

Bacterial Co-Infections: New Developments with Old Friends (C Diff, MRSA, and others)

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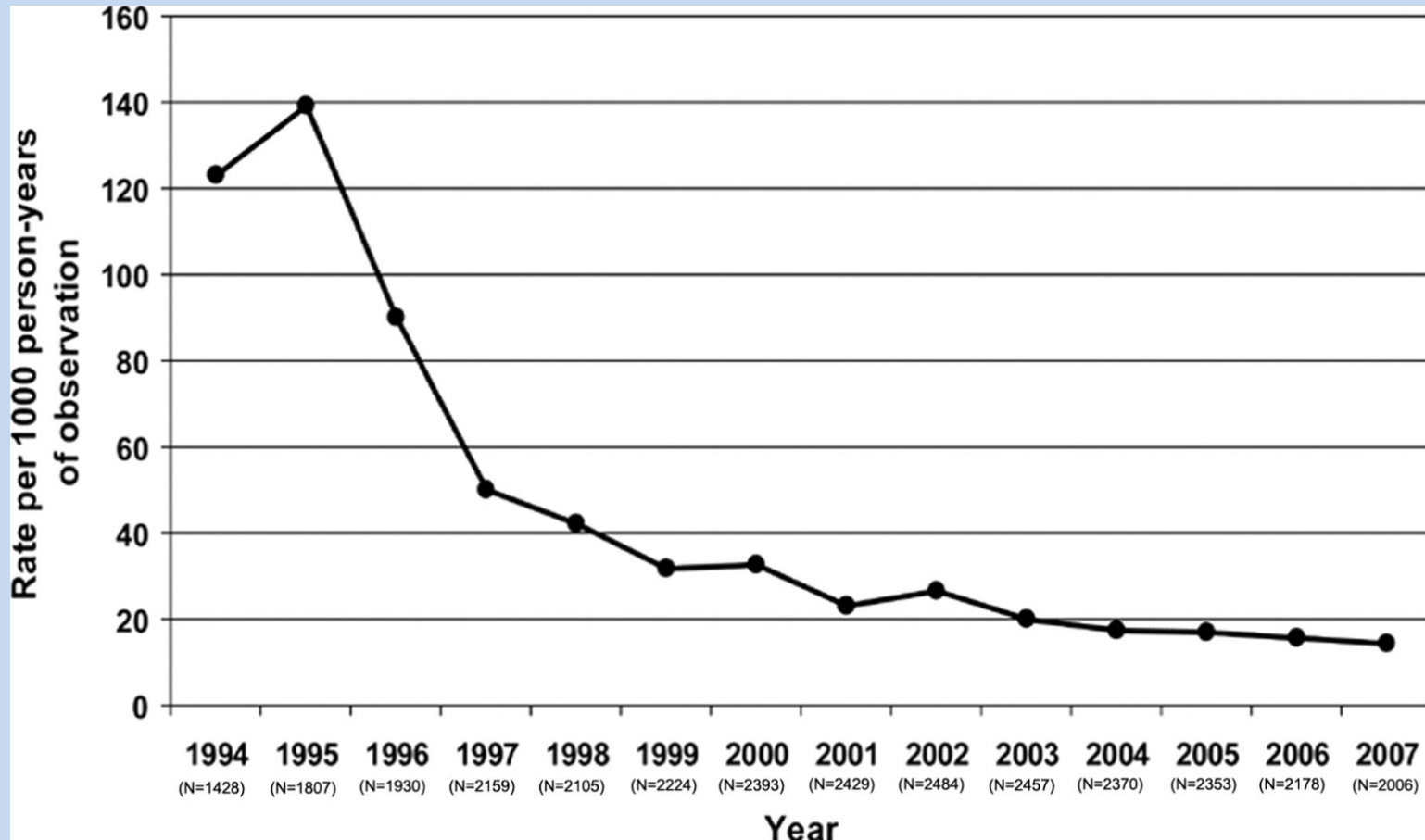
Learning Objectives

Upon completion of this presentation, learners should be better able to:

- Appraise the current trends of bacterial infections in HIV-infected individuals.
- Limit the impact of bacterial infections in HIV-infected individuals with a focus on MRSA and *Clostridium difficile*.
- Identify presentations for infection respiratory syndromes in HIV-infected individuals.



Incidences of first AIDS-defining opportunistic infection, according to year, among all patients in care, HIV Outpatient Study, 1994–2007



Hospitalization Rate by Primary Specific Cause During Study Period, 1999-2007

Cause of Hospitalization	All Periods	1999-2001	2002-2004	2005-2007	RR (95% CI) [†]	P
AIDS-defining condition						
Patients hospitalized	78	33	29	24	0.95 (0.71 to 1.27)	0.72
Total hospitalizations	133	47	49	37		
Rate	10.3 (8.7-12.2)	10.0 (8.3-11.5)	10.0 (8.3-11.3)	9.0 (7.5-10.4)		

Hospitalizations for MRSA increased > 300%.

Hospitalizations for skin and soft tissue infections increased by 50%.

Total hospitalizations	94	21	30	43		
Rate	7.3 (5.9-8.9)	4.9 (3.2-7.5)	6.6 (4.6-9.5)	10.5 (7.8-14.1)		
Pneumonia						
Patients hospitalized	84	37	32	26	0.91 (0.70 to 1.18)	0.47
Total hospitalizations	108	42	36	30		
Rate	8.3 (6.9-10.1)	9.8 (7.2-13.2)	8.0 (5.7-11.0)	7.3 (5.1-10.4)		
Liver disease [§]						
Patients hospitalized	21	4	14	7	1.71 (1.03 to 2.83)	0.04
Total hospitalizations	34	5	17	12		
Rate	2.6 (1.9-3.7)	1.2 (0.5-2.8)	3.8 (2.3-6.0)	2.9 (1.7-5.1)		
Chronic end-organ disease						
Patients hospitalized	107	41	47	33	1.02 (0.94 to 1.10)	0.62
Total hospitalizations	161	48	68	45		
Rate	12.4 (10.7-14.5)	11.1 (8.4-14.8)	15.0 (11.8-19.0)	10.9 (8.2-14.7)		
Surgery, primary reason						
Patients hospitalized	218	70	85	91	1.17 (1.01 to 1.35)	0.04
Total hospitalizations	283	75	107	101		
Rate	21.9 (19.5-24.6)	17.4 (13.9-21.8)	23.6 (19.6-28.6)	24.6 (20.2-29.2)		
Surgery, any [¶]						
Patients hospitalized	310	104	131	126	1.14 (1.01 to 1.29)	0.03
Total hospitalizations	424	115	162	147		
Rate	32.7 (29.8-36.0)	26.7 (22.2-32.1)	35.8 (30.7-41.7)	35.8 (30.4-42.0)		
Drug related [#]						
Patients hospitalized	34	16	10	12	0.89 (0.59 to 1.35)	0.59
Total hospitalizations	47	20	12	15		
Rate	3.6 (2.7-4.8)	4.6 (3.0-7.2)	2.7 (1.5-4.7)	3.6 (2.2-6.1)		
Suicide attempt						
Patients hospitalized	19	7	7	6	0.96 (0.56 to 1.64)	0.87
Total hospitalizations	20	7	7	6		
Rate	1.5 (1.0-2.4)	1.6 (0.8-3.4)	1.5 (0.7-3.2)	1.5 (0.7-3.2)		
Trauma/injury related						
Patients hospitalized	37	19	13	6	0.54 (0.35 to 0.83)	<0.01
Total hospitalizations	41	22	13	6		
Rate	3.2 (2.3-4.3)	5.1 (3.4-7.8)	2.9 (1.7-4.9)	1.5 (0.7-3.2)		

*Rates per 1000 person-years. Rates are unadjusted and based on clinically relevant diagnoses, which were not mutually exclusive from the organ and disease categories presented in Table 3.
[†]RR are estimated changes from one time interval to the next.
[‡]MRSA was based on positive culture confirmation.
[§]Liver disease defined as an admission due to cirrhosis, hepatitis B, C, or other any other form of hepatitis.
^{||}Chronic end-organ diseases included chronic obstructive lung disease, asthma, congestive heart failure, cardiomyopathy, arrhythmia, coronary artery disease, cerebrovascular disease, hypertension, pancreatitis, chronic liver disease, and chronic renal disease.
[¶]Surgery performed during hospitalization regardless if it was the primary reason for admission.
[#]Drug related defined as alcohol or illicit drug use or an overdose as the cause of admission.



Community-associated MRSA (CA-MRSA)

- CA-MRSA 1st reported in children
 - the prevalence of community-acquired MRSA without identified risk increased from 10/100000 admissions in 1988-1990 to 259/100000 admissions in 1993-1995 (P<.001),
- Most cases: cellulitis, abscesses or skin infections
- Susceptible to TMP-SMX, clindamycin

CDC Definition of Community-Acquired MRSA (CA-MRSA)

- Diagnosis made in the outpatient setting or by a culture growing MRSA within 48 hours of hospital admission
- No medical history of MRSA infection or colonization
- No medical history in the past year of:
 - Hospitalization
 - Admission to a nursing home, skilled nursing facility, or hospice
 - Dialysis
 - Surgery
- No permanent indwelling catheters or medical devices that pass through the skin

Bacterial Isolates from Purulent Skin and Soft-Tissue Infections in 11 U.S. Emergency Departments

Table 1. Bacterial Isolates from Purulent Skin and Soft-Tissue Infections in 11 U.S. Emergency Departments.*

Site	No. of Patients Enrolled (N=422)	MRSA (N=249) [†]	MSSA (N=71)	Other Bacteria (N=64) [‡]		No Bacterial Growth (N=38)
				number (percent)		
Albuquerque	42	25 (60)	10 (24)	3 (7)	4 (10)	
Atlanta	32	23 (72)	4 (12)	3 (9)	2 (6)	
Charlotte, N.C.	25	17 (68)	0	4 (16)	4 (16)	
Kansas City, Mo.	58	43 (74)	6 (10)	4 (7)	5 (9)	
Los Angeles	47	24 (51)	6 (13)	8 (17)	9 (19)	
Minneapolis	28	11 (39)	4 (14)	9 (32)	4 (14)	
New Orleans	69	46 (67)	11 (16)	9 (13)	3 (4)	
New York	20	3 (15)	8 (40)	5 (25)	4 (20)	
Philadelphia	58	32 (55)	12 (21)	12 (21)	2 (3)	
Phoenix, Ariz.	30	18 (60)	8 (27)	4 (13)	0	
Portland, Oreg.	13	7 (54)	2 (15)	3 (23)	1 (8)	

* A total of 31 cultures, including 10 cultures from which MRSA was isolated, were polymicrobial. Because of rounding, percentages may not total 100. MSSA denotes methicillin-resistant *Staphylococcus aureus*.

[†] P<0.001 for the test for homogeneity of MRSA prevalence across sites.

[‡] Other bacteria isolated were as follows: MSSA (17 percent), streptococcus species (7 percent), coagulase-negative staphylococci (3 percent), and *Proteus mirabilis* (1 percent).

Community-Associated MRSA Susceptibilities

Table 2. Number of Community-Associated MRSA Isolates That Were Susceptible to Selected Antimicrobial Agents, 2001–2002.*

Agent Tested	Atlanta	Baltimore	Minnesota	Total	P Value†‡
	<i>no. of susceptible isolates/total no. (percent)</i>				
Ciprofloxacin	408/648 (63)	6/31 (19)	146/182 (80)	560/861 (65)	<0.001
Clindamycin	840/970 (87)	78/92 (85)	211/239 (88)	1129/1301 (87)	0.58
Erythromycin	98/907 (11)	11/94 (12)	110/235 (47)	219/1236 (18)	<0.001
Gentamicin	429/444 (97)	66/71 (93)	184/188 (98)	679/703 (97)	0.59
Rifampin	682/694 (98)	6/9 (67)	179/184 (97)	867/887 (98)	0.21
Tetracycline	726/814 (89)	43/70 (61)	163/179 (91)	932/1063 (88)	0.44
Vancomycin‡	1016/1017 (100)	95/96 (99)	232/232 (100)	1343/1345 (100)	0.88
Linezolid	13/13 (100)	11/12 (92)	0	24/25 (96)	0.30
Trimethoprim– sulfamethoxazole	912/943 (97)	30/36 (83)	236/239 (99)	1178/1218 (97)	0.32

* Results were obtained at local facilities.

† P values were determined by means of the Cochran–Mantel–Haenszel summary statistic.

‡ Two isolates were nonsusceptible with the use of automated testing methods, but these results were not confirmed with the use of recommended methods.^{20,21}

MRSA treatment considerations

- Colonization vs. Infection
- Need for surgical intervention
- Medical treatment: drug & duration

Skin and soft tissue infections

- Adequate incision and drainage is critical
 - Level of evidence (A-II)
 - “crumbly”, pale, hard subcutaneous tissue
 - Stab incisions often inadequate
 - May require OR to achieve adequate anesthesia
- Cultures should be obtained to direct therapy
 - Level of evidence (A-III)
 - In 354 cases of CA-MRSA in 10 MN hospitals - 84% initially treated w/ ineffective abx (e.g., Cephalexin)

Oral antibiotics for CA-MRSA

- Should be adjunctive to adequate I&D of minor infections
 - Level of evidence (A-II)
- Clindamycin - *300-450 mg PO QID*
 - Inducible resistance has been reported
- TMP-SMX - *Bactrim DS 2-3 tabs PO BID*
 - Higher than traditional UTI dosing
 - Watch in patients w/ renal insufficiency
- Doxycycline - *100mg PO BID*

Prevention Strategies

Personal/Caregiver Hygiene

Measures:

- Shower daily using soft and hot water
- Wash hands frequently
- Cover wounds with dry, clean dressings
- Avoid contact with wound drainage
- Avoid sharing towels, razors, clothing, personal items
- Clean cuts and abrasions with soap and water

Healthcare-initiated measures:

- Use antimicrobials judiciously
- Recognize and treat CA-MRSA lesions early
- Educate and counsel patients and caregivers about appropriate wound care
- Decolonize only after consultation with ID physicians

Case 1

- 25 yo AA female with AIDS presents with diarrhea
 - CD4 ct: 16 c/mm³ (2%); HIV VL: 86,000 cp/mL
- Recently placed on therapy for *Pneumocystis jirovecki* pneumonia
- Current medications: Acyclovir, Azithromycin, Clindamycin, Primaquine
- H/O genital herpes and sulfa allergy

- Reports
 - 2 weeks diffuse abdominal pain relieved with bowel movement
 - Watery diarrhea 5-10 times daily
 - Denies melena or hematochezia
 - Intermittent nausea with vomiting
 - Denies fevers

Diarrhea and HIV

- The most common GI symptom
- Prevalence
 - 1-14% of outpatient patients
 - 50% of hospitalized HIV patients
- Increased in MSM and low CD4 counts

Potential Pathogens

Bacterial

- MAC
- Salmonella
- Shigella
- Campylobacter
- *Clostridium difficile*
- *Vibrio parahaemolyticus*

Viral

- CMV
- HSV
- Adenovirus

Fungal

- Candida
- Histoplasmosis

Protozoa/Helminths

- Cryptosporidium
- *Isospora belli*
- Leishmania
- Giardia
- Entamoeba
- Strongyloides

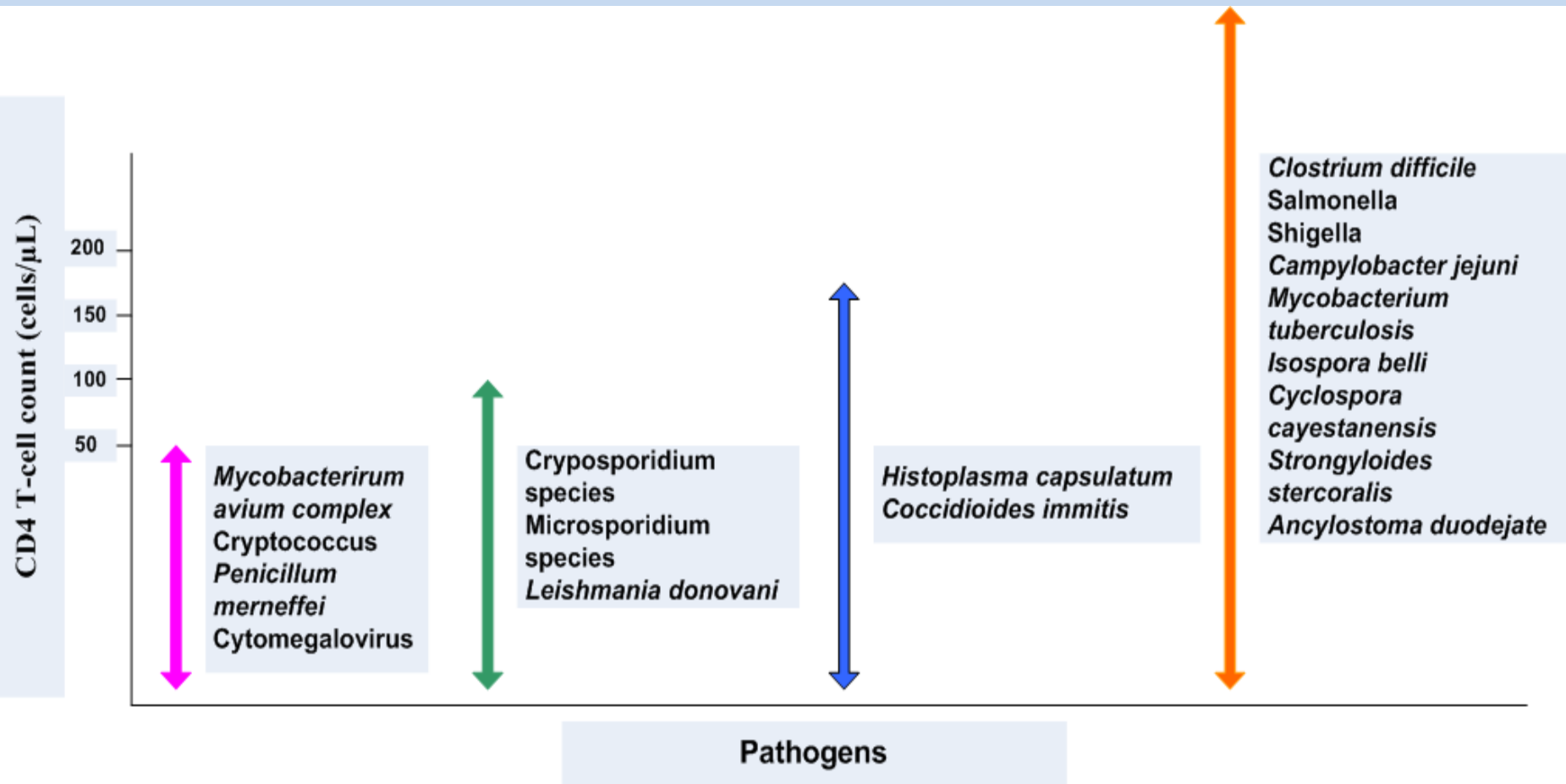
Malignancy

- Lymphoma
- Kaposi sarcoma

Other

- AIDS Enteropathy
- Small bowel flora overgrowth
- Medications

Association Between Gastrointestinal Infections and CD4+ T-cell Count in HIV-infected Patients



Evaluation of Diarrhea

- Careful history
 - Medications, Lactose intolerance, Fatty food intolerance
 - Use of cathartics
 - Symptoms of generalized/systemic disease
- Localize symptoms to area of GI tract
 - Stomach or small bowel: bloating, nausea, crampy pain
 - Large bowel: hematochezia, tenesmus
- Character, frequency, color, and odor of stool are non-specific for HIV
- Multiple sexual contacts of receptive anal intercourse: certain bacteria and STDs
- Appropriate stool evaluation
 - Stool culture for bacterial pathogens
 - C diff toxin assay (particularly if recent antibiotic exposure)
 - Ova and parasites, including acid fast and trichrome stain
 - May require multiple specimen to confirm cryptosporidiosis
- Sigmoidoscopy required if diagnosis not made (particularly for HSV or CMV)
 - Biopsy abnormal regions
- Terminal ileum biopsy may diagnose cryptosporidium



Treatment of Diarrhea

- If enteric pathogen identified, administer specific therapy
- Chronic, alternating antibiotics may be required for certain pathogens
- Once potential infectious etiologies ruled out, chronic diarrhea can be treated symptomatically.
 - Lactose free diet
 - Stool bulking agents
 - Anti-motility agents
 - IV fluids, if dehydrated
- No definitive treatment for cryptosporidiosis, microsporidiosis, or pathogen negative diarrhea
 - Initiation of HAART and subsequent immune reconstitution may improve these diarrheal diseases.

Case 1

- WBC 22.5×10^9 c/mm³
- Stool studies:
 - Culture negative
 - O&P neg
 - Bacterial culture negative
 - Cryptosporidium Ag negative

C diff toxin positive

Clostridium difficile

- Spore forming, Gram-positive, anaerobic bacillus
- Causes a toxin mediated disease by damaging the colonic mucosal epithelium
- Disruption of normal colonic flora (*Bacteroides spp*, in particular) by
 - Antibiotics (Ampicillin, amoxicillin, cephalosporins, and clindamycin)
 - Rarely, chemotherapy
- Leading cause of nosocomial acquired diarrheal disease
- Since 1996, incidence of *C difficile* colitis has doubled.
 - Estimated 3 million cases in US per year.
- Increasing mortality
 - Increasing virulence
 - Host vulnerability
- Key factors
 - Comorbidities, particularly in advanced age
 - Altered GI bacterial flora (due to antibiotics or cancer meds)
 - Exposure to spores of *C difficile*

Reports of *C diff* and HIV

Table 2. Studies of *Clostridium difficile* colitis in patients infected with human immunodeficiency virus^a

Series (ref. no.)	No. of HIV-positive patients	WBC range \pm SD in HIV-positive patients	Mean CD4 count \pm SD	Study design	Response to treatment and prognosis
Harrison and Bartlett, 1991 ¹⁵	26	—	—	Case series, retrospective	3 relapses; increased mortality (7 of 26 patients died)
Cappell and Philogene, 1993 ¹²	7	6,040 \pm 4,820	92 \pm 126	Case series	100% response, but 2 of 7 relapsed; severe symptoms
Cozart et al, 1993 ⁸	17	3,931 \pm 2,906	—	Case-control, retrospective	88% response; similar to control
Lu et al, 1994 ⁹	32	5,910 \pm 3,900	—	Control, prospective	59% response; similar to control; similar symptoms; 9.4% relapsed
Tumbarello et al, 1995 ¹¹	31	—	49 \pm 5	Case-control, prospective	9.7% relapse; more severe symptoms in HIV+ patients
Barbut et al, 1997 ¹³	34	200 to 11,000 (neutrophils)	15 (range, 1–463)	Case-control, retrospective	28% relapsed
Willingham et al, 1998 ¹⁴	24	—	<150	Case-control, prospective	Higher mortality rate (42%) compared with other causes

^aWBC is expressed as total white blood cells/mm³. HIV, human immunodeficiency virus; WBC, white blood cell count.

Harrison and Bartlett. Program and Abstracts of the 31st ICAAC. Chicago, 1991 (Abstract 190).

Cappell and Philogene. Am J Gastroenterol 1993; 88: 891–897.

Cozart, et al. J Clin Gastroenterol 1993; 16: 192–194.

Lu et al. Am J Gastroenterol 1994; 89: 1226–1229.

Tumbarello et al. Eur J Gastroenterol Hepatol 1995; 7: 259–263.

Barbut et al. J Acquir Immune Defic Syndr Hum Retrovirol 1997; 16: 176–181.

Willingham et al.. Clin Infect Dis 1998; 27: 487–493.

DeToledo and Symes. South Med J. 2004;97:388-92



C diff Presentation

- Usually presents as mild disease
- Generally responds well to treatment
- Small subset of HIV-infected persons develop severe disease with
 - Toxic colitis
 - Dehydration and renal failure
 - Colonic ischemia
 - Shock
 - Death

Predisposing Factors related to HIV

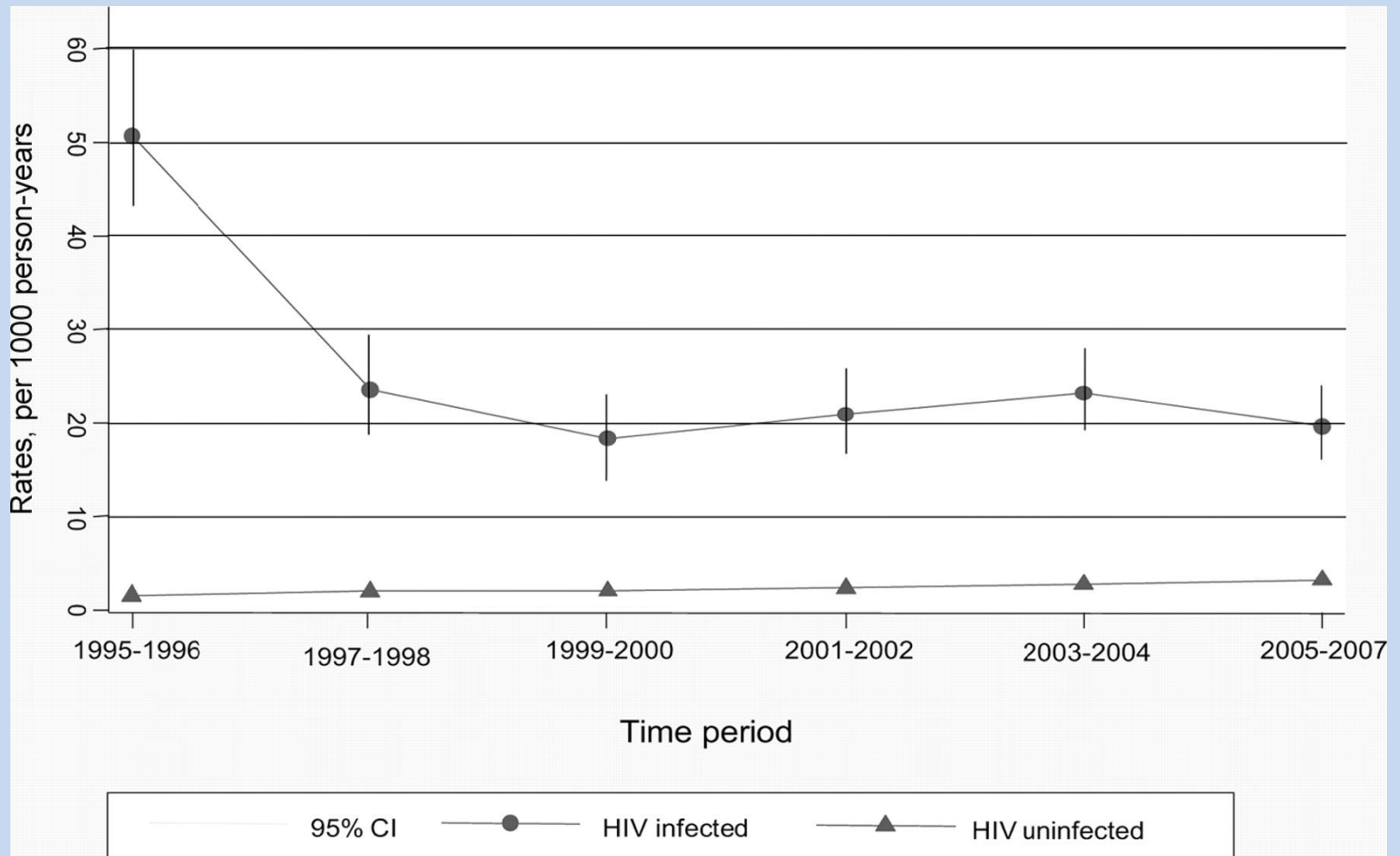
- OI prophylaxis among advanced patients
- Frequent hospitalizations, i.e. more exposure
- Relapse rate: 9-24%
 - Similar to that in the general population



Treatment of *Clostridium difficile*

- Discontinue offending agent, if possible
- Initiate appropriate therapy
 - Metronidazole 500mg tid for 10-14 days
 - Vancomycin 125mg qid for 10-14 days
- Fidaxomicin, a macrocyclic antibiotic
 - Similar efficacy to vancomycin
 - Reduction in recurrence (15% vs. 25%)

Incidence of first-time hospitalization to treat pneumonia in Denmark among individuals with and without HIV infection, 1995–2007.



Respiratory Disease Presentation

- Challenging
 - Frequent complaint
 - Broad differential
 - HIV-related
 - Neoplasm
 - OIs (bacterial, fungal, mycobacterial, viral, parasitic)
 - Non-HIV-related
- No pathognomonic constellation of symptoms
- Cigarette smoking is an important predictor of symptoms

Respiratory Symptoms	Number Patients (%)	Patients with CD4 <200
Cough	3,359 (27%)	1,395 (34%)
SOB	2,856 (23%)	1,380 (34%)
Fever	1,127 (9%)	693 (17%)
Cough & SOB	1,691 (14%)	820 (20%)
Cough & fever	719 (6%)	430 (11%)
SOB & fever	709 (6%)	447 (11%)
Cough, SOB, & fever	536 (4%)	332 (8%)

The Pulmonary Complications of HIV Infection Study Group. J Clin Epidemiol. 1993 Jun;46(6):497-507

Possible Etiologies

- Bacteria
 - *Streptococcus pneumoniae*
 - *Haemophilus influenzae*
 - Gram-negative bacilli
 - *Pseudomonas aeruginosa*
 - *Klebsiella pneumoniae*
 - *Staphylococcus aureus*
- *Mycobacteria*
 - *Mycobacterium tuberculosis*
 - *Mycobacterium kansasii*
 - *Mycobacterium avium* complex
- Fungi
 - *Pneumocystis jiroveci*
 - *Cryptococcus neoformans*
 - *Histoplasma capsulatum*
 - *Coccidioides immitis*
 - *Aspergillus* spp
- Viruses
 - Cytomegalovirus
 - Herpes simplex virus
- Parasites
 - *Toxoplasma gondii*
 - *Strongyloides stercoralis*
- Malignancy
 - Kaposi sarcoma
 - Non-Hodgkin lymphoma
 - Bronchogenic carcinoma

Madeddu G, et al. Curr Opin Pulm Med. 2010;16(3):201-7.

Huang L. Pulmonary Manifestations of HIV. @ <http://hivinsite.ucsf.edu/InSite> .

Accessed February 15, 2011.



Case 2

- 35 yo C male with HIV infection presents with cough and fever
 - CD4 ct: 416 c/mm³ (22%); HIV VL: 16,000 cp/mL
 - Reports “pneumonia” by CXR at walk-in clinic

Case 2: Pulmonary symptoms, abnormal CXR, and CD4 count >200

- DDx
 - Community acquired pneumonia
 - *Strep pneumo*, *H flu*
 - TB
 - Non-Hodgkin Lymphoma
 - Bronchogenic CA (if a smoker)
 - Influenza, if the season
- If no evidence of lower tract disease on repeat CXR →
 - Consider: bronchitis or URI

Case 3

- 35 yo C male with HIV infection presents with cough and fever
 - CD4 ct: 107 c/mm³ (8%); HIV VL: 37,000 cp/mL
 - Reports “pneumonia” by CXR at walk-in clinic

CXR reveals focal infiltrate



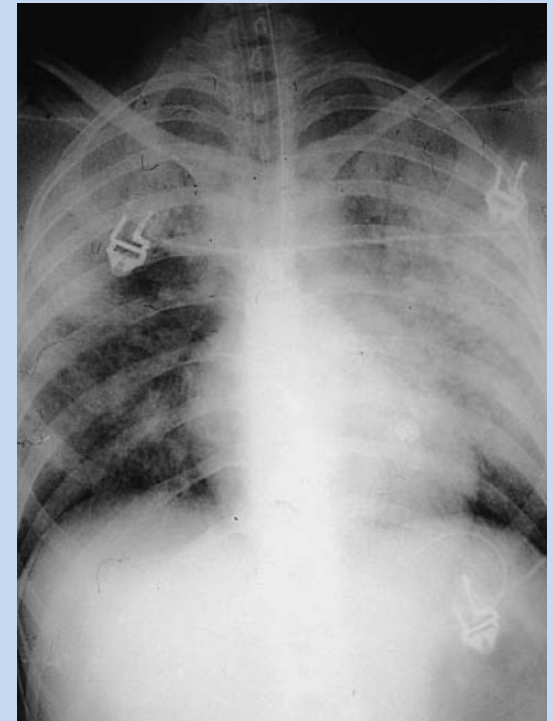
Case 3: Pulmonary symptoms, focal opacity on CXR, and CD4 count <200

- DDX
 - Community acquired pneumonia
 - *Strep pneumo*, *H flu* remain common
 - *Staph aureus* and Gram negative rods
 - PCP
 - TB (extrapulmonary disease more common)
 - Fungal infection (particularly if CD4 count <50)
 - Non-Hodgkin Lymphoma
 - Bronchogenic CA (if a smoker)
 - Influenza, if the season
- If patient has concomitant neurologic complaints
 - Consider disseminated cryptococcal disease
- PCP can present with a focal infiltrate!
 - Consider if the patient has a sub-acute onset of symptoms.

Case 4

- 35 yo C male with HIV infection presents with cough and fever
 - CD4 ct: 107 c/mm³ (8%); HIV VL: 37,000 cp/mL
 - Reports “pneumonia” by CXR at walk-in clinic

CXR reveals diffuse infiltrate



Case 4: Pulmonary symptoms, diffuse opacities on CXR, and CD4 count <200

- DDX
 - PCP
 - Bacterial pneumonia (multifocal)
 - TB (miliary)
 - Fungal infection (particularly if CD4 count <50)
 - Pulmonary KS
 - Non-Hodgkin Lymphoma
 - CMV pneumonitis
 - Influenza, if the season
- At very low CD4 counts (< 50)
 - OIs and neoplasms are more common
 - Diffuse infiltrates are also more common

Summary

- Bacterial infections remain common among HIV-infected individuals
- HIV infection, immunosuppression, and prophylaxis may predispose patients to certain pathogens
- Thorough evaluation will help identify routine and opportunistic pathogens.