## Distance Learning and CME

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Associate Director, Division of Infectious Disease,
Brigham and Women's Hospital.

Director, Center for Experimental Pharmacology & Therapeutics,

Harvard University-Massachusetts Institute of Technology, Division of Health Sciences & Technology "Knowing is not enough, we must apply; willing is not enough, we must do."

- Goethe

# Medical Education: a lifelong obligation and privilege

- The pace of medical advances and basic science discoveries has never been greater.
- Traditional education initiatives are threatened
  - Cost
  - Conflict of interest concerns
  - Accountability
- The appearance of new diseases from AIDS to SARS and the difficulty in treating age-old pathogens like influenza and cholera remind us that we must think globally.

## Wish List for Innovative Medical Education Efforts

- Broadly available ("a worldwide network")
- Can be accessed with available technology
- Can be utilized for a variety of purposes
  - "Primary learning" for students, trainees, (alternative or supplement to traditional lectures, journals, textbooks)
  - Continuing education for practitioners
  - Creation of networks of clinicians, researchers, and scholars that will share problems, ideas, and insights
  - Task forces for particular goals
    - Ethics
    - IRB and DSMB approaches
  - Rapid response needs

### Requirements for Innovative Learning

- Interactive
- Self assessment
- Certification
- Deficits → special education
- Creation of <u>communities of scholars</u>, linked by distance learning approaches, and not limited by geographic barriers

### Our Experience

- History of GCP project (cooperative effort Silva, Rodriguez, and Rubin)
  - CITP program (produce clinical scientists)
  - CME efforts in Latin America
  - Distance learning experience
    - English, Spanish, Mandarin
- Approach to clinical problems
  - State of the art lectures
  - Annotated bibliography
  - Case studies (interactive)
  - E-conference room



This web course is made possible through an unrestricted educational grant from Roche Laboratories.















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August 19, 2004

Welcome to this free Internet course on the diagnosis and treatment of Transplant Infectious Diseases.

Explore this online course module to discover the latest findings in the field:

- · View video lectures given by world-renowned experts
- Work through interactive case studies to test your knowledge and patient management skills
- Browse our extensive Reference Library
- Receive consultation from field experts and exchange ideas in our eConference Room
- Earn CME credit

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To begin, please register or go to the About page to learn more about the site.











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### Member Home - Interactive Study Guide

#### Welcome Melinda

The Study Guide will automatically track your progress through the case studies and lectures. Completion of all case studies is required for e-conference room membership. Lectures are not required for membership, but are highly recommended.

Take our Guided Tour: to see all that this course contains.



Key:	Not yet started	▼ In-progress	✓ Completed	
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Required Case Studies:		
Prog.	Course Material	
	Antimicrobial Prophylaxis in a Heart Transplant Recipient	
	51 year-old man status post stem-cell transplantation for aggressive lymphoma presenting with headache and fever	
	Adenopathy in a Haitian man 15 months after cardiac transplantation	
	Bone marrow transplant patient with febrile neutropenia	
	Fever and Deteriorating Liver Function Tests 34 Days After Orthotopic Liver Transplant	
	A 57-year-old female schoolteacher with end-stage liver disease due to sclerosing cholangitis and hepatitis C.	

Recommended Video Lectures:		
Prog.	Course Material	
	Overview of Organ Transplantation	
	Infectious Complications of Hematopoietic Stem Cell Transplantation	
	Pathogenesis and Impact of Herpes Group Viruses in Transplant Patients	
	Direct and Indirect Effects of Infection in the Transplant Recipient	
	Viral Diagnostics: The Measurement and Management of Viral Infection in the Immunocompromised Host	
	Herpes Virus and Transplantation	
	Hepatitis in the Transplant Recipient	
	Non-Hernes Viruses of Importance in Transplantation	



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August 19, 2004

### **IDT Lecture Index**

Our distinguished faculty review the essential principles of transplant infectious disease, concentrating on the latest approaches to diagnosis and treatment. Each lecture is closed captioned and divided into segments for convenient viewing and greater accessibility to specific topics of interest.

**Software Requirements:** In order to view our lectures, you must have Flash version 6 or higher installed. Please install Flash by clicking on the install button or click help for more options.

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HELP ?

Progress	Lecture	Speaker
	Overview of Organ Transplantation  This lecture offers an overview of organ transplantation and the infectious disease challenges facing the transplant recipient. Discussed in detail are patterns of illness (timetable of infection), the relation between the net state of immunosuppression and epidemiologic exposures in the causation of infection, and the most effective methods for preventing and treating infection. The concept of the therapeutic prescription (immunosuppressive and antimicrobial therapy) is emphasized.  Date Recorded: 22 January, 2004	Robert H. Rubin, MD, FACP
	Infectious Complications of Hematopoietic Stem Cell Transplantation  This lecture covers the overarching principles behind the infectious complications	

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Covering the major challenges faced in transplantation today, each case guides you through a real patient scenario, allowing you the opportunity to make decisions at critical junctures. To aid in your decisions, new information will be presented as you work through the case.

Progress	Case Study	Estimated Time to Complete
	Antimicrobial Prophylaxis in a Heart Transplant Recipient:	10-15 Minutes
	51 year-old man status post stem-cell transplantation for aggressive lymphoma presenting with headache and fever:	10-15 Minutes
	Adenopathy in a Haitian man 15 months after cardiac transplantation:	10-15 Minutes
	Bone marrow transplant patient with febrile neutropenia:	5-10 Minutes
	Fever and Deteriorating Liver Function Tests 34 Days After Orthotopic Liver Transplant:	5-10 Minutes
	A 57-year-old female schoolteacher with end-stage liver disease due to sclerosing cholangitis and hepatitis C.:	Other
	Cytomegalovirus infection in a liver transplant recipient:	15-20 Minutes
	34 year-old man with fever following an allogeneic bone-marrow transplantation (BMT) for acute myeloid leukemia (AML):	Other
	Viral Infection in a Renal Transplant Patient:	30-35 Minutes
_	Aspergillus respiratory tract colonization in a patient who had undergone bilateral lung transplantation:	5-10 Minutes
	Recurrent Fever in a Liver Transplant Recipient : Author: Atul Humar, MD	15-20 Minutes
	Abdominal Pain in a Lung Transplant Patient:	20-25 Minutess
	Fever and Rigors in a Neutropenic Human Stem Cell Transplant Patient.:	25-30 Minutes
	Fever in a liver transplant candidate:	5-10 Minutes
	Fever and Rigors Five Days Following Cadaveric Renal Transplantation.:	5-10 Minutes
	Liver Dysfunction in a Liver Transplant Patient with hepatitis C virus (HCV) Infection.:	30-35 Minutes
	19 year old Woman with Fever and Malaise 111 Days Post-transplant:	15-20 Minutes







#### ▼ Patient Chart

download, to help you work this case.

This area will link you to relevant files, available for

Aspergillus respiratory tract colonization in a patient who had undergone bilateral lung transplantation

### PRESENTING CONDITION

A 32 y.o. woman with cystic fibrosis underwent bilateral lung transplantation. Pre-transplant sputum cultures yielded three separate strains of Pseudomonas aeruginosa, each one resistant to either aminoglycosides or anti-pseudomonal beta-lactams. Perioperatively, she received imipenem, a lipid amphotericin formulation, and intravenous ganciclovir. Her immunosuppression consisted of tacrolimus 6 mg twice daily, prednisone 15 mg/day and mycophenolate 2 grams per day. After an initially stormy course (re-implantation reperfusion injury with prolonged intubation), the patient by the 4th week post-transplant was doing well. Routine surveillance bronchoscopy and sputum culture yielded Aspergillus fumigatus. Chest X-ray and CT were without evidence of invasive fungal infection.

Question: What is the significance of the finding of Aspergillus fumigatus in the sputum of this patient?

#### Possible Answers:

a.	•	Aspergillus species are fre	equent contaminants of	sputum cultures, and	have no significance i	n this setting.
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- b. Aspergillus in the sputum is a marker for an abnormal bronchial tree, particularly for chronic bronchitis and bronchiectasis, but is of little significance in terms of invasive disease.
- c. A variety of clinical syndromes can be associated with the isolation of Aspergillus species in the sputum, each of which requires different management.
- d. The finding of Aspergillus species in the sputum of an immunosuppressed patient with evidence of acute or subacute pulmonary disease should be regarded as significant.
- e. Aspergillus colonization of the respiratory tract in transplant recipients is associated with an increased risk of invasive pulmonary disease.













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August 19, 2004

Aspergillus respiratory tract colonization in a patient who had undergone bilateral lung transplantation

O Go Back to the Beginning and Start Over

**▼** Patient Chart

Aspergillus species are frequent contaminants of sputum cultures, and have no significance in this setting.

Incorrect. Although this statement has been made in the microbiology literature, it applies only to certain groups of patients. Patients with chronic lung disease, particularly those individuals with bronchiectasis and/or cavity formation, may indeed have colonization with Aspergillus species without evidence of invasive infection clinically. However, in a patient with a clinically compatible syndrome and x-ray, who is immunosuppressed, the isolation of Aspergillus species on sputum culture should be taken very seriously, with the expectation that invasive disease requiring treatment is present.

TRY AGAIN









### Aspergillus respiratory tract colonization in a patient who had undergone bilateral lung transplantation





This area will link you to relevant files, available for download, to help you work this case.

### PRESENTING CONDITION

A 32 y.o. woman with cystic fibrosis underwent bilateral lung transplantation. Pre-transplant sputum cultures yielded three separate strains of Pseudomonas aeruginosa, each one resistant to either aminoglycosides or anti-pseudomonal beta-lactams. Perioperatively, she received imipenem, a lipid amphotericin formulation, and intravenous ganciclovir. Her immunosuppression consisted of tacrolimus 6 mg twice daily, prednisone 15 mg/day and mycophenolate 2 grams per day. After an initially stormy course (re-implantation reperfusion injury with prolonged intubation), the patient by the 4th week post-transplant was doing well. Routine surveillance bronchoscopy and sputum culture yielded Asperaillus fumigatus. Chest X-ray and CT were without evidence of invasive fungal infection.

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a.	0	Aspergillus species are frequent	contaminants of sputum cultures,	, and have no significance in this	setting.
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- Aspergillus in the sputum is a marker for an abnormal bronchial tree, particularly for chronic bronchitis and bronchiectasis. but is of little significance in terms of invasive disease.
- c. A variety of clinical syndromes can be associated with the isolation of Aspergillus species in the sputum, each of which requires different management.
- d. The finding of Aspergillus species in the sputum of an immunosuppressed patient with evidence of acute or subacute pulmonary disease should be regarded as significant.
- e. Aspergillus colonization of the respiratory tract in transplant recipients is associated with an increased risk of invasive pulmonary disease.











### Aspergillus respiratory tract colonization in a patient who had undergone bilateral lung

Patient Chart HELP This area will link you to relevant files, available for download, to help you work this case.

Go Back to the Beginning and Start Over

A variety of clinical syndromes can be associated with the isolation of Aspergillus species in the sputum, each of which requires different management.

Correct. The clinical effects of Aspergillus species can be divided into five different categories:

- Colonization syndromes: Aspergillus can colonize an abnormal bronchial tree and/or preexisting cavities- most commonly bronchiectasis and/or old tuberculosis. The usual effects of this are irritative- hemoptysis, increased sputum production, and cough.
- Allergic Syndromes: Aspergillus can induce asthma, and can be a cause of hypersensitivity pneumonitis or extrinsic alveolitis. In this case, it is the host's response to organic antigens.
- 3. Allergic Bronchopulmonary Aspergillosis: This syndrome can be considered as being a combination of a colonization and an allergic syndrome. These patients have a functional defect in the bronchial tree such that colonization is maintained. The consequence of this is cough productive of sputum containing brown bits of Aspergillus, with fleeting infiltrates on chest x-ray and eosinophilia. The end result of untreated disease is central bronchiectasis.
- 4. Invasive Aspergillosis: Invasive aspergillosis is an angiovasive infection with three cardinal manifestations: infarction, hemorrhage, and metastases. A. fumigatus and, to a lesser extent, A. flavus account for the great majority of such infections, with the lungs being the primary portal of entry. Other primary sites of invasion include the nasal sinuses, and damaged skin. Invasive aspergillosis occurs in patients with severe neutropenia and/or impaired cell mediated immunity.
- Semi invasive Aspergillosis: This is a slowly progressive, necrotizing infection seen in patients without clear cut immune
  deficits, but with such systemic conditions as diabetes, liver disease, systemic viral infection, etc. It is best treated with
  surgical excision.

In addition, there is the possibility of crossover syndromes. For example, 80% of patients with bronchopulmonary aspergillosis (#3 above) become symptom free and clear the *Aspergillus* on steroids; those that do not may develop invasive disease. Aspergillomas in a cavity may have some degree of local invasion, which can become clinically important if surgical manipulation is undertaken or if immunosuppression occurs. The advent of azole therapy for invasive aspergillosis, particularly voriconazole has permitted early and aggressive therapy (preemptive therapy) to prevent disseminated infection.

CONTINUE (











transplantation

### Aspergillus respiratory tract colonization in a patient who had undergone bilateral lung transplantation

Go Back to the Beginning and Start Over

▼ Patient Chart No Chart Data Yet



Main learning points for this case:

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▼ Related Links

Clinical Course: The patient was treated preemptively with voriconazole for 2 months, and cleared the Aspergillus colonization. The dose of tacrolimus was decreased to 1 mg twice daily (achieving the same therapeutic blood level as was observed on a 6 mg twice daily regimen), while on the voriconazole. On completion of the course of voriconazole, the dose of tacrolimus was returned to its previous level.

### Summary and Conclusions:

A patient with end stage pulmonary disease due to cystic fibrosis underwent bilateral lung transplantation. This patient developed colonization of the respiratory tract with Aspergillus fumigatus. Because of the risk of subsequent invasion, he was treated with preemptive voriconazole, which eliminated the fungus. In transplant patients such as this, the addition of voriconazole to the therapeutic regimen mandates a decrease in the dosage of tacrolimus or cyclosporine, because of the down regulation of the metabolism of these drugs by hepatic cytochrome P450 enzymes caused by the azoles. As in this case, the dose of the calcineurin inhibitors must be decreased with the initiation of voriconazole, and then increased when the voriconazole is discontinued.

Please return to your study guide to continue the course.

REFERENCES:









### Reference Library

### The IDT Reference Library is a:

- Repository of over 1000 relevant journal articles
- · Powerful search engine to find specific information within the site

Searching by keyword or browsing by medical topic, you will generate a page listing all site references and related articles by author, title, publication, and date.



### Or Browse by Medical Topic:

Click on the arrow to expand each topic category. Click on the actual topic name to go to search results for that topic.

### Filter Contents By:



- First Topic Index
  - 1 Basic Principles of Transplant Infectious Disease
  - 2 Clinical Management
  - 3 Antimicrobial Drugs of Special Importance
  - 4 Clinical Syndromes Produced by Invasive Microorganisms
  - ▶ 5 Microbial Etiology of Infectious Disease Syndromes
  - ▶ 6 Drug and Radiation-induced Adverse Events
  - 7 Parasites
  - 8 Transplant Type









### ▼ First Topic Index

### ▼ 1 Basic Principles of Transplant Infectious Disease

- Survival of a patient transplanted with a kidney infected with Cryptococcus neoformans.: Ooi BS, Chen BT, Lim CH, Khoo OT, Chan DT.
- \* Severe candidal infections: Clinical perspective, immune defense mechanisms, and current concepts of therapy.: Edwards JE Jr, Lehrer RI, Stiehm ER, et al.
- ▶ 1.1 Impact of Immunosuppressive Therapy
- 1.2 Risk of Infection
- ▶ 1.3 Principles of antimicrobial therapy

### 2 Clinical Management

- \* Salmonellosis: Microbiologic, Pathologic and Clinical Features. : Rubin R, Weinstein L.
- Infectious disease problems. : Rubin R.
- Radiation reaction in the lung: Report of a fatal case in a patient with carcinoma of the lung, with studies of pulmonary function before and during prednisone therapy. : Rodman T, Karr S, Close HP.
- \*Lymphosarcoma: A review of 1269 cases. : Rosenberg SA, Diamond HD, Jaslowitz B, et al.
- \*The Nisbet Symposium: Hodgkin's disease--Radiological aspects of the disease.: Martin JJ.
- Intra-thoracic Hodgkin's disease. Part II. Peripheral manifestations of Hodgkin's disease in the chest.:
  Strickland B.
- \* Lung function in patients receiving busulphan. : Littler WA, Ogilvie C.
- Pulmonary infiltrates associated with leukoagglutinin transfusion reactions.: Ward HN.
- Pulmonary
- \* Pulmonary disease in the immunocompromised host. : Rosenow EC III, Wilson WR, Cockerill FR III.
- \*Pneumonia in febrile neutropenic patients and in bone marrow and blood stem-cell transplant recipients: use of high resolution computed tomography.: Heussel CP, Kauczor HU, Heussel GE, et al.
- Predictors of mortality in the immunocompromised patient with pulmonary infiltrates. : Poe RH, Wahl GW, Qazi R, et al.
- \*Pulmonary infections in immunocompromised patients who do not have acquired immunodeficiency syndrome: a systematic approach.: Conces DJ Jr.
- Infectious disease complications of renal transplantation. : Rubin RH.
- Advances in preventing nosocomial pneumonia.: Faling LJ.
- \* Alterations of normal gastric flora in critical care patients receiving antacid and cimetidine therapy. : Donowitz LG, Page MC, Mileur GL, et al.
- \* Effect of cimetidine on gastric bacterial flora. : Ruddell WSJ, Axon ATR, Finlay JM, et al.
- \* Enteral nutrition in patients receiving mechanical ventilation: Multiple sources of tracheal colonization include the stomach.: Pingleton SK, Hinthorn DR, Liu C.
- Gastroduodenal dysfunction and bacterial colonization of the ventilated lung. : Inglis TJJ, Sherratt MJ, Sproat LJ, et al.
- 2.1 Temporal Sequence of Infection (Timetable)
- 2.2 Antimicrobial treatment design
- 2.3 Hierarchy of diagnostic interventions
- 2.4 Linkage of diagnostics and therapeutics
- 2.5 Proven empiric strategies



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August 23, 2004

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### Or Browse by Medical Topic:

Title:

Pulmonary infections in immunocompromised patients who do not have acquired immunodeficiency

syndrome: a systematic approach.

Author(s): Conces DJ Jr.

Publication: J Thoracic Imaging; 13:234-246.

Date: 1998-00-00

Link: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\_uids=9799132

### Referenced in IDT Course Module item(s):

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<b>Key</b> : ☐ Not yet started <b>X</b> In-progress <b>✓</b> Completed
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Progress	Lecture Segement	Transcript
	Segment 1 View Low Bandwidth   View High Bandwidth Length 5:09 Key Issues Historical overview; Infectious Disease challenges posed by organ transplantation	View
	Segment 2 View Low Bandwidth   View High Bandwidth Length 5:26 Key Issues Infectious Disease challenges posed by organ transplantation; patterns illness in immunocompromised patients	s of View
	Segment 3 View Low Bandwidth   View High Bandwidth Length 8:12 Key Issues Use of antimicrobial agents in transplantation; drug interaction between antimicrobials and calcineurin inhibitors (CI); case example of antimicro	
	Segment 4 View Low Bandwidth   View High Bandwidth Length 3:54 Key Issues Modes for prescribing antimicrobial agents in transplantation; forms of preemptive markers	View
	Segment 5 View Low Bandwidth   View High Bandwidth Length 9:37 Key Issues Timetable of infection following organ transplantation; utility of the times in clinical practice; preventative strategies linked to the timetable	table View
	Segment 6 View Low Bandwidth   View High Bandwidth Length 3:52 Key Issues Classification of infectious agents; factors that determine the risk of infe effects of antibiotics in the occurrence of infection in the presence of technical/anatomic abnormalities	ction; View
	Segment 7 View Low Bandwidth   View High Bandwidth Length 8:27 Key Issues Epidemiologic exposures of importance; infections acquired through th ingestion of contaminated food/water; nosocomial exposure to potential pathogens; effects of corticosteroids; immunosuppressive effects of corticosteroids	
	Segment 8 View Low Bandwidth   View High Bandwidth  Length 4:40  Key Issues Azathioprine: Cyclosporine A: Tacrolimus: rapamycin (Sirolimus): Pathi	wave View

### Lessons from Initial Experience

- Active vs passive learning
- Fungal infection
- Transplant Infectious Disease
- Statistics
- Study Design
- Clinical Pharmacology
- Case Studies in Biomedical Ethics

Available now though HSTelearning

In production

In planning phase

"Our heads are round so that our thinking can change direction."

- Francis Picabo

"Many people say that it is the intellect which makes a great scientist. They are wrong; it is character."

- Albert Einstein

"This is not the beginning of the end; it is the end of the beginning."

- Winston Churchill