35 - Hospital Epidemiology

Speaker: Robert Weinstein, MD

2020 INFECTIOUS DISEASE BOARD REVIEW

Hospital Epidemiology

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Disclosures of Financial Relationships with Relevant Commercial Interests

- None

TOPICS

1. Healthcare-associated Infection (HAI) Pathogens
2. Isolation Precautions
3. Device- and Procedure-related Infections
4. Antimicrobial Stewardship
5. Outbreaks
6. Occupational Health

TOPIC 1: PATHOGENS

Question #1

A 50 y.o. previously healthy man developed urinary retention followed by urosepsis during admission for acute myocardial infarction. Initial antibiotic therapy appears to be failing. The most likely antimicrobial-resistant pathogen is:

A. Carbapenem-resistant *K. pneumoniae*
B. ESBL-producing *E. coli*
C. Multi-drug resistant *P. aeruginosa*
D. Vancomycin-resistant Enterococcus
E. *Candida auris*

CAUSATIVE PATHOGENS & TYPES OF INFECTION — KEY POINTS

Most Common Pathogens (% of HAIs) -- 10 states, 2011 & 2015

- *C. difficile* (12-15)
- *S. aureus* (11)
- *E. coli* (9-10)
- Candida (6)
- Klebsiella (5-10)
- Enterococcus (5-9)
- *P. aeruginosa* (5-7)
- Enterobacter (3-5)

MDR U.S. Case #s 2012-17 (hospital and community); % change

• Methicillin-R *S. aureus*	400K-320K	21% decrease
• Vancomycin-R Enterococci	85K-54K	39% decrease
• ESBL-producing Enterobacteriaceae	130K-200K	53% increase
• Carbapenem-R Enterobacteriaceae	12K-13K	no trend
• Carbapenem-R *Acinetobacter spp*	12K-9K	32% decrease
• MDR *P. aeruginosa*	46K-33K	30% decrease

N Engl J Med **2014**; 370:1198-1208 **2018**; 379:1732-44 **2020**; 382:1309-19

National Data for Acute Care Hospitals, Year 2017

Card View | Table

National Data by HAI Type

HAI Type	# OF FACILITIES THAT REPORTED DATA TO CDC'S NHSN, 2017*	2017 NATIONAL SIR VS. 2016 NATIONAL SIR	2017 NATIONAL SIR VS. NATIONAL BASELINE
CLABSI	3,576	↓ -9%	↓ -19%
CAUTI	3,679	↓ -5%	↓ -12%
VAE	2,046	↓ -3%	↓ -5%
C. difficile Events	3,669	↓ -13%	↓ -20%
MRSA Bacteremia	3,662	↓ -8%	↓ -14%
SSI: Abdominal Hysterectomy	2,970	= 2%	↓ -11%
SSI: Colon Surgery	3,158	= 3%	↓ -9%

SIR, Standardized Infection Ratios; National Baseline is 2015
https://www.cdc.gov/hai/data/portal/progress-report.html
https://www.cdc.gov/HAI/pdfs/progress-report/hai-progress-report.pdf
Magill et al, *N Engl J Med* 2018; 379:1732-44

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Question #2

An 25 y.o. man with a recent renal transplant was admitted via the Emergency Room with gross hematuria. Three days after admission he developed fever and flu-like symptoms. An NP PCR test is positive for SARS-CoV-2. The most likely source of infection is:

A. Community exposure before admission
B. Food-borne illness in the community
C. Emergency Department exposure
D. In-hospital exposure to visitors or personnel
E. In-hospital exposure to contaminated respiratory therapy equipment

Incubation Periods for Selected Pathogens

• Influenza	1-4 days
• Parainfluenza	2-7 days
• Norovirus	12-48 hrs
• Rotavirus	<2 days
• RSV	2-8 days
• SARS-CoV-2	mean 5-6 (up to 14) days
• Wound Infection	
• Clostridia	24-48 hrs
• Group A Strep	24-48 hrs
• *S. aureus*	5-7 days
• Gram-negative bacilli	>7 days (variable)

Characteristics of COVID-19, SARS, MERS and Influenza

Characteristic	COVID-19	SARS-CoV/MERS-CoV	Influenza
Clinical severity	Asymptomatic to severe	Mostly severe	Mostly mild
Infection fatality risk	0.5% to 1%	10% (to 30%)	Seasonal: ≤0.1% 1918/1919 pandemic: 2%
Incubation period	Mean 5-6 (up to 14) days	Mean 3-5 (up to 14) days	Mean 1 (up to 3) days
Basic reproductive number	1.5 to 3.0	SARS: 1.5 to 4 MERS: 0.5 to 1	1.5 to 2.0
Modes of transmission	Respiratory droplets > aerosols Possible spread via fomites and fecal-oral	Respiratory droplets and aerosols Possible fomites	Respiratory droplets, some aerosols & fomites
Infectiousness profile	Most infectious before illness onset	Most infectious 7-10 days after illness onset	Most infectious around time of illness onset
Location of person-to-person transmission	Mainly community and long-term care facilities	Mainly hospitals	Mainly community; also can spread in hospitals
Importance of children in transmission dynamics	Unclear	Not important	Very important
Possible to avoid widespread transmission?	Unlikely	Yes	Maybe

Adapted from Cowling & Aiello, *J Infect Dis* 2020; 221:1749-51 and Weinstein, *NEJM* 2004; 350:2332-4.

Question #3

A nursing home reports that over the past 2 months 25% of its 100 residents have been diagnosed with suspected gastrointestinal infections. The symptoms — low grade fever, nausea, vomiting, and occasional diarrhea — resolved for most patients within 48-96 hours. The clinical lab's diagnostic test of choice for the most likely pathogen is:

A. MALDI-TOF of blood culture
B. Aerobic culture of vomitus
C. Aerobic culture of stool
D. EIA on stool
E. PCR on stool

Norovirus (Norwalk-like virus)

- Non-enveloped single-stranded RNA viruses that cause acute, self-limited gastroenteritis; major cause of foodborne outbreaks
- Caliciviridae family (includes sapoviruses, also a cause of gastroenteritis); multiple genotypes & reinfection possible
- Incubation 12-48 hrs; duration of illness 24-72 hrs
- Vomiting > diarrhea; low grade fever, headache, myalgia
- Highly contagious; infective inoculum – 18 viral particles; spreads indirectly, directly, common source, droplet
- Lab diagnosis: PCR>EIA; culture – a research tool (2016)

Topic 2: Isolation Precautions

Control & Prevention Keyed to Modes of Transmission

- Contact
  - Direct (body-to-body)
  - Indirect (e.g., fomites/environment, HCWs' hands)
- Droplet (>5 µm; travel 3-6 feet)
- Airborne (droplet nuclei ≤ 5 µm; remain aloft)
- Endogenous (auto-inoculation & device-related)
- Common source (outbreak potential)
- Vectorborne

HCW, healthcare worker

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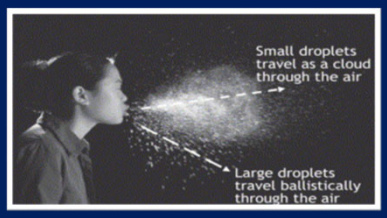
Droplet vs. Airborne Spread – Dichotomy or Continuum?



Droplet generation. A flash photo of a human sneeze, showing the expulsion of droplets that may be laden with infectious pathogens. Sneezing can produce as many as 40 000 droplets of 0.5–12 μm. These particles can be expelled at a velocity of 100 m/s, reaching distances of several metres. Smaller droplets with less mass are less influenced by gravity, and can be transported as a 'cloud' over greater distances by air flows. Larger droplets with more mass are more strongly influenced by gravity and less so by air flows, and move more 'ballistically', falling to the ground more quickly. Reproduced with the kind permission of Prof. Andrew Davidhazy, School of Photographic Arts and Sciences, Rochester Institute of Technology, Rochester NY, USA.

Tang JW et al, *J Hosp Infect* 2006; 64:100-14.

Isolation Categories & Precautions are Based on Three Modes of Transmission

		Healthcare Worker		
Category	**Private Room**	**Gloves**	**Gown**	**Mask**
Contact (Touch)	**Yes***	**Yes**	**Yes**	PRN
Droplet (3-6 ft)	**Yes***	PRN	PRN	**W/in 3-6 ft**
Airborne (Same air space)	**All**	PRN	PRN	**N95**

* When possible; cohort if not possible. Avoid rooming with immunosuppressed or high risk patients.
AII = Airborne Infection Isolation: negative pressure with no air recirculation (unless HEPA-filtered); 6-12 ACH (air changes per hour).
Hand hygiene – yes for all; eye protection – PRN for all.

Question #4

A hospitalized patient with nosocomial Influenza A was treated promptly with oseltamivir.
She should be placed on:

A. Standard Precautions in any room
B. Standard Precautions in a private room
C. Contact Precautions
D. Droplet Precautions
E. Airborne Precautions

Isolation Precautions — Examples of Indications

- Standard – All patients
- Contact – Multidrug resistant bacteria, infectious diarrhea, Ebola, chickenpox
- Droplet – Bacterial meningitis, pertussis, mumps, seasonal influenza
- Airborne – Tuberculosis, measles, chickenpox
- "Opportunistic" Airborne* – SARS, MERS-CoV, SARS-CoV-2, Pandemic flu, Ebola, Some BT agents

*e.g., increased transmission risk during aerosol generating procedures (such as intubation)

TABLE
Two Perspectives on Occupational Infections

	Infection Control	Occupational Medicine
Tradition	Nosocomial infection	Occupational exposure
Focus	Patients	Workers
Setting	Hospitals	Industries
Goal	Disease transmission	Exposure prevention
Authority	CDC	OSHA
Approach	Infection control policy	Exposure control plan
Enforcement	Voluntary guidelines	Mandatory regulations
Prevention	Isolation Behaviors Barrier precautions	Hierarchy of controls Engineering Work practices Personal protective gear

Gerberding JL, *Infect Control Hosp Epidemiol* 1993; 14:686-8.

Question #5

A 30 y.o. landscaper in Martha's Vineyard is admitted with fever and pneumonia. Blood cultures are growing gram-negative coccobacilli in the aerobic bottle. The appropriate patient placement and specimen lab containment, respectively, are:

A. Standard precautions for patient and lab containment for specimen
B. Contact precautions for patient and no lab containment for specimen
C. Droplet precautions for patient and no lab containment for specimen
D. Respiratory isolation for patient and lab containment for specimen
E. Strict (Respiratory & Contact) isolation for patient and lab containment for specimen

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CDC Category A Bioterrorism Agent Infection Control

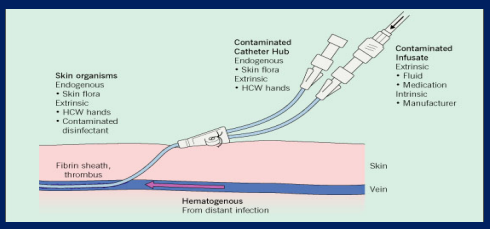
Disease	Patient Isolation	Laboratory Containment
Smallpox	AII & CP	Y
Plague	AII or DP	Y
Viral Hemorrhagic Fever	AII & CP	Y
Anthrax	SP*	N
Botulism	SP	N
Tularemia	SP	Y

AII = Airborne Infection Isolation, CP = Contact Precautions, DP = Droplet Precautions, SP = Standard Precautions

*Exception: CP if cutaneous anthrax has uncontained drainage

Topic 3: Devices & Procedures – Outcomes, Better

Potential Sources of Infection of a Percutaneous Intravascular Device (IVD)



Potential sources of infection of a percutaneous intravascular device (IVD). These include contiguous skin flora, contamination of the catheter hub and lumen, contamination of infusate and hematogenous colonization of the IVD from distant, unrelated sites of infection. HCW, health care worker. Adapted from Crnich and Maki, *Clin Infect Dis* 2002; 34:1232-4.

Question #6

You are revising your ICU's CVC-infection prevention guidelines. Which one of the following measures should not be included?

A. Maximum barrier precautions for CVC insertion
B. Removal of idle CVCs
C. Education of personnel
D. Preference for chlorhexidine for CVC site preparation
E. Regular guidewire-facilitated replacement of CVCs during prolonged use

CDC/HICPAC IV Catheter Infection Prevention Guidelines
Use this "Bundle" for a "Checklist"

- Education of personnel
- Is catheter needed?
- Avoid routine central line replacement as an infection control strategy
- Chlorhexidine skin prep (other uses of chlorhexidine?)
- Maximum barrier precautions
- Use of coated catheters (if after full implementation of above, goals are not met)

http://www.cdc.gov/hicpac/pdf/guidelines/bsi-guidelines-2011.pdf
HICPAC = Healthcare Infection Control Practices Advisory Committee

Catheter Infection Don'ts

- Don't culture catheter tips unless removed for suspected infection
- Don't order qualitative catheter tip cultures (e.g., don't stick catheter in broth)
- Don't under-fill blood culture bottles (because positivity rates are proportional to amount sampled)
- Don't start antibiotics without (re)culturing blood (peripheral & through catheter)
- Don't use thrombolytics routinely (usually case-by-case decision)
- Don't ignore infection control of peripheral IVs (PIVs)

Question #7

Which of the following patient care measures is least likely to be effective for preventing the ventilator-associated infection complication of pneumonia (VAP)?

A. Subglottic suction ports on ET tube
B. Elevation of the heads of beds to 30-45 degrees
C. Regularly scheduled changes of the ventilator tubing
D. Assessing extubation readiness daily
E. Non-invasive ventilation

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Ventilator Complication Prevention Bundle – Update

DO When Possible

- Non-invasive ventilation
- Avoid sedation/ "Sedation Vacation" daily
- Assess extubation readiness daily/ breathing trials off sedatives
- Facilitate early mobility
- Use subglottic suction ports (if >48 hr intubation)
- Avoid ventilator circuit changes
- Elevate head of bed to 30-45°

Increased Interest in Non-ventilator Healthcare-associated Pneumonia

Klompas et al, *Infect Control Hosp Epidemiol* 2014; 35(8):915-36.

Ventilator Complication Prevention Bundle – Update

Special Approaches

- Selective decontamination
- Oral chlorhexidine
- UltraThin ET tube cuffs
- Auto-control ET tube cuff pressure
- Saline instillation pre-suctioning
- Mechanical tooth brushing

Klompas et al, *Infect Control Hosp Epidemiol* 2014; 35(8):915-36.

Ventilator Complication Prevention Bundle – Update

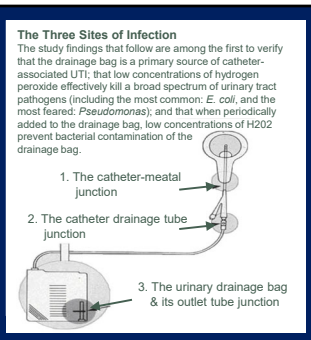
Don't Use (for infection prevention)

- Silver-coated ET tubes
- Kinetic beds
- Prone positioning
- Stress ulcer prophylaxis
- Early tracheotomy
- Gastric volume residual monitoring
- Early parenteral nutrition

No Recommendation

- Closed/in-line ET suctioning

Klompas et al, *Infect Control Hosp Epidemiol* 2014; 35(8):915-36.



Reduce CUTIs

- Avoid use of catheters (Key role for bladder ultrasound)
- Don't open or irrigate system
- Aseptic drainage of bag
- Bag below bladder

Reduce Surgical Site Infections

- Appropriate use of prophylactic antibiotics: start within 30-60 min of incision; stop within 24h
- Appropriate hair removal: no razors
- Surgical site skin prep – Chlorhexidine-alcohol
- Perioperative normothermia (colorectal surgery patients)*
- Post operative glucose control (major cardiac surgery patients cared for in an ICU)*
- Supplemental perioperative oxygen
- Nasal *S. aureus* decolonization
- Checklists
- Reporting of rates

* These interventions are supported by clinical trials and experimental evidence in the specified groups and may prove valuable for other surgical patients as well.

Being studied: Negative-pressure wound therapy
Not on list: Laminar air flow technologies; UV light use

Refs: *N Engl J Med* 2010; 362:18-26 and *JAMA Surg* 2017; 152:784-91 and 2020; 155:479.

What is Essential?*

Preventing Device and Procedure Infections:

- HAND HYGIENE — Often the answer
- CVC-BSI — CHG prep, maximum barrier precautions, daily CHG bathing, CVC removal
- PIV — Observe site daily; change post ED insertion & q ≤3 days
- VAP — Oral CHG & sedation vacations (tube removal), positioning 45°
- UTI — Closed system & catheter removal
- SSI — Skin prep, antibiotic prophylaxis timing, & capable surgeon
- REPORT RATES
- As device infection rates fall, increasing attention to other HAIs

*Qualifier: RAW's views

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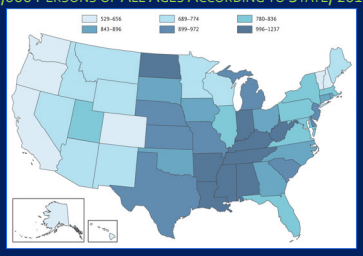
TOPIC 4: ANTIMICROBIAL STEWARDSHIP

PROFLIGATE ANTIBACTERIAL USE: ANTIBIOTIC PRESCRIPTIONS PER 1,000 PERSONS OF ALL AGES ACCORDING TO STATE, 2010



Hicks et al, *N Engl J Med* 2013; 368:1461-2.

SEVEN CORE ELEMENTS CRITICAL TO THE SUCCESS OF HOSPITAL ANTIBIOTIC STEWARDSHIP PROGRAMS

- LEADERSHIP COMMITMENT: Dedicating necessary human, financial, and information technology resources
- ACCOUNTABILITY: Appointing a single leader responsible for program outcomes. Experience with successful programs has shown that a physician leader is effective
- DRUG EXPERTISE: Appointing a single pharmacist leader responsible for working to improve antibiotic use
- ACTION: Implementing at least one recommended action, such as systemic evaluation of ongoing treatment need after a set period of initial treatment (i.e., "antibiotic time out" after 48 hours)
- TRACKING: Monitoring antibiotic prescribing and resistance patterns
- REPORTING: Regular reporting information on antibiotic use and resistance to doctors, nurses and relevant staff members
- EDUCATION: Educating clinicians about resistance and optimal prescribing

Source: CDC. Core elements of hospital antibiotic stewardship programs. Atlanta GA: US Department of Health and Human Services, 2014.
Available at http://www.cdc.gov/getsmart/healthcare/implementation/core-elements.html

TOPIC 5: OUTBREAKS

Question #8

During a 1 week period, 5 ICU patients develop fulminant sepsis. Blood cultures from each grow *Serratia marcescens*; cultures of respiratory secretions and urine are normal flora and negative, respectively. No Serratia infections have occurred in this ICU in the past 3 months. On a general medical ward 2 months ago a patient had a Serratia cUTI.
The evaluation most likely to explain this ICU cluster of infections is a(n):

A. Assessment of ICU staff hand hygiene adherence
B. Whole genome sequence (WGS) analysis of the ICU Serratia isolates
C. Case-control study focused on IV medications
D. Rectal swab culture survey of patients in the ICU
E. Environmental cultures of the ICU rooms of the infected and control patients

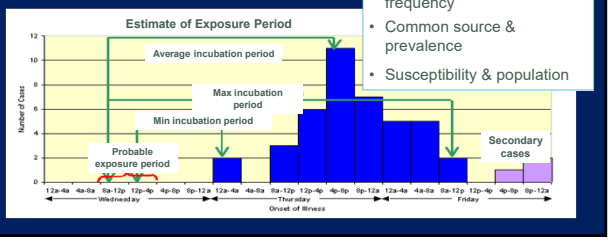
STEPS IN OUTBREAK INVESTIGATION

1. Establish existence of epidemic
2. Verify diagnosis (*preceding question was an outbreak of "primary bacteremia" with Serratia*)
3. Case count
4. Orient data into time, place, person
5. Determine size of population at risk
6. Develop hypothesis regarding source & mode of spread, e.g., indirect person-to-person, common source, personnel carrier (*e.g., primary bacteremia – possibility of contaminated IV medications/infusions*)
7. Test hypothesis, refine above, plan and implement control measures. Test may be typing (such as PFGE or WGS) of epidemic isolates; case-control study (*e.g., in primary bacteremia outbreak, assess IV exposures*)

INTERPRETING EPIDEMIC CURVES

Infer from size, shape, & repetition of curves:

- Person-to-person spread & frequency
- Common source & prevalence
- Susceptibility & population



SOME OUTBREAK ASSOCIATIONS

- Unusual bug (esp. if BSI): Think common-source contamination, e.g., *Pantoea agglomerans*, Pseudomonas spp, Flavobacterium from IV fluids or propofol; extrinsic > instrinsic contamination
- *Burkholderia cepacia* – Contaminated iodophors, benzalkonium chloride
- *Cronobacter* (formerly *Enterobacter*) *sakazakii* – yellow pigment, powdered infant formula
- Listeria – foodborne (soft cheese, dairy, cabbage); miscarriages; a psychrophile
- Yersinia – blood products, pork, hot dogs; post-infectious reactive arthritis; a psychrophile

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Key Emerging Outbreak Pathogens

- ***Candida auris***
  - Multi-continent emergence in "unrelated" outbreaks (different clades)
  - Heavy environmental contamination in affected nursing home and hospital wards
  - Some clades resistant to anti-fungals
- Mycobacteria (***M. chimera***) in CV surgery heater-cooler devices

Dry & Wet Environmental Contamination Increasingly Implicated in Outbreaks of Some Nosocomial Pathogens

Bacteria	*C. difficile*, VRE, MRSA, Acinetobacter, *P. aeruginosa*, "Water Bugs" (various gram-negative bacilli)
Virus	Norovirus, HBV, HCV
Fungi	Aspergillus, Mucor, Rhizopus, *Candida auris*
Mycobacterium	*M. chimera*

Topic 6: Occupational Health

Question #9

A healthy new resident has 12 mm of induration around a PPD skin test at 48 hours and a positive quantiferon gold assay. She says a PPD skin test in medical school 2 years ago, 12 weeks after a "tuberculosis exposure", was non-reactive. Her chest x-ray has no active disease. Which of the following is the most appropriate prophylaxis in this case:

A. 2 months of daily rifampin and pyrazinamide
B. 3 months of weekly isoniazid and rifapentine
C. 6 months of daily isoniazid
D. 9 months of daily isoniazid
E. Because no known exposure, not needed unless PPD ≥ 15 mm

MMWR Recomm Rep Feb 14, 2020; 69:1-11.

Classification of the Tuberculin Reaction (continued)
A reaction of ≥ 10 mm is positive in:

- Recent PPD converters (≥10mm increase within 2 years)
- Persons with medical risk factors (diabetes, silicosis, CKD, gastrectomy, j-i bypass, malnutrition, immunosuppressive therapy)
- Foreign-born persons from high prevalence countries
- Intravenous drug users or alcoholics

Classification of the Tuberculin Reaction (continued)
A reaction of ≥ 10 mm is positive in:

- Residents of long-term-care facilities, such as correctional institutions and nursing homes or homeless individuals
- Other high risk populations identified locally, e.g., healthcare workers

Employee Health – A Common Question:
Classification of the Tuberculin Reaction
A reaction of ≥ 5 mm is positive in:

- Close contacts to patients with infectious tuberculosis
- Persons with HIV infection
- Persons who have CXRs with fibrotic lesions consistent with healed TB
- Organ transplant recipients
- Persons on ≥15mg/day of prednisone for ≥1 month
- Persons on TNF-α antagonist treatment

Classification of the Tuberculin Reaction (continued)
A reaction of ≥ 15 mm is positive in:

- Persons with no additional risk factors for tuberculosis

But PPD tests now often replaced by IGRAs

IGRAs = Interferon gamma release assays

Question #10

A worried health care worker who is planning international travel gets a booster dose of MMR vaccine. His work restrictions during the 2 weeks after vaccination should be:

A. Furlough
B. Work in non-patient contact area
C. No contact with immunosuppressed patients
D. No restrictions unless there is evidence of vaccine-related fever or rash
E. No restrictions

Question #11

A 30 y.o. Neurosurgery resident was stuck with a bloody, brain-contaminated scalpel by a medical student during an OR procedure. The source patient was in the hospital for treatment of a febrile rash illness and confusion and was found to have positive tests for HIV antibody, HCV antibody, and HBs Ag; an RPR titre of 1:64; and a brain MRI that showed changes of PML. Appropriate viral load and PCR test results for the patient are not yet available. The surgeon has negative serologic tests for HBV, HCV, HIV, and syphilis.

Question #11

The infection most likely to be transmitted by this blood exposure is:

A. JC Virus infection
B. HBV
C. HIV
D. HCV
E. Syphilis

Healthcare Worker Post Exposure Prophylaxis (PEP)

Pathogen or Disease	Mode of Transmission	High-risk HCW	PEP	Modifying Factors
HIV	Percutaneous, splash — Blood or sterile body fluid or bloody fluids **Risk 0.3%**	Seronegative	ARVs for 4 weeks; serologic follow-up for 6 months	Sharp type, puncture depth, contaminating fluid, patient, VL & treatment, duration after exposure (24-36h or longer); pregnancy
Hepatitis C	Percutaneous **Risk 3%**	Seronegative	Pre-emptive therapy vs watchful waiting	Serologic follow-up
Hepatitis B	Percutaneous **Risk 30%**	Seronegative	HBIG & vaccine	Duration after exposure (24-48h)

Healthcare Worker PEP (continued)

Pathogen or Disease	Mode of Transmission	High-risk HCW	PEP	Modifying Factors
Hepatitis A	Fecal-oral	Seronegative	Vaccine; IG	Duration after exposure (14 days)
Parvovirus B19	Droplet, contact	Seronegative and pregnant, HIV, or hemoglobinopathy	No PEP	Exclude pregnant HCW from patient care
Pertussis	Droplet, contact	Seronegative or waned immunity	Macrolide	Duration after exposure (3 weeks)

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HEALTHCARE WORKER PEP (CONTINUED)

Pathogen or Disease	Mode of Transmission	High-risk HCW	PEP	Modifying Factors
N. meningitidis	Droplet	Close contact	Ciprofloxacin, rifampin, ceftriaxone, or azithromycin (or sulfa if S)	Duration & proximity of contact
VZV	Contact, airborne	Negative VZV history or seronegative and immunocompromised or pregnant	VZIG or valacyclovir; VZV vaccine (Furlough day 10-21 PE; 10-28 if VZIG used)	Duration of, and after, exposure
Tuberculosis	Airborne, rarely contact	PPD- or IGRA-negative	Several regimens if PPD conversion	PPD results (baseline;12 weeks post-exposure)