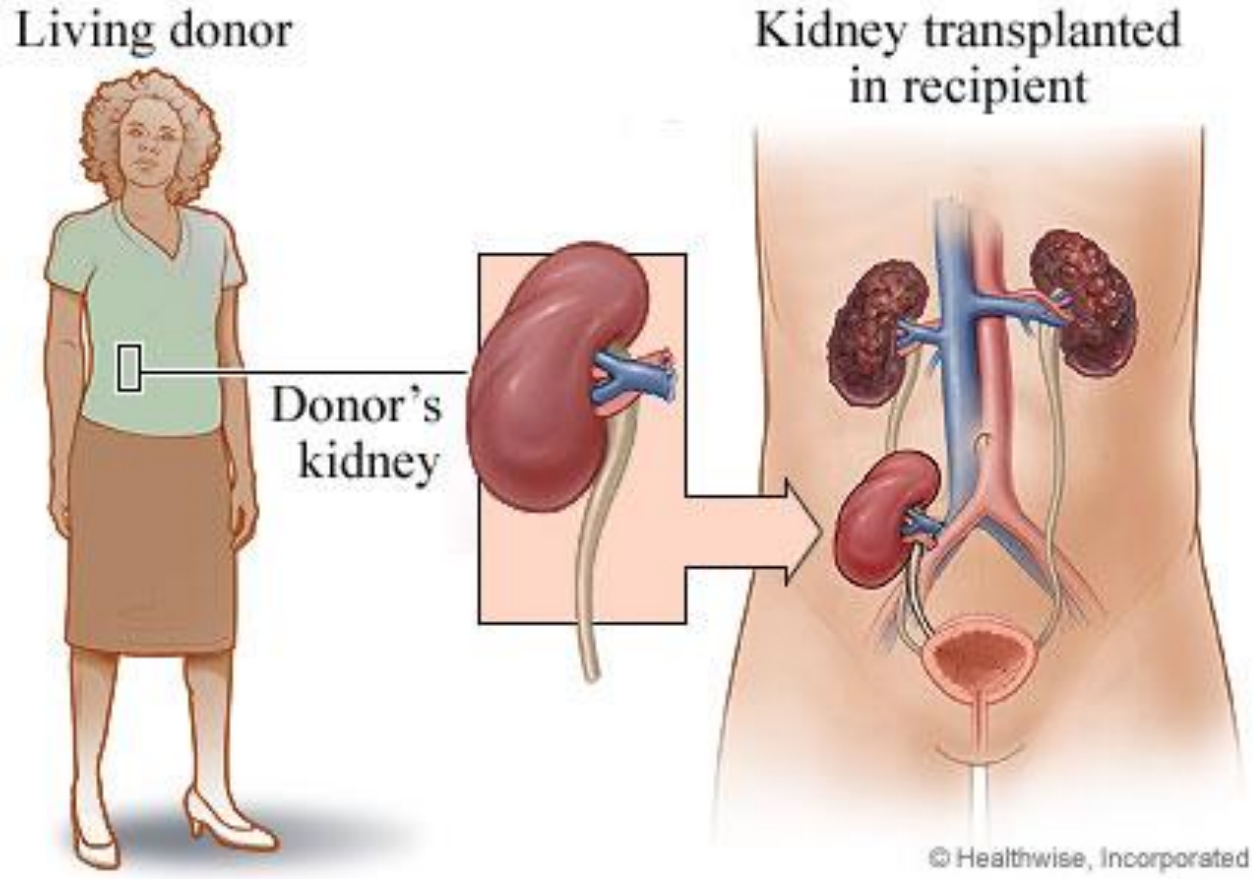

Lecture Seven

Renal Allograft

432 *Pathology* Team

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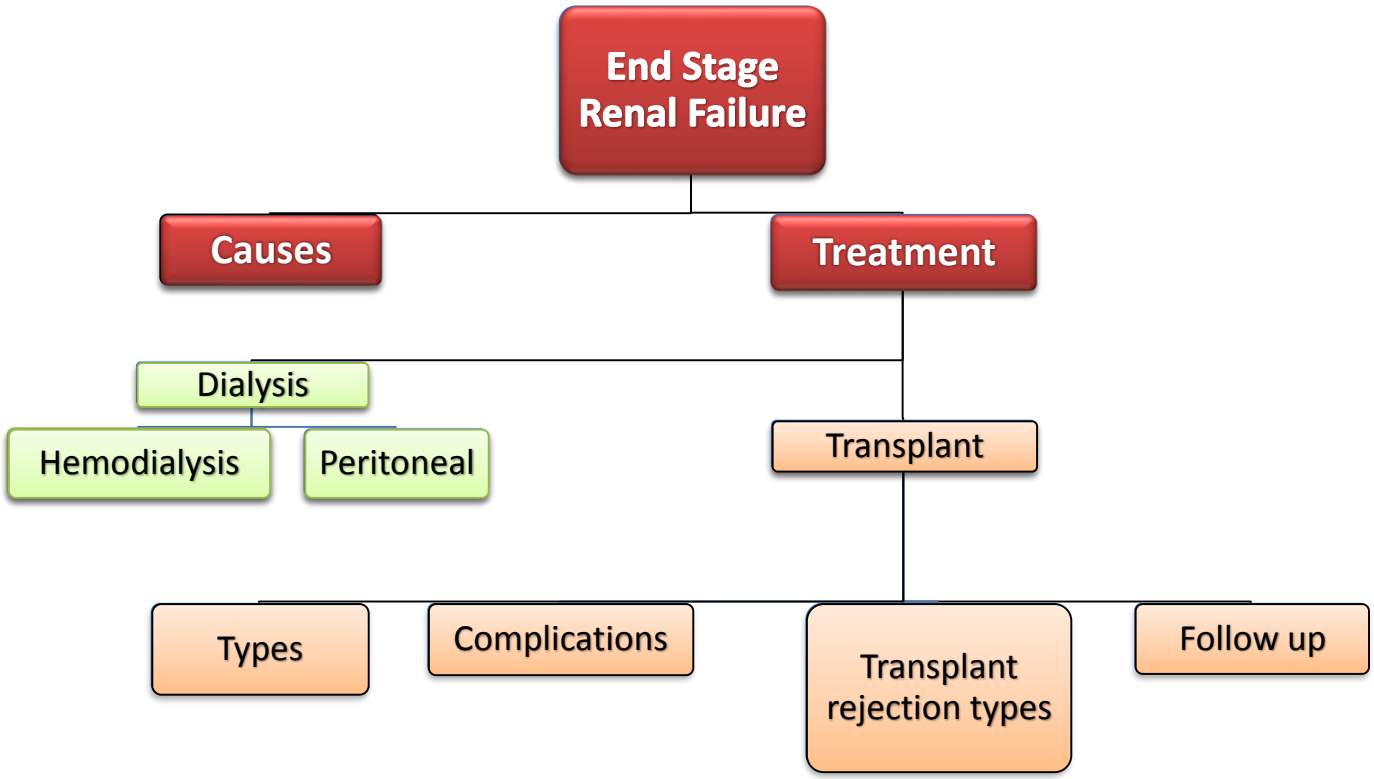
***Reviewed By: Ala'a** Baghazal*

Renal Block

NOTE: female-side notes are written in purple. Red is important. Orange is explanation. Info in the handout not mentioned by Prof. Al-Rikabi are in GREY

Renal Transplantation

Mind Map:



Introduction

Renal transplantation is increasingly being performed as a treatment for **end-stage renal failure**, (diffuse and global glomerulonephritis)

Causes of end-stage renal failure:

Secondary to any one of **Glomerular Diseases** or **Tubulointerstitial Diseases** but the most common cause in Saudi Arabia is **Diabetic nephropathy**

First thing we do to end-stage renal failure patient is dialysis

Dialysis: is a mechanical process that performs the work that healthy kidneys would do. It clears wastes and extra fluid from the body and restores the proper balance of chemicals (electrolytes) in the blood.

Types of Dialysis

1- **Hemodialysis**
2- **Peritoneal dialysis**

1) Hemodialysis

Hemodialysis is a medical procedure that uses a special machine to filter waste products from the blood and to restore normal constituents to it.

Characteristics of hemodialysis:

1- Using a special machine in the hospital
2- Inserted in the blood stream
3- Ones every few weeks to few months
4- Each Hemodialysis take a few hours

Disadvantages of hemodialysis:

1- Transmission of diseases due to poor sterilization of the dialysis machine
2- Infections
3- Thrombosis
4- Destruction of the vessels due to continuous use
5- Not available in every hospital

2) Peritoneal dialysis

(Or continuous ambulatory peritoneal dialysis (CAPD))

Peritoneal dialysis is the removal of soluble substances and water from the body by transfer across the peritoneum, utilizing a solution which is intermittently introduced into and removed from the peritoneal cavity.

Characteristic of peritoneal dialysis:

1- Catheter inserted into the peritoneal cavity surgically
2- The patient is ambulatory
3- Can be used any ware
4- Daily use

Disadvantage of peritoneal dialysis:

1- More prone to cause infections
2- 3 to 5 daily use dialysis

Transplantation

Organ transplantation is increasingly being used to treat irreversible diseases of the kidney, liver, heart, lung and bone marrow. Unfortunately, the action of the immune system can lead to the transplanted tissue being destroyed, a process termed transplant rejection. For the best chance of survival, antigens in the graft and recipient must be alike.

Types of transplantation:

1- **Allografts:** refers to transplantation of organs within the same species.

   Kidney transplants are always allografts.

2- **Xenografts:** refer to transplantation between different species.

The place of the transplanted kidney

The transplanted kidney will placed in acsseabul area (e.g. extraperitoneally in the iliac fossa) for biopsy and being easily palpated and we don't necessarily remove the old kidneys. The old kidney is not removed but if it caused any complications it should be removed. "The risks of having complications aren't high."

Note: The best way to avoid any problem in the transplantation is to have identical

A) **Immunology** For the best chance of survival with transplanted kidney the Immunologist has to do:
   1- **ABO grouping**
   2- **Lymphocytes HLA compatibility testing**: Incubating the T lymphocytes from both donor and recipient and see if there is any histocompatibility between them. To make sure that the HLA of the recipient not to recognize the lymphocytes of the donor as an antigen and react against it.

B) **Pathology** to help if there is a rejection problems

C) **Surgery** to do transplant

Transplantation complications:

1- **Harvest injury "at time of transplant"**: there can be tubular injury to the transplanted allograft kidney. It is generally due to **cold ischemia time** or the mode of donor death e.g."brain-dead". It can lead to primary non-functioning kidney in which the patient will have anuria after engraftment. These patients usually recover. **Cold ischemic time is the time where there's no blood flow to the donor's kidney, if that time was long → primary injured kidney before transplantation.**

2- **Thrombosis** of the surgical vascular anastomosis

Thrombus formation→ obstruction of the blood supply→ ischemia → hypoxia → necrosis → failure or rejection

3- Recurrent of initial disease in the transplanted kidney like membrano-proliferative glomerulonephritis.
4- Transplant rejection.
5- Acute and chronic immunosuppressive drug toxicity.
6- Infections of the renal allograft e.g. CMV and polyoma virus
7- De novo "new Disease" it's very rare

Transplant Rejection

There are four patterns of rejection seen after renal transplantation, and they are **hyperacute rejection**, **acute rejection**, **accelerated acute rejection** and **chronic rejection**

a) Hyperacute rejection

It only happen in .04% of all rejections and it occurs within minutes to a few hours after transplantation in a presensitized host and is typically recognized by the surgeon just after the vascular anastomosis is completed. Grossly, the kidney becomes cyanotic. Microscopically, there is widespread acute arteritis and arterioles, vessel thrombosis and ischemic necrosis.

It happens in a patient if the **immunologist** didn't study him well while having:

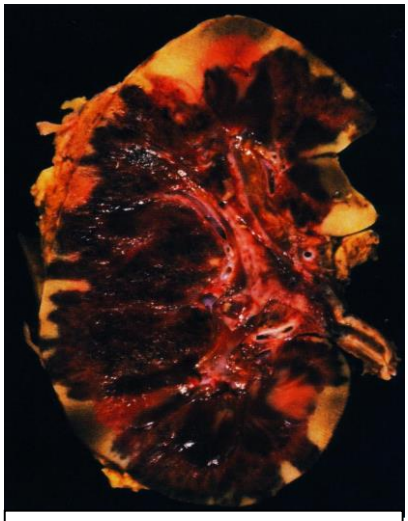
1- A preformed antibody which is in multiparous women because the embryo has different HLA than his mother so she produce antibody against it and the more she gets pregnant the more antibody being produce.

2- A lot of blood transfusion

3- ABO incompatibility

4- Subtotal renal infarction due to **hyperacute (antibody-mediated) rejection.**

Clinically: There will be no urine output



Subtotal hemorrhagic renal infarction due to hyperacute (antibody-mediated) rejection.

From "Robbins basic pathology"

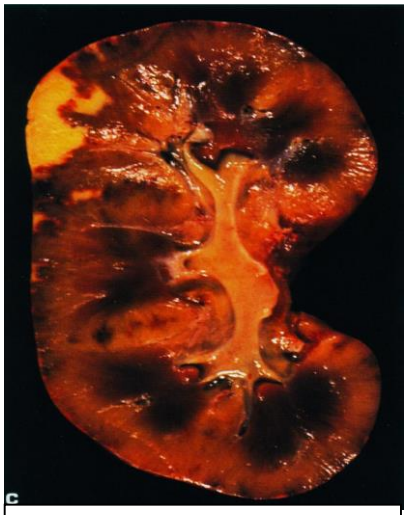
Hyperacute rejection occurs within minutes to a few hours after transplantation in a presensitized host and typically is recognized by the surgeon just after the vascular anastomosis is completed. In contrast with a nonrejecting kidney graft, which regains a normal pink color and tissue turgor and promptly excretes urine, a hyperacutely rejecting kidney rapidly becomes cyanotic, mottled, and flaccid and may excrete only a few drops of bloody fluid. The histologic picture is characterized by widespread acute arteritis and arteriolitis, vessel thrombosis, and ischemic necrosis, all resulting from the binding of preformed antibodies to graft endothelium. Virtually all arterioles and arteries exhibit characteristic acute fibrinoid necrosis of their walls, with narrowing or complete occlusion of the lumens by precipitated fibrin and cellular debris.

b) Accelerated acute rejection

Occurs in a patient who has had a previous unsuccessful graft and is therefore already sensitized to donor antigens it happen within hours.

c) Acute rejection:

Acute rejection may occur within days to weeks of transplantation and sometimes after months or years later. This rejection is divided into:



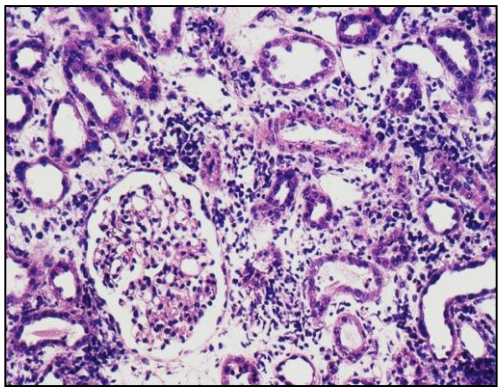
Severe acute rejection of donor kidney. Focal infarcts are present.

1- Acute Cellular rejection (direct):

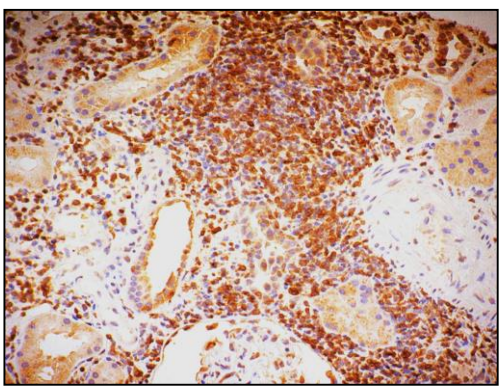
Pathophysiology:

- T lymphocytes antigen presenting cell (macrophages and dendrocytes) recognize the cell of the graft (kidney) as a foreign body → activate CD4 and CD8 → secrete lymphokynase (IL2, IF gamma) → attack the graft (blood vessels and tubular epithelium of the kidney) → graft fail → acute cellular rejection.

In this category interstitial infiltrate is more extensive involving greater than 25% of the biopsy with numerous foci of severe tubulitis with greater than 10 mononuclear T cell per tubular cross section **(more than 3 cellular rejection)**



Using immunohistochemistry stain special for T-lymphocytes, the interstitial infiltrate consists of a mixed population of T cells.



From "Robbins basic pathology"

Acute cellular rejection most commonly is seen within the first months after transplantation and typically is accompanied by clinical signs of renal failure. Histologic examination usually shows extensive interstitial CD4+ and CD8+ T cell infiltration with edema and mild interstitial hemorrhage. Glomerular and peritubular capillaries contain large numbers of mononuclear cells, which also may invade the tubules, leading to focal tubular necrosis. In addition to tubular injury, CD8+ T cells also may injure the endothelium, causing an endothelitis. Cyclosporine (a widely used immunosuppressive agent) is also nephrotoxic and induces so-called arteriolar hyaline deposits. Renal biopsy is used to distinguish rejection from drug toxicity. Accurate recognition of cellular rejection is important, because patients typically respond promptly to increased immunosuppressive therapy.

2- Acute humeral rejection (indirect):

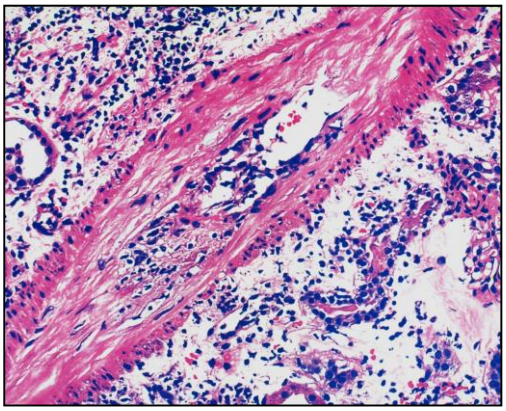
Pathophysiology:

- It caused by CD4 by 2 mechanism, either:
  1- The same mechanism of Acute Cellular rejection.
  2- After activation of CD4 → it stimulates B lymphocytes → plasma cells → immunoglobulin → bind to the antigen → immune complexes formation → they accumulate in the vessels of the kidney → inflammation and activation of C4D complement → vasculitis and rejection.

-The microvasculature "endothelium" of the kidney (i.e. glomeruli and peritubular capillaries) is the main target. → Glomerulitis and capillaritis. Acute tubular necrosis can happen in response to the injury to the blood supply.

Acute humeral rejection severity of Type II is determined by the number of vessels involved as well as the intensity of the individual lesions

We give more immunosuppressive drugs in this case; such as calcineurin inhibitors (Cyclosporins and tacrolimus) are the most common used. The doctor said it's important to know them; they might come in the MCQ's

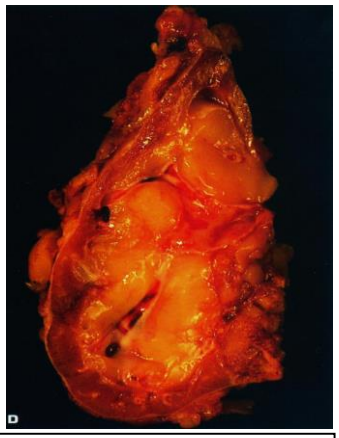


From "Robbins basic pathology"

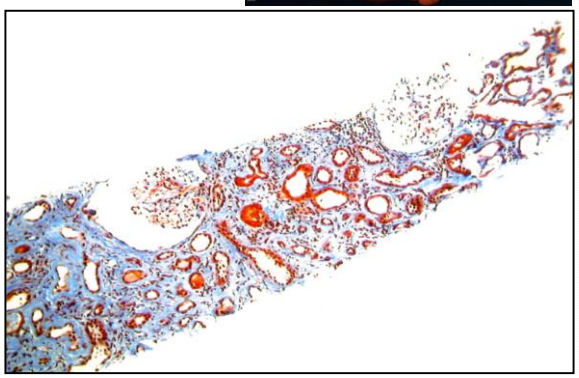
Acute humoral rejection (rejection vasculitis) caused by antidonor antibodies also may participate in acute graft rejection. The histologic lesions may take the form of necrotizing vasculitis with endothelial cell necrosis; neutrophilic infiltration; deposition of antibody, complement, and fibrin; and thrombosis. Such lesions may be associated with ischemic necrosis of the renal parenchyma. Somewhat older subacute lesions are characterized by marked thickening of the intima by proliferating fibroblasts, myocytes, and foamy macrophages. The resultant narrowing of the arterioles may cause infarction or renal cortical atrophy. The proliferative vascular lesions mimic arteriosclerotic thickening and are believed to be caused by cytokines that stimulate proliferation of vascular smooth muscle cells. Local deposition of complement breakdown products (specifically C4d) is used to detect antibody-mediated rejection of kidney allografts.

D) Chronic rejection: Chronicity = fibrosis

Patient usually presents late after transplantation (months to years) with a progressive rise in serum creatinine levels. Chronic rejection is dominated by vascular changes (subintmal fibrosis), interstitial fibrosis and loss of renal parenchyma. Chronic rejection does not respond to standard immunosuppression treatment. Acute and chronic rejection happened due to: reducing the dose of immunosuppression drugs.



Severe chronic rejection. (graft arteriopathy). Note the severe parenchymal atrophy and the thick-walled arteries



Chronic / sclerosing allograft nephropathy. An example of Grade II-III is characterized by a **diffuse increase in interstitial tissue** and marked tubular atrophy as seen on this **trichrome stain**.

How the doctor knows? The patient will have fever "sometimes" or will develop renal failure symptoms.

Tram track appearance is seen in: Membranoproliferative GN and chronic rejection

From "Robbins basic pathology"

Chronic Rejection Patients present with chronic rejection late after transplantation (months to years) with a progressive rise in serum creatinine levels (an index of renal function) over a period of 4 to 6 months. Chronic rejection is dominated by vascular changes, interstitial fibrosis, and loss of renal parenchyma; there are typically only mild or no ongoing cellular parenchymal infiltrates. The vascular changes occur predominantly in the arteries and arterioles, which exhibit intimal smooth muscle cell proliferation and extracellular matrix synthesis. These lesions ultimately compromise vascular perfusion and result in renal ischemia manifested by loss or hyalinization of glomeruli, interstitial fibrosis, and tubular atrophy. The vascular lesion may be caused by cytokines released by activated T cells that act on the cells of the vascular wall, and it may be the end stage of the proliferative arteritis described earlier.

Follow up:

- We follow up the patient with biopsies and urinalysis.

Rejection findings:

If we found:

1- More than 3 T cell in the tubular epithelium, that mean → Acute Cellular rejection
2- C4D complements by IF (immunofluorescence) → Acute humeral rejection
3- Subintmal (of the vessels) or interstitial fibrosis → chronic rejection

In all rejection types, there is an increase in creatinine and urea levels in the urine.

Treatment:

- Most Important drug we use after kidney transplant is cyclosporine.
- MOA: Inhibition of the T lymphocyte gene that secret interleukin 2 (IL2)
- ADRs:
    1. Interstitial nephritis.
    2. Opportunistic infection: which is an infection of an organism that not usually causes an infection in people with normal immune system.
    3. Feature similar to the rejection in the biopsy.

Summary (from Robbins)

Recognition and Rejection of Organ Transplants (Allografts)

- The graft rejection response is initiated mainly by host T cells that recognize the foreign HLA antigens of the graft, either directly (on APCs in the graft) or indirectly (after uptake and presentation by host APCs).
- Types and mechanisms of rejection comprise the following:
  - *Hyperacute rejection*: Pre-formed antidonor antibodies bind to graft endothelium immediately after transplantation, leading to thrombosis, ischemic damage, and rapid graft failure.
  - *Acute cellular rejection*: T cells destroy graft parenchyma (and vessels) by cytotoxicity and inflammatory reactions.
  - *Acute humoral rejection*: Antibodies damage graft vasculature.
- *Chronic rejection*: Dominated by arteriosclerosis, this type is probably caused by T cell reaction and secretion of cytokines that induce proliferation of vascular smooth muscle cells, associated with parenchymal fibrosis.

Questions from Pathology Recall book

1/ What clinical indicator is used to follow possible rejection?

- Plasma creatinine.

2/ What type of rejection occurs most often?

- Acute cellular rejection.

3/ What is the time course and mechanism of hyperacute rejection?

- Usually occurs in first 72 hours due to preformed antibody.

4/ What are the histopathological findings of acute cellular rejection?

- Interstitial and peritubular infiltrate of neutrophils, monocytes, and lymphocytes.

5/ What is the overall histopathological theme of chronic rejection?

- Fibrosis of various areas

6/ What are the vascular microscopic findings of chronic rejection?

- Medial thickening and intimal fibrosis.

اللهم إني استودعتك ما قرأت و ما حفظت و ما تعلمت فرده عليَ عند حاجتي اليه انك على كل شيء قدير

432 Pathology Team

Good Luck ^_^