & electrolyte complications.
  - Small children: 0.5 L/hr or 25 ml/kg/hr
  - Adolescents and Adults: 1.5-2 L/hr over a 4-6 hr period

Rapid Toxicology Review

Drug Toxicity	Antidote(s)	Notes
Acetaminophen	N-acetylcysteine (Acetadote IV, Mucomyst)	• Check level at 4 hrs post ingestion, plot on nomogram • IV takes at least 21 hrs vs. 72 hrs with oral • IV associated with more anaphylactoid rxns especially in pediatrics
Anticholinergics	Physostigmine	• Check pulse first as it can cause bradycardia • Can worsen secretions and cause bronchospasm
Antifreeze (Ethylene glycol)	_____ (or) 10% ethanol IV	• Both will inhibit alcohol dehydrogenase and reduce the metabolism to glycolic acid and oxalic acid that can cause acid/base disorder

Rapid Toxicology Review

Drug Toxicity	Antidote(s)	Notes
Neuroleptic Malignant Syndrome	Diphenhydramine _____	• Counter acts the excessive imbalance of cholinergic response from dopamine antagonism • May also benefit from benzodiazepine +/- propranolol
Aspirin (Salicylic Acid)	Alkalization of urine Dialysis	• Increasing pH causes ion trapping in urine • Most need ICU admission with HD • ASA causes initial respiratory alkalosis followed by metabolic acidosis
Benzodiazepine	Flumazenil (Romazicon)	• Competitive inhibition for GABA receptor • Not for chronic users who OD as it can precipitate seizures, but only for acute overdose in naïve patients
Beta-Blockers	Glucagon Insulin + Glucose	• Glucagon can increase inotropy outside of beta-receptor • Insulin/glucose improve energy substrate availability to increase effectiveness

Rapid Toxicology Review

Drug Toxicity	Antidote(s)	Notes
Calcium Channel Blockers	Calcium IV Glucagon Insulin/Glucose	• Calcium IV usually not effective • Glucagon improves inotropy • Insulin/glucose improve energy substrate use and cardiac activity
Carbon Monoxide	O2 via NRB mask Hyperbaric O2	• CO causes metabolic acidosis • High conc O2 reduces half-life of CO • If pregnant, hyperbaric O2 and for longer due to greater affinity by fetal Hgb
Cyanide	Amyl nitrate or Na nitrite, then Na thiosulfate (or) _____	• CN results in metabolic acidosis • Amyl nitrate or Na nitrite cause initial MetHgb than binds to CN, then Na thiosulfate converts to thiocyanate for elimination • Hydroxocobalamin binds to CN to become vit B12

Rapid Toxicology Review

Drug Toxicity	Antidote(s)	Notes
Digoxin	Digibind DigiFAB	• FAB fragments of Abs that bind to digoxin • Acute OD can see hyperK and need larger doses (10 vials) vs chronic toxicity • Historically people avoid Ca "stone heart"
Heparin	Protamine sulfate	• Every 1 mg neutralizes 100 IU of heparin • Max dose is 50 mg due to anticoagulant effect at higher doses
Isoniazid (INH)	_____	• Replenishes levels of vit B6 • DOC of INH induced seizures

Rapid Toxicology Review

Drug Toxicity	Antidote(s)	Notes
Methanol	Fomepizole (Antizol) 10% ethanol IV	• Competitive inhibition of alcohol dehydrogenase to reduce formation of formic acid (causes optic nerve damage & blindness) • Methanol found in windshield wiper fluid, Sterno (used for portable fires), pain solvent
Methotrexate	Leucovorin Glucarpidase (Voraxaze)	• FH4 derivative that bypasses DHFR • Glucarpidase (IV or intrathecal) in an enzyme that metabolizes MTX quickly
Neuromuscular Blockers	Edrophonium (Enlon) Neostigmine (Prostigmin Sugammadex (Bridion)	• Cholinesterase inhibitors to increase conc of ACH present at NMJ • Not for succinylcholine

Rapid Toxicology Review

Drug Toxicity	Antidote(s)	Notes
Nitrates	Methylene Blue	• Goal methemoglobin < 20% • Less effective in pts with G6PD
Opioids	Naloxone (Narcan)	• Competes directly with mu receptor • Give slowly (0.1 mg at a time) until RR improves • Avoid with meperidine induced seizures • Duration only 30 min – 2 hrs
Pesticides (Organophosphates)	Body decontamination Atropine Pralidoxime (2-PAM)	• SLUDGE: (salivation, lacrimation, urination, diarrhea, GI upset, emesis) • Atropine antagonizes muscarinic receptor • 2-PAM reactivates acetylcholinesterase
Snake Bite	Crotalidae polyvalent immune Fab ovin (CroFab)	• IgG antibody that neutralizes venom toxins • Best used within 6 hrs of bite

Rapid Toxicology Review

Drug Toxicity	Antidote(s)	Notes
Sulfonylureas	Initial correction of glucose with D50 x1 _____	• Inhibits insulin secretion of beta-islet cells in pancreas • Avoid glucose infusions
TCAs	Sodium Bicarbonate Hypertonic saline Lipid Emulsion Benzodiazepines	• First 3 options will reduce Na blockade cause QRS widening • Benzodiazepines if seizures occur (avoid phenytoin)
Valproic acid	Naloxone _____	• Naloxone for AMS • L-carnitine for hyperammonemia
Warfarin	Vitamin K K-centra (Prothrombin Complex Concentrate II, VII, IX, X, C, & S)	• Vit K is not immediate effect; given PO or IV • K-centra is four factor complex concentrate for rapid reversal
Dabigatran (Pradaxa)	Idarucizumab (Praxbind)	• Humanized monoclonal Ab fragment (Fab); most get reversal within 4hrs

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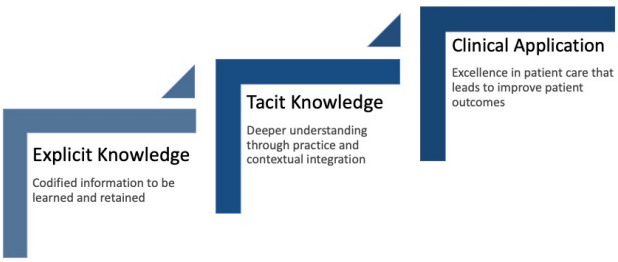
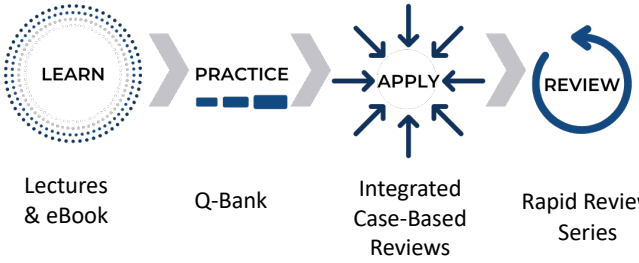


Knowledge Transfer

The High-Yield Approach



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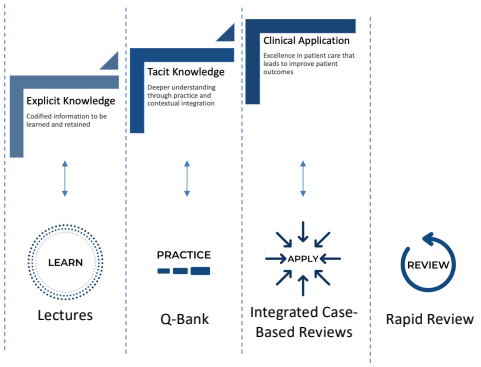

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