
NATIONAL INISTITUTE OF UROLOGY & NEPHROLOGY
المعهد القومي للكلى
والمسالك البولية

Post Kidney Transplantation Fungal Infection

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Annual International Conference of
National Institute of Urology & Nephrology
February 2022
المؤتمر السنوي
للمعهد القومى للكلى والمسالك البولية
فبراير 2022
SILVER JUBILEE & 1K KIDENY TRANSPLANTS CELEBRATING
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Disclosure

I have no conflicts of interest to disclose

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3 Prevention Strategies

4 Diagnosis

5 Treatment

6 Common fungal infections post KTx.

Our Agenda

Introduction

- Infections are a major cause of morbidity & mortality in KTX. recipients ranking 2nd as the cause of death in patients with functioning allograft.

Modern immunosuppressives → better outcomes and patient's survival → increased opportunistic infections.

- After transplant, the extent of the immune response is influenced by the amount of (IL-2) being produced by the T-helper cells.
- Immunosuppressive therapy primarily targets T cell-mediated graft rejection.
- Calcineurin inhibitor impairs calcineurin-induced up-regulation of IL-2 expression, resulting in increased susceptibility to invasive fungal diseases.
- The overall mortality due to invasive fungal infections (IFIs) in SOTR 25% - 80%.

- Most fungal infections occur in the first 6 months after transplant.
- *Candida* spp. and *Cryptococcus* spp. are the yeasts most frequently isolated, while most frequent filamentous fungi (molds) isolated are *Aspergillus* spp.
- The symptoms of systemic fungal infections are non-specific and early detection of fungal infections and proper therapy are important in improving survival and reducing mortality.
- According to the Transplant-Associated Infection Surveillance Network, the most common IFIs is candidiasis (53%), aspergillosis (IA) (19%), cryptococcosis (8%), non-Aspergillus molds (8%), endemic fungi (5%), and zygomycosis (2%)

Pappas PG, et al 2010

Evaluation for infection before Kidney transplantation

❖History:

- ❑ **Travel** to or residence in areas with unique endemic infections.
- ❑ **Animal exposures** including cats, dogs, rodents, or birds.
- ❑ Potential or known **exposure** to patients with **fungal infection.**
- ❑ Risk factors for **HIV** infection.
- ❑ **Surgical history** (eg, **sinus** surgery).
- ❑ **Dietary exposures** including well water & contaminated food.
- ❑ **Jobs & hobbies** e.g. exposures to **soil, birds**, & **toxins (endemic fungi).**
- ❑ **Drug** abuse.
- ❑Bad **personal hygiene.**

Prophylaxis of infections in solid organ transplantation

- **Universal prophylaxis:** TMP-SMX for the prevention of *PCP.*
- **Pre-emptive therapy:** Using sensitive assays (eg, antigen detection or molecular assays).
- **Hybrid approach:** Some period of prophylaxis & subsequent monitoring.
- **Perioperative prophylaxis:** With azole or echinocandin must be considered.
- **Treatment of active or recurrent infections.**
- **Peri-transplantation prophylaxis:** Using antifungal agents.
- **Post-transplantation prophylaxis:** Nosocomial infections, prolonged hospitalizations or mechanical ventilation particularly high risk.

Risk of infection following kidney transplant

1-Epidemiologic exposures.

2-Community-acquired pathogens.

3-Reactivation of infections.

4-Nosocomial infections.

5-Donor-derived infections.

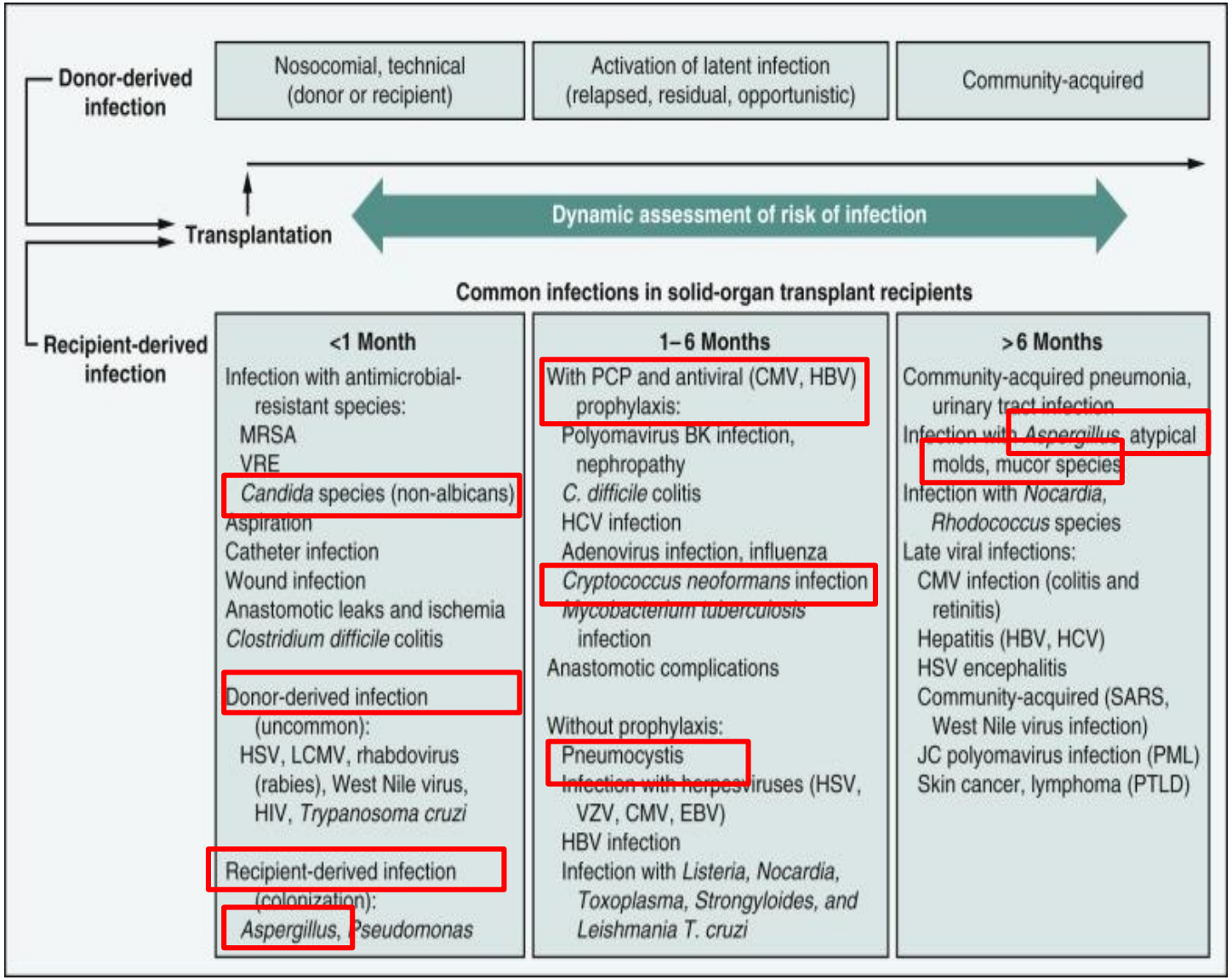
6-Bloodstream infection.

7-Unexpected infections accelerated by immunosuppression.

Net state of immunosuppression

It is a conceptual assessment of factors contributing to the risk for infection in an individual.

- Type, dose, duration, and temporal sequence of immunosuppressants.
- Underlying diseases or comorbid conditions.
- Presence of devitalized tissues or fluid collections.
- Invasive devices such as vascular access or urinary catheters, surgical drains.
- Other host factors affecting immune function: neutropenia, hypogammaglobulinemia, and metabolic problems.
- Concomitant infection with immunomodulating viruses.



Timeline of common infections in transplant recipients. CMV, cytomegalovirus; EBV, Epstein-Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HSV, herpes simplex virus; LCMV, lymphocytic choriomeningitis; MRSA, methicillin-resistant *Staphylococcus aureus*; PCP, *Pneumocystis jiroveci* pneumonia; PML, progressive multifocal leukoencephalopathy; PTLD, post-transplant lymphoproliferative disorder; VRE, vancomycin-resistant enterococci; VZV, varicella-zoster virus. Reprinted from reference 3, with permission.

Fungal infections in transplantation

Organ transplanted	Estimated incidence (percent)	Mortality *Aspergillus* (percent)	Mortality *Candida* (percent)
Kidney	0 to 20	20 to 100	23 to 71
Liver	5 to 40	50 to 100	6 to 77
Heart	5 to 20	78	27
Lung	10 to 36	21 to 100	27
Pancreas/pancreas-kidney	6 to 38	100	20 to 27
Small bowel	33 to 59	0 to 100	0 to 5

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Diagnosis

- **Clinical Evaluation:** Fever, cough, or oral thrush in.
- **Laboratory:** Cultures from blood, urine, or sputum; special stains; and molecular assays.
- **Imaging Studies:** Chest X-rays or CT scans for lung involvement.
- **Biopsy:** Sometimes necessary if other less invasive tests are inconclusive.

- The European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) defines **invasive fungal infection** when **histological analysis or culture of a specimen of tissue taken from a site of disease can reveal fungus.**

- In case of ***Cryptococcus neoformans***, a positive result of an **India ink** preparation of **CSF** or detection of capsular antigen in CSF is sufficient.

De Pauw B, e al 2008

- About 30% of the IFI cases at death remain undiagnosed or untreated**.**

- An elevated creatinine level in RTR indicates a state of chronic rejection and/or opportunistic infection.

Maertens J, et al 2001

Laboratory testing

- **Cultures** (blood, CSF, peritoneal fluid)
- **Quantitative** tests (such as **sandwich** ELISA or molecular assays).
- The **galactomannan** assay detect aspergillosis before symptoms appear, but sensitivity and specificity in SOTR are lower than in hematological patients.
- Testing **biweekly** for increasing galactomannan antigen levels can monitor therapeutic response.
- **Invasive** procedures that provide tissues for culture and histologic testing should be performed early.
- **Potassium hydroxide** wet mount smear is the most sensitive screening test for the rapid detection.
- Tissues from patients with a suspected IFI should be stained with a fungal stain as acridine orange, periodic acid-Schiff reaction, Grocott-Gomori methenamine silver staining, lectins….etc.

Badiee P, et al 2011

Treatment

Drugs Frequently Used to Treat Renal Mycoses

Fluconazole

- Fluconazole is a triazole antifungal drug used in the treatment and prevention of superficial and systemic fungal infections.
- It is available in both oral and I.V. formulations.
- It is the most common antifungal prophylactic agent.
- Empirical treatment with fluconazole in neutropenic patients with suspected fungal infection is inappropriate as prior exposure (treatment or prophylaxis) is associated with resistant candida strains.
- In addition, fluconazole has limited activity against IA.

Pappas PG, et al 2004

Voriconazole

- It is a triazole with broad antifungal spectrum, good against all Candida species, including resistant strains.
- It should not replace fluconazole or other antifungal agents due tonmore side effects and drug interactions.
- It has also shown activity against Aspergillus, including amphotericin B-resistant Aspergillus strains.
- Reversible **“disturbance of vision”** occurs in **30%** of patients.
- **Co-administration** with **cyclosporine** increase plasma concentration of cyclosporine by **1.7 folds.**
- Blood cyclosporine concentrations should also be monitored and increased if voriconazole is discontinued.
- Of interest, patients are advised to avoid fatty meals as they decrease the bioavailability of voriconazole.

Johnson LB, et al 2003

Amphotericin B

- **Amphotericin B deoxycholate (AmB-D)** is a polyene with a very broad spectrum of activity, including most yeasts and filamentous fungi.

- **Liposomal amphotericin B (L-AmB) :**

  - It is a lipid-associated formulation of the broad-spectrum amphotericin B.
  - Indicated for treatment of severe systemic mycoses if nephrotoxicity limits the use of amphotericin B.
  - It is active against *Candida* spp., *Aspergillus* spp. and filamentous molds such as zygomycetes.

Leenders AC, et al 1998

Azole

- All azoles interrupt the cell membrane ergosterol synthesis by inhibition of cytochrome P450.

- Rising liver enzymes occur with azole therapy hence, liver function testing prior to therapy, within the first 2 weeks of therapy and then every 2 - 4 weeks throughout therapy should be performed.

Johnson LB, et al 2003

Itraconazole

- It has a wider spectrum than fluconazole being active against both yeasts and molds.

- Itraconazole has fewer adverse events (5% versus 54%), and less withdrawal because of adverse events (19% versus 38%) and nephrotoxicity (5% versus 24%) compared with AmB-D.

Boogaerts M, et al 2001

Posaconazole

- It is the newest triazole approved by FDA as prophylaxis for invasive Aspergillus and Candida infections in patients aged ≥ 13 years.
- It is only found in oral formulation and predominantly eliminated in the feces, so dose adjustment is not required in renal and hepatic insufficiency.
- It inhibits hepatic cytochrome P 450-3A4; therefore dose adjustments must be made to immunosuppressive drugs.
- It is more effective in prevention of IA, when compared to other azoles ($P < 0.001$).

Boogaerts M, et al 2001

Candins

- They are a new class that disrupts the biosynthesis glycan polymers in fungal cell wall.
- Specificity for glycan linkage makes it less toxic with a high therapeutic index.

Micafungin

It is as effective as fluconazole and poses as an alternative for antifungal prophylaxis.

Caspofungin

- It is licensed for the treatment of IA in refractory to or intolerant of AmB-D, L-AmB and/or itraconazole.
- Also for empirical therapy for presumed fungal infections in febrile neutropenic adults.

Van Burik JA, et al 2004

Anidulafungin

- It is not metabolized by or eliminated through the liver or kidney.
- It is free of interactions with other drugs such as prednisone, CyA, TAC, MMF or sirolimus.
- Dosage adjustments are not required in renal impaired patients and in patients with severe liver disease.

Nystatin

- It is a polyene that is active against molds and yeast infections, most notably Candida.
- It is inferior to fluconazole in preventing invasive fungal infection.
- It cannot be recommended for prophylaxis or treatment of IFI.

Gotzsche PC, et al 2002

Flucytosine

- It is used in the treatment of systemic fungal infections mainly Candida and Cryptococcus.
- It shows rapid emergence of resistance when used alone; so it is given in combination with other antifungals.
- Side effects include nausea, diarrhea, hepatotoxicity and bone marrow suppression all are reversible.

Human Interferon (IFN)-γ Therapy

- T cell-based immune responses are important for protective immunity against IFI in transplant patients.

Granulocyte-Colony Stimulating Factor (G-CSF)

The use of G-CSF and granulocyte monocyte-colony stimulating factor (GM-CSF) can shorten the period of neutropenia, and improve the overall immune status of the patient.

Management of Common post transplantation fungal Infections

Candidiasis

Types of Candidiasis Post-Transplant:

- **Oropharyngeal and Esophageal** Candidiasis.
- **Urinary Tract** Candidiasis: Candida can colonize the urinary tract due to prolonged catheterization.
- **Invasive** Candidiasis: Severe form can affect the bloodstream (candidemia), CVS, or other vital organs.

Diagnosis

- **Clinical Examination:** Oral white patches, sore throat, or difficulty swallowing.
- **Laboratory Testing:** Cultures from relevant samples.
- **Serological Tests:** May be needed if invasive candidiasis is suspected.
- **Endoscopy:** In cases of suspected esophageal involvement.

Treatment

- **Oropharyngeal/Esophageal** Candidiasis: Topical antifungals like nystatin or oral fluconazole.
- **Urinary Tract** Infections: Fluconazole, with attention to any Foley catheter issues.
- **Invasive** Candidiasis: Aggressive treatment, starting with echinocandins (e.g., caspofungin) or amphotericin B, followed by azoles such as fluconazole once the patient stabilizes.

Pneumocystis jirovecii (formerly carinii) pneumonia (PCP)

Life-threatening infection that occurs in immunocompromised individuals.

- Colonized individuals may be at risk of developing pneumonia or transmitting infection.
- Colonized individuals receiving *PCP* prophylaxis are at risk for developing drug resistance mutations.
- Ongoing colonization may trigger inflammation and local alveolar damage leading to lung diseases, such as chronic obstructive pulmonary disease.

❑ **Clinical manifestations:** Most commonly gradual in onset & characterized by fever (80 to 100%), cough (95%) & dyspnea (95%) progressing over days. Patient has pulmonary symptoms for 3 weeks before presentation.

❑ **Oxygenation**: Progressive Hypoxia, alveolar-arterial oxygen gradient is widened, ranging from mild (alveolar-arterial O_2 difference <35 mmHg) to severe (O_2 difference >45 mmHg).

- **Identifying the organism**: Since *Pneumocystis* cannot be cultured, the diagnosis relies upon the visualization of the cystic or trophic forms in appropriate specimens.

- **Stains** used selectively stain the cell wall of the cystic form, and include Gomori silver, cresyl violet, Gram-Weigert & toluidine blue.

- **Polymerase chain reaction (PCR)** of respiratory fluid, in particular **(BAL).**

- **Sputum induction**: The least invasive method of definitively diagnosing PCP by analysis of sputum induced via the inhalation of hypertonic .

- **Bronchoalveolar lavage.**

- **Tissue biopsy**

TREATMENT :

Drugs used in the treatment of *Pneumocystis* pneumonia (PCP) in adults and adolescents

Drug	Dose	Major adverse reactions
Preferred regimen		
TMP-SMX	TMP-SMX (15 to 20 mg/kg/day of the trimethoprim component) orally or IV given in three or four divided doses*¶	Rash (rarely SJS/TEN), fever, neutropenia, hyperkalemia, transaminase elevations, photosensitivity, increased serum creatinine
Alternative regimens		
TMP **plus** dapsone$^{\Delta}$	TMP: 5 mg/kg orally three times daily¶	Trimethoprim: Rash, gastrointestinal distress, transaminase elevation, neutropenia, hyperkalemia
	Dapsone: 100 mg orally once per day	Dapsone: Rash, fever, lymphadenopathy, transaminase elevations (sulfone hypersensitivity syndrome), gastrointestinal upset, methemoglobinemia, hemolytic anemia
Primaquine$^{\Delta}$ **plus** clindamycin*	Primaquine: 30 mg (base) orally once per day	Primaquine: Rash, fever, gastrointestinal distress, methemoglobinemia, hemolytic anemia, leukopenia, neutropenia
	Clindamycin: 900 mg IV every eight hours **OR** 600 mg IV every six hours **OR** 600 mg orally three times daily **OR** 450 mg orally four times daily	Clindamycin: Rash, diarrhea, *Clostridioides* (formerly *Clostridium) difficile* colitis, abdominal pain
Atovaquone suspension	750 mg orally twice daily (must be taken with food)	Gastrointestinal distress, fever, transaminase elevation, rash (less frequently than with other regimens)
Pentamidine$^{\diamond}$	4 mg/kg IV once daily¶	Nephrotoxicity, infusion reactions, hyperkalemia, hyperglycemia, pancreatitis, cardiac arrhythmias (including TdP), transaminase elevations, hypotension, hypoglycemia, hypokalemia, hypocalcemia Certain adverse effects can be life threatening (eg, hypoglycemia and hypotension)§
Adjunctive glucocorticoids§		
Prednisone	40 mg orally twice daily for five days, followed by 40 mg orally once daily for five days, followed by 20 mg orally once daily for 11 days	

Aspergillosis

Presentations

- Vague clinical symptoms of infection and early laboratory reveals are normal.
- High index of suspicion is necessary in renal transplant recipients.
- Unexplained fever despite broad-spectrum antibiotic treatment for more than 3 - 6 days, recurring febrile episodes or the presence of pulmonary infiltrates during antibiotic treatment.
- Early symptoms of invasive pulmonary aspergillosis include cough, fever and hemoptysis.
- Preventive measures using sensitive assays at given interval to stop progression to invasive disease.
- A positive assay will require initiation of therapy and reduction in the anti-suppression medication, with frequent monitoring of the patient.

Gavalda J, et al 2005

Risk Factors in Renal Transplant Recipients

- **Hospital constructions** or at adjacent sites predispose the hospital ventilation systems to become concentrated with Aspergillus spores.

- The use of **vascular amines for > 24 h after surgery**, (ICU) readmission, AKI, need for hemodialysis, and occurrence of > 1 episode of bacterial infection after transplantation were the major risk factors for early-onset IA.

- Late-onset IA was contributed to **age > 50** years, chronic impaired graft function, use of immunosuppressive drugs and occurrence of an immunosuppression-related neoplasm.

- Other risk factors are diabetes and prolonged dialysis promote serious fungal infections.

Gavalda J, et al 2005

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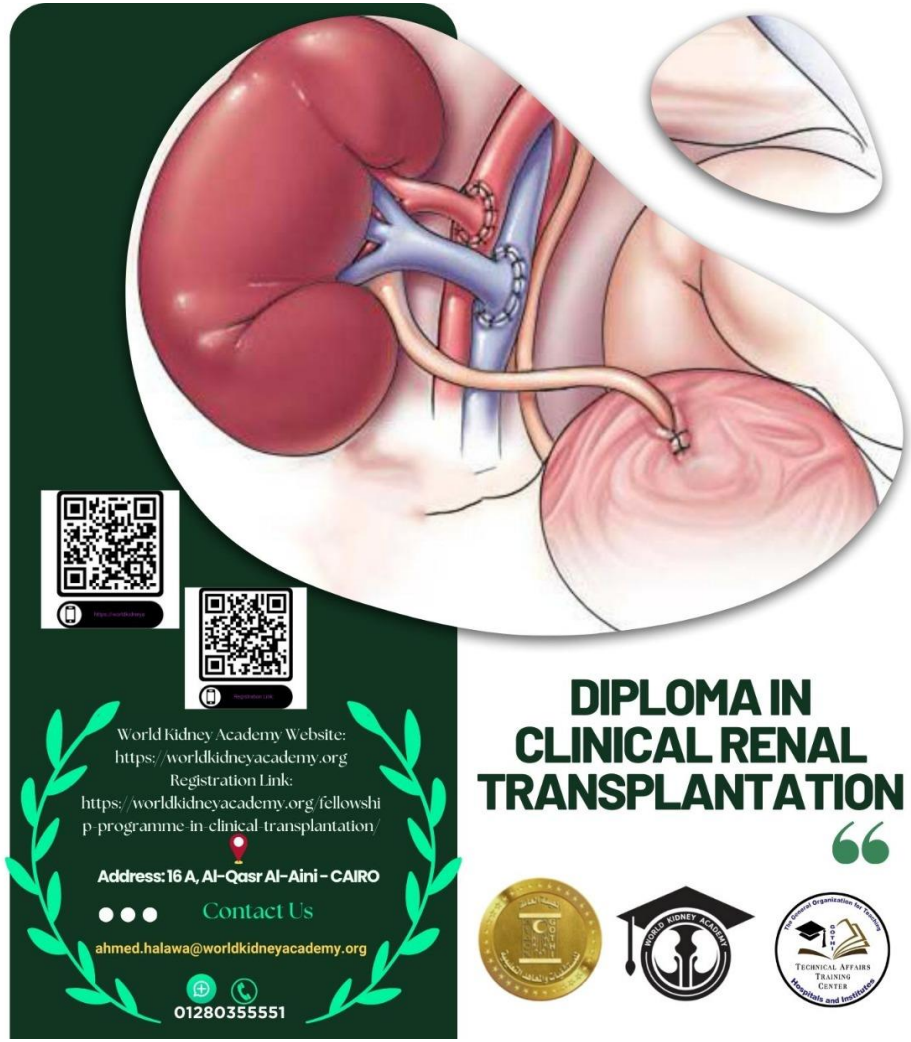

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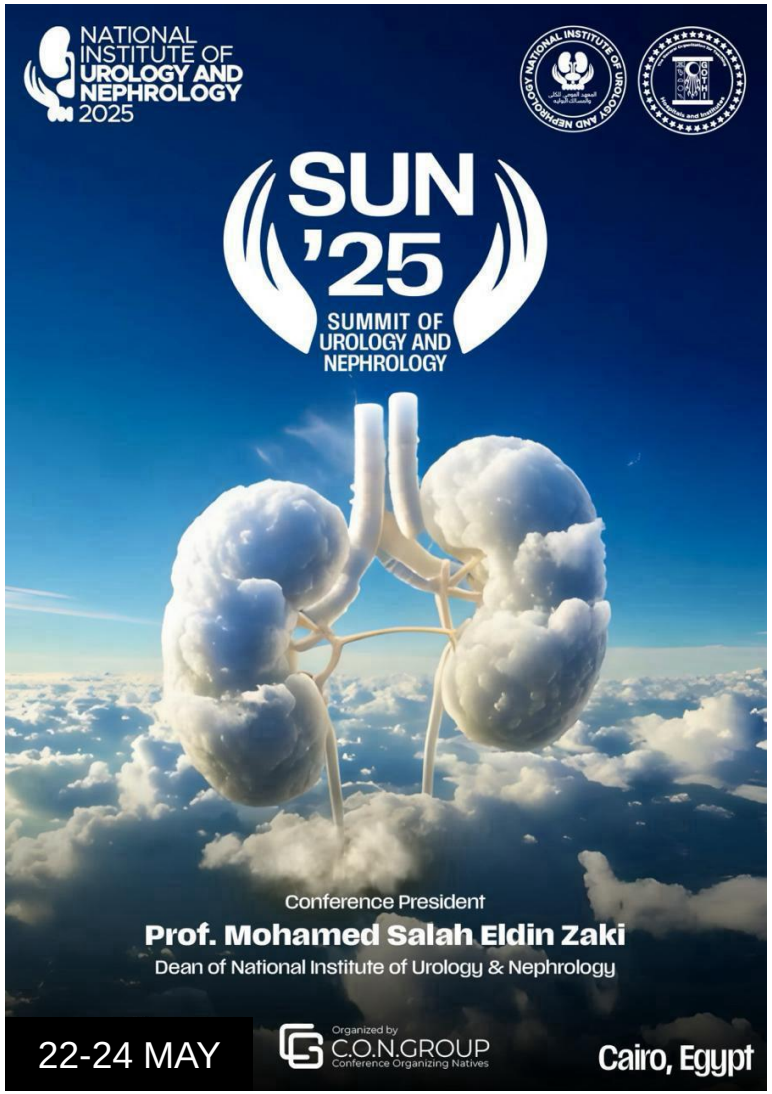

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