Transplant Surgery Curriculum

1. Type of transplant in terms of location, relation of donor to recipient, timing.
2. History of organ transplantation: dates of first transplants for each organ.
3. Main immunosuppression medications and their side effects.
4. Rules of pre-transplant donor/recipient matching and testing.
5. Indications for dialysis and abdominal organ transplantation.
6. Diagnosis of kidney, pancreas, liver graft dysfunction.
7. Methods of organ preservation.

Questions

1. Why do we do organ transplantation?
2. What is allogeneic, autologous, xenogeneic orthotopic organ Tx? What is an isograft?
3. What is heterotopic vs orthotopic organ Tx? Examples.
4. List organs and tissues which are currently being transplanted as a standard of care (SOC).
5. Which organs are transplanted from living donors?
6. When was the first successful organ transplant? Which organ? Where? Who did it?
7. When was the first allo- kidney, pancreas, liver, heart Tx?
8. Who first transplanted liver successfully?
9. What type of immunosuppression medications were used during first transplants in the 60s?
10. What type of immunosuppression medications do we use today?
11. What is the difference between monoclonal and polyclonal antibodies?
12. What are the types of rejection that relate to timing?
13. What are the types of rejection that relate to mechanism?
14. Which cell types are involved in rejection?
15. What is the cause of hyperacute rejection and mechanism of tissue damage? How soon after Tx does it happen?
16. How can we prevent hyperacute rejection?
17. Why do we do cross match?
18. What is the difference between real X-match and virtual X-match?
19. What does PRA stand from and what does it mean?
20. Why is it that incompatible ABO antibodies can cause hyperacute rejection, if they bind to antigens on erythrocytes and the organ is completely flush of erythrocytes?
21. How do we prevent acute rejection?
22. 4 sides effects of tacrolimus.
23. 2 side effects of Cellcept.
24. 4 side effects of Thymoglobulin.
25. 3 side effects of large doses of steroids.
26. Reasons for rising creatinine level on day 7, after kidney Tx (3 prerenal, 6 renal, 3 postrenal).
27. What is an opportunistic infection? Examples.
28. How does one prevent and treat CMV infection?
29. What is PTLD?
30. What is the most common cancer after kidney Tx? What is its incidence? How soon does it occur after Tx?
31. What is the typical incision for kidney Tx? What is the anatomical space?
32. To which vessels is the kidney graft connected?
33. Where is the blood supply to kidney graft ureter coming from?
34. Most common urological complications after kidney Tx.
35. How long do Foley and stent stay after kidney Tx?
36. How does one recognize that patient is bleeding after kidney Tx?
37. When does one suspect DVT?
38. Postoperative day (POD) 0 evening, patient after incisional hernia repair, in severe abdominal pain. What do you do first?
39. POD 1 after liver Tx — how do we know that the liver graft is working just by looking at the patient?
40. POD 2-3 after liver Tx — what is the expected trend of AST/ALT and bilirubin?
41. What lab values are used to calculate MELD (Model of End Stage Liver Disease)?
42. MELD score ranges and their meaning.
43. Indications for dialysis (what GFR?).
44. Indications for kidney Tx.
45. Causes of kidney failure.
46. When does a recurrent primary disease cause kidney graft failure?
47. Indications for liver Tx (main groups).
48. Indications for SPK (simultaneous pancreas-kidney) Tx.
49. Indications for PTA (pancreas transplant alone).
50. Indications for PAK (pancreas after kidney) Tx.
51. Indication for intestine Tx.
52. Kidney graft half-life (DD, LD).
53. Heart graft half-life.
55. What organs /tissues are being transplanted as experimental procedures?
56. Brain death criteria.
57. Maximum cold storage preservation time for organs for Tx.
58. Methods of controlling variceal bleeding.
59. What is TIPS and what are the indications for it?
60. What are the signs of pancreas graft dysfunction?

Answers

1. To replace function of the organ, which has failed.
2. Allogenic: same species, autologous: own tissue, xenogeneic: different species. Isograft - genetically identical (i.e. monozygotic twins).
3. Heterotopic -- organ transplanted in the same site as native organ (liver, heart). Orthotopic -- organ transplanted at a different site (kidney, pancreas).
5. Kidneys, liver, small bowel.
8. Thomas Starzl in Pittsburg, PA.
9. Imuran (antimetabolite) and steroids.
10. Calcineurin inhibitor (cyclosporine, tacrolimus), antibodies (Thymoglobulin, basiliximab), proteasome inhibitor (bortizemib).
11. Monoclonal: against single antigens, vs polyclonal: against multiple antigens.
13. Cellular rejection, antibody mediated rejection.
14. Antigen presenting cells (macrophages, monocytes), lymphocytes (T, B, plasma cells)
16. Test the donor and the recipient before the transplant surgery for any antibodies that might be incompatible (performing cross match, checking for blood group compatibility).
17. To test for the presence of donor specific antibodies (mixing recipient serum with donor cells and checking for rejection).
18. Real X-match — see above, virtual X-match — comparing information about identified donor HLA antigens with information about recipient HLA antibodies identified previously during HLA testing.
19. PRA -- panel of reactive antibodies -- test on recipient serum, which detects HLA antibodies. The PRA score is expressed in a range of 0-100%. It provides practical information about frequency of donors in population with antigens which are unacceptable for the recipient (recipient has those HLA antibodies); PRA 0%: patients has no HLA antibodies, PRA 100%: recipient has HLA antibodies against 100% of the population.
20. The same antigens are on the surface of endothelium of organ blood vessels; their binding activates complement and causes thrombosis.
21. Induction (Thymoglobulin or basiliximab) and maintenance immunosuppression (tacrolimus, mycophenolate, steroids).
22. Nephrotoxicity (hyperkalemia, rising creatinine), neurotoxicity (headache, tremor, seizure), hyperglycemia, HTN.
23. GI (diarrhea, nausea, vomiting), neutropenia, anemia, thrombocytopenia.
24. 1) Fever, malaise, 2) rash, 3) cytokine release symptoms (tachycardia, hypotension), 4) lymphopenia, anemia, thrombocytopenia.
25. Elevated WBC, hyperglycemia, depression/manic attack.
27. Usually does not develop in healthy people (CMV, EBV, BK, PCP).
29. Post Transplant Lymphoproliferative Disease: often in EBV IgG negative patients, positive blood EBV PCR; clinically: recurrent fever, SBO, diarrhea; treatment: lower immunosuppression, Rituxan, chemotherapy; incidence: 2-10%.
30. Basal cell skin cancer; 5-10 years after Tx; 20-40% of patients.
31. A) Retroperitoneal space: 1) Gibson (hokey stick) incision through oblique abdominal muscles, 2) lateral rectus sheath incision (not muscle incision), 3) midline with pushing peritoneum medially; B) intraperitoneal space: midline.
32. External iliac vessels, common iliac vessels.
33. Renal artery.
34. Urine retention, stenosis of the ureter, urine leak.
35. Foley 3 days, double J stent 4-6 weeks.
36. 1) Look for/at: blood in the bed, basin, dressing, wound, drain, NGT, rectal bleeding, hematuria, hematemesis, skin color, eyes, agitation; 2) ask nurse and patient for the same, 3) vital signs, 4) labs.
37. Unilateral swelling.
38. Open the abdominal binder and assess.
39. Patient is waking up, making urine, drains are dry, no pressors required.
40. AST/ALT down, bilirubin up.
41. Serum bilirubin, creatinine (HD), INR.
42. MELD 6-40; chance for 3 months survival without liver Tx; 90% -7%.
   MELD <15 — transplant differed; MELD>17 — indication for Tx.
43. No GFR value alone is indication for dialysis. Indications are clinical based on kidney failure and a) fluid overload, b) metabolic acidosis, c) hyperkalemia d) uremia (uremic coagulopathy, uremic encephalopathy, pericarditis) e) poisoning (eg. ethylene glycol which can cause AKF and anion gap metabolic acidosis).
44. Indication for kidney Tx:
   • ESRD: patient on dialysis or GFR<20; 2.
   • GFR<15 -- CKD stage 5; 3.
   • GFR 15-20 — CKD stage 4 (GFR 15-30).
45. Most common causes of kidney disease leading to kidney failure:
   • Diabetes
   • HTN
   • GN (glomerulonephritis), SLE
   • Congenital (eg. polycystic kidney disease, congenital renal hyperplasia)
   • Infectious — pyelonephritis
46. Years after Tx: 1) diabetes, 10 years after; 2) FSGS can recur right away; 3) next day after Tx: proteinuria, biopsy, plasmapheresis.
47. Below
   • Acute liver failure,
   • acute on chronic liver disease,
   • decompensated cirrhosis (recurrent ascites, recurrent hemorrhage, encephalopathy, hepatopulmonary syndrome, hepatorenal syndrome),
   • liver graft failure.
48. Diabetes (T1DM, lean T2DM with low c-peptide) with GFR<20.
49. Highly selected T1DM with problematic hypoglycemia and uncontrolled glycemia despite optimal medical therapy with good kidney function.
50. T1DM with a stable kidney graft function.
51. Short gut syndrome, functional bowel problems.
52. DD: 12 yrs, LD: 15 yrs.
53. 12-15 years.
54. 1) Islet auto- Tx: islets are isolated from patient's own pancreas and infused into portal vein; no immunosuppression required, indication: during total pancreatectomy in patients with chronic pancreatitis and intractable pain. 2) Islet allo- Tx: islets are isolated from cadaveric pancreas and infused into portal vein of T1DM; patients need lifelong immunosuppression.
55. Experimental Tx:
   o VCA (Vascularized Composite Allotransplantation) — transplantation of multiple tissues such as muscle, bone, nerve and skin, as a functional unit (e.g. a hand, or face) from a deceased donor to a recipient with a severe injury.
   o Allogeneic islets
   o Abdominal Wall
   o Head and Neck: Craniofacial
   o Head and Neck: Scalp
56. Clinical criteria included in establishing brain death diagnosis are:
   a) coma with cerebral unresponsiveness,
   b) lack of brain stem reflexes and
   c) apnea test with persistence of this conditions for 6-24 hours.
   d) additional testing may be necessary to confirm the diagnosis:
      i) somatosensory and brainstem auditory evoked potentials
      ii) electroencephalogram
      iii) transcranial Doppler USG,
      iv) magnetic resonance imaging and
      v) cerebral blood flow

57. Maximum time of cold storage organ preservation:
   heart: 6hrs, lungs:8 hrs, pancreas, liver:12hrs, kidney: 48 hrs (72hrs on pump).

58. 1) endoscopic bands, sclerotherapy, injections, 2) TIPPS 3) Sengstaken-Blakmore tube or Linton-Nachlas tube (in the past)

59. TIPS: Transjugular Intrahepatic Portosystemic Shunt; indications:
   • Recurrent/persistent esophageal variceal bleeding
   • Refractory ascites or hepatic hydrothorax (resistant to diuretics)
   • Budd-Chiari syndrome
   • As the bridging procedure for patient on the waiting list for liver transplant (disadvantage: encephalopathy)

60. Rising blood glucose, pain over the graft, rising amylase/lipase.

Some more reading
Fig 1. Pancreas and kidney transplantation

In most cases, the allograft pancreas is transplanted along with a segment of duodenum, which is anastomosed to the recipient’s jejunum to establish drainage of bile.

Most pancreas transplants are done simultaneously with a kidney transplant.

Fig 2. Pancreatic Islet allotransplantation
Fig 3. Liver transplantation

Piggy back anastomosis of donor cava to IVC
Criteria for Tx

<table>
<thead>
<tr>
<th>Indications for transplantation</th>
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<tbody>
<tr>
<td><strong>Kidney</strong></td>
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<tr>
<td>□ ESRD: patient on dialysis or</td>
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<td>□ GFR&lt;20,</td>
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<td>3. GFR&lt;15 — CKD stage 5</td>
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<td>4. GFR 15-30 — CKD stage 4</td>
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<td>The most common kidney diseases that lead to kidney failure:</td>
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<td>1. Diabetes</td>
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<td>3. GN (glomerulonephritis), SLE,</td>
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<td>4. Congenital (eg. polycystic kidney disease, congenital renal hyperplasia,</td>
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<td>Pancreas/Kidney (SPK)</td>
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PTA or Islet Transplant Alone (experimental)  
- Highly selected T1DM with problematic hypoglycemia and uncontrolled glycemia despite optimal medical therapy **with** good kidney function

PAK or Islet After Kidney (experimental)  
- T1DM with a stable kidney graft function

Intestine  
- Short gut syndrome, functional bowel problems

<table>
<thead>
<tr>
<th></th>
<th>Graft survival (%) Cadaveric</th>
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<th>Graft survival (%) Living donor</th>
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<tbody>
<tr>
<td></td>
<td>1 year</td>
<td>5 year</td>
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<td>1 year</td>
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<tr>
<td>Kidney</td>
<td>93</td>
<td>74</td>
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<tr>
<td>SPK –</td>
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<tr>
<td>PAK –</td>
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<td>PTA –</td>
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<td>Heart</td>
<td>90</td>
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<th>Half-life median life (in years)</th>
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<tr>
<td>Kidney</td>
<td><strong>DD (KDPI 85-100)</strong> 9</td>
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<td></td>
<td><strong>DD (KDPI 0-85)</strong> 12</td>
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<tr>
<th></th>
<th>LD</th>
<th>15 years</th>
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<tr>
<td></td>
<td>LD</td>
<td>20 years</td>
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<td>0 mismatch</td>
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<tr>
<td>Heart</td>
<td></td>
<td>12-15</td>
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<tr>
<td></td>
<td>PTA</td>
<td>5-7</td>
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<tr>
<td>Islets</td>
<td>insulin independence</td>
<td>1-5 years</td>
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KDPI — index indicating quality of the kidney donor which correlates with graft survival,
- range 0-100%
- 0% — the best, young donor
- 0-85% — standard donors (half-life 12 years)
- 85-100% — extended criteria donors with shorter half-life (9 years)

**Immunosuppression**
Current forms of immunosuppression for transplantation, their mechanism of action and side effects.

1. **Calcineurin inhibitors** (cyclosporine, tacrolimus – FK506) — block T-cell activation by preventing IL-2 transcription.
   Side effects:
   - Both: Nephrotoxicity, hyperlipidemia, hypertension, neurotoxicity
   - Cyclosporine: gingival hyperplasia, hirsutism
   - Tacrolimus: more GI symptoms, mood changes and diabetes than cyclosporine

2. **Antimetabolites**
   **Azathioprine** — inhibits lymphocyte proliferation by blocking nucleotide synthesis. Side effects: Pancreptiopenia
   **Mycophenolate (MMF, CellCept)**: prevention of purine synthesis for B and T cells by reversible inhibition of IMP dehydrogenase (inhibits de novo purine synthesis)
   Side effects: Pancreptiopenia, hypertension, hyperglycemia, GI upset.

3. **mTOR inhibitors** (sirolimus/rapamycin) — block T-cell activation and B-cell differentiation by preventing response to IL-2.
   Side effects: Pancrptiopenia, hyperlipidemia, insulin resistance, mouth ulcers, poor wound healing, hernia (avoid during the surgery).

   Used for induction after Tx, maintenance and acute rejection episodes.
   Side effects: Osteoporosis, Cushing syndrome, hyperglycemia and diabetes – increased
insulin resistance, peptic ulcers, amenorrhea, adrenal cortex atrophy and secondary adrenal insufficiency when abrupt withdrawal, cataracts, avascular necrosis of the femoral head.

Graft Definition

**Autograft** — Organ graft or tissue in which recipient and donor is the same individual (e.g. autologous pancreatic islet transplantation after total pancreatectomy, autologous skin grafts in burn victims, autologous bone marrow transplants, saphenous vein in CABG).

**Isograft** — (or syngeneic graft) organ graft or tissue transplanted from a donor who is genetically identical to the recipient (e.g. first kidney transplantation was performed between monozygotic twins in 1954 by Joseph E. Murray at Peter Bent Brigham Hospital in Boston – no immunosuppression was needed).

**Allograft** — organ graft or tissue transplanted to a recipient from a genetically non-identical donor of the same species.

**Xenograft** — organ graft or tissue transplanted from a donor of a different species from the recipient.

**Orthotopic** — organ graft or tissue transplanted in the position of previously removed native organ (e.g. native liver is removed and replaced by the donor organ in the same anatomic position as the original liver).

**Heterotopic** — organ graft or tissue transplanted in the different location than existing/native organ (e.g. kidney graft transplanted on iliac fossa, the existing kidneys are not usually removed unless they are causing problems like recurrent infections, uncontrolled hypertension or they are greatly enlarged as they can present in PKD).

**CIT — cold ischemia time** — refers to the time from when the organ is cooled with preservation solution (organ procurement – after cross clamp of the aorta) to the release of the vascular clamp of anastomosis.

1) **WIT** — warm ischemia time — for Donation after Cardiac Death, it is the time between donor extubation and initiation of the cold perfusion of the organ.

- For kidneys should not exceed 90 mins.
- For liver or pancreas should not exceed <30 mins.

**Methods of preservation:**

- Flushing organs and storage with preservation solution (e.g. UW – University of Wisconsin fluid).
- Storage in hypothermic conditions (so called “cold storage”) or mechanical pulsatile perfusion pumps with preservation solution imitating physiologic circulation (pressure, flow, resistance) of the donor (Lifeport machine for kidneys). Pulsatile perfusion can be hypothermic or normothermic, optionally oxygenated.
Table – acceptable cold ischemia times for transplanted organs

<table>
<thead>
<tr>
<th></th>
<th>Optimal</th>
<th>Up to</th>
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<tbody>
<tr>
<td>Heart</td>
<td>4 hours</td>
<td>6 hours</td>
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<tr>
<td>Lungs</td>
<td>4-6 hours</td>
<td>8 hours</td>
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<tr>
<td>Liver</td>
<td>6-10 hours</td>
<td>12 hours</td>
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<tr>
<td>Pancreas</td>
<td>&lt;8 hours</td>
<td>&lt;12 hours</td>
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<tr>
<td>Intestines</td>
<td>6-12 hours</td>
<td>-</td>
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<tr>
<td>Kidneys</td>
<td>36 hours</td>
<td>Up to 48 ice storage, 72 hours on pump</td>
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<tr>
<td>Pancreatic islets</td>
<td>&lt;8 hours</td>
<td>&lt;12 hrs</td>
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Type of rejection

a) **Hyperacute rejection** — within minutes or first few hours after transplantation, necrotic ischemia to the graft due to graft vessel thrombosis. Mediated by preformed antibodies present before transplantation with specificity to the graft endothelial cells. Nowadays hyperacute rejection is not a big problem in transplantation since every donor and recipient are matched for blood type and serum of recipient is tested for preformed antibodies against the prospective donor (cross match).

b) **Accelerated acute rejection** — mechanism similar as above, has been used to categorize episodes of renal dysfunction occurring during the first several days (3-7 days) after transplantation.

c) **Acute rejection** — within days or weeks after transplantation, main cause for early graft failure. Maintenance immunosuppression play very crucial role in prevention of this rejection by blocking the activation/proliferation of alloreactive T cells.

d) **Chronic rejection** — within months to years, indolent type of rejection, gradual, insidious loss of graft function.

Controlling upper GI variceal bleeding

1) **Endoscopic therapies** (advantage — minimal invasive)
   a. endoscopic esophageal band ligation — current treatment of choice for bleeding and nonbleeding esophageal varices
   b. endoscopic injection (adrenaline)
   c. endoscopic sclerotherapy – vascular obliteration by injection of a sclerosing agent
No longer used: esophageal tamponade (Sengstaken-Blakemore tube or Linton-Nachlas tube); was used in the past in emergent variceal bleeding; nowadays rarely needed since endoscopy is available.

High recurrence rate (re-bleeding) after esophageal tamponade, risk of aspiration and esophageal perforation limits use of tamponade.

2) **TIPS** indications:

- Recurrent/persistent esophageal variceal bleeding – rescue treatment in patients with recurrent bleeding despite combination therapy with endoscopic band ligation
- Refractory ascites or hepatic hydrothorax (resistant to diuretics)
- Budd-Chiari syndrome
- As the bridging procedure for patient on the waiting list for liver transplant

Complication is encephalopathy. Needed specialized IR team experienced in those procedures, usually available in high reference liver centers.

**Surgical anatomy of common liver resections:**
left hepatic lobectomy, right hepatic lobectomy, extended right hepatic lobectomy (right trisegmentectomy)

“A good knowledge of the anatomy of the liver is a prerequisite for modern surgery of the liver” H. Bismuth

The plane of division between the right and left lobe of the liver is not, as it seems, the falciform ligament, but rather a plane passing through the bed of the gallbladder and the notch of the IVC with no clear indications on the surface (Cantlie line).

We divide liver into functional lobes and segments based on arterial blood supply, portal venous blood supply and biliary drainage. The most well-known and clinically used is the hepatic segmentation proposed by Couinaud and modified by Bismuth. Eight segments are described: one for the caudate lobe (segment I), three on the left (II, III and IV) and four on the right (V, VI, VII and VIII).

- Left hepatectomy: removal of all the liver tissue to the left of Cantle’s line.
- Right hepatectomy: removal of all the liver tissue to the right of Cantle’s line.
- Extended right hepatectomy — when indicated segment IV can be included in resection alongside with the right liver. Initial steps similar for right hepatectomy. The plane for transection is along the right side of the falciform ligament – from the groove separating the middle and left hepatic veins (cranially) to the right side of the umbilical fissure caudally. Transection is directed towards the medial aspect of the right hilar plate while avoiding the confluence of the left and right hepatic ducts.
Segment I corresponds to the caudate lobe, close proximity to IVC, venous blood directly drained to IVC through small veins.

In about 17% the right (replaced of accessory) hepatic artery branches from superior mesenteric artery and pass to the right/behind (or occasionally in front of) the common bile duct in front of the portal vein

☐ Describe the standard methods of implantation/revascularization for liver and kidney allograft.

**Kidney allograft** — implanted extra-peritoneally on left or right iliac fossa of the recipient (some transplant surgeons prefer right iliac fossa since the vessels are more superficial on the right side — this side might be used first during 1st kidney transplant). After exposition of recipient’s iliac vessels, donor’s renal vein is anastomosed with external iliac vein of the recipient (end-to-side anastomosis). Next, renal artery is anastomosed with recipient’s external iliac artery (end-to-side). Renal artery in deceased donor kidney is procured with an aortic patch (so called “Carell patch”) which helps during implantation. This, as opposed to living donor kidneys, which are procured without a patch. After completion of anastomoses, “Satinsky clamp” is released from recipient’s external iliac artery and blood starts to flow to the transplanted kidney (reperfusion). Procedure ends with implantation of ureter into the bladder on J-J catheter (in most of the cases urine can be observed ?? from ureter immediately after reperfusion).

**Liver allograft**

*Portal flow: end-to-end portal anastomosis*

**Systemic outflow**
1. IVC to IVC end-to-end (requires complete clamping of recipient IVC -- blood flow halted)
2. piggy-back technique (partial clamping of IVC, flow through recipient IVC maintained -- patient more stable)
   - (a) side-to-side IVC to IVC or
   - (b) hepatic veins to hepatic vein at orifice in recipient IVC

**Arterial inflow**
- donor celiac trunk to the recipient common hepatic artery end-to-end or
- donor celiac trunk to the recipient aorta via arterial conduit (donor iliac artery)

**Prevention of wound infection in transplant recipients**
- ERAS in transplant surgery — proper preparation of the patient (nutritional status, strict control of diabetes, smoking cessation, weight control, bariatric approach first if morbid obesity).
- Perioperative antibiotic prophylaxis — 1st dose 60 min prior to incision, continued up to 24 hours postoperatively.
  - Cefazolin 1-2 g IV every 8 hours (if < 60 kg – 1g, if ≥ 60 kg – 2g).
  - If beta lactam allergy: Ciprofloxacin 400 mg IV every 12 hours AND Clindamycin 600 mg IV every 8 hours.
  - Do not use Gentamycin due to nephrotoxicity!
Skin decontamination, preoperative shaving and skin preparation.
Operative factors — changing scrubs, separation of back table in order to avoid cross-contamination of recipient’s surgical site, optimal perioperative temperature management (hypothermia prevention).
Optimal timing of removal of surgical drains.
Proper surgical technique: avoiding tissue trauma, proper hemostasis, diligent obliteration of dead spaces in the wound.
Minimize the length of pre- and postoperative stay.
Appropriate antibiotic timing and antibiotic selection to prevent multidrug resistance.

Leak from the surgical wound after kidney Tx:
Early (day 1-6):
- Minimal/moderate — fluid overload, fat necrosis.
- Substantial — requiring constant dressing changes, worse in vertical position - suspect dehiscence.

Later, after day 6:
- Wound infection? -- send culture
- Wound dehiscence
- Urine leak -- send for creatinine

Wound hematoma -- do not open at the bed side (watch or OR)!