Antibiotics: New Drugs - How You'll See Them, and How They Should be, Used

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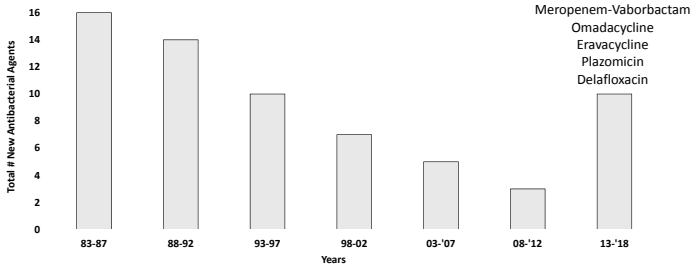
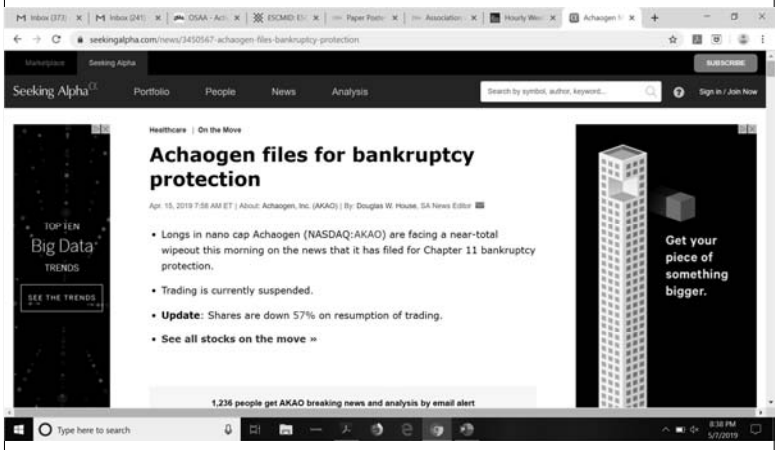
Disclosures

- Consultant with honorarium:
  - Merck
  - Tetraphase

FDA Reboot of Antibiotic Development: Antibacterial Agents Approved



Shlaes DM, et al. *Antimicrob Agents Chemother.* 2013;57(10):4605-4607.
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/default.htm - accessed 3/2019



Why Big Pharma has Gotten Out

- $12.9 billion vs $1 billion
- Resistance
- Cheap generics / satisfied market
- Durations of therapy
- Ever seen a "statin stewardship team"?
- The FDA
- Indications

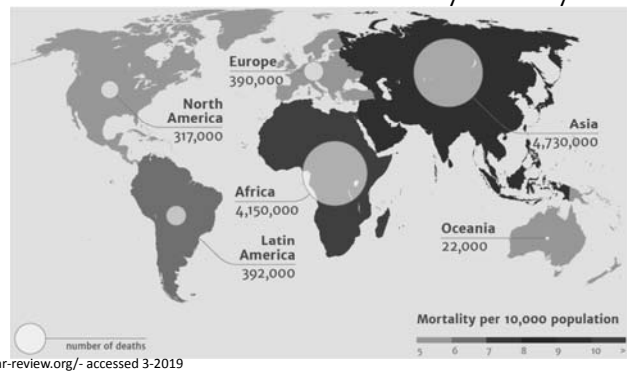
Rex JH, et al. *Ann NY Acad Sci* 2014;1323:11-20

Table 2. Meta-analyses and Examples of Randomized Clinical Studies Comparing Shorter Versus Longer Duration of Antibiotics

Reference	Clinical Condition/Population	Treatment Duration, d	Clinical Outcome[a]
Meta-analyses			
Dimopoulos et al, 2008 [123]	Adults and children with CAP	3–7 vs 5–10	Clinical success, relapse, mortality, adverse events
Pugh et al, 2011 [124]	Adults with VAP	7–8 vs 10–15	Antibiotic-free days[b], recurrence[b]
Dimopoulos et al, 2013 [125]	Adults with VAP	7–8 vs 10–15	Relapse, mortality, antibiotic-free days[c]
Randomized clinical trials			
Chastre et al, 2003 [127]	Adults with VAP	8 vs 15	Mortality, recurrent infections[d]
El Moussaoui et al, 2006 [128]	Adults with CAP	3 vs 5	Clinical and radiological success
Greenberg et al, 2014 [129]	Children with CAP	5 vs 10	Treatment failure[e]
Hepburn et al, 2004 [130]	Adults with cellulitis	5 vs 10	Clinical success
Sandberg et al, 2012 [131]	Adult females with acute pyelonephritis	7 vs 14	Clinical efficacy, adverse events
Talan et al, 2000 [132]	Women with acute uncomplicated pyelonephritis	7 vs 14	Bacteriologic and clinical cure[f]
Runyon et al, 1991 [133]	Adults with spontaneous bacterial peritonitis	5 vs 10	Mortality, bacteriologic cure, recurrence
Saini et al, 2011 [134]	Neonatal septicemia	2–4 vs 7 (with sterile culture)	Treatment failure
Sawyer et al, 2015 [135]	Adults with intra-abdominal infection	4 vs ≤10	Composite of surgical site infection, recurrent intra-abdominal infection, or death
Bernard et al, 2015 [136]	Adults with vertebral osteomyelitis	42 vs 84	Cure at 1 y by independent committee and secondary outcomes

Barlam TF, et al. *Clin Infect Dis* 2016;62:e51-e77

Deaths Attributable to AMR Every Year By 2050



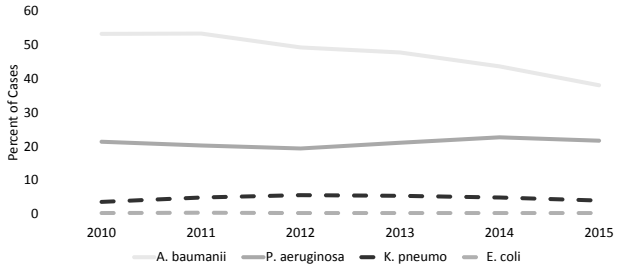
https://amr-review.org/- accessed 3-2019

2017 WHO Priority Pathogens List for R&D of New Antibiotics

- **Priority 1: CRITICAL**
  - *Acinetobacter baumannii*, carbapenem-resistant
  - *Pseudomonas aeruginosa*, carbapenem-resistant
  - *Enterobacteriaceae*, carbapenem-resistant, ESBL-producing

http://www.who.int/mediacentre/news/releases/2017/bacteria-antibiotics-needed/en/ - Accessed 3/2019

% of Total of Carbapenem Resistant Cases Contributed By Pathogen



Cai B, et al. *Open Forum Infect Dis* 2017;4: DOI: 10.1093/ofid/ofx176

A colistin crisis in India

Despite some global progress in limiting the use of antimicrobials in animals, inappropriate colistin use is still widespread. Madlen Davies and Timothy R Walsh report.

"In India, at least five animal pharmaceutical companies advertise products containing colistin as growth promoters or to be used metaphylactically"

"…57% of *Klebsiella pneumoniae* are thought to be resistant to carbapenems…"

Lancet Infect Dis 2018. http://dx.doi.org/10.1016/ S1473-3099(18)30072-0

Comment

Evidence to improve the treatment of infections caused by carbapenem-resistant Gram-negative bacteria

- "The high patient mortality rate (44% at 28 days)… is sobering – considering that infection with bacteria susceptible to colistin was a criterion for inclusion and that colistin dosing was carefully controlled – but is not surprising."
- "…low Charlson and SOFA scores…"
- "…colistin, either as monotherapy or combined with a carbapenem, is not that effective."

Perez F & Bonomo R. *Lancet Infect Dis* 2018; epub 2/15/18

MAJOR ARTICLE

Ceftolozane/Tazobactam Plus Metronidazole for Complicated Intra-abdominal Infections in an Era of Multidrug Resistance: Results From a Randomized, Double-Blind, Phase 3 Trial (ASPECT-cIAI)

Joseph Solomkin,[1] Ellie Hershberger,[2] Benjamin Miller,[2] Myra Popejoy,[2] Ian Friedland,[2,a] Judith Steenbergen,[2] Minjung Yoon,[2] Sylva Collins,[2] Guojun Yuan,[2] Philip S. Barie,[3] and Christian Eckmann[4]

Ceftolozane-tazobactam compared with levofloxacin in the treatment of complicated urinary-tract infections, including pyelonephritis: a randomised, double-blind, phase 3 trial (ASPECT-cUTI)

Florian M Wagenlehner, Obiamiwe Umeh, Judith Steenbergen, Guojun Yuan, Rabih O Darouiche

Clin Infect Dis 2015;60:1462
Lancet 2015;385:1949

"We're Gonna Need a Bigger Boat." – Part 1

- 21 patients treated with ceftolozane-tazobactam (tol-tazo)
- MDR *P. aeruginosa:* Mostly pneumonia/RTI – 86% of patients (18/21)
- Non FDA approved indication & inconsistent Dosing – 1.5g Q8h vs 3.0g Q8h
- Median duration of therapy 14 days
- 71% of isolates R to all anti-pseudomonal beta lactams
- 30 day mortality: 10%, attributable mortality: 5%, 90 day mortality: 48%
- Only variable associated with clinical failure: SAPS-II score

Spellberg B, Bonomo R. *Clin Infect Dis* 2016;63:1619
Haidar G, et al. *Clin Infect Dis* 2017; https://doi.org/10.1093/cid/cix182

Ceftolozane-Tazobactam: Outcomes in Complicated *P. aeruginosa* Infections

- Emergence of resistance in 14% (3) patients
- Dose did not impact resistance selection
- AmpC mutations → resistance
- 90 days mortality rate, complexity of patients, multiple antibiotics
- Are you really surprised?

Haidar G, et al. *Clin Infect Dis* 2017; https://doi.org/10.1093/cid/cix182

Ceftazidime-Avibactam Phase 3 Trials

- cUTI
- cIAI
- And…

Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): a randomised, double-blind, phase 3 non-inferiority trial

Antoni Torres, Nianshen Zhong, Jan Pachl, Jean-François Timsit, Marin Kollef, Zhangjing Chen, Jie Song, Dianna Taylor, Peter J Laud, Gregory G Stone, Joseph W Chow

Torres A, et al. *Lancet Infect Dis* 2018. http://dx.doi.org/10.1016/S1473-3099(17)30747-8

Ceftazidime-Avibactam HAP/VAP Trial – An Interesting Finding

- Increasing MICs (≥4X baseline)
- Same genotype as the baseline isolate
- 1 patient ceftaz/avi – *K. pneumoniae*
- 11 patients meropenem – 10 *P. aeruginosa*
- Consistent theme with *P. aeruginosa* & carbapenems?

Torres A, et al. *Lancet Infect Dis* 2018. http://dx.doi.org/10.1016/S1473-3099(17)30747-8

Clinical Infectious Diseases
MAJOR ARTICLE

Colistin Versus Ceftazidime-Avibactam in the Treatment of Infections Due to Carbapenem-Resistant Enterobacteriaceae

David van Duin,[1] Judith J. Lok,[2] Michelle Earley,[2] Eric Cober,[2] Sandra S. Richter,[4] Federico Perez,[5,6] Robert A. Salata,[5] Robert C. Kalayjian,[7] Richard R. Watkins,[8,9] Yohei Doi,[10] Keith S. Kaye,[11] Vance G. Fowler Jr,[12,13] David L. Paterson,[14] Robert A. Bonomo,[15,16,17] and Scott Evans[2]; for the Antibacterial Resistance Leadership Group

- 38 patients ceftaz-avi vs 99 colistin
- Often used in combination
- 30 day after start of treatment mortality
  - Ceftaz-avi: 9%
  - Colistin 32%
  - 95% CI = 9-35%, P=.001

Clin Infect Dis 2018;66:163-71.

Ceftazidime-Avibactam Resistance in KPC+ Enterobacteriaceae

Clinical Infectious Diseases

BRIEF REPORT

Clinical Outcomes, Drug Toxicity, and Emergence of Ceftazidime-Avibactam Resistance Among Patients Treated for Carbapenem-Resistant Enterobacteriaceae Infections

Ryan K. Shields,[1,2,4,a] Brian A. Potoski,[1,2,3,a] Ghady Haidar,[1] Binghua Hao,[4] Yohei Doi,[1] Liang Chen,[4] Ellen G. Press,[1] Barry N. Kreiswirth,[4] Cornelius J. Clancy,[1,4,5] and M. Hong Nguyen[1,2,4]

- 37 patients
- 10/37 – microbiologic failure
- Resistance in 3/10 failures
- Complex, sick patients
- PK/PD issues?

Clin Infect Dis 2016;63:1615

Research

JAMA | Original Investigation

Effect of Meropenem-Vaborbactam vs Piperacillin-Tazobactam on Clinical Cure or Improvement and Microbial Eradication in Complicated Urinary Tract Infection

The TANGO I Randomized Clinical Trial

- Vaborbactam - the first boronic acid BLI to reach clinical use
- Activity vs.
  - Carbapenem-resistant (CR) *P. aeruginosa* – N/A
  - CR *A. baumannii* – N/A
  - CR *Enterobacteriaceae* – MIC50/90 = 0.06/1mcg/mL
- Indicated for cUTI
  - Phase 3 data TANGO-1: Both EMA and FDA endpoints achieved
  - Superior to piperacillin-tazobactam using the FDA endpoint
  - Dose = 2.5g every 8 hours as a 3 hour infusion

Kaye KS, et al. *JAMA* 2018;319:788. Hackel M, et al. *IDWeek* 2016:Poster 1830

Plazomicin – a novel aminoglycoside (AG)

- Resists most AG modifying enzymes – except methylases
- Active against the vast majority of U.S. CRE.
- No additional benefit for *P. aeruginosa* or *Acinetobacter* sp.

Figure 2. Mortality-Based Outcomes

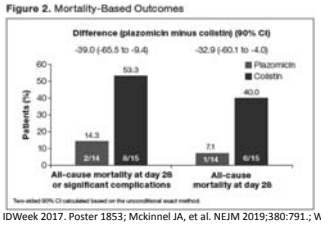
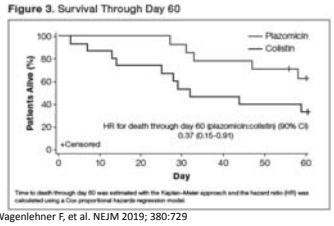


Figure 3. Survival Through Day 60



McKinnell JA, et al. IDWeek 2017. Poster 1853; Mckinnel JA, et al. NEJM 2019;380:791.; Wagenlehner F, et al. NEJM 2019; 380:729

Research

JAMA | Original Investigation

Effect of 5-Day Nitrofurantoin vs Single-Dose Fosfomycin on Clinical Resolution of Uncomplicated Lower Urinary Tract Infection in Women

A Randomized Clinical Trial

- Clinical response through day 28 – 70% nitro vs 58% fosfo (CI 4-21%)
- Microbiologic resolution: 74% nitro vs 63% fosfo (CI 1-20%)
- *E. coli* subgroup – clinical response 78% vs 50% (CI 15-40%)
- ADRs similar
- $5.00 nitro for 5 days vs $75.00 for fosfo X 1

JAMA 2018;319:1781

IV Fosfomycin – The ZEUS trial

- Complicated UTI or acute pyelonephritis, multi-center, double blind
- Randomized to:
  - 6g Q8h fosfo OR 4.5g Q8h pip-tazo for 7d
  - Up to 14 days allowed for bacteremia
  - No oral switch allowed
- CrCl <20mL/min excluded from study
- MICs at central laboratory using agar dilution method
- Clinical and microbiological response at test of cure:
  - 64.7% Fosfo vs 54.5% pip-tazo (95% CI = -0.4 – 20.8)

Kaye KS, et al. *Clin Infect Dis* 2019;epub AOP 3/19

Fosfomycin: When and Where, but…

Verified Date/Time: 8/25/2018 07:40 PDT
Urine colony count >100,000 CFU/ml E. coli , ESBL producer & 2nd *E. coli*

***E. Coli* #1**		
Antibiotic	MIC	MIC Interp
Ampicillin	>=32	Resistant
Ampicillin/Sulb	**8**	**Susceptib**
Cefazolin	>=64	Resistant
Cefepime		Resistant
Ceftazidime		Resistant
Ceftriaxone	>=64	Resistant
Ciprofloxacin	>=4	Resistant
Gentamicin	**<=1**	**Susceptible**
Levofloxacin	>=8	Resistant
Meropenem	**<=0.25**	**Susceptible**
Nitrofurantoin	**<=16**	**Susceptible**
Piperacillin/Tazo	**<=4**	**Susceptible**
TMP/SMX	>=16/304	Resistant
ESBL	Positive	

E.coli #2		
Antibiotic	MIC	MIC Interp
Ampicillin	>=32	Resistant
Ampicillin/Sulb	16	Intermediate
Cefazolin	**<=4**	**Susceptible**
Ciprofloxacin	**<=0.25**	**Susceptible**
Gentamicin	**<=1**	**Susceptible**
Levofloxacin	**0.5**	**Susceptible**
Meropenem	**<=0.25**	**Susceptible**
Nitrofurantoin	**<=16**	**Susceptible**
Piperacillin/ Tazobactam	**<=4**	**Susceptible**
TMP/SMX	**1/19**	**Susceptible**
ESBL	Negative	


EDITORIALS

Omadacycline — The Newest Tetracycline

Henry F. Chambers, M.D.

Clinical Infectious Diseases
EDITORIAL COMMENTARY

IDSA hivma

Another New Antibiotic for Skin Infections and Why Infectious Disease Specialists Are Hypocrites

- "…one must ask: So what?"
- "…we shun the use of new and novel drugs that we have been begging for."

New Drugs I'm Not Sure What to Do With Yet: Delafloxacin

- Want a new FQ?
- $200.00/day
- ABSSSI indication
- Pneumonia & UTI in the works
- No QT warning
- MRSA activity

- Issues:
  - Not better for gram negatives
  - *P. aeruginosa* indication = weak
  - Anaerobe activity look amazing…
  - Are those moxiflox R anaerobes?
  - Tendons, confusion, etc…

New Drugs I'm Not Sure What to Do With Yet: Eravacycline

- IV only tetracycline class
- Twice daily dosing
- Spectrum = tigecycline
- Failed 2 cUTI trials
- Equivalent to mero and erta in IAI phase 3 studies
- Carbapenem sparing?

- Issues:
  - = tigecycline spectrum
  - No *P. aeruginosa* activity
  - No oral formulation
  - Nausea still an issue
  - Price = tigecycline

New Drugs I'm Not Sure What to Do With Yet: Omadacycline

- IV and Oral tetracycline class
- Once daily dosing
- Spectrum = tigecycline
- Equivalent to moxifloxacin for CAP
- Equivalent to linezolid for SSSTI

- **Issues**:
- Fast for at least 4 hours and then take with water[1] can be taken at bedtime or upon waking
- No food or drink (except water) for 2 hours after dosing[1]
- No dairy products, antacids, or multivitamins for 4 hours after dosing[1]
- Efficacy and safety of an oral loading dose was not evaluated in CABP – day 1 IV required per label

What's New on the Gram + Side?


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 5, 2014 VOL. 370 NO. 23

Once-Weekly Dalbavancin versus Daily Conventional Therapy for Skin Infection

Helen W. Boucher, M.D., Mark Wilcox, M.D., George H. Talbot, M.D., Sailaja Puttagunta, M.D., Anita F. Das, Ph.D., and Michael W. Dunne, M.D.

DICINE

ORIGINAL ARTICLE

Single-Dose Oritavancin in the Treatment of Acute Bacterial Skin Infections

G. Ralph Corey, M.D., Heidi Kabler, M.D., Purvi Mehra, M.D., Sandeep Gupta, M.D., J. Scott Overcash, M.D., Ashwin Porwal, M.D., Philip Giordano, M.D., Christopher Lucasti, M.D., Antonio Perez, M.D., Samantha Good, Ph.D., Hai Jiang, Ph.D., Greg Moeck, Ph.D., and William O'Riordan, M.D., for the SOLO I Investigators*

So What's New About These?

Oritavancin 1200mg

Parameter	Mean (%CV)
$T_{1/2\alpha}$	2.3h (50%)
$T_{1/2\beta}$	13.4h (10%)
$T_{1/2\gamma}$	**245h (15%)**

Dalbavancin 1000mg

Parameter	Mean (%CV)
$T_{1/2\alpha}$	-
$T_{1/2\beta}$	-
$T_{1/2\gamma}$	**346h (17%)**

That is 10.2 and 14.4 **DAYS** respectively

Oritavancin Prescribing Information – Revised 8/2014
Dalbavancin Prescribing Information – Revised 5/2014

Dalbavancin – Strengths & Weaknesses

- Strengths:
  - Rapidly bactericidal
  - Faster infusion time (30-60min)
  - Administer w/o regard to dialysis
  - Dosing recommendation for CrCl<30
  - Better stability
  - No QT prolongation
  - No coagulation test problems
- Weaknesses:
  - LFTs?
  - Cross resistance/VISA

Oritavancin Strengths and Weaknesses

- Strengths
  - VRE activity
  - Rapidly bactericidal
- Weaknesses
  - Drug interactions (P450 activity!!)
  - Interference with anticoagulation assays
  - Stability
  - Infusion time and volume
  - Cross resistance/VISA
  - PK in severe renal dysfunction and dialysis - unclear

Prices

Agent	Inpatient Price/Outpatient
Daptomycin 500mg vial	$175/60
Dalbavancin 500mg vial	$950/675
Oritavancin 400mg vial	$950/620

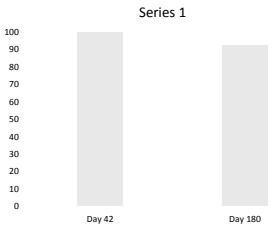
- Remember dapto is 6-10mg/kg daily
- Dalbavancin is 1500mg X1
- Oritavancin is 1200mg X1
- So for 10 days of therapy inpatient
  - Dapto = $1750-3500
  - Dalba = $3850
  - Orita = $3850

Dalbavancin for Osteomyelitis in Adults

Concentrations ± SD at day 14

- Synovium - 15.3 ± 7.9mcg/g
- Synovial fluid– 6.2 ± 1.7mg/L
- Bone – 4.1 ± 1.6mcg/g
- Skin – 13.8 ± 2.1mcg/g
- MIC = ???

Clinical Response: N=54



Jandourek, A, et al. Eur Congress Clin Micro Infect Dis (ECCMID) 2017. OS-0130
Dunne MW , et al. *Antimicrob Agents Chemother* 2015;59:1849

The long-acting lipo-glycopeptides: Where We're Going?

Clinical Infectious Diseases

BRIEF REPORT

Dalbavancin as Primary and Sequential Treatment for Gram-Positive Infective Endocarditis: 2-Year Experience at the General Hospital of Vienna

Selma Tobudic,[1] Christina Forstner,[1,2] Heinz Burgmann,[1]

- 27 patients
- 92.6% clinical success rate
- Only used after bacteremia cleared

Clin Infect Dis 2018;67:795

Open Forum Infectious Diseases

BRIEF REPORT

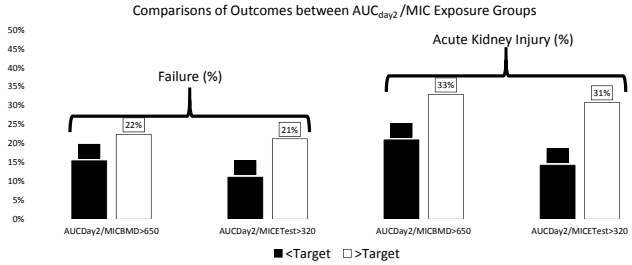
Dalbavancin as Secondary Therapy for Serious *Staphylococcus aureus* Infections in a Vulnerable Patient Population

Chloe Bryson-Cahn,[1,2] Alison M. Beieler,[1,2] Jeannie D. Chan,[1,2,3] Robert D. Harrington,[1,2] and Shireesha Dhanireddy[1,2]

[1]Division of Allergy and Infectious Diseases, Department of Medicine, University of Washington, School of Medicine, Seattle, Washington; [2]Harborview Medical Center, Seattle, Washington; [3]School of Pharmacy, University of Washington, Seattle, Washington

DOI: 10.1093/ofid/ofz028

What's New With Vanco? The ARLG PROVIDE Study



Lodise TP et al. IDWeek 2017 Abstract 985.

Conclusions

- Antibiotic development is tough and needs to be incentivized
- Gram negative resistance is a challenge and colistin is not the answer
- The new gram negative drugs have holes in their spectrum
- The long acting lipo-glycopeptides are intriguing but expensive
- Do we know what we're doing with vancomycin?

Osteomyelitis

Jina Makadia MD
Assistant Professor
Infectious Diseases OHSU
5/30/19

OBJECTIVES

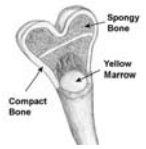
1) CLASSIFICATION OF OSTEOMYELITIS
2) MECHANISM AND PATHOGENESIS
3) IMAGING MODALITIES
4) APPROACH TO TREATMENT

Introduction

- Etymology
- ✓ Greek in origin
- ✓ Osteon – Bone
- ✓Myelos – Marrow
- ✓Itis – Inflammation

Osteomyelitis

- Inflammation of bone due to a pathogenic organism leading to destruction of bone
- It is a common disease with a variety of clinically and microbiologically distinct characteristics



Classification

- Traditionally:
- Hematogenous
- Direct contiguous spread without vascular insufficiency - eg open fracture, contaminated prosthesis
- Contiguous infection with vascular insufficiency – eg DFI

- Acute:
  - Signs and symptoms < 2 weeks
  - Acute hematogenous seeding or penetrating injury
- Chronic:
  - Signs and symptoms ≥2 weeks
  - Usually occurs by contiguous spread

Osteomyelitis - Mechanism

- Ongoing inflammatory cytokines lead to **bone destruction**
- Vascular channels are compressed and obliterated by the inflammatory process - resulting ischemia contributes to bone **necrosis**
- Segments of bone devoid of blood supply can become separated to form **sequestra**
  - Antibiotics and inflammatory cells cannot reach this avascular area
- **Biofilms**
  - Microbial community characterized by cells that attach to substratum or to each other, embedded in a matrix of extracellular polymeric substance
  - Alters phenotype in terms of growth, gene expression, and protein production
  - Fibrinogen covering evades host defense mechanisms and antimicrobial penetration
  - Allows bacteria to hide intracellularly and achieve slow metabolic rate

Lew and Waldvogel. Lancet 2004; 364: 369–79

Clinical Presentation

- Signs and symptoms vary depending on the category of infection, anatomic location and host.
- Hematogenous – mostly in long bones,
- In adults – vertebral osteomyelitis is more common followed by long bones, pelvis and clavicle
- Vertebrae blood supply is by segmental arteries that divide and perfuse segments of 2 adjacent vertebrae, thus vertebral osteomyelitis occurs in 2 contiguous bodies in intervertebral discs.

Clinical Presentation

- Fever, chills, pain at site of infection, purulent drainage are some of the symptoms that the patient complain about.
- Back pain could be the only complain in a patient with vertebral osteomyelitis
- Infections of the feet are more commonly seen in patients with osteomyelitis in the setting of vascular insufficiency
- In a diabetic foot – pain may be absent or minimal

Osteomyelitis - Diagnosis

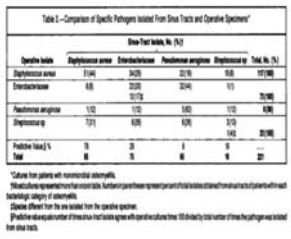
- Nonspecific pain around the involved site with the absence of systemic signs and symptoms is normal
- Labs
  - ESR/CRP often elevated
  - WBC normal or high
- Imaging
- Culture

Technique	Advantages	Disadvantages	Sensitivity	Specificity
X-ray	Cheap, accessible	Late diagnosis, confusion	**43-75%**	**75-83%**
CT	Excellent spatial resolution	Cost, radiation, availability	**~67%**	**~50%**
US	Accessibility, cheap, guided aspiration	Operator dependent, US beam can't cross cortical bone	**TBD**	**TBD**
MRI	Excellent spatial resolution, early detection, can assess extent	Cost, availability, time requested	**82-100%**	**75-96%**
3-phase bone scintigraphy	Sensitive, availability, early detection	Nonspecific, need further imaging	**~85%**	**~25%**
Combo bone and gallium scintigraphy	Reliable when clearly + or -	Need 2 isotopes w/ mult imaging over few days, high radiation	**~60%**	**~80%**

Pineda et al. Semin Plast Surg. 2009; 23(2): 80–89.

Swab Culture

- Mackowiak et al. JAMA. 1978 Jun 30;239(26):2772-5.
- Sinus-tract cultures compared with operative specimens in 40 pts with chronic osteo
  - 35 (87.5%) had a single pathogen isolated from operative specimens
  - Only 44% of the sinus-tract cultures contained the operative pathogen
- Isolation of *S. aureus* from sinus tracts correlated with the presence of *S. aureus* in the operative specimen
  - However, less than half of the sinus-tract cultures obtained from patients with *S. aureus* osteo contained this organism
- Isolation of bacteria other than *S aureus* from sinus tracts had a low likelihood of predicting the pathogen isolated from bone



Treatment Of Osteomyelitis

- Multidisciplinary approach

✓ surgical debridement
✓ antibiotics
✓ duration of antibiotics

- Surgical debridement of necrotic debris +/- ROH, revascularization
- When possible – delay abx until cx are obtained.

Antibiotic therapy for acute osteomyelitis in adults

Infectious agent	Antibiotic	Dosing
MSSA	Nafcillin	2 g IV every 4 hours
	Oxacillin	2 g IV every 4 hours
	Cefazolin	2 g IV every 8 hours
MRSA*	Vancomycin¶	30 to 40 mg/kg IV every 24 hours in two or three divided doses; not to exceed 2 g/dose
Coagulase-negative staphylococci	Vancomycin¶	30 to 40 mg/kg IV every 24 hours in two or three divided doses; not to exceed 2 g/dose unless serum trough levels are inappropriately low
Gram-negative organisms (including *Pseudomonas*)	Ciprofloxacin	750 mg orally twice daily or 400 mg IV every 12 hours; if treating *Pseudomonas*, increase IV dose to 400 mg IV every 8 hours&
	Levofloxacin	750 mg orally or IV once daily
	Ceftazidime	2 g IV every 8 hours
	Cefepime	2 g IV every 8 to 12 hours
Empiric therapy	Vancomycin PLUS an agent with activity against gram-negative organisms	

In stable patients, antibiotics may be held pending establishment of microbiologic diagnosis or obtaining cultures from bone debridement or biopsy. Total duration of antibiotic therapy (IV and step-down oral) is four to eight weeks. The doses in this table are intended for patients with normal renal function. The doses of many of these agents must be adjusted in the setting of renal insufficiency; refer to the Lexicomp drug-specific monographs for renal dose adjustments.

MSSA: methicillin-susceptible *Staphylococcus aureus*; MRSA: methicillin-resistant *S. aureus*; IV: intravenously.

* For alternative agents with activity against MRSA, refer to the topic on treatment of invasive infections due to methicillin-resistant *S. aureus* infection in adults.

¶ In adults, vancomycin is dosed based on actual body weight. Vancomycin dose should be adjusted for target trough concentration of 10 to 20 mcg/mL. Refer to the UpToDate topic review on vancomycin parenteral dosing and serum concentration monitoring in adults.

Δ Oral ciprofloxacin at dose shown in table achieves therapeutic levels for treatment of *Pseudomonas*.

Data from:

1. Calhoun JH, Manring MM. Adult osteomyelitis. Infect Dis Clin North Am 2005; 19:765.
2. Berbari EF, Kanj SS, Kowalski TJ, et al. 2015 Infectious Diseases Society of America (IDSA) clinical practice guidelines for the diagnosis and treatment of native vertebral osteomyelitis in adults. Clin Infect Dis 2015; 61:e26.

UpToDate®

- Staph Osteo
- ✓ empirically – should consist of anti mrsa coverage initially
- ✓ adjunctive treatment - ? Combination with Rifampin for biofilms, hyperbaric oxygen.

❖ In one series including 142 patients with refractory osteomyelitis treated with HBO, successful healing without relapse was observed in 73 percent of patients

- Gram Neg osteo
- ✓ FQ are excellent if no resistance exists.
- ✓ Other abx based on susceptibility

- Duration
- ✓ optimal duration of antibiotic therapy is not certain
- ✓ some suggest cont iv until debrided bone is covered by vascularized tissue
- ✓ usually 6 weeks from last debridement
- ✓ suppression if hardware present 3-6 months. ? If longer is helpful
- ✓ if amputation - shorter course

- Complications
- ✓ infection of contiguous structures
- ✓ sinus tracts
- ✓ Pathological fractures
- ✓ Hematogenous spread/ sepsis – rare

Native Vertebral Osteomyelitis

- ✓ dx often delayed
- ✓ persistent back pain with elevated esr or crp
- ✓ Unresponsive to conservative measures
- ✓ MRI often required
- ✓ Hold off empiric treatment unless septic and have neurologic compromise
- ✓ image guided or OR aspiration or biopsy
- ✓ Commonly monomicrobial
- ✓ concomitant bacteremia may preclude need for biopsy
- ✓ many pts do well with 6 weeks of abx
- ✓ 3 months for Brucella (strepto X 3 weeks and doxy for 3 months OR doxy/rif 3 months)

- Surgical indications
- ✓ neurological deficits
- ✓ Cord compression
- ✓ Progression despite abx

- Repeat imaging for worsening clinical symptoms
- Fungal, mycobac, Brucella cx – based of epidemiology clues.
- May need specimen broad pcr testing

Table 2. Parenteral Antimicrobial Treatment of Common Microorganisms Causing Native Vertebral Osteomyelitis

Microorganism	First Choice[a]	Alternatives[a]	Comments[a]
Staphylococci, oxacillin susceptible	Nafcillin sodium or oxacillin 1.5–2 g IV q4–6 h or continuous infusion or Cefazolin 1–2 g IV q8 h or Ceftriaxone 2 g IV q24 h	Vancomycin IV 15–20 mg/kg q12 h or daptomycin 6–8 mg/kg IV q24 h or linezolid 600 mg PO/IV q12 h or levofloxacin 500–750 mg PO q24 h and rifampin PO 600 mg daily [122] or clindamycin IV 600–900 mg q8 h	6 wk duration
Staphylococci, oxacillin resistant [122]	Vancomycin IV 15–20 mg/kg q12 h (consider loading dose, monitor serum levels)	Daptomycin 6–8 mg/kg IV q24 h or linezolid 600 mg PO/IV q12 h or levofloxacin PO 500–750 mg PO q24 h and rifampin PO 600 mg daily [122]	6 wk duration
Enterococcus species, penicillin susceptible	Penicillin G 20–24 million units IV q24 h continuously or in 6 divided doses, or ampicillin sodium 12 g IV q24 h continuously or in 6 divided doses	Vancomycin 15–20 mg/kg IV q12 h (consider loading dose, monitor serum levels) or daptomycin 6 mg/kg IV q24 h or linezolid 600 mg PO or IV q12 h	Recommend the addition of 4–6 wk of aminoglycoside therapy in patients with infective endocarditis. In patients with BSI, physicians may opt for a shorter duration of therapy. Optional for other patients [124, 125]. Vancomycin should be used only in case of penicillin allergy.
Enterococcus species, penicillin resistant	Vancomycin IV 15–20 mg/kg q12 h (consider loading dose, monitor serum levels)	Daptomycin 6 mg/kg IV q24 h or linezolid 600 mg PO or IV q12 h	Recommend the addition of 4–6 wk of aminoglycoside therapy in patients with infective endocarditis. In patients with BSI, physicians may opt for a shorter duration of aminoglycoside. The additional of aminoglycoside is optional for other patients [124, 125].
Pseudomonas aeruginosa	Cefepime 2 g IV q8–12 h or meropenem 1 g IV q8 h or doripenem 500 mg IV q8 h	Ciprofloxacin 750 mg PO q12 h (or 400 mg IV q8 h) or aztreonam 2 g IV q8 h for severe penicillin allergy and quinolone-resistant strains or ceftazidime 2 g IV q8 h	6 wk duration. Double coverage may be considered (ie, β-lactam and ciprofloxacin or β-lactam and an aminoglycoside).
Enterobacteriaceae	Cefepime 2 g IV q12 h or ertapenem 1 g IV q24 h	Ciprofloxacin 500–750 mg PO q12 h or 400 mg IV q12 hours	6 wk duration
β-hemolytic streptococci	Penicillin G 20–24 million units IV q24 h continuously or in 6 divided doses or ceftriaxone 2 g IV q24 h	Vancomycin IV 15–20 mg/kg q12 h (consider loading dose, monitor serum levels)	6 wk duration. Vancomycin only in case of allergy.
Propionibacterium acnes	Penicillin G 20 million units IV q24 h continuously or in 6 divided doses or ceftriaxone 2 g IV q24 h	Clindamycin 600–900 mg IV q8 h or vancomycin IV 15–20 mg/kg q12 h (consider loading dose, monitor serum levels)	6 wk duration. Vancomycin only in case of allergy.
Salmonella species	Ciprofloxacin PO 500 mg q12 h or IV 400 mg q12 h	Ceftriaxone 2 g IV q24 h (if nalidixic acid resistant)	6–8 wk duration

Abbreviations: BSI, bloodstream infection; IV, intravenous; PO, take orally; q, every.

[a] [illegible]

[illegible]

Table 3. Selected Oral Antibacterial Agents With Excellent Oral Bioavailability Commonly Used to Treat Patients With Native Vertebral Osteomyelitis

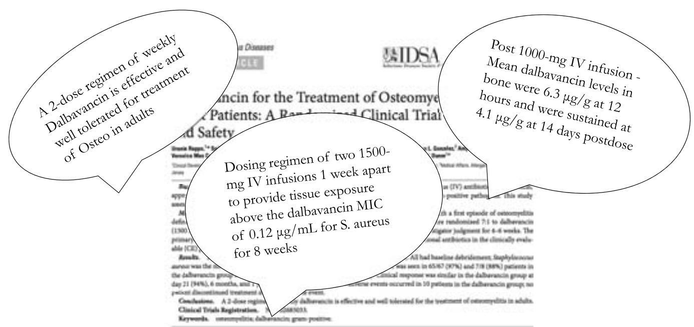
Oral Agents	Comments
Metronidazole 500 mg PO tid to qid	Can be used in the initial course of NVO due to *Bacteroides* species and other susceptible anaerobes.
Moxifloxacin 400 mg PO once daily	Is not recommended for use in patients with staphylococcal NVO, but may be used in patients with NVO due to Enterobacteriaceae and other susceptible aerobic gram-negative organisms.
Linezolid 600 mg PO bid	Can be used in the initial course of NVO due to oxacillin-resistant staphylococci when first-line agents cannot be used.
Levofloxacin 500–750 mg PO once daily	Is not recommended for use in patients with staphylococcal NVO as monotherapy but may be used in patients with NVO due to Enterobacteriaceae and other susceptible aerobic gram-negative organisms.
Ciprofloxacin 500–750 mg PO bid	Is not recommended for use in patients with staphylococcal NVO but may be used in patients with NVO due to Enterobacteriaceae and other susceptible aerobic gram-negative organisms including *Pseudomonas aeruginosa* and *Salmonella* species.
TMX-SMX 1–2 double strength tabs PO bid	Is not recommended for use in patients with staphylococcal NVO but may be recommended as a second-line agent in patients with NVO due to Enterobacteriaceae and other susceptible aerobic gram-negative organisms. May need to monitor sulfamethoxazole levels.
Clindamycin 300–450 mg PO qid	Recommended as second-line choice for sensitive staphylococcal NVO.
Doxycycline and rifampin	Mostly used in patients with brucellar NVO.

Dosages need to be adjusted based on patients' renal and hepatic function. Antimicrobials should be chosen based on in vitro susceptibility as well as patient allergies, intolerances, and potential drug interactions or contraindications to a specific antimicrobial.

Abbreviations: bid, twice daily; NVO, native vertebral osteomyelitis; PO, take orally; qid, 4 times daily; tid, 3 times daily; TMP-SMX, trimethoprim-sulfamethoxazole.

Dalbavancin

- A lipoglycopeptide with an antibiotic spectrum similar to that of vancomycin
- Long half-life (180–240 hours, allowing weekly or biweekly dosing) and achieves high concentrations in bone.
- Approved for the treatment of acute bacterial skin and skin structure infection (ABSSSI) as a 30-minute IV infusion in a single dose (1500 mg IV) or as 2 doses (1000 mg IV followed 1 week later by 500 mg IV)
- Potent activity against gram-positive pathogens that cause bone and joint infection, with a minimum inhibitory concentration (MIC) required to inhibit the growth of 90% of S. aureus isolates.



THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral versus Intravenous Antibiotics for Bone and Joint Infection

H.-K. Li, I. Rombach, R. Zambellas, A.S. Walker, M.A. McNally, B.L. Atkins, B.A. Lipsky, H.C. Hughes, D. Bose, M. Kümin, C. Scarborough, P.C. Matthews, A.J. Brent, J. Lomas, R. Gundle, M. Rogers, A. Taylor, B. Angus, I. Byren, A.R. Berendt, S. Warren, F.E. Fitzgerald, D.J.F. Mack, S. Hopkins, J. Folb, H.E. Reynolds, E. Moore, J. Marshall, N. Jenkins, C.E. Moran, A.F. Woodhouse, S. Stafford, R.A. Seaton, C. Vallance, C.J. Hemsley, K. Bisnauthsing, J.A.T. Sandoe, I. Aggarwal, S.C. Ellis, D.J. Bunn, R.K. Sutherland, G. Barlow, C. Cooper, C. Geue, N. McMeekin, A.H. Briggs, P. Sendi, E. Khatamzas, T. Wangrangsimakul, T.H.N. Wong, L.K. Barrett, A. Alvand, C.F. Old, J. Bostock, J. Paul, G. Cooke, G.E. Thwaites, P. Bejon, and M. Scarborough, for the OVIVA Trial Collaborators*

- Oral versus Intravenous Antibiotics for Bone and Joint Infection.*Li HK, Rombach I, Zambellas R, Walker AS, McNally MA, Atkins BL, Lipsky BA, Hughes HC, Bose D, Kümin M, et al.* N Engl J Med. 2019 Jan 31; 380(5):425-436.

OVIVA TRIAL

- Multicenter, open label, randomized, controlled non-inferiority trial
- Investigated Po vs IV antibiotics for complex orthopedic infection
- 26 UK centers, adults with bone and joint infections with/without surgical intervention
- Randomly assigned to IV or PO to complete the first 6 weeks with po followup in both groups if needed
- Primary end point – Rx failure within 1 year after randomization
- Antibiotics were selected by ID specialists

- Factor – local epidemiology, antimicrobial susceptibility, bioavailability, previous infections, contraindications, allergy, drug-drug interactions were taken into account
- Rifampin was permitted at ID discretion

- 1054 pts were randomized – 527 in each group
- End point available for 1015(96.3%)
- Treatment failure – 14.6% in the IV group and 13.2% in the oral

CONCLUSIONS

Oral antibiotic therapy was noninferior to intravenous antibiotic therapy when used during the first 6 weeks for complex orthopedic infection, as assessed by treatment failure at 1 year. (Funded by the National Institute for Health Research; OVIVA Current Controlled Trials number, ISRCTN91566927.)

Adjunctive Therapy

- Even with standard care, therapeutic failures and recurrences are common, often in the range 20 to 30%
- Consequences of treatment failure may escalate to limb loss most commonly seen in our diabetic pts

- Outcomes of osteomyelitis among patients treated with outpatient parenteral antimicrobial therapy. *Tice AD, Hoaglund PA, Shoultz DA Am J Med. 2003 Jun 15; 114(9):723-8.*
- Diagnosis and treatment of diabetic foot infections. *Lipsky BA, Berendt AR, Deery HG, Embil JM, Joseph WS, Karchmer AW, LeFrock JL, Lew DP, Mader JT, Norden C, Tan JS, Infectious Diseases Society of America. Plast Reconstr Surg. 2006 Jun; 117(7 Suppl):212S-238S.*

➢ **Hyperbaric oxygen therapy (HBOT)**

- Has perhaps the longest history of reported efficacy in treating refractory cases of osteomyelitis
- HBOT involves the intermittent inhalation of 100% oxygen in specialized chambers at pressures greater than that at sea level
- The arterial partial pressure of oxygen rises to ~1500 mm Hg under these hyperbaric conditions; oxygen tensions can approach 500 mm Hg in soft tissue and 200 mm Hg in bone
- Osteomyelitic bone has been shown to be hypoxic, and hyperbaric oxygen (HBO) enhances bactericidal activity just like neutrophils during an infection.

Hyperbaric oxygen therapy in the treatment of chronic refractory osteomyelitis: a preliminary report. *Chen CE, Shih ST, Fu TH, Wang JW, Wang CJ Chang Gung Med J. 2003 Feb; 26(2):114-21.*

Hyperbaric oxygen: its uses, mechanisms of action and outcomes. *Gill AL, Bell CN, QJM. 2004 Jul; 97(7):385-95.*

Hyperbaric oxygen therapy in orthopedic conditions. *Kawashima M, Yamura H, Nagayoshi I, Takao K, Yoshida K, Yamaguchi T, Undersea Hyperb Med. 2004 Spring; 31(1):155-62.*

➢ **Growth factors such as the bone morphogenetic proteins (BMPs)**

- studied extensively for their effects in modulating osteogenesis.
- Play important roles in skeletal development and bone formation
- Multiple studies have demonstrated the positive effects of exogenous BMPs in accelerating osteogenesis and bone healing in animal models.
- Only recently received attention as potential therapeutic adjuncts to the management of chronic osteomyelitis, and their clinical utility remains speculative at this time.

Osteogenic protein-1 induced bone formation in an infected segmental defect in the rat femur. *Chen X, Kidder LS, Lew WD J Orthop Res. 2002 Jan; 20(1):142-50.*

Angiogenic gene therapy as a potential therapeutic agent in chronic osteomyelitis. *Rusc JJ Med Hypotheses. 2006; 67(1):161-3.*

➢ **Pulsed Electromagnetic Field (PEMF)**

- PEMFs are believed to simulate the endogenous electrical fields that are produced by bone in response to mechanical strain. This response of bone to physical loads is believed to stimulate new bone growth.
- It has also been suggested that electrical fields or ultrasound can be efficacious in disrupting the attachment of biofilms

Engineering approaches for the detection and control of orthopaedic biofilm infections. *Ehrlich GD, Stoodley P, Kathju S, Zhao Y, McLeod BR, Balaban N, Hu FZ, Sotereanos NG, Costerton JW, Stewart PS, Post JC, Lin Q Clin Orthop Relat Res. 2005 Aug; (437):59-66.*

➢ **Platelet rich plasma**

- concentrate of autologous blood containing the plasma fraction with a platelet concentration above baseline levels
- improve healing, primarily in periodontal and oral surgery, maxillofacial surgery, aesthetic surgery, spinal fusion, heart bypass surgery, and chronic wound
- Given the vulnerary effects that are apparent in soft tissue healing and also bone healing, one may speculate that these effects may also enhance healing in a wound or fracture complicated by osteomyelitis.

Platelet-rich plasma: a review of biology and applications in plastic surgery. *Eppley BL, Pietrzak WS, Blanton M Plast Reconstr Surg. 2006 Nov; 118(6):147e-159e*

Platelet-rich plasma: evidence to support its use. *Marx RE J Oral Maxillofac Surg. 2004 Apr; 62(4):489-96.*

When there is Balance in the Force

ID MD and ID PharmD Perspectives on Common ID topics in Primary Care

DATE: February 2019 PRESENTED BY: Erin Bonura MD, MCR & James Lewis PharmD

Objectives

- Select antimicrobial therapy for common primary care infections using an antibiogram
- State which conditions do not need antibiotics
- State the duration of therapy for common primary care infections

Outpatient Antibiogram

	Gram Negative Aerobes						Gram Positive Aerobes						
	Pseudomonas aeruginosa (168)	Enterobacter cloacae (50)	E.coli (1018)	Proteus mirabilis (72)	Klebsiella pneumoniae (148)	Klebsiella oxytoca (49)	Enterococcus faecalis (133)	MRSA (methicillin-resistant Saureus) (161)	MSSA (methicillin-susceptibe Saureus) (560)	Staphylococcus coagulase-negative (59)	Staphylococcus lugdunesis (48)	Streptococcus pneumoniae (non-meningitis) (35)	Streptococcus pneumoniae (meningitis) (35)
Ampicillin	-	-	62	86	-	-	99	-	-	-	-	-	-
Amoxicillin/clavulanate	-	-	87	96	92	84	-	-	-	-	-	-	-
Cefazolin	-	-	93	96	95	28	-	-	100	64	92	-	-
Cefepime	93	92	99	99	97	100	-	-	-	-	-	-	-
Ceftriaxone	-	84	97	99	95	96	-	-	-	-	-	100	96
Ciprofloxacin	88	98	89	96	94	94	84*	-	-	-	-	-	-
Clindamycin	-	-	-	-	-	-	-	65	80	71	85	-	-
Erythromycin	-	-	-	-	-	-	-	-	-	-	-	76	-
Gentamicin	90	100	95	94	95	94	-	-	-	-	-	-	-
Levofloxacin	82	98	89	99	96	94	91*	-	-	-	98	100	-
Meropenem	90	100	100	100	100	100	-	-	-	-	-	-	-
Nitrofurantoin	-	66	97	-	37	96	100	-	-	93	100	-	-
Oxacillin (Nafcillin)	-	-	-	-	-	-	-	-	100	64	92	-	-
Penicillin (intravenous)	-	-	-	-	-	-	-	-	-	-	-	98	84
Piperacillin/tazobactam	90	86	97	100	95	88	-	-	-	-	-	-	-
Tetracycline	-	92	82	-	79	90	24	98	95	85	94	-	-
Tobramycin	96	100	94	96	93	92	-	-	-	-	-	-	-
Trimethoprim/ sulfamethoxazole	-	82	82	90	92	92	-	92	97	58	98	80	-
Vancomycin	-	-	-	-	-	-	100	100	100	100	100	100	-

* Use for urine pathogens only

RESEARCH

OPEN ACCESS

Check for updates

Appropriateness of outpatient antibiotic prescribing among privately insured US patients: ICD-10-CM based cross sectional study

Kao-Ping Chua,[1] Michael A Fischer,[2] Jeffrey A Linder[3]

- 19,203,264 privately insured U.S. kids & adults
- 15,455,834 outpatient antibiotic Rxs
- Among all antibiotic prescriptions filled:
  - 23.2% were inappropriate
  - 35.5% were potentially appropriate
  - 28.5% not associated with a recent diagnosis code

 BMJ 2019;364:k5092

Case 1: Rey

Rae is a 21 year old Jedi Padawan who presents with an abscess on her left arm after a recent lightsaber injury. On exam her vitals are normal but she does have a 3x5 cm abscess with surrounding erythema on her L forearm that is warm and very tender to touch. What would you do?

A. Start clindamycin
B. Perform an Incision and Drainage only
C. Perform an I&D then start doxycycline
D. Start IV vancomycin

Categorization of Skin & Skin Structure Infections

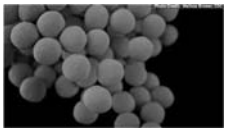
NONPurulent: Erysipelas, Cellulitis, Necrotizing

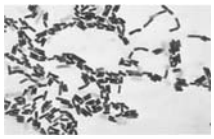
Purulent: Furuncle, Carbuncle, Abscess

	Mild	Moderate	Severe
	Localized	Purulent/Non-purulent + systemic signs*	(1) Failed I&D + abx (2) Immunocompromised (3) Severe systemic signs (4) Deeper infection, organ dysfunction, hypotension
* Systemic signs = T>38C, HR>90, RR >24, WBC >12k or <400 cells			

Clin Infect Dis. 2014 Jul 15;59(2):147-59.

Pathogens Associated with **NON**-purulent SSSI

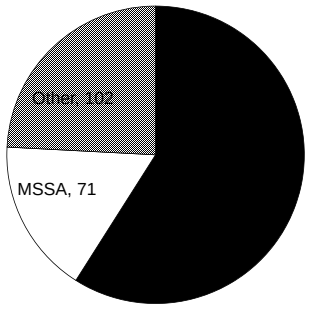




Pathogens Associated with PURULENT SSSI

MSSA/MRSA

Evidence of MSSA/MRSA epidemiology



N Engl J Med. 2006;355(7):666

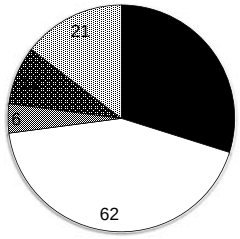
Bacterial Epidemiology in IVDU vs Non-IVDU Patients

Location	IVDU # (%)	Non-IVDU # (%)
Upper Extremity	**59 (69)**	24 (32)
Lower Extremity	13 (15)	**23 (31)**
Buttock/Perirectal	9 (11)	9 (12)
Axilla	---	5 (7)
Breast	2 (2)	4 (5)
Pilonidal	---	4 (5)
Abdomen	3 (3)	2 (3)
Other	---	3 (4)
Total	86	74

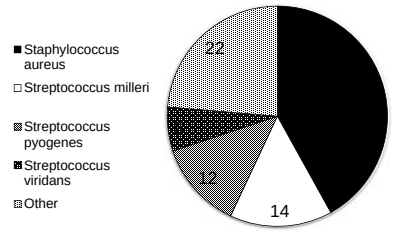
Clin Infect Dis. 1995 Jun;20 Suppl 2:S279-82.

Bacterial Epidemiology in IVDU vs Non-IVDU Patients

IVDU



Non-IVDU



Clin Infect Dis. 1995 Jun;20 Suppl 2:S279-82.

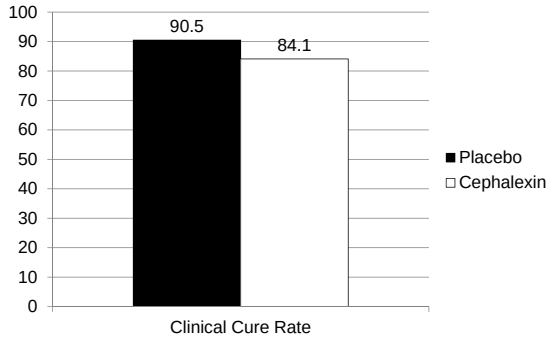
Antibiotic Choice for Outpatient Management of SSSI

	Gram Negative Aerobes						Gram Positive Aerobes						
	Pseudomonas aeruginosa (168)	Enterobacter cloacae (50)	E.coli (1018)	Proteus mirabilis (72)	Klebsiella pneumoniae (148)	Klebsiella oxytoca (49)	Enterococcus faecalis (133)	MRSA (methicillin-resistant Saureus) (161)	MSSA (methicillin-susceptible S.aureus) (569)	Staphylococcus coagulase-negative (59)	Staphylococcus lugdunesis (48)	Streptococcus pneumoniae (non-meningitis) (35)	Streptococcus pneumoniae (meningitis) (35)
Ampicillin	-	-	62	86	-	-	99	-	-	-	-	-	-
Amoxicillin/clavulanate	-	-	87	96	92	84	-	-	-	-	-	-	-
Cefazolin	-	-	93	96	95	28	-	-	100	64	92	-	-
Cefepime	93	92	99	99	97	100	-	-	-	-	-	-	-
Ceftriaxone	-	84	97	99	95	96	-	-	-	-	-	100	96
Ciprofloxacin	88	98	89	96	94	94	84*	-	-	-	-	-	-
Clindamycin	-	-	-	-	-	-	-	65	80	71	85	-	-
Erythromycin	-	-	-	-	-	-	-	-	-	-	-	76	-
Gentamicin	90	100	95	94	95	94	-	-	-	-	-	-	-
Levofloxacin	82	98	89	99	96	94	91*	-	-	-	98	100	-
Meropenem	90	100	100	100	100	100	-	-	-	-	-	-	-
Nitrofurantoin	-	66	97	-	37	96	100	-	-	93	100	-	-
Oxacillin (Nafcillin)	-	-	-	-	-	-	-	-	100	64	92	-	-
Penicillin (intravenous)	-	-	-	-	-	-	-	-	-	-	-	98	84
Piperacillin/tazobactam	90	86	97	100	95	88	-	-	-	-	-	-	-
Tetracycline	-	92	82	-	79	90	24	98	95	85	94	-	-
Tobramycin	96	100	94	96	93	92	-	-	-	-	-	-	-
Trimethoprim/ sulfamethoxazole	-	82	82	90	92	92	-	92	97	58	98	80	-
Vancomycin	-	-	-	-	-	-	100	100	100	100	100	100	-

* Use for urine pathogens only

Why Do Providers Love Clinda?

Do We Need Antibiotics for Purulent SSSI?



Antimicrob Agents Chemother. 2007 Nov;51(11):4044-8.

Case 2: Shmi

Shmi has a history of recurrent UTI and has been in a remote area without much access to health care for some time where she developed fever, dysuria and back pain. She is brought to the ER by her son and found to have a fever of 101 (other vitals stable), costovertebral tenderness and 100,000 cfu of e.coli in her urine. What would you do?

A. Start nitrofurantoin
B. Treat with fosfomycin
C. Treat with cipro x 7 days
D. Treat with IV ertapenem x 14 days
E. Do not treat, she has asymptomatic bacteriuria

JCM

Urine Is Not Sterile: Use of Enhanced Urine Culture Techniques To Detect Resident Bacterial Flora in the Adult Female Bladder

Evann E. Hilt,[a] Kathleen McKinley,[b] Meghan M. Pearce,[c] Amy B. Rosenfeld,[d] Michael J. Zilliox,[d] Elizabeth R. Mueller,[e] Linda Brubaker,[e] Xiaowu Gai,[d] Alan J. Wolfe,[a,c] Paul C. Schreckenberger[a,b]

Infectious Disease and Immunology Institute,[a] Department of Pathology,[b] Department of Microbiology and Immunology,[c] Department of Molecular Pharmacology and Therapeutics,[d] and Departments of Obstetrics & Gynecology and Urology,[e] Stritch School of Medicine Loyola University Chicago, Maywood, Illinois, USA

Review Article

Page 1 of 7

The female urinary microbiota, urinary health and common urinary disorders

Linda Brubaker[1], Alan J. Wolfe[2]

[1]Departments of Obstetrics & Gynecology and Urology, [2]Department of Microbiology and Immunology, Loyola University Chicago Stritch School of Medicine, Maywood, IL 60130, USA

Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Linda Brubaker, MD, MS. Departments of Obstetrics & Gynecology and Urology, Stritch School of Medicine Loyola University Chicago, 2160 South First Avenue, Maywood, IL 60153, USA. Email: LBrubaker@luc.edu.

MAJOR ARTICLE

Asymptomatic Bacteriuria Treatment Is Associated With a Higher Prevalence of Antibiotic Resistant Strains in Women With Urinary Tract Infections

Tommaso Cai,[1] Gabriella Nesi,[5] Sandra Mazzoli,[7] Francesca Meacci,[7] Paolo Lanzafame,[2] Patrizio Caciagli,[3] Liliana Mereu,[4] Saverio Tateo,[4] Gianni Malossini,[1] Cesare Selli,[8] and Riccardo Bartoletti[6]

- 550 patients
- 257 not treated, 293 treated
- Antibiotic treatment associated with higher occurrence of antibiotic-resistant bacteria

Clin Infect Dis 2015;61:1655[19]

2 Pages of Pure Genius

TEACHABLE MOMENT

LESS IS MORE

Asymptomatic Bacteriuria, What Are You Treating?

Jennifer Weisdorf, MD
University of Colorado, Internal Medicine Residency Program, Aurora.

Serena Scott, MD
University of Colorado, Hospital Medicine Group, Department of Medicine, Aurora.

Story From the Front Lines

A man in his 80s with a history of interstitial lung disease, deep venous thrombosis treated with warfarin, and chronic venous stasis presented to the emergency department with swelling of his bilateral lower extremities. He had no other symptoms, and his vital signs were normal. As part of the workup, a urinalysis was obtained, the results of which demonstrated pyuria and positive leukocyte esterase. His urine was sent for culture, and in the meantime he

The increased risk of symptomatic UTI in patients with ABU was likely due to host factors that support bacterial colonization rather than the current strain becoming virulent. Intervening in such cases with antibiotics only increases the risk of progressively resistant infections with no observable clinical benefit.[3] A recent prospective randomized clinical trial[4] that studied sexually active young women indicated that the presence of ABU may even be protective. The study found that colonization

JAMA Internal Medicine 2015; epub 1/15/15

Outpatient Antibiogram

	Gram Negative Aerobes						Gram Positive Aerobes						
	Pseudomonas aeruginosa (168)	Enterobacter cloacae (50)	E.coli (1018)	Proteus mirabilis (72)	Klebsiella pneumoniae (148)	Klebsiella oxytoca (49)	Enterococcus faecalis (133)	MRSA (methicillin-resistant Saureus) (161)	MSSA (methicillin-susceptibe Saureus) (568)	Staphylococcus coagulase-negative (59)	Staphylococcus lugdunesis (48)	Streptococcus pneumoniae (non-meningitis) (35)	Streptococcus pneumoniae (meningitis) (35)
Ampicillin	-	-	62	86	-	-	99	-	-	-	-	-	-
Amoxicillin/clavulanate	-	-	87	96	92	84	-	-	-	-	-	-	-
Cefazolin	-	-	93	96	95	28	-	-	100	64	92	-	-
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Ciprofloxacin	88	98	89	96	94	94	84*	-	-	-	-	-	-
Clindamycin	-	-	-	-	-	-	-	65	80	71	85	-	-
Erythromycin	-	-	-	-	-	-	-	-	-	-	-	76	-
Gentamicin	90	100	95	94	95	94	-	-	-	-	-	-	-
Levofloxacin	82	98	89	99	96	94	91*	-	-	-	98	100	-
Meropenem	90	100	100	100	100	100	-	-	-	-	-	-	-
Nitrofurantoin	-	66	97	-	37	96	100	-	-	93	100	-	-
Oxacillin (Nafcillin)	-	-	-	-	-	-	-	-	100	64	92	-	-
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Tetracycline	-	92	82	-	79	90	24	98	95	85	94	-	-
Tobramycin	96	100	94	96	93	92	-	-	-	-	-	-	-
Trimethoprim/ sulfamethoxazole	-	82	82	90	92	92	-	92	97	58	98	80	-
Vancomycin	-	-	-	-	-	-	100	100	100	100	100	100	-

* Use for urine pathogens only

7 vs 14 Days of Ciprofloxacin (Cip) for Pyelonephritis

- **Randomized, open-label and double-blind, placebo-controlled, non-inferiority trial**

	Cip for 7 days (n=73)	Cip for 14 days (n=83)
Age	46 (27-62)	41 (23-58
Recurrent UTIs	11 (15%)	10 (12%)
E. Coli	64 (88%)	79 (95%)
Positive blood cultures	16 (22%)	26 (32%)
Initial IV dose of cip	14 (19%)	26 (32%)

Data are number (%) or median (IQR). All blood cultures grew *Escherichia coli*.

Sandberg T, et al. *Lancet* 2012;380:484-90.

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7 vs 14 Days of Ciprofloxacin (Cip) for Pyelonephritis

	Cip 7 days	Cip 14 days	Difference (90% CI)	Non-Inferiority test P value
Cure	93%	93%	-0.3% (-7.4 to 7.2)	0.015
Clinical failure or recurrent UTI symptoms	7%	7%	-	-

- The take home – quit treating pyelo for 14 days with quinolones!
- Even bacteremic pyelo!
- Questions when using non-quinolone agents

Sandberg T, et al. *Lancet* 2012;380:484-90.

Other Considerations

- FQs – Tendons, Neuropathy, CNS effects. Do not use for uUTI, ABECB, Sinusitis
- What to treat elderly UTI with
  - Nitrofurantoin issues
  - Bactrim issues
  - 3GC oral issues
  - Fosfomycin issues
- Altered mental status? - https://thecurbsiders.com/podcast/134-uti-delirium-voltaire

Case 3: Saw

Saw is a 57 year old man with diabetes and emphysema on 2L home O2 presents with fever, cough, and shortness of breath. T 100.4, HR 92, RR 20, BP 130/82, pO2 94% on 2L. His CXR is notable for a left lower lobe pneumonia. How do you manage this case?

A. Treat with ceftriaxone and azithromycin x 10 days
B. Treat with levofloxacin x 5-7 days
C. Treat with Azithromycin x 5 days
D. Treat with piperacillin-tazobactam x 5 days

Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults

Lionel A. Mandell,[1,a] Richard G. Wunderink,[2,a] Antonio Anzueto,[3,4] John G. Bartlett,[5] G. Douglas Campbell,[6] Nathan C. Dean,[3,10] Scott F. Dowell,[11] Thomas M. File, Jr.,[12,13] Daniel M. Musher,[1,4] Michael S. Niederman,[14,15] Antonio Torres,[16] and Cynthia G. Whitney[11]

Duration of antibiotic therapy.

32. Patients with CAP should be treated for a minimum of 5 days (level I evidence), should be afebrile for 48–72 h, and should have no more than 1 CAP-associated sign of clinical instability (table 10) before discontinuation of therapy (level II evidence). (Moderate recommendation.)

33. A longer duration of therapy may be needed if initial therapy was not active against the identified pathogen or if it was complicated by extrapulmonary infection, such as meningitis or endocarditis. (Weak recommendation; level III evidence.)

Clin Infect Dis 2007;44:s27-72

Research

JAMA Internal Medicine | Original Investigation | LESS IS MORE

Duration of Antibiotic Treatment in Community-Acquired Pneumonia
A Multicenter Randomized Clinical Trial

Ane Uranga, MD; Pedro P. España, MD; Amaia Bilbao, MSc, PhD; Jose María Quintana, MD, PhD; Ignacio Arriaga, MD; Maider Intxausti, MD; Jose Luis Lobo, MD, PhD; Laura Tomás, MD; Jesus Camino, MD; Juan Nuñez, MD; Alberto Capelastegui, MD, PhD

- 312 patients – 4 teaching hospitals in Spain
- Minimum of 5 days of antibiotics vs standard of care
- Intervention arm stopped based on
  - Tmax < 37.8C for 48h
  - ≤ 1 CAP associated sign of clinical instability – WHAT ARE THESE?

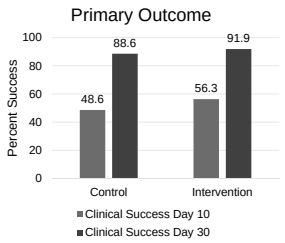
JAMA Internal Medicine 2016;176:1257-65

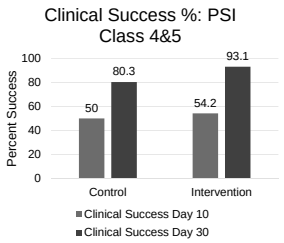
CAP Associated Signs of Instability

- No more than one of the following
  - SBP<90
  - HR >100/min
  - Respiratory rate >24/min
  - Arterial O2 saturation <90% or PaO2 <60mm Hg on room air
- Recommended by IDSA/ATS in 2007 CAP guidelines
  - Weak evidence
  - Poor uptake of recommendation
  - How often do you still see 10-14 days?

JAMA Internal Medicine 2016;176:1257-65

Outcomes



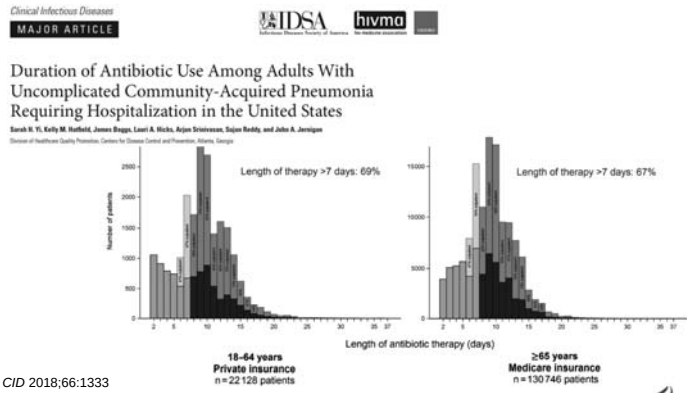


JAMA Internal Medicine 2016;176:1257-65

Results for Secondary Outcomes

Outcome	Control group (n=137)	Intervention group (n=146)	P Value
Time, median (IQR), days			
Taking antibiotics	10 (10-11)	5 (5-6.5)	<.001
Until clinical improvement	12 (8-18)	12 (7-15)	.41
Return to normal activity	18 (9-25)	15 (10-21)	.12
30 day mortality	3 (2.2%)	3 (2.1%)	>.99
30 day readmission	9 (6.6%)	2 (1.4%)	.02
Length of hospital stay, mean (sd)	5.5 (2.3)	5.7 (2.8)	.69

JAMA Internal Medicine 2016;176:1257-65


Clinical Infectious Diseases
MAJOR ARTICLE

IDSA hivma

Duration of Antibiotic Use Among Adults With Uncomplicated Community-Acquired Pneumonia Requiring Hospitalization in the United States

Length of therapy >7 days: 69%

Length of therapy >7 days: 67%

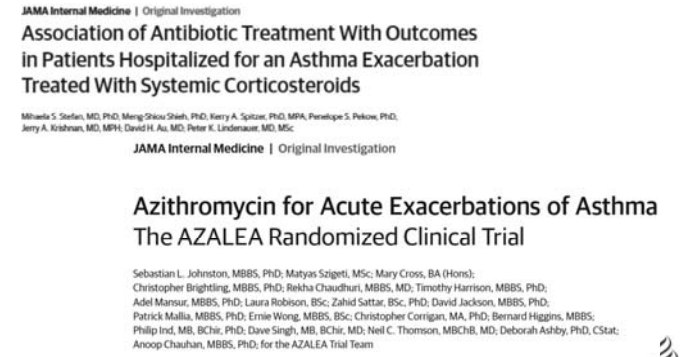
Length of antibiotic therapy (days)

18–64 years
Private insurance
n = 22 128 patients

≥65 years
Medicare insurance
n = 130 746 patients

CID 2018;66:1333

A Couple of Thoughts on Asthma Exacerbations


JAMA Internal Medicine | Original Investigation

Association of Antibiotic Treatment With Outcomes in Patients Hospitalized for an Asthma Exacerbation Treated With Systemic Corticosteroids

Mihaela S. Stefan, MD, PhD; Meng-Shiou Shieh, PhD; Kerry A. Spitzer, PhD, MPA; Penelope S. Pekow, PhD; Jerry A. Krishnan, MD, MPH; David H. Au, MD; Peter K. Lindenauer, MD, MSc

JAMA Internal Medicine | Original Investigation

Azithromycin for Acute Exacerbations of Asthma
The AZALEA Randomized Clinical Trial

Sebastian L. Johnston, MBBS, PhD; Matyas Szigeti, MSc; Mary Cross, BA (Hons); Christopher Brightling, MBBS, PhD; Rekha Chaudhuri, MBBS, MD; Timothy Harrison, MBBS, PhD; Adel Mansur, MBBS, PhD; Laura Robison, BSc; Zahid Sattar, BSc, PhD; David Jackson, MBBS, PhD; Patrick Mallia, MBBS, PhD; Ernie Wong, MBBS, BSc; Christopher Corrigan, MA, PhD; Bernard Higgins, MBBS; Philip Ind, MB, BChir, PhD; Dave Singh, MB, BChir, MD; Neil C. Thomson, MBChB, MD; Deborah Ashby, PhD, CStat; Anoop Chauhan, MBBS, PhD; for the AZALEA Trial Team

JAMA Intern Med 2019; doi:10.1001/jamainternmed.2018.5394.
JAMA Intern Med 2016;176:1630

Case 4: Jyn

Jyn is a 27 year old female in military special ops with no PMH who presents to you in between missions with headache, sinus pressure and colored nasal discharge for the past 2 days. She is concerned she has sinusitis and is asking for "a z-pak" because her friend Cassian had the same thing and improved after taking this for a couple days. She leaves on her next mission in 2 days and is worried this will decrease her function. What do you do?

A. Provide reassurance
B. Prescribe amoxicillin for 7 days
C. Prescribe amoxicillin-clavulanate for 10 days
D. Send a nasal culture to rule out MRSA

ABRS Common Factors

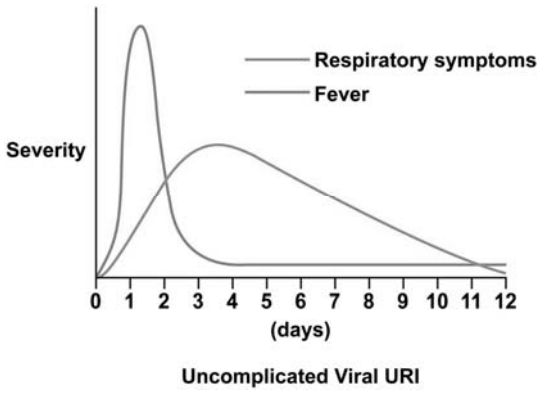
Major Criteria	Minor Criteria
Purulent Anterior Discharge	Headache
Purulent Posterior Discharge	Ear pain, fullness, pressure
Nasal obstruction/congestion	Halitosis
Facial fullness/ congestion	Dental pain
Hyposmia/Anosmia	Fever
Fever (acute sinusitis)	Fatigue

How Good are the Common Factors in Diagnosis of ABRS

- Based on Expert Panel
- Purulent rhinitis and facial pain most important together
- Sensitivity and specificity of "Top 3"
  - Purulent Rhinitis: 72%/52%
  - Facial pressure or pain: 52%/48%
  - Nasal Obstruction: 41%/80%

Williams JW et al. Rational Clinical Exam JAMA.1993;270(10):1242-1246

Signs and Symptoms of URI Over Time

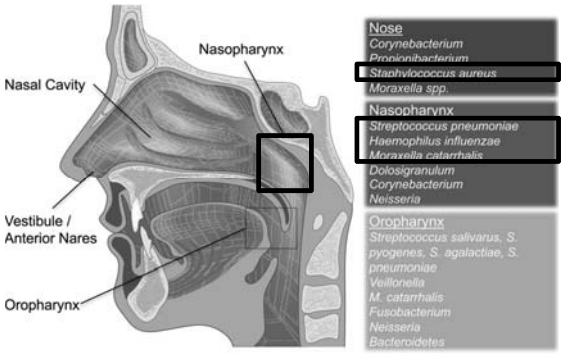


Pediatr Rev. 2013 Oct;34(10):429-37;

Indications for Treatment with Antibiotics

1. Persistent symptoms ≥10 days
2. Symptoms with T≥39 + purulent discharge or facial pain x 3-4 days
3. Double Sickening
   1. Typical viral URI
   2. Initially improved after 5-6 days
   3. New worsening (fever, headache, discharge)

Pathogens associated with ABRS



Should I get cultures?

Yes, IF…

- Failed first and second line treatment
- Immunocompromised
- Concern for complications
- Obtained by direct sinus aspiration
  - Not: nasopharyngeal swabs

Clin Infect Dis. 2012;54(8):e71-e112.

Should I Get Imaging?

Standardly, no, unless…

- No response after multiple antibiotics
- Concern for complications
- Immuncompromised

Clin Infect Dis. 2012;54(8):e71-e112.

Penicillin Resistance Rates

	Gram Negative Aerobes						Gram Positive Aerobes						
	Pseudomonas aeruginosa (168)	Enterobacter cloacae (50)	E.coli (1018)	Proteus mirabilis (72)	Klebsiella pneumoniae (148)	Klebsiella oxytoca (49)	Enterococcus faecalis (133)	MRSA (methicillin-resistant S.aureus) (161)	MSSA (methicillin-susceptible S.aureus) (560)	Staphylococcus coagulase-negative (59)	Staphylococcus lugdunesis (48)	Streptococcus pneumoniae (non-meningitis) (85)	Streptococcus pneumoniae (meningitis) (35)
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Cefazolin	-	-	93	96	95	28	-	-	100	64	92	-	-
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Erythromycin	-	-	-	-	-	-	-	-	-	-	-	76	-
Gentamicin	90	100	95	94	95	94	-	-	-	-	-	-	-
Levofloxacin	82	98	89	99	96	94	91*	-	-	-	98	100	-
Meropenem	90	100	100	100	100	100	-	-	-	-	-	-	-
Nitrofurantoin	-	66	97	-	37	96	100	-	-	93	100	-	-
Oxacillin (Nafcillin)	-	-	-	-	-	-	-	-	100	64	92	-	-
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Tetracycline	-	92	82	-	79	90	24	98	95	85	94	-	-
Tobramycin	96	100	94	96	93	92	-	-	-	-	-	-	-
Trimethoprim/ sulfamethoxazole	-	82	82	90	92	92	-	92	97	58	98	80	-
Vancomycin	-	-	-	-	-	-	100	100	100	100	100	100	-

* Use for urine pathogens only

Drug Resistance and Sinusitis

Increase in *H. influenza* beta-lactamase production

Risk factors for Pneumococcal resistance

- Region with resistance rates >10%
- >65 YOA
- Hospitalization in last 5 years
- Antibiotic use last month
- Immunocompromised
- Comorbidities
- Severe Infection (toxicity)

Mini-Break

Case 5: Leia Organa

Leia is an 18 month year old girl who is brought in by her father with complaints of fussiness and pulling at her left ear over the last 24 hours. On exam you notice that she has a T38.4F and a bulging slightly red TM with effusion but no otorrhea. No perforation noted.

- What is your next step in management?
  A. Symptomatic care for next 24-48 hours
  B. Start amoxicillin
  C. Start cephalexin
  D. Refer to ENT

Do Antibiotics Decrease Failure Rates?


The NEW ENGLAND JOURNAL of MEDICINE

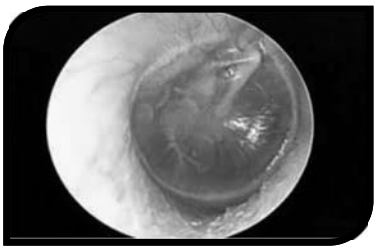
ORIGINAL ARTICLE

A Placebo-Controlled Trial of Antimicrobial Treatment for Acute Otitis Media

Paula A. Tähtinen, M.D., Miia K. Laine, M.D., Pentti Huovinen, M.D., Ph.D., Jari Jalava, Ph.D., Olli Ruuskanen, M.D., Ph.D., and Aino Ruohola, M.D., Ph.D.

ABSTRACT

What About Observation?



What Does the AAP Say?

Age	Otorrhea w/AOM	Unilateral or B/L AOM Severe Sx	B/L AOM No Otorrhea	Unilateral AOM No Otorrhea
6m-2Y	Antibiotics	Antibiotics	Antibiotics	Antibiotics **or** Observation
≥2Y	Antibiotics	Antibiotics	Antibiotics **or** Observation	Antibiotics **or** Observation

Acknowledgement of Dr. Dawn Nolt (OHSU Peds ID)
Pediatrics 2013;131:e964–e999

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≥2Y	Antibiotics	Antibiotics	Antibiotics **or** Observation	Antibiotics **or** Observation

- Properly Selected Patients
- Ensure Follow up

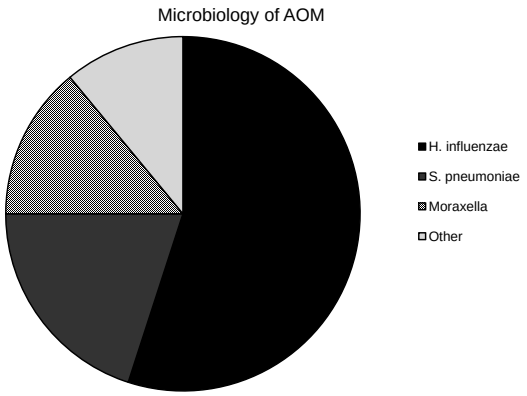
Acknowledgement of Dr. Dawn Nolt (OHSU Peds ID)
Pediatrics 2013;131:e964–e999

But, it isn't that simple… Children < 2 may do worse

No. of Children <2 Y With Treatment Failure (%)				
Presentation	**Amox/Clav N (%)**	**Placebo N (%)**	**ARR**	**NNT**
Unilateral NS	10/72 (14)	26/65 (40)	0.27	4
Unilateral Sev	11/77 (14)	33/70 (47)	0.34	3
B/L nonsevere	13/60 (22)	29/55 (53)	0.31	4
B/L severe	17/68 (25)	44/75 (59)	0.34	3

JAMA Pediatr. 2013;167(12):1171-1172

Effect of Vaccinations on Microbiology



Antibiotic Choice for Outpatient Management

	Gram Negative Aerobes						Gram Positive Aerobes						
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Cefepime	93	92	99	99	97	100	-	-	-	-	-	-	-
Ceftriaxone	-	84	97	99	95	96	-	-	-	-	-	100	96
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Tetracycline	-	92	82	-	79	90	24	98	95	85	94	-	-
Tobramycin	96	100	94	96	93	92	-	-	-	-	-	-	-
Trimethoprim/ sulfamethoxazole	-	82	82	90	92	92	-	92	97	58	98	80	-
Vancomycin	-	-	-	-	-	-	100	100	100	100	100	100	-

* Use for urine pathogens only

Duration of Therapy?

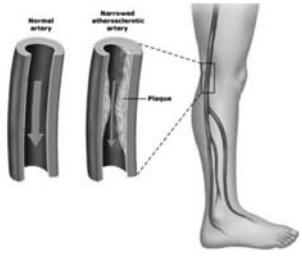
	1-3 doses	5 days	5-7 days	10 days
Antimicrobials	Ceftriaxone	Azithromycin	Amoxicillin, Amox-clav, clarithromycin, oral cephalosporins, clindamycin levofloxacin	
			• Age ≥2 • Intact TM • No hx of recurrent AOM	• Age ≤2 • TM perf • Recurrent AOM

Case 6: Luke Skywalker

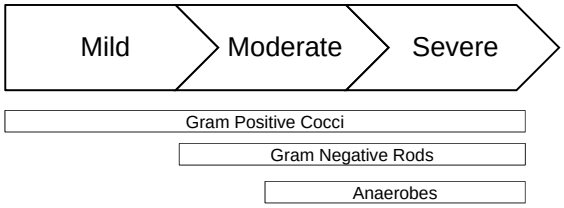
Luke has been off the grid for many years living on a remote rocky island who now presents with uncontrolled diabetes II and a 3x5cm non healing ulcer on the plantar surface of his left first metatarsal head with surrounding erythema. MRI shows osteomyelitis and he undergoes debridement. Cultures are pending. What is your next step in management?

A. Start trimethoprim-sulfamethoxazole
B. Start vancomycin and piperacillin-tazobactam
C. Start ampicillin-sulbactam
D. Wait for culture data

Diagnosing the problem



Microbiology of DFIs May Depend on Severity



Clinical Infectious Diseases 2012;54(12):132–173

Do I Need to Cover for Pseudomonas?

Diabetologia 2011;54:58–64.
Clin Microbiol Infect 2007; 13:351–3.

Do I Need to Cover for Pseudomonas?

Severe SSTI

Diabetologia 2011;54:58–64.
Clin Microbiol Infect 2007; 13:351–3.

Do I Need to Cover MRSA?

- Prior MRSA
- High Prevalence of MRSA
- Sufficiently Severe Infection

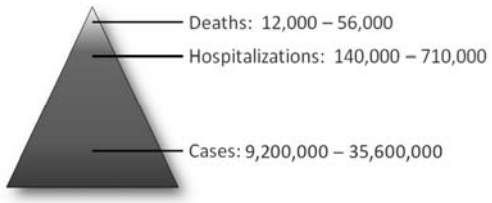
Clin Microbiol Infect 2007; 13:351–3

Case 7: Maz

Maz is an elderly woman with a history of cataracts who presented to clinic with fevers, myalgias and shortness of breath. Her vitals are notable for T100.6, HR 85, BP 120/65, RR 18, p02 94%. CXR notable for hazy air space disease bilaterally. You check an Influenza PCR and it is positive for influenza A. What do you do?

A. Treat with oseltamivir x 5 days
B. Treat with zanamivir x 7days
C. Admit and treat with oseltamivir x 14 days
D. Give Maz the high dose flu vaccine
E. Provide reassurance and treat symptomatically

Influenza Morbidity and Mortality: Annual US Rates, 2010–2016 Influenza Seasons

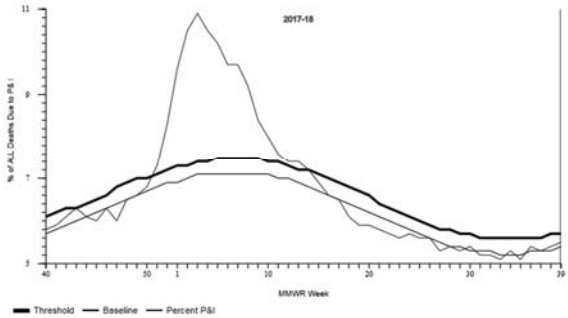


*Data on respiratory and circulatory deaths are available with a 3-y lag; therefore, estimates on averted respiratory and circulatory deaths are available for the 2010-2011 through 2013-2014 influenza seasons but not for the 2014-2015 or 2015-2016 seasons.

Rolfes MA et al. 12/9/16. www.cdc.gov/flu/about/disease/2015-16.htm. Accessed 9/13/18.

2017-2018 Influenza Season: The Deadliest in Decades

Percentage All Deaths Due to Pneumonia and Influenza, National Summary



FluView. https://gis.cdc.gov/grasp/fluview/mortality.html. Accessed 10/22/18.

All Patients With Influenza-like Illness at High Risk of Complications Should Receive Antiviral Therapy[1]

- Hospitalized
- Younger age (6–59 mo)
- Older age (≥50 y)
- Chronic diseases
  - Pulmonary (eg, asthma)
  - Cardiovascular*
  - Renal
  - Hepatic
  - Neurologic
  - Hematologic
  - Metabolic disorders (eg, diabetes)
- Immunocompromised
- Pregnant or postpartum
- <19 y of age receiving long-term aspirin therapy
- LTC facility residents
- American Indians/Alaska Natives
- Obese patients (BMI ≥40 kg/m^2)

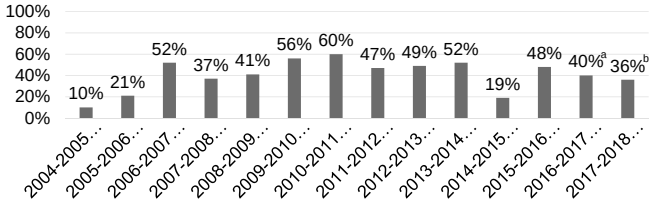
*Excluding isolated hypertension

BMI, body mass index; LTC, long-term care

Grohskopf LA et al. *MMWR Recomm Rep*. 2018;67(No.RR-3):1-20.

Fact: Influenza Vaccination Is Effective, But Not Foolproof

Vaccine Effectiveness (%) Across Influenza Seasons



[a]Interim 2016-2017 vaccine effectiveness estimates (4/20/2016-4/9/2017) were presented to the Advisory Committee on Immunization Practices in June 2017

[b]Interim early estimates may differ from final end-of-season estimates

CDC. 8/30/18. www.cdc.gov/flu/about/season/flu-season-2018-2019.htm. Accessed 9/13/18.

Key Educational Points for Patients and Clinicians

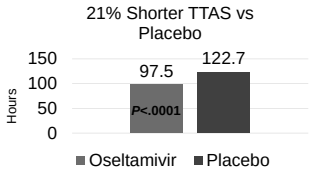
- Encourage all patients to be vaccinated!
- Consider a diagnosis of influenza in patients with signs and symptoms, even when laboratory test results are negative and the patient has been vaccinated
- RT-PCR has greater diagnostic accuracy than RIDT and is thus preferred
- Antiviral therapy should be initiated as soon as possible in patients with influenza who are at high risk for complications—*without waiting for laboratory results*
- People who are not at high risk may also be treated with antiviral drugs, especially if treatment can begin within 48 h

Antiviral Therapy Is Recommended as Soon as Possible for Patients With Influenza

- All hospitalized patients and all high-risk patients (either hospitalized or outpatient) with suspected influenza should be treated as soon as possible with a neuraminidase inhibitor antiviral
- While antiviral drugs work best when treatment is started within 2 days of symptom onset, clinical benefit has been observed even when treatment is initiated later

CDC. 8/30/18. www.cdc.gov/flu/about/season/flu-season-2018-2019.htm. Accessed 9/13/18.

Oral Oseltamivir: Efficacy and Safety



Reduced risk of lower respiratory tract complications and hospital admissions vs placebo[1]

Outcome	RR	95% CI	*P* Value
Lower respiratory tract complications	0.56	0.42 to 0.75	*P*=.0001
Hospital admissions	0.37	-1·4 to -0·3	*P*=.013

- **Prophylaxis** decreases incidence of symptomatic influenza in healthy adults by 55%[2]
- **Adverse events**
  - Nausea, vomiting, headache[1,3]
  - Post marketing reports of serious skin reactions and sporadic, transient neuropsychiatric events[4]

CI, confidence interval; RR, risk ratio; TTAS, time to alleviation of symptoms

1. Dobson J et al. Lancet. 2015;385(9979):1729-1737. 2. Jefferson T et al. *Cochrane Database Syst Rev*. 2014;4:CD008965. 3. Tamiflu (oseltamivir) [package insert]. South San Francisco, CA: Genentech, Inc.; 4/2018. 4. CDC. 2/23/18. www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm. Accessed 9/14/18.

Use of Influenza Antiviral Medications Among Outpatients at High Risk for Influenza-Associated Complications During the 2013–2014 Influenza Season

Fiona Havers,[1] Brendan Flannery,[1] Jessie R. Clippard,[1] Manjusha Gaglani,[2] Richard K. Zimmerman,[3] Lisa A. Jackson,[4] Joshua G. Petrie,[5] Huong Q. McLean,[6] Mary Patricia Nowalk,[3] Michael L. Jackson,[4] Arnold S. Monto,[5] Edward A. Belongia,[6] Heather F. Eng,[7] Lois Lamerato,[8] Angela P. Campbell,[1] and Alicia M. Fry[1]

- 6004 outpatients aged ≥6 months
- Acute respiratory illness
- 30% presented within ≤2 days of symptoms
- 15% prescribed antivirals
- 2012-2013 3 antibiotic drugs were prescribed > antivirals

Clin Infect Dis 2015;60:1677

High-Dose compared to standard dose seasonal flu vaccines for adults 65 years and older?

- Stronger immune response (i.e., higher antibody levels) occurs after vaccination with High-Dose.
- NEJM: high-dose 24.2% more effective in preventing flu in adults 65 years of age and older relative to a standard-dose vaccine. 95% CI = 9.7% to 36.5%.
- Lancet Resp Med:
  - lower risk of hospital admissions compared with standard-dose for >65 yo,
  - especially those living in long-term care facilities.
  - >38,000 residents of 823 nursing homes in 38 states during the 2013-14 flu season.

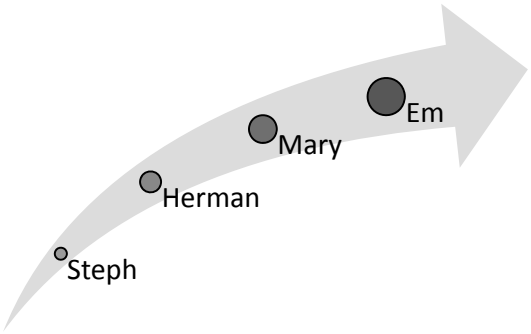
https://www.cdc.gov/flu/prevent/qa_fluzone.htm - Accessed 5/2019

Thank You

Questions From the Coffee Line

Erin Bonura, MD, MCR
Assistant Professor, Infectious Diseases
Oregon Health and Science University

Today's Curbsides



Steph Oryus

Mr Oryus is a 37 year old man with a history of substance abuse disorder (heroin) who presented to clinic with a 3x5 cm left arm abscess, pain and fever. He had a temperature of 102F, HR 96, RR18, BP 140/76, pO2 98% on RA. Exam was notable for a 3x6cm abscess. Urine screen was sent and pt was started on bactrim/cephalexin. You are called the next day because his urine is growing MSSA.

What management would you recommend?

A. Drain the abscess and start dalbavancin
B. Admit for IV Vancomycin
C. Admit, drain the abscess, start cefazolin
D. Obtain CT of the arm and blood cultures in the clinic.

Staph Bacteriuria is Associated with Bacteremia

Data	No.
Bacteremia	76
Bacteremic with Ucx obtained	59
+ Staph aureus ucx	16/59 (27%)
Ucx no growth	33/59 (56 %)

Site	+ Ucx (16)	Neg Ucx (31)	P
Bone/Joint	1	2	NS
Endocarditis	5	8	NS
Genitourinary	6	1	<0.01
IV device	2	9	NS
Respiratory	0	4	NS
Other	2	7	NS

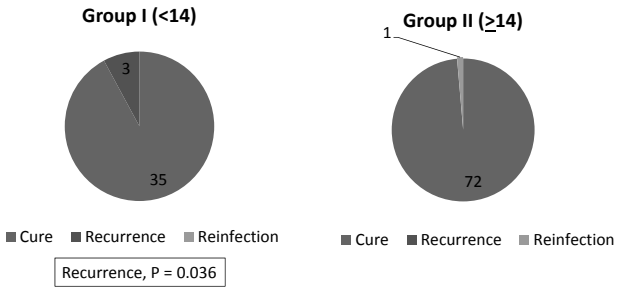
Am J Med. 1978 Aug;65(2):303-6.

S. aureus Bacteremia Categories

Uncomplicated	Complicated
☐ Exclusion of endocarditis	☐ Everyone else
☐ No prosthesis	
☐ Bcx neg 2-4 days later	
☐ Defervesce in 72hrs	
☐ No metastatic sites	

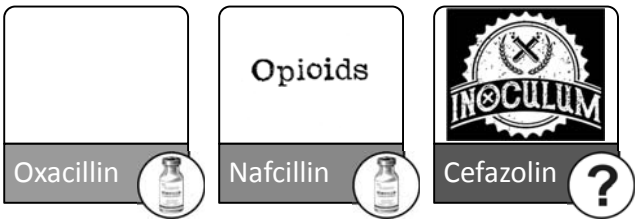
Liu C. Clin Infect Dis. 2011;52: 1-38

S. aureus Outcomes for **Uncomplicated** Bacteremia with Short Course

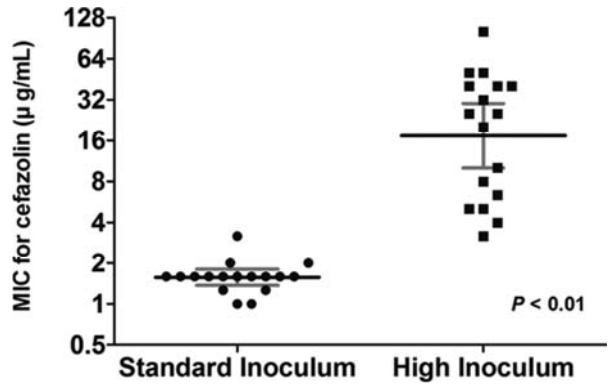


Chong YP, et al. AAC. 2013;57(3):1150-6

Antibiotic Choice for MSSA Bacteremia



Comparison of cefazolin MICs of MSSA clinical isolates positive for the type A blaZ gene at SI (●) versus HI (■).



Sun Hee Lee et al. Antimicrob. Agents Chemother. 2016;60:6928-6932

Antimicrobial Agents and Chemotherapy

Clinical Outcomes in Patients with Standard vs High Inoculum Treated with Cefazolin

Variable	Standard	High	P value
7 day all cause mortality	2 (5.7)	5 (11.9)	0.455
30 day all cause mortality	5 (15.2)	15 (39.5)	0.034

Adjusted Risk Ratio = 2.65

Miller WR, et al. OFID, ofy123, https://doi.org/10.1093/ofid/ofy123

Herman Ivey

H. Ivey is a 45 year old man living with HIV (CD4 478, VL UD) and HTN on Biktarvy (bictegravir, emtricitamine, tenofovir alafenamide) and norvasc who presents with his partner in follow up. His partner is HIV negative and they want to know what the chances are of transmitting the virus to his HIV negative partner. What do you say?

A. With continued use of condoms, it is unlikely you will transmit the virus to your partner
B. If you remain undetectable, you will not transmit the virus to your partner
C. Your partner should start PrEP to prevent transmission
D. It is likely you will transmit the virus in the next 5-10 years despite your best efforts.

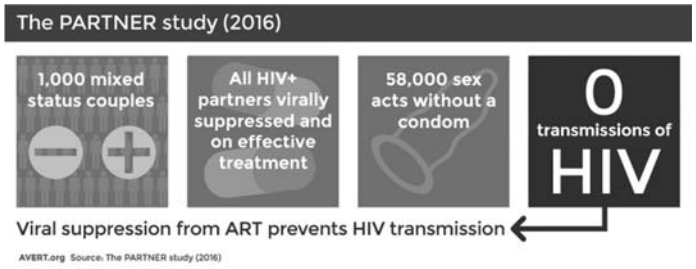


Figure 1. Rate of HIV Transmission According to Sexual Behavior Reported by the HIV-Negative Partner

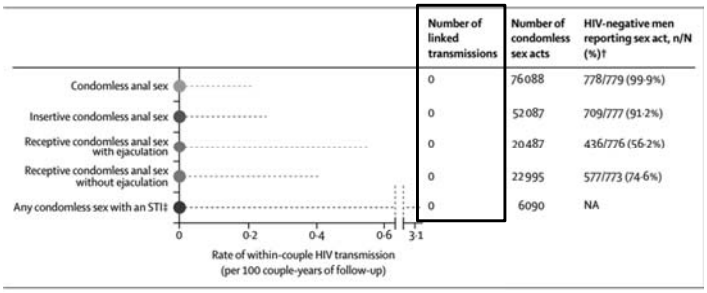
PARTNER 1

	HIV-Negative Members of Eligible Couples Reporting Specific Sex Act, No./Total (%)	Couple-Years of Follow-up	Upper 95% Confidence Limit
All			
Any sex	863/866 (99.7)	1238	0.30
Vaginal sex	532/878 (60.6)	629	0.59
Anal sex	449/849 (52.9)	522	0.71
Insertive anal sex	363/862 (42.1)	417	0.88
Receptive anal sex with ejaculation	185/864 (21.4)	166	2.23
Heterosexual women			
Any sex	261/262 (99.6)	381	0.97
Vaginal sex with ejaculation	193/259 (74.5)	246	1.50
Vaginal sex without ejaculation	207/257 (80.5)	238	1.55
Anal sex	61/256 (23.8)	60	6.16
Receptive anal sex with ejaculation	37/255 (14.5)	29	12.71
Receptive anal sex without ejaculation	55/253 (21.7)	45	8.14
Heterosexual men			
Any sex	272/274 (99.3)	418	0.88
Vaginal sex	271/275 (98.5)	383	0.96
Anal sex	60/264 (22.7)	47	7.85
Insertive anal sex	60/264 (22.7)	47	7.85
Men who have sex with men			
Any sex	330/330 (100)	439	0.84
Anal sex	328/329 (99.7)	415	0.89
Insertive anal sex	303/329 (92.1)	370	1.00
Receptive anal sex with ejaculation	148/329 (45.0)	137	2.70
Receptive anal sex without ejaculation	217/324 (67.0)	220	1.68

0 2 4 6 8 10 12
Rate of Within-Couple Transmission, per 100 Couple-Years of Follow-up

JAMA. 2016;316(2):171-181.

PARTNER 2: MSM



Mary Teabe

M. Teabe is a 32 year old oncology nurse sees you in line and asks you to read her PPD. You strike up a conversation about LTBI. Select the most correct statement below:

A. All health care personnel (HCP) should be screened annually with either a PPD or IGRA
B. HCP groups with exposure to TB can be considered for serial screening
C. HCP with LTBI should be referred to ID to determine if treatment is warranted
D. HCP no longer need annual screenings for TB

So who with infection (LTBI) is more likely to progress to disease?

The risk of progression is 7-10% each year!!

Risk Factor	Relative Risk (95% CI)
Advanced untreated HIV	9.9 (8.7-11)
Close Contacts	**6.1 (5.5-6.8)**
CXR c/w prior healed TB	**5.2 (3.4-8.0)**
Prednisone ≥15mg/day	2.8 (1.7-4.6)
Chronic Renal Failure	2.4 (2.1-2.8)
TNF alpha inhibitor	2.0 (1.1-3.5)
Poorly controlled diabetes	1.7 (1.5-2.2)
Weight <10% below normal	1.6 (1.1-2.2)
Smoking	1.5 (1.1-2.2)
Kids are the double whammy: Risk may double if <4 years old, 40% risk if < 12mo	

Horsburgh and Rubin, NEJM. 2011;364(15):1441-8
LTBI guide for primary care providers. CDC. 2013

TB immune-based testing (PPD/IGRA) is imperfectly sensitive

- PPD is similar in sensitivity although less specific

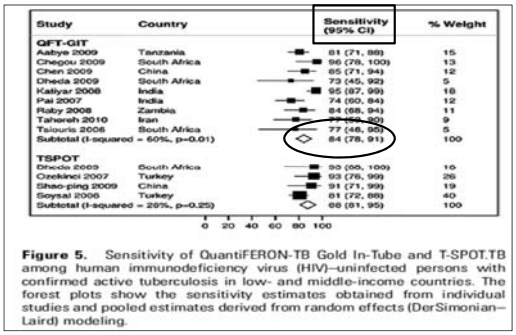


Figure 5. Sensitivity of QuantiFERON-TB Gold In-Tube and T-SPOT.TB among human immunodeficiency virus (HIV)–uninfected persons with confirmed active tuberculosis in low- and middle-income countries. The forest plots show the sensitivity estimates obtained from individual studies and pooled estimates derived from random effects (DerSimonian–Laird) modeling.

Metcalf, et al. Interferon-gamma Release Assays for Active Pulmonary Tuberculosis Diagnosis in Adults in Low- and Middle-Income Countries: Systematic Review and Meta-analysis. JID. 2011;204:S1120–29

LTBI Testing: imperfect science

A positive test is 50/50

- With imperfect sensitivity and specificity, positive and negative predictive value depends on prevalence…
  - Two hypothetical scenarios…

	Disease+	Disease-		
			10% Prevalence	
Test+	90	90	Total	1000
Test-	10	810	Disease	100
Total	100	900	Not Disease	900
Sensitivity	0.9			
Specificity	0.9			

	Disease+	Disease-		
			80% Prevalence	
Test+	720	20	Total	1000
Test-	80	180	Disease	800
Total	800	200	Not Disease	200
Sensitivity	0.9			
Specificity	0.9			

A negative test is 70/30

"CDC discourages use of diagnostic tests for LTBI among individuals and populations at low risk for infection with *M. tuberculosis*." – CDC 2013

AND… You May Not Need Annual PPD Testing!

Tuberculosis Screening, Testing, and Treatment of U.S. Health Care Personnel: Recommendations from the National Tuberculosis Controllers Association and CDC, 2019

Weekly / May 17, 2019 / 68(19):439–443

Sosa LE, Njie GJ, Lobato MN, et al. Tuberculosis Screening, Testing, and Treatment of U.S. Health Care Personnel: Recommendations from the National Tuberculosis Controllers Association and CDC, 2019. MMWR Morb Mortal Wkly Rep 2019;68:439–443.

Updated Recommendations

Category	2005 Recommendation	2019 Recommendation
Baseline (preplacement) screening and testing	TB screening of all HCP, including a symptom evaluation and test (IGRA or TST) for those without documented prior TB disease or LTBI.	TB screening of all HCP, including a symptom evaluation and test (IGRA or TST) for those without documented prior TB disease or LTBI **(unchanged)**; individual TB risk assessment **(new)**.
Postexposure screening and testing	Symptom evaluation for all HCP when an exposure is recognized. For HCP with a baseline negative TB test and no prior TB disease or LTBI, perform a test (IGRA or TST) when the exposure is identified. If that test is negative, do another test 8–10 weeks after the last exposure.	Symptom evaluation for all HCP when an exposure is recognized. For HCP with a baseline negative TB test and no prior TB disease or LTBI, perform a test (IGRA or TST) when the exposure is identified. If that test is negative, do another test 8–10 weeks after the last exposure **(unchanged)**.
Serial screening and testing for HCP without LTBI	According to health care facility and setting risk assessment. Not recommended for HCP working in low-risk health care settings. Recommended for HCP working in medium-risk health care settings and settings with potential ongoing transmission.	Not routinely recommended **(new)**; can consider for selected HCP groups **(unchanged)**; recommend annual TB education for all HCP **(unchanged)**, including information about TB exposure risks for all HCP **(new emphasis)**.
Evaluation and treatment of positive test results	Referral to determine whether LTBI treatment is indicated.	Treatment is encouraged for all HCP with untreated LTBI, unless medically contraindicated **(new)**.

Updated Recommendations

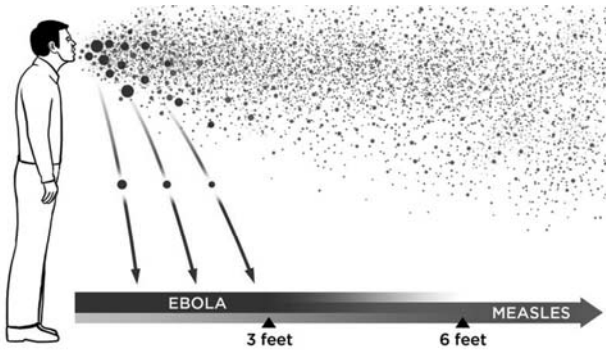
- Baseline Individual TB Risk assessment
- Annual screening for HCP without LTBI **NOT** routinely recommended
- Annual TB education for all HCP with **information about TB exposure risks**
- Treatment is encouraged for all HCP with LTBI

Emily (Em) Emmar

Em is a 4 year old with leukemia from Clark County, WA who is about to undergo a bone marrow transplant presented to her PCP in January 2019. Her mom is concerned about the measles outbreak and what she is reading online. She asked how transmissible the virus is and what she can do to protect her daughter. Which of the following is correct?

A. Measles is highly transmissible but less so than SARS
B. Though there is currently an isolated outbreak in her county, the vaccination rate is high enough to provide herd immunity, thus she is unlikely to get measles.
C. You will talk to the health department who is likely to recommend Em be excluded from school
D. Though the social media information she is seeing posted by her "friends" is concerning, it is generally correct given the regulations and oversight of social media platforms.

Measles Transmission



NPR.org

Measles Transmission

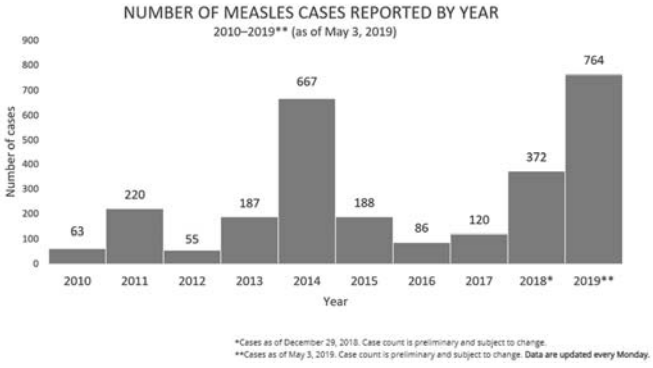
R_0	12 to18	12 to 17	6 to 7	5 to 7	4 to 7	2 to 4
DISEASE	Measles	Pertussis (Whooping cough)	Rubella	Smallpox	Mumps	SARS
HOW IT SPREADS	Airborne	Airborne droplets	Airborne droplets	Airborne droplets	Airborne droplets	Airborne droplets

http://graphics.thomsonreuters.com/15/measles/index.html

The Herd: 94.5% Immune

http://graphics.thomsonreuters.com/15/measles/index.html

Measles in the U.S.



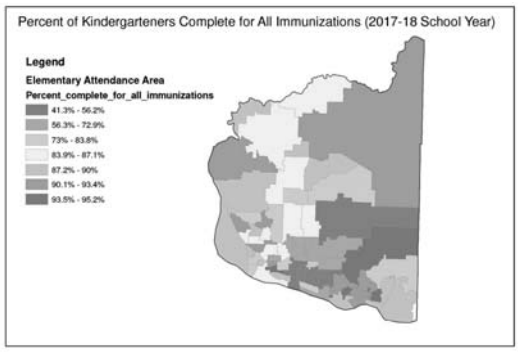
Measles in the U.S. 2019

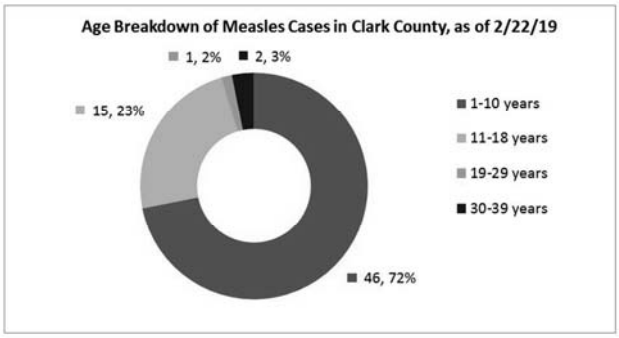
https://www.nytimes.com/2019/02/20/us/measles-outbreak.html

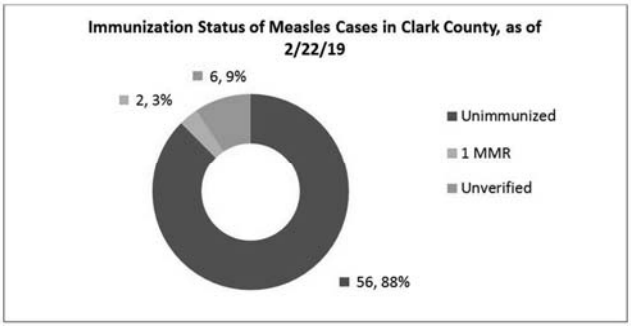
Clark County, Washington

- Dec. 31st: First case visited Memorial Urgent Care
- Jan. 4th: Lab confirmed measles in child with unknown immunization history
- Jan. 15th: 2 more confirmed and 11 suspected cases
- Jan 15th: Incident Command System activated
- Jan 25th: State of Emergency

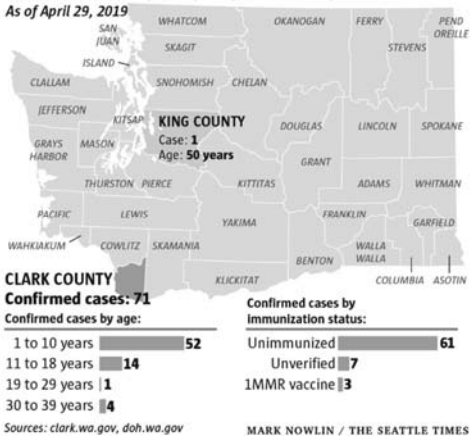
Immunization Rates







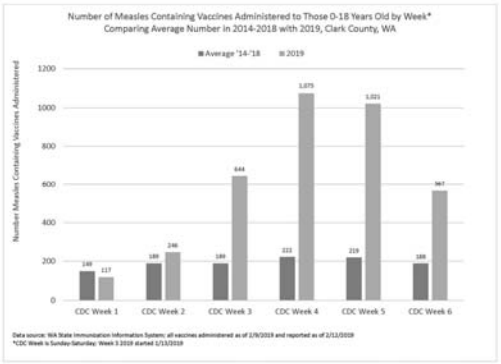
Outbreak Totals



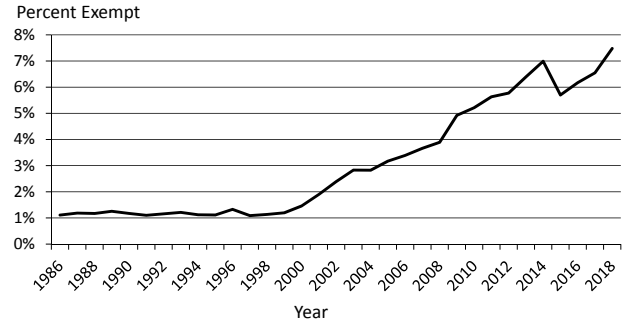
Outbreak Totals

- Cases: 71
- Exposure sites: 54
- School Exclusions: 849 students
- Responders: 219
- Cost: $510,000

Immunization increases



Exemptions to vaccination requirements hit 7.5% among kindergartners in 2018.



Oregon Immunization Program

Overall, 96% of K – 12 students are vaccinated against measles.

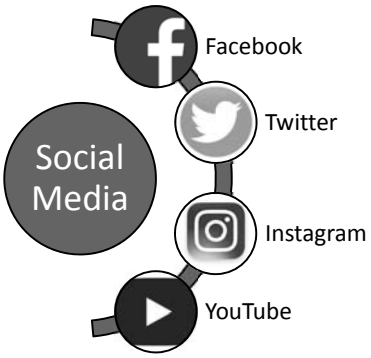
- First dose coverage >95% for children attending preschool or certified daycare
- 2nd dose coverage >95% for kindergarteners
- 2nd dose coverage >97% for 7th graders

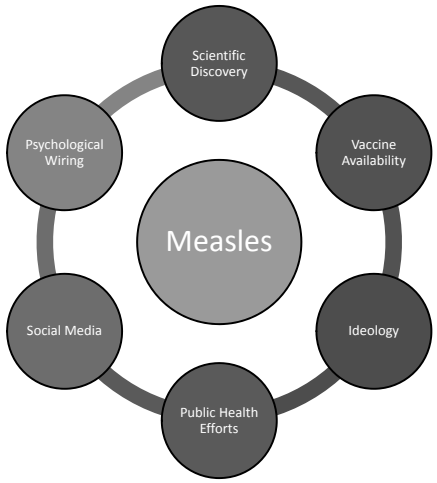
"Arguments" Can Change Minds

Beliefs | Trusted Sources | Values

Hugo Mercier, TED-Ed. https://www.youtube.com/watch?v=58jHhNzUHm4

(Mis)information Highways





Acknowledgements:
Luke Strnad, MD
Alan Melnick, MD, MPH, CPH
Paul Lewis, MD, MPH
Paul Cieslak, MD

Take Home Points

- Treatment for *S.aureus* bacteremia **does** require IV antibiotics for 2-6 weeks
- Undetectable = Untransmittable
- Vaccine preventable diseases are here but conversations can be impactful
- You may not need annual screening for TB

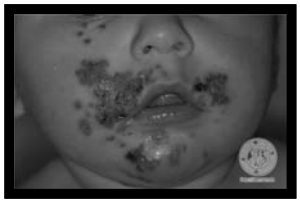
Difficult Skin and Soft tissue Infections

Erin Bonura, MD, MCR
Oregon Health & Science University

Objectives

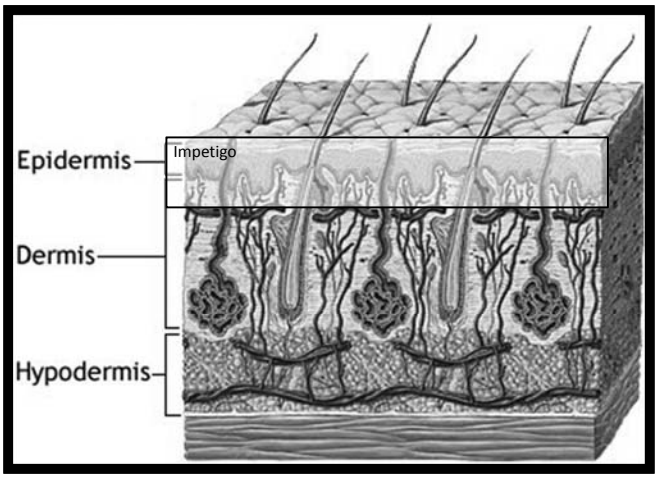
- Compare and contrast the epidemiology and clinical presentation of common skin and soft tissue diseases
- State the management for skin and soft tissue infections
- Differentiate true infection from infectious disease mimics of the skin

Casey

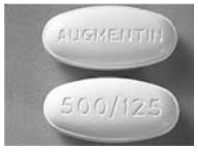


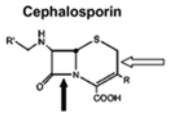
Casey is a 2 year old boy who presents with this rash. What is the best treatment?

A. Soap and Water
B. Ibuprofen, it will self resolve
C. Dicloxacillin
D. Mupirocin

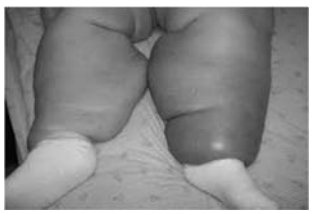


Impetigo Epidemiology and Treatment



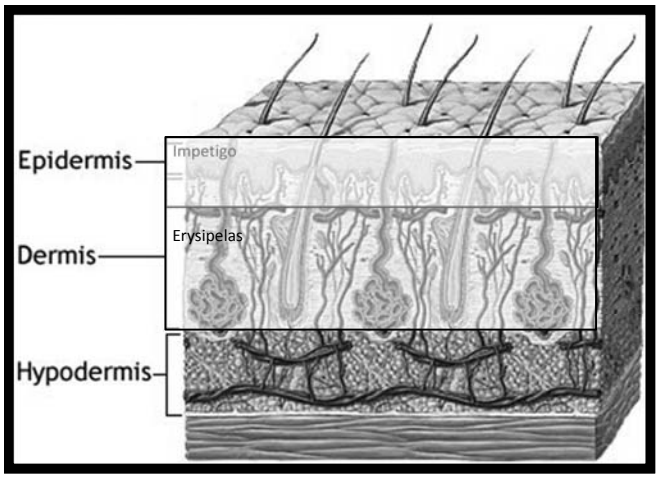


Ellen

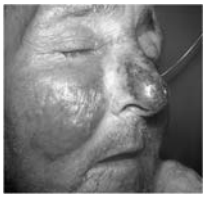


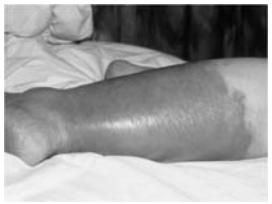
Ellen is a 54 year old morbidly obese woman with DM, HTN and venous stasis who presented with a painful left leg and fever. She has had 3 episodes in the last 6 months. What do you recommend?

A. Cefazolin followed by oral amoxicillin prophylaxis
B. Vancomycin – this is likely MRSA
C. Amoxicillin – this is likely erysipelas
D. Clindamycin to cover staph and strep cellulitis

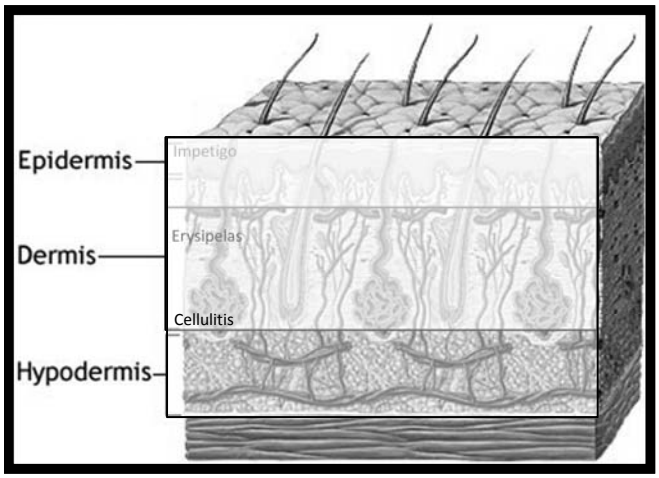


Erysipelas

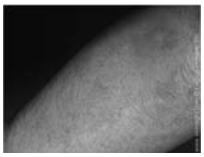




Risk: lymphedema, stasis, obesity, paresis, DM, ETOH
Recurrence rate: 30% in 3 yrs
Treatment: Penicillin



Cellulitis



- DEEPER than erysipelas
- **Microbiology**:
  - 6-48hrs post op: think GAS… too early for staph (days in the making)!
  - Periorbital – Staph, *Strep pneumoniae*, GAS
  - Post Varicella - GAS
  - Skin popping – Staph + almost anything!

Framework for Skin and Soft Tissue Infections (SSTIs)

NONPurulent
Necrotizing/Cellulitis/Erysipelas

Severe	Moderate	Mild
I&D C&S Vanc + Pip-tazo	IV Rx	Oral Rx

Purulent
Furuncle/Carbuncle/Abscess

Severe	Moderate	Mild
I&D C&S	I&D C&S	I&D C&S
Empiric IV MRSA	Empiric Oral MRSA TMP/SMX Doxy	

What Are Your "Go-To" Oral Options For Non-Purulent SSTI?

Amoxicillin	✚	Doxycycline
Cephalexin	✚	Doxycycline
Trimethoprim-Sulfamethoxazole		

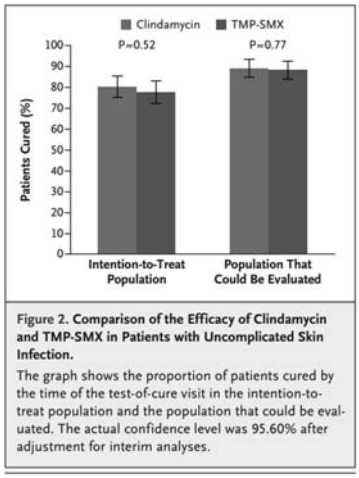


Figure 2. Comparison of the Efficacy of Clindamycin and TMP-SMX in Patients with Uncomplicated Skin Infection.

The graph shows the proportion of patients cured by the time of the test-of-cure visit in the intention-to-treat population and the population that could be evaluated. The actual confidence level was 95.60% after adjustment for interim analyses.

Miller LG, et al. Clindamycin versus Trimethoprim-Sulfamethoxazole for uncomplicated skin infections. NEJM.2015;372(12):1093-1103

Cure rate: Clinda vs TMP/SMX vs Placebo

		Clindamycin	TMP-SMX	Placebo
All	- ITT	83.1	81.7	68.9
	- Evaluated	92.9	92.7	80.5
Children	- ITT	89.1	82.4	68.5
	- Evaluated	97.8	92.6	82.4
Adults	- ITT	79.4	81.4	69.0
	- Evaluated	89.7	92.7	79.5
No *S. aureus*	- ITT	83.8	91.9	83.1
	- Evaluated	90.5	90.8	90.8

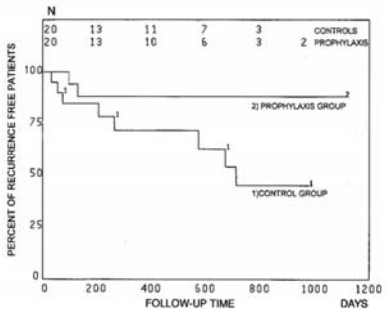
Daum RS., et al. A placebo-controlled trial of antibiotics for smaller skin abscesses. NEJM. 2017;376(26):2545-2555

What About Prophylaxis?

	Erythromycin x 18 m	No prophylaxis
Complete Prevention	16	
Relapse	------	8
(One Relapse)		(7)
(Two Relapses)		(1)

Kremer M, et al. Long-term antimicrobial therapy in the prevention of recurrent soft-tissue infections. J Infect. 1991;22(1):37-40.

More Data on Prophylaxis



Sjoblom AC et al. Antibiotic prophylaxis in recurrent erysipelas. Infection 1993;21:390–3.

When Should We Give Prophylaxis?

- 1st: Identify and treat predisposing conditions
- *If* still 3-4 episodes per year
- Penicillin or erythromycin BID x 4-52 weeks or IM benzathine PCN every 2-4 weeks
- Continue as long as predisposing factors present

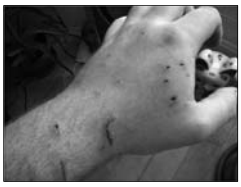
IDSA Practice Guidelines for SSTI. 2014

Jessie is a 32 yo radio host at NPR who volunteers at the local animal shelter. She was bitten by a cat 2 hours ago and comes in for evaluation. She has 2 puncture marks on her L thenar eminence without spreading erythema. Her last tetanus shot was 3 years ago. What should you do?

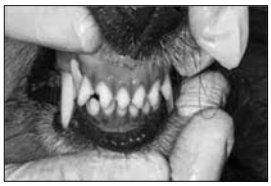
A. Treat with amoxicillin
B. Treat with amoxicillin-clavulanate
C. Send her to the ED for IV antibiotics
D. Wash the wound, give a tetanus booster, and do not give antibiotics

Cats….





Dogs….


Microbiology of cat and dog bites

Dog Bites

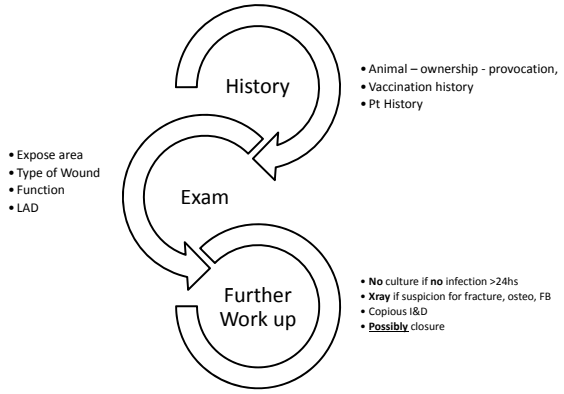
- ***Pasteurella spp*** (50%)
- *Streptococci (46%)*
- *Staphylococci (46%)*
- *Neisseria spp (32%)*
- *Fusobacterium spp (32%)*
- ***Capnocyphaga canimorsus***

Cat Bites

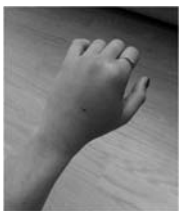
- ***Pasteurella spp*** (75%)
- *Streptococci* (46%)
- *Staphylococci* (35%)
- *Neisseria spp* (35%)
- *Fusobacterium spp* (33%)
- ***Bartonella henslae***

Clin Microbiol Rev. 2011 Apr; 24(2): 231–246.

Evaluation and management of animal bites



Who do you treat?


When to give toxoid and Tetanus Ig

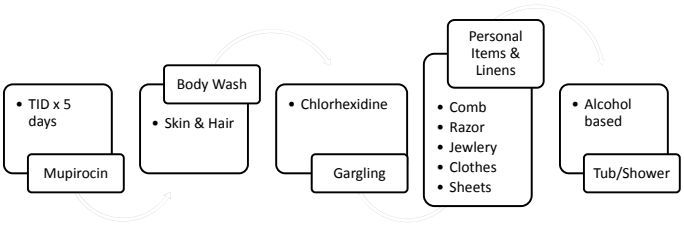
Previous # Toxoid Doses	Clean and Minor Wounds		All other Wounds (dirt, feces, soil, saliva, puncture, avulsions, crushing, burns, frostbite)	
	Tetanus toxoid vaccine	Tetanus Ig	Tetanus toxoid vaccine	Tetanus Ig
<3 doses	**YES**	NO	**YES**	**YES**
≥3 doses	If **≥10yrs** ago	NO	If **≥ 5yrs** ago	NO

Jane is a 62 yo female with lupus on prednisone 10 and azathioprine who presents with recurrent MRSA abscesses. She has undergone numerous I&Ds and rounds of antibiotics.

What do you suggest?

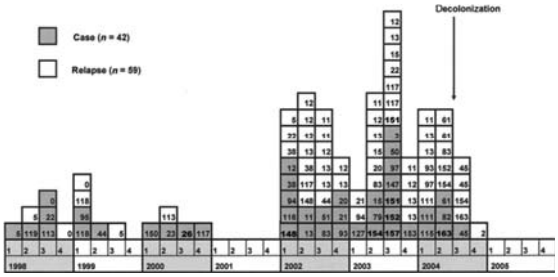
A. Decolonize with mupirocin and chlorhexidine
B. Decrease her immunosuppression
C. Start suppressive antibiotics
D. Treat what comes

Stringent Decolonization in a German Village (2002-2005)



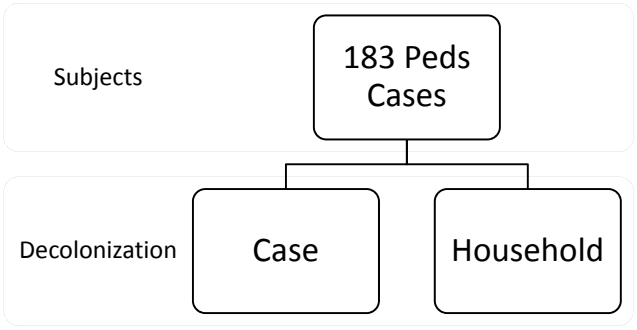
Wiese-Posselt M, et al. Clin Infect Dis. 2007;44(11):e88-95

Stringent Decolonization in a German Village (2002-2005)



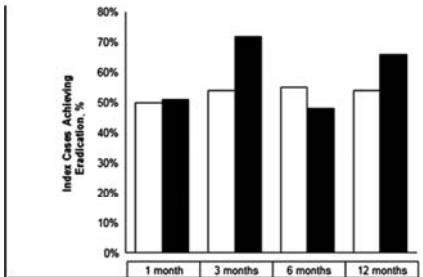
Wiese-Posselt M, et al. Clin Infect Dis. 2007;44(11):e88-95

Eradication of Carriage versus Recurrence of Disease



Fritz SA, et al. Clin Infect Dis. 2012;54(6):743-51

Eradication versus Recurrence



	1 month	3 months	6 months	12 months
Index Group (%)	39/78 (50)	39/72 (54)	39/71 (55)	37/68 (54)
Household Group (%)	35/69 (51)	41/57 (72)	31/64 (48)	38/58 (66)
P value	1.00	.05	.49	.28
OR (95% CI)	1.03 (.54, 1.97)	2.17 (1.03, 4.55)	0.77 (.39, 1.52)	1.59 (.77, 3.28)
AOR (95% CI)	1.03 (.52, 2.02)	2.02 (.95, 4.31)	0.77 (.38, 1.55)	1.38 (.66, 2.91)

Recurrence Rate At 12 months
- 72% in case
- 52% in household (P=0.02)

Fritz SA, et al. Clin Infect Dis. 2012;54(6):743-51

Management of Recurrent Abscesses

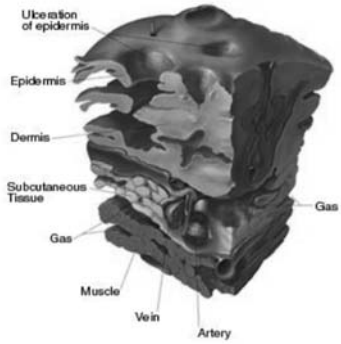
- ***If*** occur since childhood, evaluate for defect
- ***If*** at the same site, evaluate for local cause
- Drain and culture
- Treat 5-10 days
- *Consider* decolonization

Practice Guidelines SSSI. CID. 2014

Al, is a 65 yo diabetic man with a HbA1c of 10 on insulin. He presents to the ED with a rash over his L buttock that is warm, and extremely tender. He states there was a pimple that popped and over the next few hours this developed. He has a fever to 101 with other vitals stable. On exam, he has a warm, erythematous area of 20x16 cm which is more tender than you would expect on exam and does not have clear demarcations. There is no crepitus.

- Pair up with the person next to you.
- What is the working diagnosis?
- What is your management?

- Look like cellulitis
- Spreads along fascia
- Pain **out of proportion**
- Rapidly progressive
- Surgical emergency

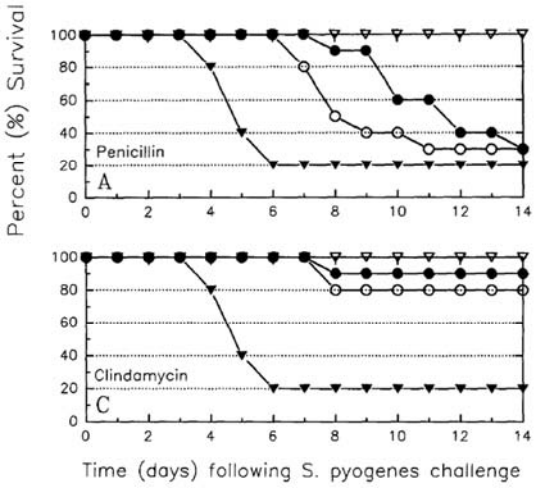


	Type I	Type II	Type III
Conventional Name	**Fournier's (GU)**	**Streptococcal gangrene**	**Gas Gangrene**
Pathogens	Polymicrobial	Group A Strep *S. aureus*	*Clostridium pyogenes*
Host	Diabetics Immunocompromised Peripheral Vascular Disease Recent Surgery	Varicella	Traumatic injury

Empiric Antibiotic Choice

Suspected pathogens	Option 1	Option 2	Option 3
Mixed	Pip-tazo + vanc	Carbapenem	Cefotaxime+ metro or clinda
Streptococcal	Penicillin + Clinda		
Staph aureus	Nafcillin	Vancomycin	Clindamycin*
Clostridial	Penicillin + Clinda		

*Bacteriostatic; potential cross-resistance and emergence of resistance in erythromycin resistant strains; inducible resistance in MRSA



Stevens DL., et al. International Journal of Antimicrobial Agents 4 (1994) 297-301

Clindamycin data

Table 1. Effects of antibiotics on the viability of *Clostridium perfringens* and on production of α-toxin.

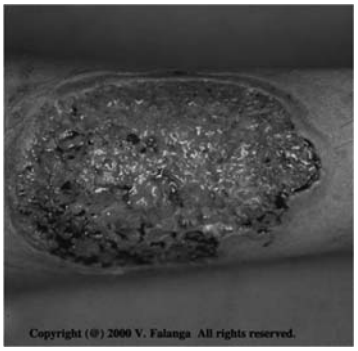
Drug	Viable *C. perfringens* (cfu/mL) at 30 minutes	α-Toxin level (U/mL) at 30 minutes
None	7.5×10^6	100
Penicillin	0.2×10^6	80
Clindamycin	0.5×10^6	0
Metronidazole	0	0

NOTE. Initial bacterial concentration was 2.5×10^6/mL. Antibiotic concentrations were 10 times the MIC of the respective antibiotic used. Data adapted from [6].

Stevens, DL., et al. Clinical Infectious Diseases, Vol. 20, Supplement 2. Proceedings of the 1994 Meeting of the Anaerobe Society of the Americas (Jun., 1995), pp. S154-S157

New Case of PG

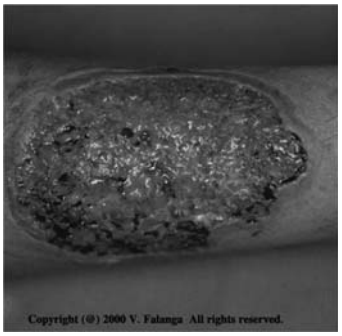
Sarah is a 32 yo female with a history of IBS who presents to you with this wound. She states it started as a pustule that progressed. She has tried multiple course of antibiotics but nothing works.

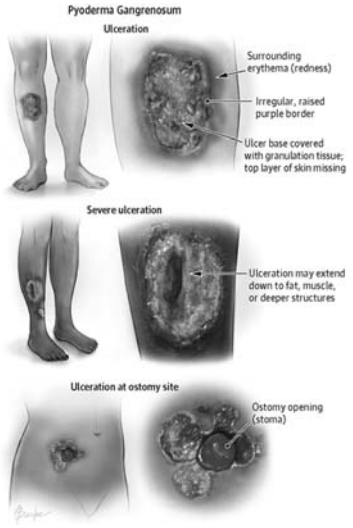


Case of the Non-healing Wound

What is the cause?

1. MRSA
2. Mycobacteria marinum
3. Vascular disease
4. Sweet's Syndrome
5. Pyoderma gangrenosum





Thank you for your participation!!
I would like to acknowledge Dr. Bill Messer & Dr. Melissa Nyendak

Rabies testing, Oregon, 2000–2013 (number of positive/total tested)

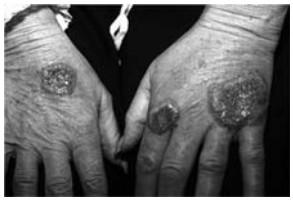
Year	Bat	Cat	Dog	Fox	Other
2000	8/73	0/79	0/56	1/4	0/4
2001	4/59	0/67	0/46	0/1	0/41
2002	12/134	0/102	0/27	2/4	0/29
2003	6/61	0/75	0/36	1/5	0/39
2004	7/88	0/105	0/42	0/2	0/27
2005	8/83	0/100	0/48	0/1	0/23
2006	23/126	0/72	0/26	2/4	0/41
2007	12/153	0/80	0/33	0/1	0/26
2008	13/128	0/58	0/23	0/3	0/53
2009	11/117	0/73	0/27	0/1	0/42
2010	10/104	0/67	0/41	6/15	1/48 (goat)
2011	11/143	0/84	0/32	5/44	1**/61 (coyote)
2012	14/203	0/79	0/37	3**/28	0/45
2013	7/193	0/90	0/36	2/34	1/53 (coyote)
Totals 2000–2013	146/1,665 8.7%	0/131	0/510	22/147 14.9%	3/532 (0.56%)

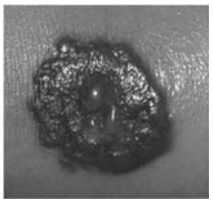
** enhanced surveillance due to positive goat and foxes in 2010–2012

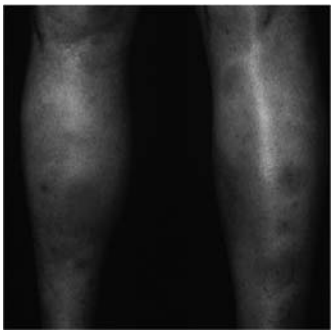
When to give toxoid and Tetanus Ig

Previous # Toxoid Doses	Clean and Minor Wounds		All other Wounds (dirt, feces, soil, saliva, puncture, avulsions, crushing, burns, frostbite)	
	Tetanus toxoid vaccine	Tetanus Ig	Tetanus toxoid vaccine	Tetanus Ig
<3 doses	**YES**	NO	**YES**	**YES**
≥3 doses	If ≥**10yrs** ago	NO	If ≥ **5yrs** ago	NO

Sweet Syndrome



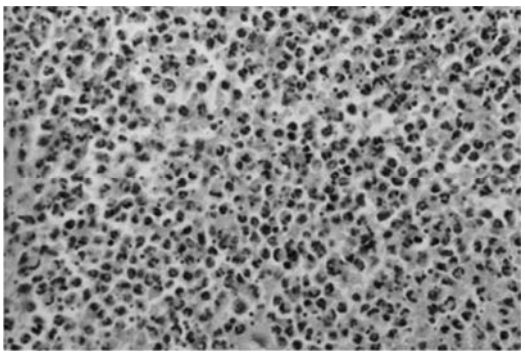




Sweet Syndrome

• Inflammatory Bowel Disease • URI, GI • Pregnancy	• 87% Heme	• Many!
Classical	Malignancy	Drug

Neutrophilic Infiltration



HIV Management
Updates in HIV Primary Care

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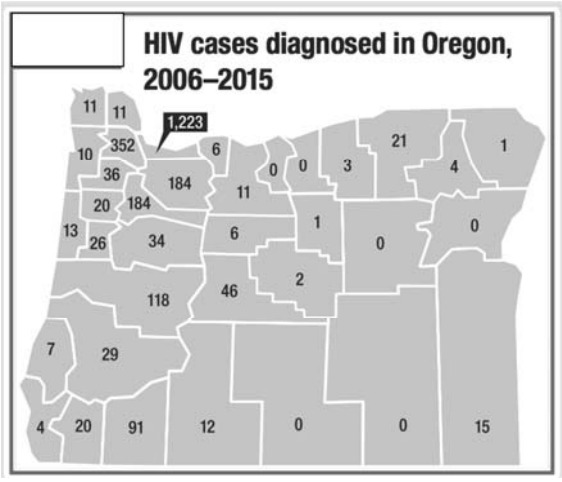
Learning Objectives

- Understand the role of role of **Primary Care** in HIV
- Understand the epidemiology of HIV in the United States
- Appreciate the multiple comorbidities in patients living with long term HIV infection
- Understand current guidelines and screenings for the health maintenance of HIV patients
- Understand the role of Pre Exposure Prophylaxis (PreP) in at risk patients for HIV
- Appreciate the future science of an HIV Cure

HIV Testing Recommendations

- USPSTF recommends that clinicians screen adolescents and adults 15-65 years and all pregnant women for HIV infection (Grade A)
  - Younger adolescents and older adults who are at increased risk should also be screened
  - Repeat screening should be considered for those known to be at risk for HIV infection
- Rationale for updated recommendations:
  - ART reduces progression to AIDS, AIDS-related events and death and substantially reduces transmission of HIV
  - Data support earlier initiation of ART, and routine testing helps identify patients earlier

Moyer VA. Screening for HIV: U.S. Preventive Services Task Force Recommendation. Ann Intern Med 2013;159 (1):1-10, w1-

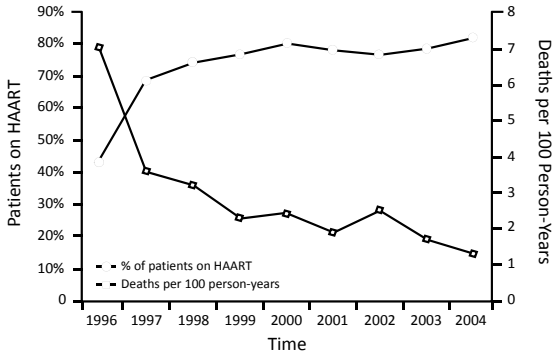


Late Diagnosis of HIV in Oregon

- 41% of Oregon adults have ever been tested for HIV
- 2008 – 2012 (39%) of Oregonians newly diagnosed with HIV infection had severe enough immune suppression to meet AIDS criteria within 12 months of diagnosis
- Most have likely had been infected for ≥7 years
- These individuals reported missed opportunities for testing, often because they didn't recognize or report their HIV risks.

CD Summary: Screen Your Patients for HIV, Oregon Public Health Division, Oregon Health Authority. February 13, 2015 Vol. 64, No. 2

Mortality and HAART Over Time



Palella FJ Jr, Baker RK, Moorman AC, et al; *J Acquir Immune Defic Syndr*. 2006;43:27-34.

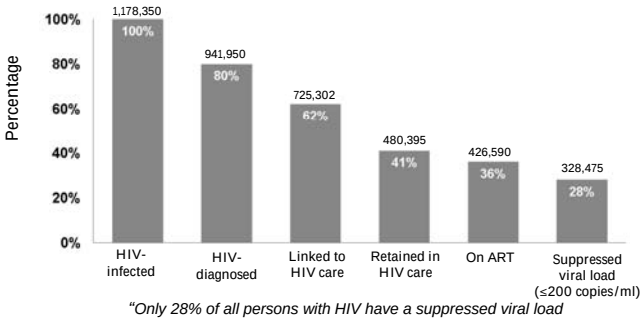
Life Expectancy is Not "Normal"

Slide 5

At HAART Initiation	CD4 Cell Count (mm^3)		
	<100	100-199	≥200
A 20 yr old will live to	52	62	70
A 35 yr old will live to	62	65	72
% Remaining Life Lost (all ages)	46%	27%	14%

Adapted from *ART-CC, Lancet 2008;372:293-99* by adding additional expected survival to age at treatment initiation.

The Continuum of HIV Engagement in care

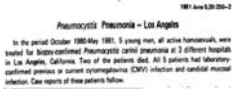


"Only 28% of all persons with HIV have a suppressed viral load because the best possible levels have not been reached for 1) testing, 2) ongoing HIV medical care, and 3) adherence."

Adapted from CDC, MMWR 2011;60:1618-1623

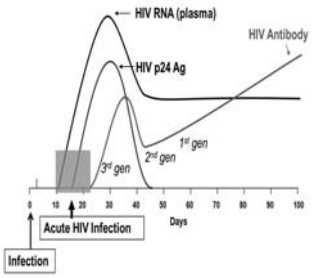
HIV...The Early Years

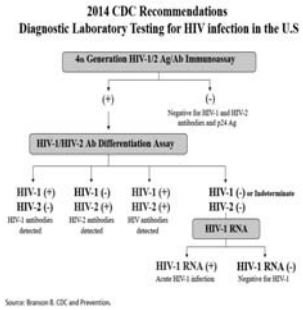
David Kirby 1990 Life magazine Picture



HIV Care Today

Window Period and HIV Infection





Source: Branson B. CDC and Prevention.

Busch MP, et al. *American Journal of Medicine*. 1997; 102(5B):117-124. Modified diagram based on first iteration in stated source and updated using several publications since 1997.

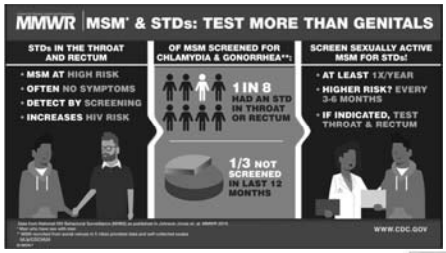
Starting HAART Early

- **START trial**
  - Subjects who initiated ART with a CD4 > 500 cells/mm3 experienced statistically significant reduction in
  - Risk to Death
  - Cancer
  - Tuberculosis
  - Other serious health end points
- **HPTN-052**
  - Early use of HAART (CD4+ cell count >350 cells/mm3) was show to decrease transmission between partners by 93%
- CD4 + cell recovery directly associated with CD4 count nadir at initiation on HAART

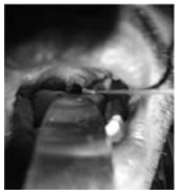
INSIGHT/START Group. N. England J Med. 2015;373: 795-807. Cohen MS, El al N. Engl J Med. 2011;365:293-505
Cohen MS, et al. IAS 2015. Abstact MOAC0101LB. Cohen MS, et al N Engl J Med. 2016, 275:830-839

HIV – Initial Clinic Visit and Labs

- CD4 Count
- HIV viral RNA PCR
- CMP and CBC with diff
- Lipid Panel
- HIV Resistance Testing (GENOTYPE)–selected patient
- Hepatitis A, B & C serology
- Tuberculin skin testing or IGRA (QuantiFERON Gold)
- Sexually transmitted disease (GC/chlamydia + RPR) 3 point testing in MSM
- Toxoplasma serologic test
- HLA-B5701 if considering Abacavir

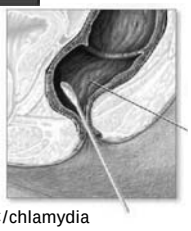


Pharyngeal



Aptima swab

Rectum



3 point testing: Especially in MSM and asymptomatic disease GC/chlamydia

http://emedicine.medscape.com/article/212100
4-overview#aw2aab6b4. https://www.scripps.org/articles/907-rectal-culture

Genotype Report (GART)


GuideLines™ Rules 13.0
RESISTANCE REPORT
State Central Labs

Before Starting :
- Transmitted resistance in 6-16% of HIV + patients

Failing medications:
- Perform while patient is taking ART, or ≤4 weeks after stopping therapy

- **NRTI, NNRTI AND PI**
  - GENOTYPE
  - PHENOTYPE
  - Genotype Archive – DNA, virologically suppressed.
- **INTEGRASE INHIBITORS**
  - GENOTYPE
  - PHENOTYPE
- **Co-Receptor Tropism Assay**
  - RNA
  - DNA

Antiretroviral Therapy What to Start in 2019

- **Nucleoside and nucleotide RTIs (NRTI)**
  - Zidovudine, AZT
  - Abacavir, ABC
  - Lamivudine, 3TC
  - Didanosine, ddI
  - Stavudine, d4T
  - Tenofovir, TDF
  - Emtricitabine, FTC
  - AZT/3TC
  - AZT/3TC/ABC
  - ABC/3TC (HLA B5701 testing)
  - TDF/FTC
  - TAF/FTC
- **CCR5 receptor blocker**
  - Maraviroc
- **Integrase inhibitor (INSTI)**
  - Raltegravir, RAL
  - Elvitegravir, EVG
  - Dolutegravir, DTG

Non nucleoside NRTIs: (NNRTI)
- Delavirdine (DLV)
- Nevirapine, NVP
- Efavirenz, EFV
- Etravirine
- Rilpivirine

Fusion inhibitors:
- Enfuvirtide, ENF or T20

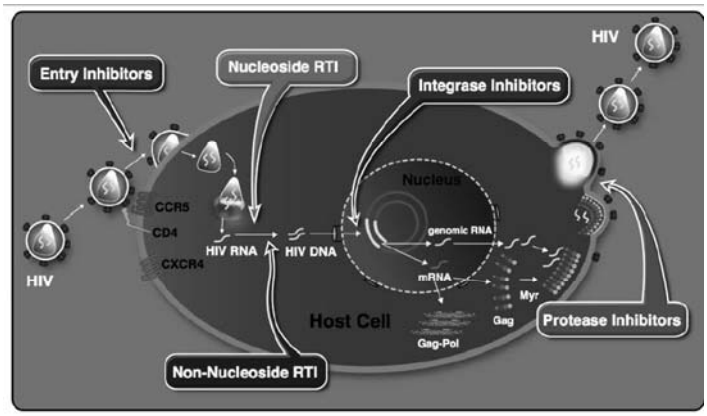
Protease inhibitors (PIs):
- Indinavir, IDV
- Saquinavir, SQV
- Nelfinavir, NFV
- Amprenavir, APV
- Atazanavir, ATV
- Fosamprenavir, FPV
- Lopinavir/ritonavir
- Tipranavir
- Darunavir
- Darunavir/cobicistat
- Atazanavir/cobicistat

Red – combination agents

Single pill regimens
- EFV/FTC/TDF
- RPV/FTC/TDF
- EVG/cobi/FTC/TDF
- DTG/ABC/3TC
- EVG/cobi/FTC/TAF
- Rilpivirine/FTC/TAF
- Bictegravir/FTC/TAF
- DRV/c/TAF/FTC

Picture Credit: https://www.choice.com.au/health-and-body/medicines-and-supplements/prescription-medicines/articles/the-dangers-of-mixing-medicines

HIV Drug Targets



Antiretroviral Therapy What to Start in 2019?

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

Developed by the HHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council (OARAC)

DHHS, IAS-USA, EACS, and WHO guidelines include recommended first-line ART regimens

	US DHHS[1]	IAS-USA[2]	EACS[3]	WHO[4]
INSTI	• BIC/TAF/FTC* • DTG/ABC/3TC* • DTG + TDF/FTC or TAF/FTC • EVG/c/TDF/FTC* • EVG/c/TAF/FTC* • RAL + TDF/FTC or TAF/FTC	• DTG/ABC/3TC* • DTG + TAF/FTC • EVG/c/TAF/FTC* • RAL + TAF/FTC	• DTG/ABC/3TC* • DTG + TDF/FTC or TAF/FTC • EVG/c/TDF/FTC* • EVG/c/TAF/FTC* • RAL + TDF/FTC or TAF/FTC	• TDF+ 3TC (or FTC) + EFV
Boosted PI			• DRV/r or DRV/c + FTC/TAF or FTC/TDF	
NNRTI			• RPV/TDF/FTC* • RPV/TAF/FTC*	

*Single-tablet regimens.

- Recommendations may be altered based on baseline HIV-1viral load, CD4+ count, CrCl, eGFR, HLA-B*5701 status, HBsAg status, and osteoporosis status

Recommended Regimens	
Integrase inhibitor + 2 NRTI	Bictegravir/TAF/FTC Dolutegravir/abacavir*/3TC Dolutegravir + TDF/FTC or TAF/FTC Elvitegravir/cobi/TDF (or TAF)/FTC Raltegravir +TDF/FTC or TAF/FTC

HLA-B5701 Testing needed for ABC – HSR (If negative safe to use ABC).
Chronic Hepatitis B, consider using TAF or TDF based regimens

http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf

HIV medications
Patient Characteristics & Considerations

Patient Characteristics

- Cardiovascular disease
- Hyperlipidemia
- Renal Disease
- Osteoporosis
- Chronic Hepatitis B
- Psychiatric illness
- Substance Use

Regimen Considerations

- Genetic Barrier to resistance
- Food requirements for absorption
- Elimination /metabolism
- Once daily vs twice daily
- Drug interactions !!!!!!!

Monitoring Labs

Laboratory	On HAART
CD4 & HIV RNA	q 3-6 months
BMP & LFT (with total bilirubin)	q 3-6 months
CBC w/differential	q 3-6 months
Fasting Lipid Panel	q 6-12 months
Fasting BG	q 3-6 months
Urinalysis	q 6 months (if HIVAN) or q 12 months (if on Tenofovir [TDF])
*for patients who have just started a new regimen, VL and safety labs should be checked 2-8 weeks following ARV initiation	

CD4 count monitoring for those on *ART for at least 2* years with consistent viral suppression:

- CD4 count between 300 and 500 cells/mm3: CD4 count monitoring every 12 months
- CD4 count >500 cells/mm3: CD4 count monitoring is optional

Common Drug Interactions

Anticonvulsants

- Protease inhibitor/PKE
- phenytoin, carbamazepine, phenobarbital-monitor levels
- Oral contraceptives
- PI/PKE, nevirapine, efavirenz

Miscellaneous

- methadone-some Protease inhibitors/PKE
- sildenafil, vardenafil-most Protease inhibitors/PKE
- warfarin-most Protease inhibitors/PKE, efavirenz
- Fluticasone, Protease inhibitors/PKE (Cushings)
- Antacids, rilpivirine and ATV (lowers HIV medication levels)

Opportunistic Infection Prophylaxis for Adults with HIV

	Criteria for Initiating Primary Prophylaxis	Criteria for Discontinuing Primary Prophylaxis	Criteria for Restarting Primary Prophylaxis	Criteria for Initiating Secondary Prophylaxis	Criteria for Discontinuing Secondary Prophylaxis	Criteria for Restarting Secondary Prophylaxis
PCP	CD4 < 200 or oral candidasis	CD4 > 200 for 3 mos	CD4 < 200	Prior PCP	CD4 > 200 for 3 mos	CD4 < 200
Toxoplasmosis	+ serum IgG CD4 < 100	CD4 > 200 for 3 mos	CD4 < 100 – 200	Prior toxoplasmic encephalitis	CD4 > 200 sustained and completed initial therapy and is asymptomatic	CD4 < 200
MAC	CD4 < 50	CD4 > 100 for 3 mos	CD < 50 – 100	Documented disseminated disease	CD4 > 100 sustained and completed 12 mos of MAC tx and asymptomatic	CD4 < 100
Cryptococcosis	none	n/a	n/a	Documented disease	CD4 > 100 – 200 sustained and completed initial therapy and asymptomatic	CD4 < 100 - 200
Histoplasmosis	none	n/a	n/a	Documented disease	No criteria recommended for stopping	n/a
CMV	none	n/a	n/a	Documented end-organ disease	CD4 > 100 – 150 sustained and no evidence of active disease and regular exams	CD4 < 100 - 150

HIV & Cancer Screening

- Breast Cancer
  - HIV Primary Care recommend that HIV + women follow the same breast cancer screening guidelines as for the general population.
- Colon Cancer
  - HIV infection may have a slightly higher risk for developing colon cancer. No additional screening recommendations
- Prostate Cancer
  - Men with and without HIV infection have a similar risk of prostate cancer. No additional screening

Cervical Cancer Screening in Women with HIV

- Abnormal cervical cytology is nearly x 11 times more common with HIV compared to HIV negative female population
- < 30 years
  - Cervical pap smear at the HIV diagnosis
  - If normal, repeat every 12 months
  - If 3 consecutive apps are normal →every 3 years
  - Co-testing (Pap and HPV) not recommended
  - Refer for colposcopy if ACUS on pap and reflex HPV test positive or if pap result LSIL or worse

https://aidsinfo.nih.gov/contentfiles/lvguidelines/glchunk/glchunk_343.pdf

Cervical Cancer Screening in Women with HIV

- >= 30 years
  - Pap alone or pap with HPV co-testing

Pap alone:

- At time of HIV diagnoses, then annually
- If 3 consecutive pap smears normal, then every 3 years

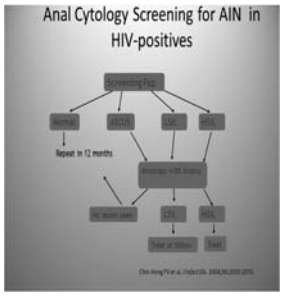
Pap with HPV co-testing

- If pap and HPV negative, screening every 3 years
- If pap normal and HPV positive, repeating testing in 1 years' if HPV
- Type 16 and 18 positive, refer for colposcopy
- If ASCUS and HPV positive, refer to colposcopy
- For LSIL or worse, refer for colposcopy

https://aidsinfo.nih.gov/contentfiles/lvguidelines/glchunk/glchunk_343.pdf

HIV & Anal Cancer

- Anal cancer incidence among HIV+ MSM has been estimated to be 2x that of HIV negative MSM (131/100,000)
- Anal Pap smears (Controversial) in MSM & women with a history of receptive anal intercourse OR abnormal cervical Pap test results, AND all individuals with HIV infection who have genital warts with DRE



Daling JR, et al. N Engl J Med. 1987;317(16):973.

JA Aberg Et al. Clinical Infectious Diseaes. 2014 Jan;58(1):e1-34. doi: 10.1093/cid/cit665. Epub 2013 Nov 13.

Recommendations for vaccination in HIV-infected adults

Vaccine	Age group (years)					CD4 cell count (cells/microL)	
	13 to 18	19 to 26	27 to 39	60 to 64	≥65	<200	≥200
Influenza*	1 dose annually					1 dose annually	
Tetanus, diphtheria, acellular pertussis (Tdap)/ tetanus, diphtheria (Td)¶	1 dose Tdap, then Td booster every 10 years					1 dose Tdap, then Td booster every 10 years	
Measles, mumps, rubella (MMR)Δ	2 doses if CD4 cell count ≥200					Contraindicated	2 doses if born in 1957 or later
Varicella (VAR)◊	2 doses if CD4 cell count ≥200					Contraindicated	2 doses
Herpes zoster (HZV)§						Contraindicated	
Human papillomavirus (HPV)ǂ	3 doses					3 doses through age 26 years	
Pneumococcal conjugate (PCV13)#	1 dose					1 dose	
Pneumococcal polysaccharide (PPSV23)#	2 doses				1 dose	Up to 3 doses depending on age	
Hepatitis A (HepA)†	2 or 3 doses depending on vaccine					2 or 3 doses depending on vaccine	
Hepatitis B (HepB)**	3 doses					3 doses	
Meningococcal (MenACWY)¶¶	2 doses, then booster every 5 years					2 doses, then booster every 5 years	
Meningococcal B (MenB)¶¶	2 or 3 doses depending on vaccine					2 or 3 doses depending on vaccine	
Haemophilus influenzae type b (Hib)ΔΔ	1 or 2 doses depending on indication					1 or 2 doses depending on indication	

Recommended for adults and adolescents with HIV infection | Recommended for adults and adolescents with HIV infection and other indications | Contraindicated | No recommendation

Adapted from the Advisory Committee on Immunization Practices (ACIP) recommended immunization schedules for adults and adolescents. These immunization schedules are available at https://www.cdc.gov/vaccines/schedules/hcp/index.html. Detailed information on these and other vaccines can be found at https://www.cdc.gov/vaccines/hcp/acip-recs/index.html.

HIV & Pneumococcal Vaccine

Invasive pneumococcal infection x 20 higher

- No History of Pneumococcal vaccine
  - PCV-13 followed by PPV 23 at least 8 weeks later
  - 5 years later, revaccinate with PPSV-23
- Previously Received PPSV23
  - Give PCV 13 x 1 dose 1 year later
  - PPSV-23 given 5 years later
    - booster at 65 years old

HIV & Meningococcal Vaccine

- Meningococcal vaccine is x 5 - 14 times greater in HIV than the general population
- (Greatest risk if CD4 is low and HIV viral load high)
  - 2 dose of meningococcal conjugate vaccine MenACWY-CRM (Menveo) or MenACWY-D (Menactra) at least 2 months apart
  - Booster every 5 years
  - Serotype B if indicated (Outbreaks or Asplenia)

ACIP. Recommended. Adult immunization Schedule US 2017

HIV & HPV vaccine

- Recommended for females and males with HIV from 9 to 26 years
  - 9 valent vaccine, 3 doses, at 0, 1-2 and 6 months
  - For those who have completed vaccination with bi or quadrivalent vaccine, may consider additional vaccine with the 9 valent
  - Pick up additional serotypes associated with some cancers in men and women.

HIV & the Zoster vaccine

- Live zoster vaccine (Zostervax)
  - CD4 < 200 Contraindicated
  - CD4 > 200 – no recommendation
- Recombinant Vaccine (Shingrix)
  - >90 % efficacy at prevention
  - Immunocompetent adults aged > 50 years, irrespective or prior zoster vaccine live (ZVL) o previous zoster
  - 2 doses, 2-6 months apart
  - Local and systemic reactions reported > 10%
  - Data on immunocompromised host coming
    - Recommended if low dose immunosuppression (< 20 mg/d prednisone)

Adapted from the Advisory Committee on Immunization Practices (ACIP) recommended immunization schedules for adults and adolescents. These immunization schedules are available

HIV & Hepatitis Vaccine (A + B)

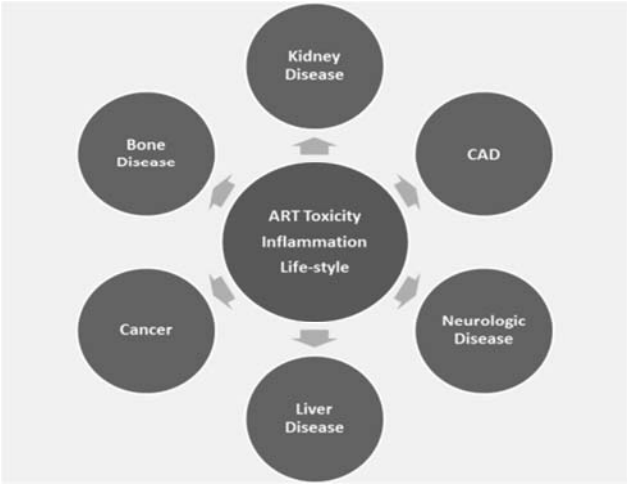
- Hepatitis A vaccine (MSM population)
- All HIV + patient should be screened for HBV
  - If non-immune give vaccine, 0, 1, 6 months
  - If vaccine series is interrupted don't restart.
  - Give 2nd & 3 doses at least 8 weeks apart
- Check anti-Hep B s after completing series
  - If non-immune- 2nd series Hep B vaccine
  - Consider revaccinating with double dose (Stop)
- Isolated Hep B core (common in HIV +)
  - Check Hep B DNA to rule out occult Hep B (rare)
  - If negative consider vaccine

http//www.cdc.gov/hepatitis/HBVfaq.htm

HIV & Influenza vaccine

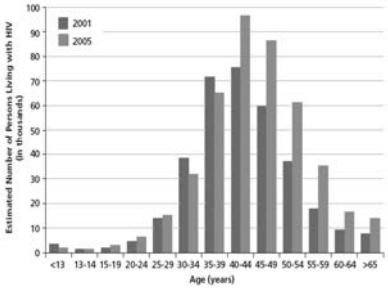
- All persons with HIV infection should receive a annual dose influenza vaccine [inactivated] (trivalent or quadrivalent)
  - **Contraindicated Vaccine**: No live attenuated influenza
- Lower CD4 count with poorer response
- More studies need for the efficacy of the high-dose influenza vaccine in HIV-infected adults
- **> 65 years**: Adults with HIV infection aged 65 years or should get standard-dose or high-dose inactivated influenza vaccine.

Yamanaka et al J Acquir Immune Defic Syndr. 2005;39(2):167.



Reference: Chang et al., Archives of Gerontology and Geriatrics, 2012

Another Kind of AIDS Crisis…

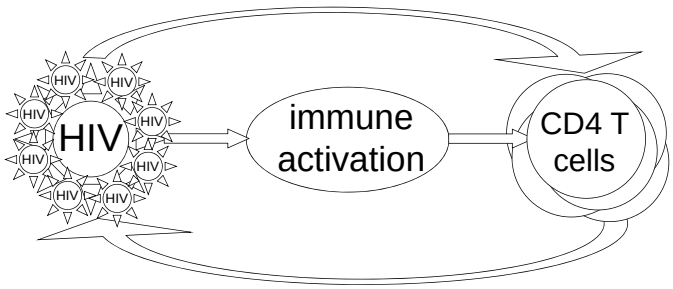


Left: **Russell Steinke**. Age: 56 / HIV: 23 years / Has suffered from: memory loss, nerve damage in feet, lipodystrophy, fatigue.
Right: **Enrico McLane**. Age: 52 / HIV: 17 years / Has suffered from: short-term memory loss, two hip replacements.

(David France, published Nov 1 2009. New York Magazi

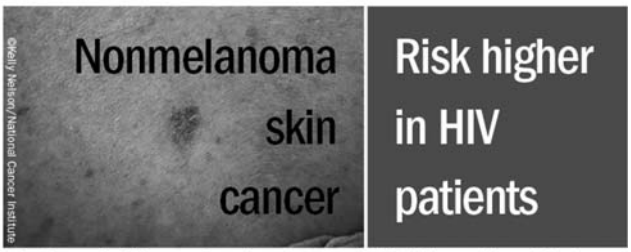
2015 > 50% of HIV patients in the USA are > 50 years old

Immune Activation Drives HIV Replication



- HIV drives a cycle of immune activation, CD4 T-cell infection and death, and more virus
- Inflammatory markers like CRP may not improve with HAART

Slide courtesy D Douek, MD, PhD, at New York, NY: March 13, 2009, IAS–USA.
Shikuma, et al, AIDS Res Hum Retroviruses. 2010 Sep 23.

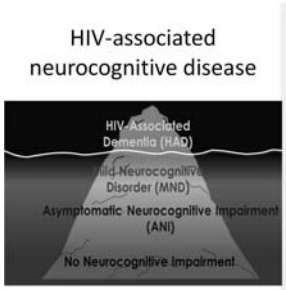


Carcinoma incidence rate ratios, compared with HIV-negative subjects:

Basal cell	Basal cell	Squamous cell
1.79	2.3	5.4
All HIV-positive patients	Men who have sex with men	All HIV-positive patients

Source: Omland S et al. J Am Acad Dermatol. 2018 Mar 24. pii: S0190-9622(18)30475-4.

INCREASED RISK of Non-AIDS Defining Cancers



The CNS Penetration-Effectiveness Score may reflect better efficacy in CNS[1,2]

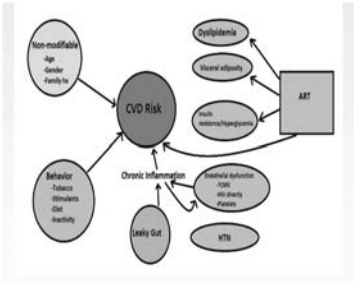
	4	3	2	1
NRTIs	• Zidovudine	• Abacavir • Emtricitabine	• Didanosine • Lamivudine • Stavudine	• Tenofovir • Zalcitabine
NNRTIs	• Nevirapine	• Delavirdine • Efavirenz	• Etravirine	
PIs	• Indinavir/r	• Darunavir/r • Fosamprenavir/r • Indinavir • Lopinavir/r	• Atazanavir • Atazanavir/r • Fosamprenavir	• Nelfinavir • Ritonavir • Saquinavir • Saquinavir/r • Tipranavir/r
Entry/Fusion Inhibitors		• Maraviroc		• Enfuvirtide
Integrase Inhibitors	• Dolutegravir	• Raltegravir	• Elvitegravir/cobi	

Changes in memory, concentration, attention, and motor skill issues
Progression by history & exam or by neuropsychological testing
Deficits cannot be fully explained by alternate conditions

HAND
- Asymptomatic neurocognitive impairment (ANI)
- HIV-associated mild neurocognitive (MND)
- HIV-associated dementia (HAD)

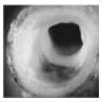
Thompson Neuroimaging Laboratory, UCLA (2005(Ellis et al., 2003) J. Neurovirology 2011 Feb; 17(1): 3–16. Letendre SL. Et al Top HIV Med. 2010; 18, 45-55. Letendre SL et al HIV management 2014. The New York Course.

HIV and Heart Disease
Chronic inflammation

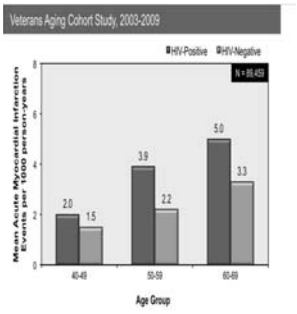


Deeks, Gandhi, Chae, Lewandrowski, NEJM 2012

HIV + Persons are at risk for CVD



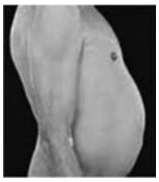
- 4th leading cause of death in HIV patient ins the D:A:D cohort
- High levels of markers of immune activation and inflammation → even with suppressed HIV
- Some ARVs found to be associated with increased risk for MI



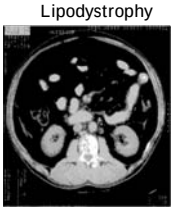
Triant, VA Curr HIV/ADIS Rep. 2013; 10;199-206. 2. Morgello, S et a. Arch Path Labs Med. 2002;126 182-190. 3. Subramanian S. et al. Jama, 2012. 308:379-386. 4. Post WS et al. Ann Internal Med 2014;160:458467. Deeks S. et al. Lancet 2013: 15250-1533. 6. Hunt PW. Curr HIV/AIDS Rep. 2012. 9:139-147. 7. Worms S. et al. J Infect Dis. 2010;201:318-330. 8. Drozd DR et. Al. JAIDS . 2017 Aug 15;75(5):586-576 . Source: Freiberg MS, Chang CC, Kuller LH, et al. HIV infection and the risk of acute myocardial infarction. JAMA Intern Med. 2013;173:614-22.

HIV + and Cardiovascular Disease

- Obesity is a much more common problem than wasting in the current therapeutic era
- Lipodystrophy with an increase in central adiposity and metabolic syndrome.



Lipodystrophy



Amorosa V, et al. 11th CROI. San Francisco, 2004. Abstract 879.
Seaberg EC et al, Multicenter AIDS Cohort Study AIDS. 2005;19(9):953.

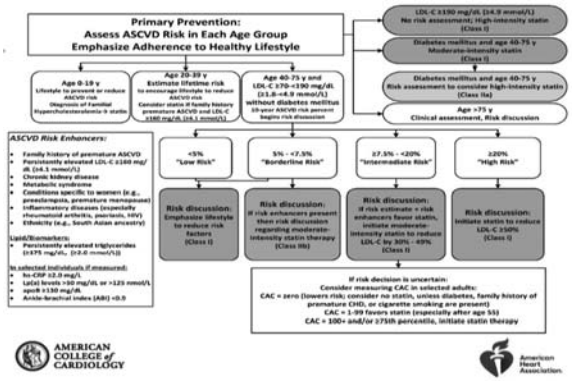
Impact of Antiretroviral Medication on Lipids

Class	Impact on Lipids
NRTIs	• Stavudine > Zidovudine > Abacavir: ⇧TG and ⇧LDL • Tenofovir alafenamide > Tenfovir DF: ⇧TG, ⇧LDL, ⇧HDL (no change TC:HDL ratio)
NNRTIs	• Efavirenz: ⇧TG, ⇧LDL, ⇧HDL
PIs	• All ritonavir- or cobicistat-boosted PIs: ⇧TG, ⇧LDL, ⇧HDL • Lopinavir-ritonavir = Fosamprenavir + Ritonavir: ⇧TG • Lopinavir-ritonavir > Darunavir + Ritonavir: ⇧TG • Atazanavir + Ritonavir: ⇧TG
ISTIs	• Elvitegravir-Cobicistat: ⇧TG, ⇧LDL, ⇧HDL
EIs	• NA

Abbreviations: NRTIs = nucleoside reverse transcriptase inhibitors; NNRTIs = nonnucleoside reverse transcriptase inhibitors; PIs = protease inhibitors; ISTIs = integrase strand transfer inhibitors; EIs = entry inhibitors

HIV & Cigarette Smoking

- HIV-infected patients are more likely to smoke and less likely to quit compared to general population
- Drug options include nicotine replacement (e.g., patch, gum, lozenge), bupropion, and varenicline, which can be used alone or in combination
- No important HIV drug interactions for commonly used smoking cessation drugs



In Adults 40 to 75 years of age without diabetes and 10 year risk for 7.5 % to 19 %, (intermediate risk), risk enhancing factors favor starting of a statin
Risk enhancing factors may favor statin therapy in patient wat 10 year risk of 5-7.5% (borderline risk)

HIV- and ART-induced dyslipidemia

Fibrates **Fluvastatin** **Pravastatin*** **Ezetimibe** **Fish oil**	**Low interaction potential**	• HIV + can persistently low HDL cholesterol • HIV have a poorer response to statin and fibrate therapies • **Beware of Drug interactions !!!**
Statin + fibrate **Atorvastatin** **Rosuvastatin** **Niacin**	**Use cautiously**	
Lovastatin **Simvastatin**	**Contraindicated**	

*AUC □ with DRV

Aptivus [package insert]; 2005. Carr RA, et al. ICAAC 2000. Abstract 1644. Fitchenbaum CJ, et al. AIDS. 2002;16:569-577. Gerber JG, et al. CROI 2004. Abstract 603. Gerber J, et al. IAS 2003. Abstract 870. Hsue PH, et al. Antimicrob Agents Chemother. 2001;45:3445-3450. Lexiva [package insert]; 2007. Prezista [package insert]; 2006. Reyataz [package insert]; 2007.

General Approach to CV Risk in HIV Positive Patients

Obtain fasting lipid profile, prior to starting antiretrovirals and within 3 to 6 months of starting new regimen

↓

Count number of CHD risk factors and determine level of risk.
If ≥2 risk factors, perform a 10-year risk calculation

↓

Intervene for modifiable non-lipid risk factors, including diet and smoking

↓

If above the lipid threshold based on risk group despite vigorous lifestyle interventions, consider altering antiretroviral therapy or lipid-lowering drugs

↓

IF LIPID-LOWERING DRUGS ARE NECESSARY

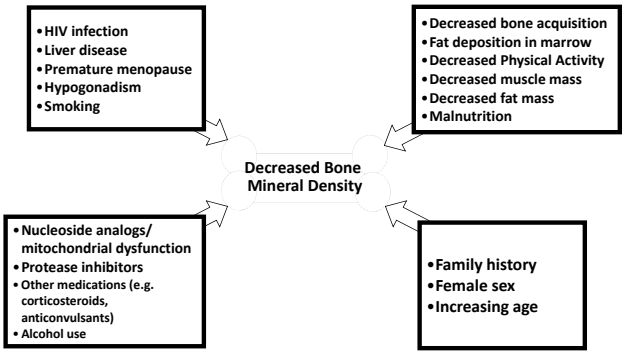
Be Aware of Drug-Drug Interactions

Dubé MP et al. *Clin Infect Dis*. 2003;37:613-627.

IDSA = Infectious Diseases Society of America.

Bone Mineral Density in HIV Patients

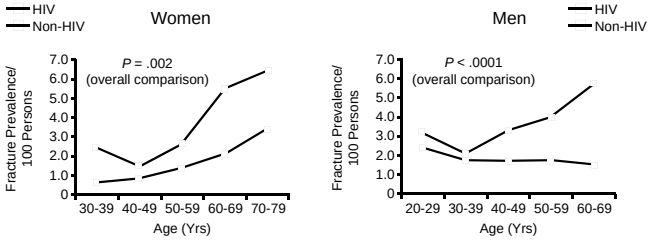
47



Glesby M et al. *CID* supplement September 2003.

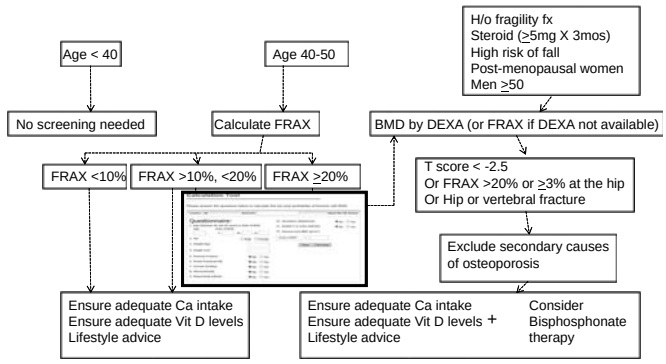
HIV-Positive Pts Have Increased Risk of Bone Loss and Fractures

- HIV-positive patients had 6.4-fold increased risk of low BMD and 3.7-fold increased risk of osteoporosis
- 8525 HIV-infected pts compared with 2,208,792 uninfected pts in Partners HealthCare System, 1996-2008



1. Brown TT, et al. AIDS. 2006;20:2165-2174.
2. Triant V, et al. J Clin Endocrinol Metab. 2008;93:3499-3504.

HIV+ & Bone Health
Screening Recommendations



Brown TT, et.al. Recommendations for evaluation and management of bone disease in HIV Clin Infect Dis, January 21, 2015

US National Osteoporosis Foundation (NOF) Guidelines for DXA Screening (2008)

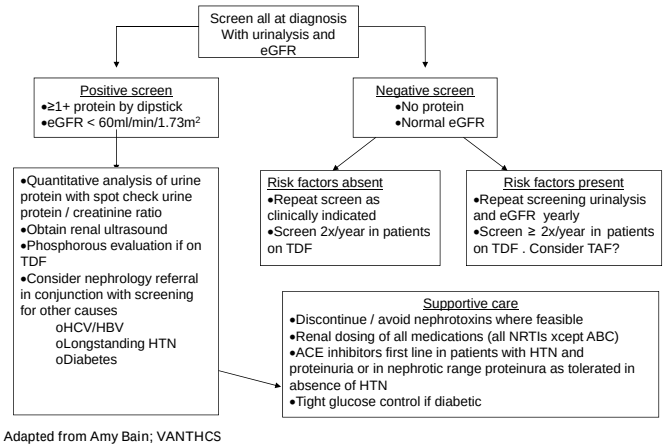
- Those with a history of fragility fracture
- Women ≥65 years, Men ≥70
- Postmenopausal women and men 50-70 years, if there is concern based on risk factor profile

Screening in HIV-infected Patients:

All post-menopausal women
Men ≥50 years

Slide Credit courtesy Todd Brown

Evaluation of Renal Disease in HIV



Adapted from Amy Bain; VANTHCS

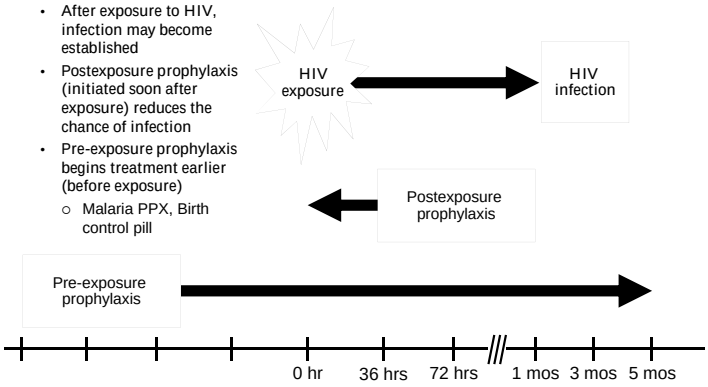
Drug Related Renal Disease in HIV
Tenofovir Nephrotoxicity (TDF vs TAF)

- Tenofovir nephrotoxicity: proximal tubular cell dysfunction that may be associated with AKI or chronic kidney disease
  - Fanconi was 60% of AKI with TDF use in one report. Most resolved with cessation, but a few incompletely
- Biopsy might be helpful: typically shows ATN without glomerular or interstitial changes
- TAF: pro-drug of tenofovir that concentrates in cells, converted to tenofovir (TFV) and is virologically as effective as TDF.
- TAF has more favorable effects on renal (CrCl > 30 cc/min) and bone markers.

Zimmermann. Clin Infect Dis 2006; 42:283-290

Pre- vs Post-exposure Prophylaxis

- After exposure to HIV, infection may become established
- Postexposure prophylaxis (initiated soon after exposure) reduces the chance of infection
- Pre-exposure prophylaxis begins treatment earlier (before exposure)
  - Malaria PPX, Birth control pill



What is PrEP?

- A prevention strategy in which a high-risk individual takes medication regularly to prevent infection
- Tenofovir-emtricitabine (*Truvada*) approved for HIV PrEP by the FDA in July 2012
- Added benefits: provides some protection against HSV and hepatitis B

Monitoring for Patients taking PrEP

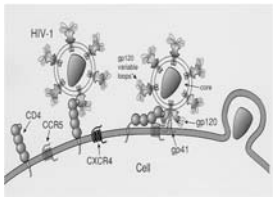
Recommended Laboratory Testing and Frequency for Patients Taking PrEP				
Laboratory test	**Baseline**	**Every 3 months**	**At least every 6 months**	**Notes**
HIV screening assay	✓	✓		Consider need for HIV RNA PCR
HBV antibody panel and HCV antibody	✓			Offer HBV vaccination if not immune
Basic Metabolic Profile	✓		✓	Avoid PrEP if CrCl <60 mL/min
General STI screen	✓		✓	**Include oral/rectal * screen for MSM if risk**
Pregnancy test for women*	✓	✓		
*The safety of PrEP in pregnancy has not been established				

Source: US Public Health Service. Clinical practice guidelines for PrEP. May 2014.

Guidance for PrEP Use With HIV-Uninfected Sexually-Active Adults

	MSM	HRH
At Very High Risk of Acquiring HIV Infection	HIV+ partner STI history, high number of sex partners History of inconsistent or no condom use Commercial sex work	
		In high prevalence area or network
Clinically Eligible	Documented negative HIV test before prescribing PrEP No signs/symptoms of acute HIV infection Normal renal function, no contraindicated medications Documented hepatitis B virus infection/vaccination status	
Prescription	(Truvada®), daily # 90 day supply	
Other services	• Follow-up visits at least every 3 months to provide: HIV test, medication adherence counseling, behavioral risk reduction support, side effect assessment, STI symptom assessment • At 3 months and every 6 months after, assess renal function • Every 6 months test for bacterial STIs	
	Do oral/rectal STI testing	Assess pregnancy intentions Every 3 months do pregnancy test Consider use for safer conception Consider continuing during pregnancy

***Main points only. See source documents:**
CDC. *MMWR*. 2011;60(3):65-68 and
CDC. *MMWR*.2012;61(31):586-590.



The New York Times

H.I.V. Is Reported Cured in a Second Patient, a Milestone in the Global AIDS Epidemic

Scientists have long tried to duplicate the procedure that led to the first long-term remission 12 years ago. With the so-called London patient, they seem to have succeeded.

- He underwent aggressive chemotherapy to clear the leukemia
- Received two bone marrow transplants from a CCR5-Δ32 individual.
- The new immune cells were not susceptible HIV, and the virus in currently HIV undetectable post-transplant.

HIV enters cells by binding to CD4 and a "corecepter" (often CCR5).

CCR5 is not functional in approximately 1% of Caucasians, which means they are highly resistant (but not completely immune) to infection with most strains of HIV.

This mutation is called CCR5Δ32.

Reference:http://www.thefullwiki.org/Discovery_and_development_of_CCR5_receptor_antagonists

Conclusions: HIV management for the Non-specialist

- Remember that early diagnosis of HIV is important
- HIV accelerates Aging—be aware of Comorbidities
  - Cardiovascular, Renal and Bone Disease
- Poly pharmacy and drug-drug interactions
- More STR Options (HAART) – More Tolerable regiments
- Prevention- Pre Exposure Prophylaxis
- Don't forget Preventable screenings and Vaccines - & cancer screening.
- HIV Cure: Promising but not ready for Prime-Time

Ali Maalin

Thanks for Listening

The Challenges of Vaginitis

Amy L Stenson MD, MPH
Associate Professor Obstetrics and Gynecology
Residency Program Director
Program in Vulvar Health, Oregon Health & Science University

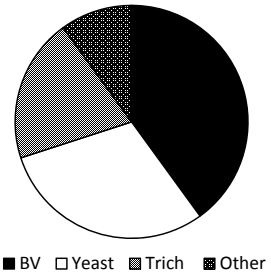
- No disclosures

Objectives

- Review common vaginitis
  - Pathogenesis
  - Diagnosis
  - Treatment
- Discuss difficult/unusual cases
  - Recurrent Yeast and BV
  - Resistant Trichomonaisis
  - Non-infectious vaginitis
- Understand when to refer to gyn/vulvar

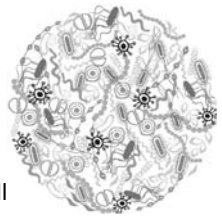
Vaginitis Basics

- Caused by infection, inflammation or changes in the normal vaginal flora
- Most common causes
  - Yeast (17-39%)
  - BV (22-50%)
  - Trich (4-35%)
  - Other (7-10%)



- Symptoms include: vaginal discharge, odor, pruritus, irritation or discomfort

Vaginal Health and the Microbiome



- Estrogen promotes mature epithelial cell
- Glycogen in epithelial cells supports lactobacilli
- Lactobacilli produce lactic acid and lower pH
  - Normal vaginal pH is <4.5
- Acidic environment is protective
- Normal flora is heterogeneous, but in balance
  - Commonly includes *Gardrenella, E. Coli, GBS, Mycoplasma, Candida, but dominated by lactobacilli*

Prepuberty and Menopausal Women

- lack of estrogen inhibits normal growth of the vaginal bacterial ecosystem;
- microscopy typically shows a paucity of epithelial cells and background bacteria
- Rare to see BV or yeast in these patients, so consider alternate diagnosis

Case 1

- 36yo G0 single woman with Mirena IUD who presents with concerns of vulvovaginal itch and burn

Office Evaluation: History

Quality: onset, frequency, duration, location, severity, consistency, color, & odor

Exposure to contact irritants: soaps, spermicide, bathing products or intra-vaginal products

Vulvar Hair Hygiene: shave, laser, wax

Hormonal status : Relation to Menstrual cycle? Estrogen depleted? (postpartum, menopausal, birth control)

Sexuality: partners, barrier BCMs, lubes, toys, other

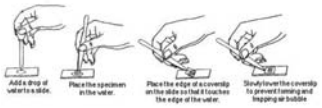
Treatments: OTC, CAM or prescribed medications

Tools for Evaluation

- **Physical Exam**
  - Visual inspection of vulva , perineum, anus & vagina (speculum)
- **Microscopy**
  - pH immediately
  - Saline/KOH prep
  - Whiff test: amine odor with application of KOH
- **Vaginal Culture**: vaginal side walls or fornix, not cervix
  - Fungal culture helpful
  - General bacterial culture generally not helpful
- **Rapid tests:** when indicated or unable to do microscopy
  - BV, GC/CT,
- **Vulvar Biopsy**
  - Only when notable skin changes
  - Random biopsy not helpful and can be traumatic for the patient

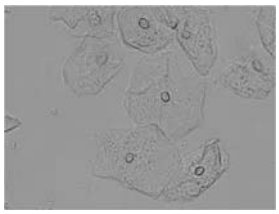
Wet Prep

1. Check Vaginal pH
   - prior to using lidocaine, gel etc ideally
   - Using pH paper graded from 3-5.5
   - Ask about bleeding, sex and intravaginal products (affect pH)
2. Collect specimen
   - From vaginal side walls
   - Consider recollecting, I usually collect twice
3. Place specimen in saline on 2 slides (or in carrier container)
   - Check to ensure that it appears cellular, if not recollect and add more cells
4. On second slide add KOH
5. Place cover slips



What can we see in a Saline Prep?

- Epithelial Cells
  - mature squamous cells
- WBCs
- RBCs
- Parabasal Cells
  - immature squamous
- Trichomonas
- Clue Cells
- Hyphae/spores
- Debris



	pH	WBC	Para-basals	Features	Discharge
Normal	3.5-4.5	Few or none	no	Mature epithelial cells lactobacilli	Creamy white

	pH	WBC	Para-basals	Features	Discharge
Normal	3.5-4.5	Few or none	no	Nl lactobacilli	Creamy, mucousy, white
Yeast	3.5-4.5	no	no	Hyphae Spores (400x)	White, Curdy
BV	>4.5	no	no	Clue Cell	Yellow, grey w/ odor
Trich	>5.0	yes	maybe	Motile trich	Greenish yellow, frothy
DIV	>5.0	yes	yes	Mixed bactertia, reduced lacto	Yellow, profuse
GSM	>5.0	maybe	yes	Scant cells, few bacteria	Scant, dry

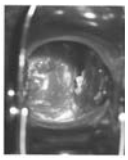
Vaginal Culture

- Appropriate for recurrent, difficult vaginitis
- Culture for **recurrent yeast**
  - Request sensitivity and speciation
- Culture for **resistant trichomonads**
- Not helpful for recurrent or resistant BV
  - Unsure role of other coliforms, therefore not recommended to obtain bacterial culture of vagina in most cases

Vulvovaginal candidiasis

Vulvovaginal Candidiasis (VVC)

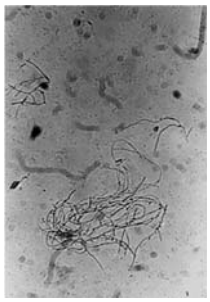
- 13 million cases annually in the USA
- Second most common cause of vaginitis
- Primary symptoms
  - Itching
  - Thick, curdy, white discharge
- 29-49% of women w/ at least 1 lifetime episode
- 5% of women develop recurrent infection



Foxman, 2013, CDC 2010 STD Treatment Guidelines

Diagnosis

- Microscopy, convenient and specific
  - Only 50-70% sensitive
- Culture
  - resistant/recurrent infection
- PCR (39-99% sensitive)
  - BD AFFIRM (candida y/n)
  - BD MAX (subtype)



Vulvovaginal Candidiasis (VVC)

- **<u>Uncomplicated</u>**
- Sporadic, infrequent
- Mild-moderate
- Likely *C. albicans*
- Non-immunocompromised

- **<u>Complicated</u>**
- Recurrent (>3/year)
- Severe (clinical exam)
- Non-albicans
- Diabetes, immunocompromise

2015 CDC STD Treatment Guideline

Treatment of uncomplicated yeast

- Topical (vaginal) OTC azole preparation x 3-7d
- Oral fluconazole 150mg as single dose
- Very Effective >90%

- Topical tx recommended in pregnancy, as oral fluconazole was associated with increased miscarriage rate.

Quiz Question 1

Candida albicans is the most common cause of recurrent vulvovaginal yeast infections. Several **uncommon** species of yeast can also cause recurrent infection. Which species of fungus is the most common in THIS category?

a. Candida parapsilosis
b. Candida glabrata
c. Saccharomyces cerevisiae
d. Tinea

Acute Infection: non-*albicans*?

- ~5-10% women with recurrent VVC have non-*albicans* species
  - *C. glabrata* ***
  - *C. parapsilosis*
  - *C. krusei*
  - *Saccharomyces cerevisiae*

Spinillo, A, 1995. **85**(6): p. 993-8
Sobel, Am J Obstet Gynecol, 2001

How to treat non-*albicans*?

- Fluconazole? >50% non-response if *Candida glabrata*
- Itraconazole 200mg QD or 100mg BID x 3-7d
- Boric acid 600mg capsules intra-vaginally QHS-BID x 14ds
  - 92 women failed conventional treatment with -azoles had 98% mycologic cure with boric acid
  - Case series of resistant VVC , 81% pt responded to 600mg QDx14d boric acid compared to <50% -azole
- Flucytosine 5% cream intravaginally 5g QHS x 14d

Nyirjesy, Am J Obstet Gynecol, 1995
Guaschino, Am J Obstet Gynecol, 2001
Van Slyke, Am J Obstet Gynecol, 1981
Sobel, Am J Obstet Gynecol, 2003
Sobel JD, Clin Infect Dis 1997
Jovanovic, J Reprod Med, 1991

Recurrent VVC Diagnosis

- Defined as 4 or more episodes/year
- Begin with office evaluation
  - Data supports women poor at self-diagnosis
- Microscopy, KOH increases sensitivity
- Consider rapid point of care test (AFFIRM®)
- Vaginal culture, most will be *C. albicans*
  - Consider ID & sensitivities for difficult case

Ferris, Obstet Gynecol 2002;99:419; Ferris, J Fam Pract. 1996;42(6):595. Sobel, AJOG 1985; 152:924
Allen-Davis, Obstet Gynecol 2002;99:18; CDC 2010 STD Treatment Guidelines

Can a Woman Accurately Diagnose Herself?

Ferris, Obstet Gynecol, Vol 99 (3), 2002.

Final Diagnosis	N	%
Normal	13	13.7
VVC	***32***	***33.7***
Trichomonas	2	2.1
BV	18	18.9
Other*	10	10.5
VVC+BV	18	**18.9**
BV+Trich	1	1.1
VVC+Trich	1	**1.1**

Recurrent VVC: Risk Factors

- Antibiotic use
- Estrogen excess (pregnancy, vaginal estrogen)
- Immune suppression (SLE, HIV, oral steroids)
- Vulvar dermatoses (LS, LP, psoriasis)
  - Likely due to steroid use
- Diabetes mellitus

2010 CDC STD Treatment Guideline
Sobel, JD. Candida vaginitis. Infect Dis Clin Pract 1994; 3:334.

Complicated/Recurrent Infection

- Topical OTC azole preparation x 14days
- Oral fluconazole 150mg x 2, 3d apart
- Oral fluconazole 150mg q 3-5days x 14days
- Topical 5-Flucytosine 5g intra-vag QHSx14days

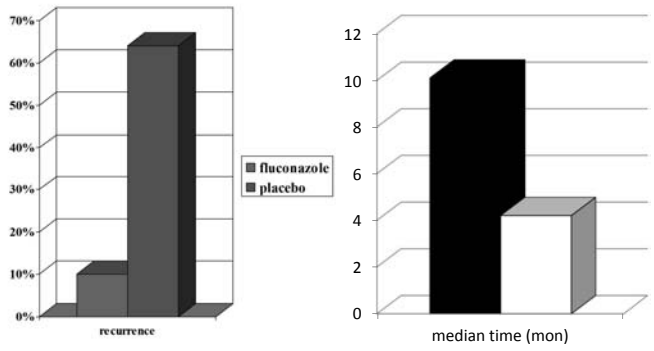
Sobel, Am J Obstet Gynecol, 2001
Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America, Clin Infect Dis. 2009 Mar 1;48(5):503-35
Rodgers, C.A. and A.J. Beardall, Int J STD AIDS, 1999.

Preventing Recurrence: Suppression

- Begin prophylaxis:
  - **Fluconazole 150mg Q week x 6 mon
  - Clotrimazole 500mg vag supp weekly x 6 mon
  - Boric acid 600mg intravag 2x/week x 6 mon
- Weekly oral fluconazole is very effective and safe
- Recurrence after suppression up to 30%
- Safety profile of long term use of boric acid not proven

Sobel, 1992 2015 CDC STD Treatment Guideline

VVC: Why Suppression?



Sobel, NEJM 2004; 351:876

What Predicts Recurrence?

Patel et al, AJOG 2004; 190:644

- Prospective cohort: 65 with RVVC despite maintenance, classic risks controlled, logistic regression for behaviors associated with recurrence
- **RISK:** panty-liners, pantyhose, cranberry juice, consumption of acidophilus products (oral & vaginal), hx of BV, <40yo
- **NO RISK:** OCPs, oral sex, vaginal sex

Preventing Recurrence?

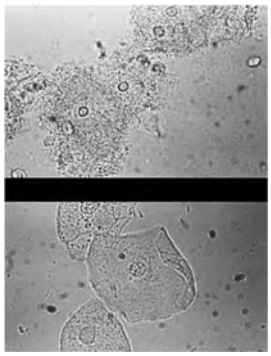
- Control Classic risk factors:
  - uncontrolled DM
  - Immuno-suppression
  - HIV+
  - antibiotic use
- Data does not support
  - use of probiotics
  - treatment of male partner

Fong 1992, William 2001, Priotta 2004, Witt, 2009

Summary: Recurrent VVC

- Defined as 4 infections/year
- Office evaluation/culture to confirm dx & species
- Treat acute infection aggressively (*Candida albicans)*
  - Fluconazole 150mg x 3 doses, Days 1, 4 and 7
  - Intra-vaginal –azole QHS x 14d
- Suppression x 6 months
  - Fluconazole 150mg weekly
  - Intra-vaginal –azole weekly
- 30% will recur after 6 months suppression
- Long term safety established with oral Fluconazole
- Look at behaviors for risk factors

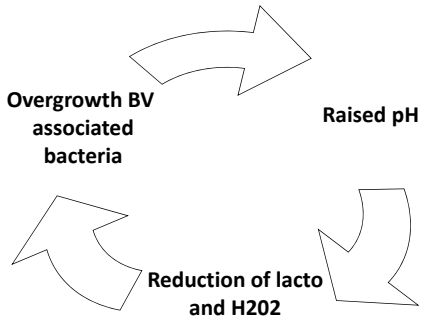
Bacterial Vaginosis



Quiz Question 2

True or False: Most bacterial vaginosis is asymptomatic.

BV: Etiology



Wilson, STI 2004;80: 8-11; Ling BMC Genomics 2010; 11: 488.

BV: Risk Factors & Associations

- Sexual activity (hetero and lesbian)
- AA ethnicity
- Multiple sex partners
- Douching
- Smoking
- STIs (CDC recommends STI testing)

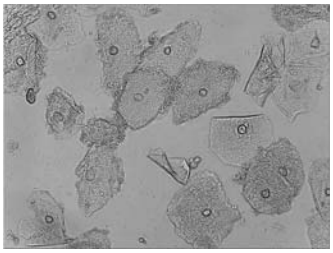
2015 CDC STD Treatment Guidelines

BV: Diagnosis

Amsel criteria: 3 of 4 findings

(1) Homogeneous, thin grayish-white vaginal discharge
(2) clue cells > 20%
(3) positive whiff test
(4) vaginal pH >4.5

A positive test for gardrenella on BD affirm, is not diagnostic for BV.



Gardnerella vaginalis, *Prevotella* species, *Porphyromonas* species, *Bacteroides* species, *Peptostreptococcus* species, *Mycoplasma hominis*, and *Ureaplasma urealyticum*, as well as *Mobiluncus*, *Megasphaera*, *Sneathia*, and *Clostridiales* species *Fusobacterium* species and *Atopobium vaginae* are also common

Other Tests

- Gram Stain with Nugent scoring
- Non-amplified nucleic-acid test for *Gardnerella*
  - BD affirm
- Chromogenic test of sialidase enzyme activity
  - OSOM BV Blue
- PCR testing
  - Evaluates presence of lactobacilli and BV assoc bacteria
  - self or clinician collected
- Over diagnosis of BV is common!

BV: Treatment

Recommended Treatment Regimens

1. Metronidazole 500mg PO BID x7d
   - most effective treatment with **90% clinical cure**
2. Metronidazole Gel 0.75% 5g vaginal once daily x 5d
   - **as effective** as oral metronidazole
3. Clindamycin 2% cream 5g intravaginally daily x 7d

Alternatives

- Tinidazole 2g PO daily x 2 d
- Tinidazole 1g PO daily x 5d
- Clindamycin 300mg oral bid x 7d
- Clindamycin ovules 100mg intravaginally daily x 3d

CDC 2015

BV: Recurrence

- 30% women recur within 3 month
- 58% recur within 12 months
- Chronic defined as 3 episodes/year

Wilson, 2004 Bradshaw, 2006, Powell 2014

Recurrent BV:

Step 1: Treat the Acute Infection

- Treat longer, 10-14d
- Change agent

Step 2: Consider Suppression

- Twice weekly MetroGel (or Clindamycin)

Baylson, Obstet Gynecol 2004; 104:931-2
2010 CDC STD Treatment Guidelines

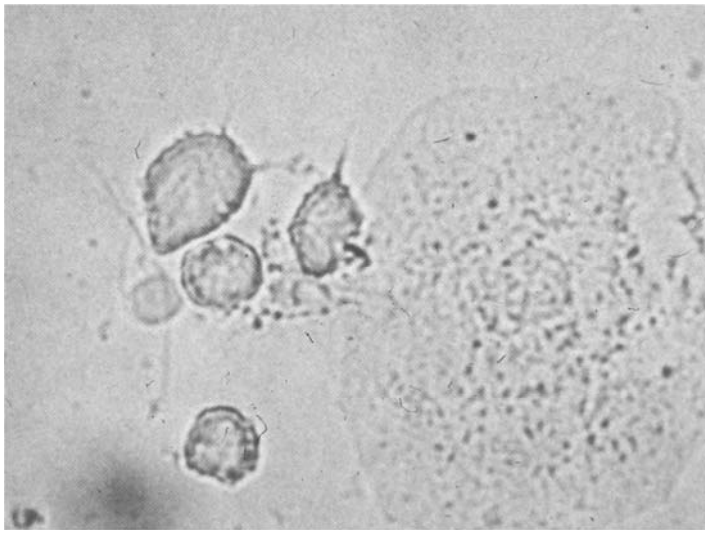
Probiotics or Alternative Treatments?

Data lacking therefore unclear benefit

- Evidence does not support replacing lactobacilli oral or vaginally
- Difficult to obtain specific species (*L. crispatus* and *L jensenii*) that adhere to vaginal walls and produces H202 used to maintain ecosystem
- Douching with H202 may exert a short term disinfection but does nothing to restore balance and can actually kill *Lactobacillus*
- Role of boric acid is unclear, may have some benefit in supporting vagina but not primary treatment

Recurrent BV: Helpful Hints

- Treat longer 10-14d for acute infection
- Consider suppression with MetroGel
- Condom first 4 weeks after treatment
- Clean sex toys
- Careful hygiene, no douching
- Suppress periods

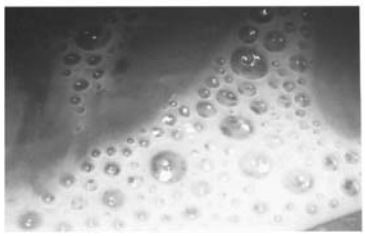


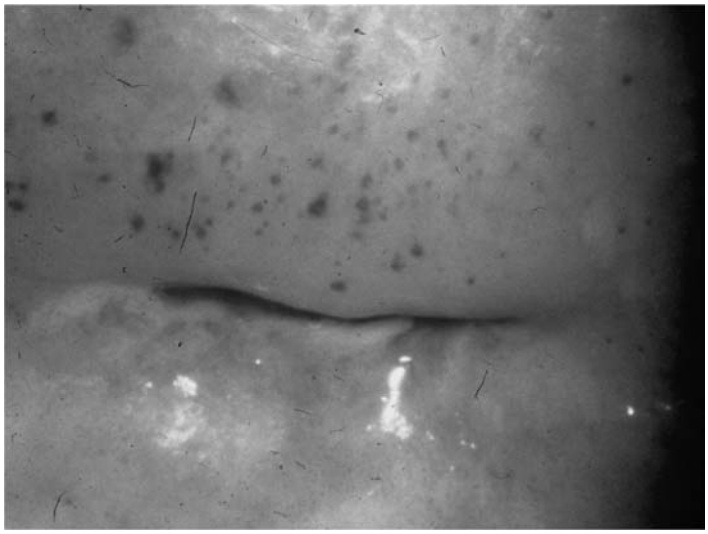
Trichomonas vaginalis: Fast facts

- Prevalence **3.1%**
- Virtually always sexually transmitted, assoc w/ other STIs
- Asymptomatic carriage for prolonged periods of time possible. . . . ? Not always able to establish vector
- If female diagnosed, most male partners +
- Risk Factors
  - Black race
  - Number of sex partners
  - Low SE status
  - douching

Symptoms

- Symptoms range from none to severe
- <10% have classic frothy discharge, suspect if pH>5.0 and WBC on wet mount





Diagnosis

- Basic microscopy
  - Elevated pH, WBCs on wet mount, trichomonads
  - Low sensitivity (50-60%), not first line
- Gold Standard
  - NAAT
  - antigen-detection
  - PCR test
  - Culture (alternative)

Perks & Pitfalls of Making the Diagnosis

	Wet mount	Diamond's Medium	AFFRIM Culture Kit	OSOM Trich Rapid Test	Pap Smear
Sensitivity Specificity	60-70%	>95%	>95% >95%	>88% 98%	50%
Pitfall	High false negative Dry slide	Obtain culture, Takes 7d	Not office based, sent to lab	Purchase kit	unreliable
What is it?	Slides + microscope	Culture medium	Swab inoculated into tube	Swab + dipstick + reagent	Slides, ? Liquid base
Perk	Available most offices	Accurate	<2 hrs Yeast&BV	In office kit, <10 min	Increase suspicion
Logistics	Office + lab	Office swab then incubate in micro lab	Becton Dickenson, San Jose, CA	GenZyme 1-800-330-3591, Office	Office + lab

Quiz Question 3

True or False: Trichomoniasis can be equally and effectively treated with either oral or vaginal medicines.

Treatment of Trichomoniasis

Recommended Regimens:

1. **Metronidazole 2 g** orally as single dose
2. **Tinidazole 2 g** orally as single dose

Alternative Regimen

Metronidazole 500 mg orally twice a day for 7 days

CDC 2015 STD Treatment Guidelines

Treatment of Trichomoniasis

- **90-95% cured**
  - with Metronidazole or Tinidazole
- MUST treat partner
  - Concurrent partner ~75% positive trich by PCR
- NO VAGINAL preparations
- No ETOH for 1-3d after use of medication
- Refrain from sex for 7d AFTER completed

- **Re-infection & Noncompliance are COMMON**
- Compliance enhanced with single 1 DAY Tx

Sena, Clin Infect Dis. 2007 Jan 1;44(1):13-22.
CDC 2010 STD Treatment Guidelines

Resistant Trichomoniasis

- If resistant then try. . . .
  - 1. Tinidazole 2g x 5d
    - Some Metro-resistant trich (2-5%) respond to high dose Tinidazole
  - 2. Metronidazole 500mg BID x 7d
- Most will respond to higher and longer doses
- If not, consider culture for resistant strain (1-2%)
- In patients with suspected resistance to Metronidazole, CDC recommends in vitro culture and drug susceptibility testing (CDC, # 404-718-4141)

Schwebke , Antimicrob Agents Chemother. 2006 Dec;50(12)
2015 CDC STD Treatment Guideline

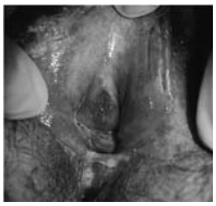
Recurrent Vaginitis: think outside the box!

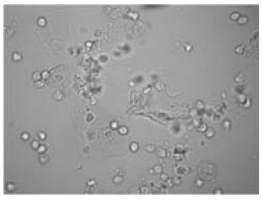
- Chemical, allergic or hypersensitivity reaction
- Foreign body, retained tampon
- Mucopurulent cervicitis (GC/CT)
- Vulvar Skin diseases
  - Erosive Lichen planus
  - Lichen sclerosus
- Vulvodynia
- Genitourinary Syndrome of Menopause (Atrophy)
- Desquamative inflammatory vaginitis (DIV)

Sobel, NEJM 1997 Vol 337

Desquamative Inflammatory Vaginitis

- Symptoms
  - Burning
  - Pain with sex
- Exam
  - Profuse purulent discharge
  - Erythema, petichiae
  - Elevated vaginal pH >4.5
- Microscopy
  - WBCs, parabasal cells
- Treatment
  - 6 week course of intravaginal clindamycin 2% or hydrocortisone 10%





Genitourinary Syndrome of Menopause

- Symptoms
  - Dryness, irritation, itching
  - Burning, Pain with sex
- Exam
  - Erythema, lack of rugae
  - Elevated vaginal pH >4.5
- Microscopy
  - Lack of cellularity,
  - Parabasal cells
- Treatment
  - Topical or systemic estrogen
  - Vaginal moisturizers
  - Topical Lidocaine

Stronger than Pills: Communication Skills that Make a Difference

Theresa Liao MD, FACP
Portland VA Medical Center
Assistant Professor of Medicine, OHSU

Disclosures

- Spouse- Clinical Research with UCB and Xenon, travel support for research meetings
- Not relevant to today's topic

Goals

- Appreciate the role of effective communication for a variety of clinical outcomes
- Utilize specific evidence-informed communication techniques in communicating with patients
  - when antibiotics are not needed
  - when there is hesitancy about vaccinations
- Develop greater awareness of larger societal communications around antibiotics and vaccines

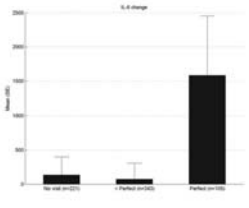
Systematic Review: Empathy

- 7 studies, >3,000 patients, 225 physicians
- Positive associations
  - Improved patient satisfaction and adherence
  - Decreased patient anxiety and distress
  - Better diagnostic and clinical outcomes
  - Stronger patient enablement

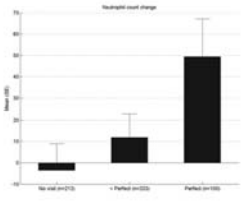
Derksen Br J Gen Pract, 2013; Jan:376-84.

UW Cold Study: Perception of Perfect Empathy

IL-8



Neutrophils



Rakel, Hoeft, Barrett, et al. Fam Med. 2009; 41(7):494-501.
Rakel, Barrett, Zhang, et al. Patient Ed & Counseling, 2011;85:390-7.

UW Cold Study: Effects of Perceived Empathy

	No Visit	< Perfect	Perfect	P Value
Duration	6.75 days	7.0 days	89 days	0.003
Severity	262.19	270.58	223.38	0.04

Rakel, Hoeft, Barrett, et al. Fam Med, 2009; 41(7):494-501.
Rakel, Barrett, Zhang, et al. Patient Ed & Counseling, 2011;85:390-7.

Listening Research

- The average doc interrupts after 18 seconds (1984 study)
  - Improved to 23 seconds (2002 study)
- How long will patients talk with no interruption?
  - Mean: 92 seconds
  - Median: 59 seconds
  - **In all 335 sessions, the info was rated as 'useful.'**

We have two ears and one mouth so we can listen twice as much as we speak.
-Epictetus

Beckman et al, Ann Intern Med, 1984;101:692-6.
Langewitz et al. BMJ, 2002;325:682-3.

Generous Listening

Communication and Antibiotics

Problem: Antibiotic Overuse

- Children with acute respiratory tract infections (ARTIs) receive Abx 50% of the time
  - ARTI bacterial etiology only 27%

Hersh AL, Pediatrics 2011; 128: 1053-61.

- Over 1 in 4 antibiotic prescriptions in adults in ambulatory settings not indicated

Shapiro,,Journal of Antimicrob Chemotherapy *2014;* 69:234–240,.

They won't be satisfied unless they get their antibiotics…

Receiving a prescription for antibiotics increases patient satisfaction.

a) True
b) False

Provider perception

- Providers believe parents want antibiotics
- Providers are concerned about negative impact on clinician-patient relationship if they don't prescribe

Szymczak JE, Infect Control Hosp Epidemiol 2015; 35 (Suppl 3): S69-78
Tonkin-Crine, J Antimicrob Chemother 2011; 66:2215-23.

- Parents generally want Abx only when absolutely necessary

Finkelstein JA, Clin Pediatr 2014; 53:145-50.

Provider Behaviors

- Providers more likely to prescribe antibiotics when they perceive parents want this
  - Viral ARTI's –
    - Abx given 52% of time when providers believed parents expected this
    - Abx given 9% when providers didn't perceive this parental expectation
- Providers not skillful at determining who expects Abx
  - 24-41% concordance

Szymczak JE, Infect Control Hosp Epidemiol 2015; 35 (Suppl 3): S69-78
Mangione-Smith R. Pediatrics 1999;103:711-8.

Patient Dissatisfaction

- Failure to acknowledge concerns
- No contingency plan if symptoms persist
- Quality of communication with provider

Cabral C, Ann Fam Med 2016; 14:141-7.
Cabral C, BMC Fam Pract 2014; 15:63.Tonkin-Crine, J Antimicrob Chemother 2011; 66:2215-23.

Improving Communication: Effective Recommendations

- Negative Recommendations
- Positive Recommendations
- Combination

Gain Framing

Putting it all together

- I know you're worried about your child being sick and that you want to do whatever you can for her health *(acknowledge, validate)*
- For the infection she has, which is caused by a virus, antibiotics aren't necessary. Antibiotics won't help her feel better or get over this illness sooner (negative recommendation).
- By avoiding them when you don't need them, you'll also be helping to make sure that if she does ever need them, her body won't be resistant and they will be effective *(gain framing)*

Putting it all together (cont'd)

- Helping her get enough rest, drink enough liquids, and giving her some acetaminophen if her fever gets high and she's uncomfortable, are things that you can do to help her feel better *(positive recommendation).*
- If she isn't much better by the end of the week, please give us a call back and we will talk by phone and see if she needs to come in to be checked out again or if she has developed something that might need an antibiotic. How does that sound? *(contingency plan)*

Communication and Vaccinations

Vaccines:
Victim of their own success

Epidemiologic methods in immunization programs. Epidemiol Rev. 1996; 18 (2):102.

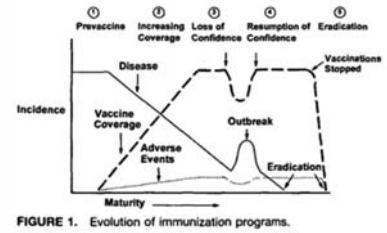
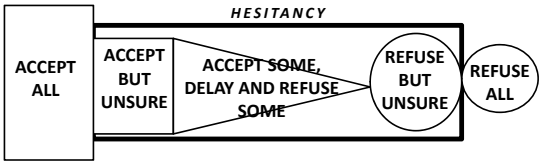


FIGURE 1. Evolution of immunization programs.

National Health Interview Survey 2016- Adults

- >=65 yo
  - Influenza vaccination 70.4%
  - Pneumococcal vaccination 66.9%
- >=19 yo
  - Tdap 26.6%
- >=60 yo
  - Herpes zoster 37.4%
- Females and males 19-26 who had not received HPV prior to 19 yo
  - 8.6% and 2.7%

What is vaccine hesitancy?



- **A delay in acceptance** or **refusal of vaccines,** despite availability of vaccination services
- **Complex and context** specific, varying across time, place and vaccine

WHO Conversations to build trust in vaccination: A training module for health workers May 2017
https://www.who.int/immunization/programmes_systems/vaccine_hesitancy/en/

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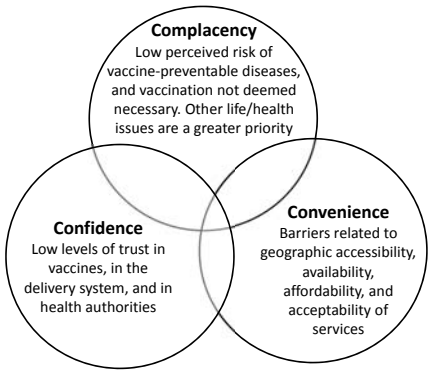
Factors contributing to vaccine hesitancy



WHO Conversations to build trust in vaccination: A training module for health workers May 2017
https://www.who.int/immunization/programmes_systems/vaccine_hesitancy/en/

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What factors influence decisions about vaccination?

Contextual	Individual and group influences	Vaccine/vaccination -specific issues
• Media and public communication • Local politics • Religion, culture • Accessibility of services • Trust in authorities	• Beliefs and attitudes about health and disease prevention • Knowledge and awareness • Poor quality health service experience	• Mode of administration • Source of the vaccine • Vaccination schedule • Any costs associated with vaccination • Knowledge/attitudes of healthcare professionals

WHO Conversations to build trust in vaccination: A training module for health workers May 2017
https://www.who.int/immunization/programmes_systems/vaccine_hesitancy/en/

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Patient Concerns

- Vaccine Safety
  - Too many, autism, additives, adverse effects
- Necessity of vaccines
  - Disease more natural, risk of disease low, vaccines not effective
- Freedom of choice
  - Risks > benefits, Lack of trust, Religious reasons

Edwards KM, Jackell JM, AAP The Committee on Infectious Diseases, The Committee on Practice and Ambulatory Medicine, Countering Vaccine Hesitancy, Pediatrics. 2016; 138 (3):e20162146.

WHO Strategic Advisory Group of Experts on Immunization – 2014 Report on Vaccine Hesitancy

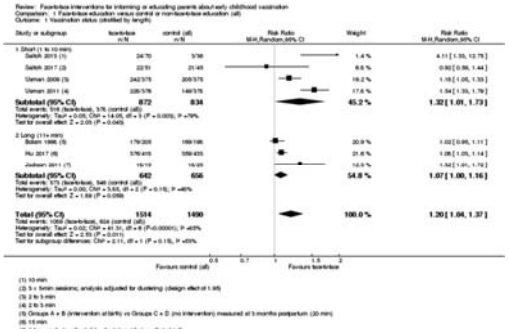
- Dialogue-based interventions, particularly those incorporating a focus on community engagement…and the improvement of health care worker communication, were most effective
- Passive interventions (e.g., posters, radio announcements, websites and media releases) less effective

Cochrane Review 2018

- 10 studies, 1997-2017, 4527 partipipants
- International, including 3 studies from low/middle-income countries
- Most studies- single intervention
  - Short (10 min or less)
  - Longer (several hours)
- Moderate-high risk of bias

Kaufman J, Ryan R, Walsh L, Horey D, Leask J, Robinson P, Hill S. Face-to-face interventions for informing or educating parents about early childhood vaccination. Cochrane Database of Systematic Reviews 2018, Issue 5. Art. No.: CD010038. DOI: 10.1002/14651858.CD010038.pub3.

Vaccination Status: Face-to-face interventions vs. Control



Cochrane Review 2018

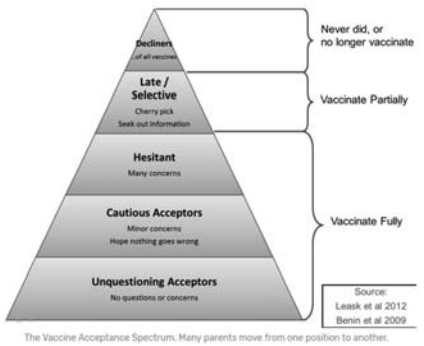
Cochrane Review 2018-Authors' conclusions about Face-to-Face Interventions

- Low- to moderate-certainty evidence - may improve or slightly improve:
  - children's vaccination status
  - parents' knowledge
  - parents' intention to vaccinate
- May be more effective with lack of awareness or understanding (e.g. new or optional vaccines).
  - Unclear efficacy with vaccine hesitancy

Kaufman J, Ryan R, Walsh L, Horey D, Leask J, Robinson P, Hill S. Face-to-face interventions for informing or educating parents about early childhood vaccination. Cochrane Database of Systematic Reviews 2018, Issue 5. Art. No.: CD010038. DOI: 10.1002/14651858.CD010038.pub3.

Unvaccinated children more likely to be white
have mother who is married, college-educated
higher income
compared to undervaccinated children.

Smith, Pediatrics. 2004;114:187-195.



The Vaccine Acceptance Spectrum. Many parents move from one position to another.

Benin, Pediatrics. 2006; 117:5.
Leask, BMC Pediatrics. 2012; 12: 154.

Announcement vs Participatory Approach

- Looks like you are due for your HPV vaccine today.
- Announcement style has been shown to result in greater vaccine acceptance.
  - Has been associated with lower patient satisfaction scores

Debunking myths- carefully

- Correcting misinformation- Not necessarily effective, may be harmful.
  - Randomized trial flu vaccine, correction significantly reduced intent to vaccinate
- Avoid repeating misinformation to avoid reinforcing it.
- Use fewer, simpler arguments.
  - Easier to understand=easier to accept
- Challenge untrustworthy sources of information

Nyhan, Vaccine. 2015; 33:459-464; 33:459-464
Lewandowsky, Psychol Sci Public Interest. 2012;13:106-131.
Horne, Proceedings of the National Academy of Sciences. 2015; 112: 10321-10324.

For conversations with hesitant individuals:

Motivational interviewing

- **A method of interacting** with patients
- Aimed at **exploring** reasons for hesitancy and **changing attitudes and behaviour**

Collaborative

Patient-centred

With a specific objective

WHO Conversations to build trust in vaccination: A training module for health workers May 2017
https://www.who.int/immunization/programmes_systems/vaccine_hesitancy/en/

Motivational Interviewing

- Open-ended questions
- Affirmations
- Reflections
- Summaries

Reflective Listening

- Repeating, paraphrasing
- Inferring meaning
- Appreciating emotion
- Trying to go deeper
  - Sometimes a guess

Downward Inflections

MI Microskills- Use Your OARS
- **Open-ended questions**
- **Affirmations**
- **Reflections**
- **Summaries**

Remember to use Reflective Listening when agenda-setting!

Elicit-Provide-Elicit

- Ask-Provide-Verify

Storytelling

For the greater good

Vaccine Adverse Event Reporting System

Provider Pursuit

- Half of patients who initially resisted vaccination ultimately accepted the initial recommendation if provider continued to recommend it.

Opel. Pediatrics. 2013; 132:e20162526.

Values

- Attitude- context-specific
- Values- more enduring
- Effective in other behavior change

Unintended consequences

- Decreased patient satisfaction
- Increased resistance

Societal Communication

- Media
- Internet
- Law
- Policy

Take-Home Points

- Skillful communication around antibiotic use and vaccination recommendations can impact important patient behaviors, clinical outcomes and patient/provider satisfaction.
- When talking with patients about antibiotic use both negative and positive recommendations as well as gain-framing.
- When talking with patients about vaccinations, announcement approach coupled with provider pursuit using motivational interviewing may be an effective strategy for both increasing vaccination rates and patient satisfaction.
- Motivational interviewing is a potentially useful tool in working with vaccine hesitancy.
- Reflective listening so patients feel their concerns are being heard is a critical skill in many patient encounters.

Thank you!

Bronchitis: Mimics and Management

Anna K. Brady, MD
Assistant Professor, Division of Pulmonary and Critical Care Medicine
OHSU

Disclosures

- I have nothing to disclose

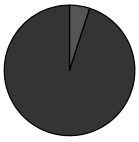
Objectives

1)Recognize common presentation of acute bronchitis and distinguish it from mimics.

1)Describe which patients merit diagnostic testing (and what that testing should be) in acute bronchitis.

1)Explain the role of non-antibiotic therapies for management of cough in acute bronchitis.

Acute bronchitis: recognizing it



5% of US adults annually

9th most common reason for outpatient visit

But cough itself is so common – how to distinguish acute bronchitis from the other common cause of cough?

Wenzel N Engl J Med 2006;355:2125-30.

Acute bronchitis: mimics

Acute

URI

Pneumonia

Acute Bronchitis

- Cough >= 5-7 days
- Normal vital signs
- Normal chest exam

Exacerbations of chronic problems

Bronchiectasis

Asthma

Acute bronchitis: mimics

Acute

URI

Pneumonia

Acute Bronchitis

- Cough >= 5-7 days
- Normal vital signs
- Normal chest exam

Exacerbations of chronic problems

Bronchiectasis

Asthma

Acute bronchitis: mimics

URI

Pneumonia*
- Fever
- Tachycardia
- Tachypnea
- Crackles or rhonchi

Acute Bronchitis
- Cough >= 5-7 days
- Normal vital signs
- Normal chest exam (but wheezing common)

Bronchiectasis Exacerbation
- Chronic sputum production

Asthma
- Wheezing?
- History of suggestive episodes

*elderly patients may present differently

Case

A 40 year-old woman presents with four weeks of nonproductive cough that is harsh and barking. Prior to this, she spent a vacation with her teenage nephew who had a cold. She initially had sore throat and rhinorrhea, which are now gone. She thinks she has whooping cough and asks whether she can have antibiotics to treat it. She is afebrile, with RR 14, HR 80, SpO2 99%, and a normal lung exam. What advice should you give her?

A. Empiric azithromycin without testing is reasonable given the high likelihood of pertussis.
B. Her cough is inconsistent with pertussis, so treatment is not needed.
C. Given the duration of her symptoms, testing and treatment for pertussis is warranted.
D. Given the duration of her symptoms, treatment is unlikely to help if this is pertussis.

Etiology of acute bronchitis

Influenza A
Influenza B
Parainfluenza
RSV
Metapneumovirus
Coronavirus
Adenovirus
Rhinovirus

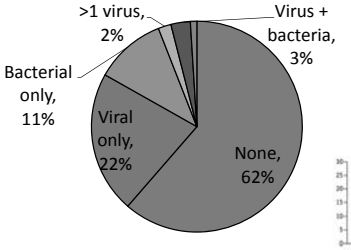
Chlamydophila pneumoniae

Mycoplasma pneumoniae

Bordetella pertussis

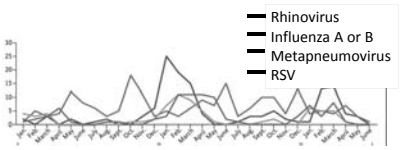
Wenzel N Engl J Med 2006;355:2125-30. Gonzales *Ann Intern Med.* 2000;133:981-991.

Viruses predominate even in pneumonia



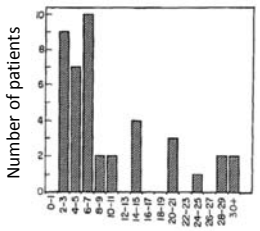
Often no pathogen recovered.

Dominant viruses changes with time of year:



Jain et al. N Engl J Med 2015; 373:415-427

Duration of cough in acute bronchitis



Typical duration of cough: 10-20 days

Median = 18 days of cough in one study

Boldy. *Respiratory Medicine* 1990:84,377-85.

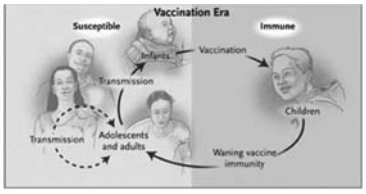
Wenzel N Engl J Med 2006;355:2125-30

Testing for pathogens: *Bordetella pertussis*

Bordetella pertussis is the cause of 1% of cases of acute bronchitis in some series, 10-20% in others.

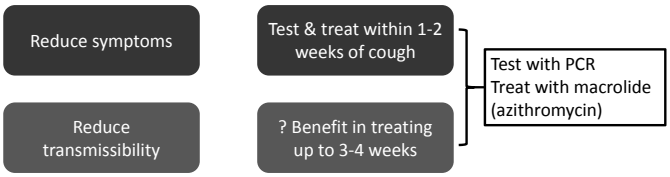
Prolonged cough
+/- post tussive emesis
Few patients really have "whoop"

Highly transmissible.



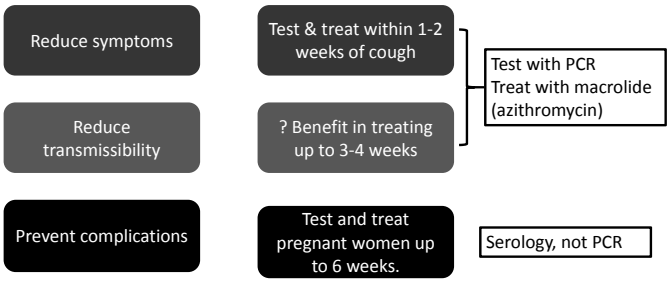
Hewlett EL, Edwards KM. N Engl J Med 2005;352:1215-1222.

Pertussis treatment



https://www.cdc.gov/pertussis/clinical/treatment.html

Pertussis treatment



https://www.cdc.gov/pertussis/clinical/treatment.html

What advice should you give her?

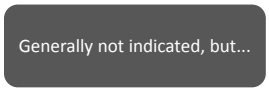
Case

A 55 year-old woman with rheumatoid arthritis presents in February 2019 with 2 days of malaise and bothersome cough productive of thick, yellow sputum. She is afebrile, with respiratory rate 16, HR 85 and BP 130/75. SpO2 is 97%. She coughs frequently during the visit. Her lungs are clear to auscultation. She is on prednisone 15mg daily and rituximab for her rheumatoid arthritis.

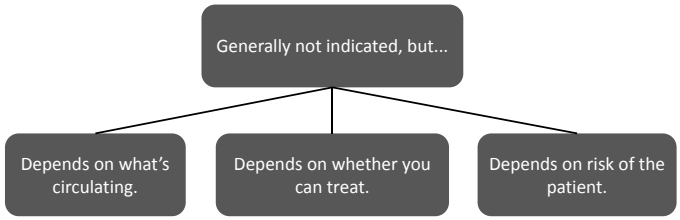
What is the next best step in her management?

A. Begin azithromycin
B. Obtain influenza PCR
C. Obtain sputum culture
D. Provide reassurance

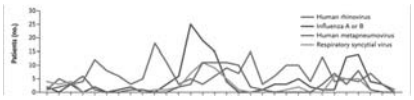
Diagnostic testing in acute bronchitis



Diagnostic testing in acute bronchitis



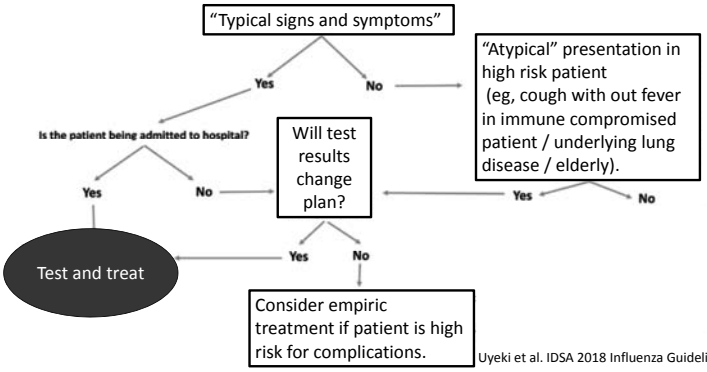
Diagnostic testing in acute bronchitis



It's flu season!

This patient is immune compromised; even out of flu season she should be tested & treated.

Influenza as a cause of acute bronchitis



Uyeki et al. IDSA 2018 Influenza Guidelines. *CID*.

Sputum characteristics

sputum production ≠ bacterial infection

Viruses can denude the respiratory epithelium (eg, influenza)

Sputum purulence not necessarily helpful

- 50% of patients with acute bronchitis have purulent sputum
- Low positive predictive value for pneumonia

Wenzel N Engl J Med 2006;355:2125-30. Gonzales *Ann Intern Med.* 2000;133:981-991.

Other diagnostic tests

Sputum culture	Reserved for inpatients with pneumonia and outpatients with bronchiectasis, not acute bronchitis.
Respiratory pathogen PCR	Generally not needed unless immunocompromised; even then, unlikely to change management.

Antibiotics in acute bronchitis

No clear benefit in multiple RCTs.

<1 day difference in cough in some meta analyses

Assuming you have not identified a treatable etiology (pertussis, influenza), there is no role for antimicrobial therapy.

Gonzales *Ann Intern Med.* 2000;133:981-991.

What is the next best step in her management?

Diagnostic testing in acute bronchitis

- No role for sputum culture
- Test & treat pertussis & flu in right situation
- Exclude pneumonia – exam, chest radiograph
- Respiratory pathogen PCR rarely helpful

If I can't give antibiotics, what can I do?

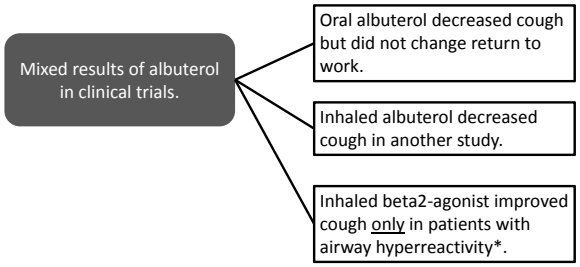
Case

A 42 year-old man presents to your office with one week of cough productive of mostly white, yellow-tinged sputum. He initially had rhinorrhea and sore throat, but those have resolved. He was seen in urgent care 3 days ago and had a negative flu swab. He is afebrile, with RR 12, HR 70, BP 124/68, and SpO2 98%. He has clear lungs. He has been using cough drops "around the clock" and says he is being kept up at night. He asks for antibiotics to "really kick this cough."

What can you recommend for his cough?

A. Albuterol
B. Codeine
C. Guaifenesin
D. Honey
E. Prednisone

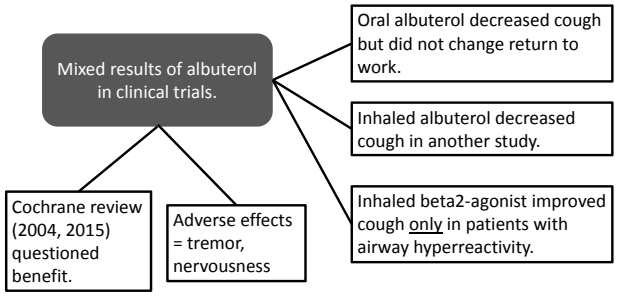
Bronchodilators



*wheezing, decline in FEV_1

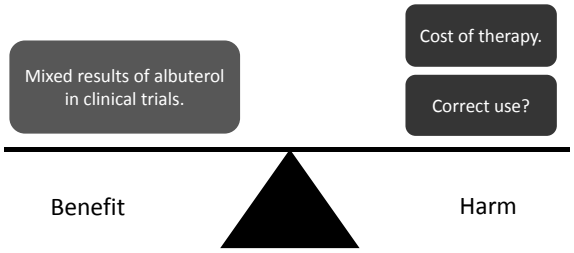
Gonzales. *Ann Intern Med.* 2000;133:981-991

Bronchodilators



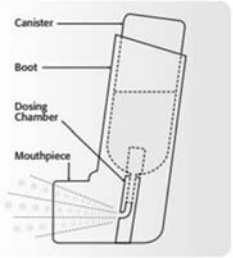
Gonzales. *Ann Intern Med.* 2000;133:981-991

Bronchodilators



If you're going to order a bronchodilator…

- Consider reserving for patients with wheezing in addition to cough.
- Teach them how to use it: http://use-inhalers.com
- Give them a spacer to go with the inhaler.



https://www.thoracic.org/patients/patient-resources/resources/metered-dose-inhaler-mdi.pdf

Steroids?

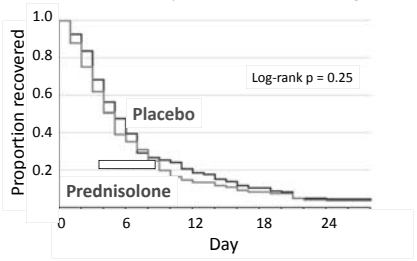
- 400 patients with acute bronchitis seen in primary care in the UK
  - Cough < 28 days
  - No prior history of lung disease / lung rx
  - No one getting antibiotics / admission
- Randomized to 40mg prednisolone PO x 5 days vs placebo
- Main outcome = severity and duration of cough

Hay et al. *JAMA*. 2017;318(8):721-730.

Steroids?

- 400 patients with acute bronchitis seen in primary care in the UK
- Randomized to 40mg prednisolone PO x 5 days vs placebo
- No significant difference in severity / duration of symptoms.

Time to recovery from "moderately bad or worse" cough



Hay et al. *JAMA*. 2017;318(8):721-730.

Mucolytics and cough suppressants

- Mucolytics
  - Limited effectiveness; unlikely to hurt.
- Cough suppressants
  - Less likely to be helpful in acute bronchitis than in chronic cough?
  - Don't want to completely suppress cough

Gonzales. *Ann Intern Med.* 2000;133:981-991

Take home points: managing symptoms

1. Consider albuterol for patients with wheezing – and set them up for success!
2. Avoid steroids.
3. Mucolytics and cough suppressants are unlikely to help OR hurt.
4. Anticipatory guidance.

Bronchitis: Take Homes

1. Use history & exam to distinguish between bronchitis and its mimics which require different treatment.
2. Diagnostic testing is rarely helpful; test and treat for *B pertussis* and influenza in the right clinical setting.
3. Unless it's pertussis, antibiotics will not help and should not be used.
4. Consider albuterol for a patient with significant hyperresponsiveness – and teach them how to use it.

Resources

Gonzales. *Ann Intern Med.* 2000;133:981-991

Hay et al. *JAMA*. 2017;318(8):721-730.

Uyeki et al. *CID.* IDSA 2018 Influenza Guidelines.

Wenzel *N Engl J Med* 2006;355:2125-30

https://www.cdc.gov/pertussis/clinical/treatment.html

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PROSTATITIS

GRAEME FORREST, MBBS, FIDSA

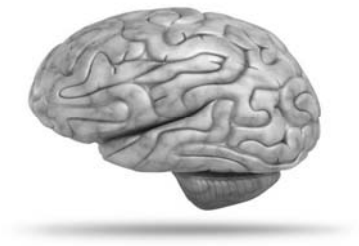
VA PORTLAND HEALTHCARE SYSTEM

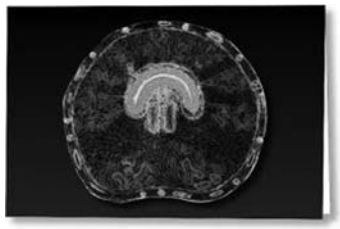
CONFLICTS OF INTEREST

- NO CONFLICTS WITH THIS TALK

QUESTION: WHAT PERCENTAGE OF PATIENTS WITH PROSTATITIS HAVE A BACTERIAL CAUSE?

- A) 10%
- B) 25%
- C) 50%
- D) 65%
- E) 80%





COMMONALITIES

- BOTH BRAIN AND PROSTATE HAVE A BLOOD-ORGAN BARRIER
- IMPACTS ANTIBIOTIC PENETRATION IN UNINFLAMED ORGAN
- DURATION OF THERAPY IS OFTEN LONGER
- DIAGNOSING INFECTION IS DIFFICULT IN BOTH
- RARE INFECTIONS CAN HIDE IN THEM
  - CRYPTOCOCCUS, TUBERCULOSIS
- BIOPSY OFTEN NEEDED FOR DIAGNOSIS

CASE 1

- 25 YO MAN, MULTIPLE SEXUAL PARTNERS
- PRESENTS WITH DYSURIA, BURNING PAIN, URGENCY AND FREQUENCY AND PERINEAL PAIN
- HAS FEVER TO 101F
- SUPRAPUBIC TENDERNESS, PROSTATE BOGGINESS
- WCC 12K
- UA 3+ WBC, 1+ RBC, 1+ LE
- URINE CULTURES NEGATIVE

CASE 2

- 65 YO MAN, MARRIED, NO ACTIVITIES. DIABETES AND HTN
- HAVING URINARY SYMPTOMS LAST 3 MONTHS. 3 VISITS NOW
- TREATED WITH 7 DAYS OF BACTRIM, OR LEVOFLOXACIN EACH VISIT
- PAIN ON ERECTIONS AND EJACULATION, SOME BLOOD SEEN
- NO FEVERS
- PROSTATE EXAM SOME BOGGINESS
- UA – 10 WBC, 1+ LE
- URINE CULTURE – *KLEBSIELLA PNEUMONIA* > 10^5, PAN SUSCEPTIBLE

CASE 3

- 43 YO PORTLAND BICYCLE ENTHUSIAST. MARRIED, NO OTHER PARTNERS
- RIDES 40 MILES EVERY SUNDAY
- NOW HAS FULLNESS IN PERINEUM, PENILE PAIN, ERECTILE DYSFUNCTION
- AFEBRILE
- PROSTATE NORMAL ON EXAM
- UA – 5 WBC, NO LE OR RBC
- URINE CULTURE NEGATIVE, GC AND CHLAMYDIA NEGATIVE

HISTORY

- FIRST DESCRIBED IN 1815 BY LEGNEAU.
- MAIN TREATMENT WAS REPEATED PROSTATE MASSAGE.
- IN 1930'S ANTIBIOTICS CAME INTO REGULAR USE.
- EVIDENT THAT MOST FORMS OF PROSTATITIS DID NOT RESPOND TO AB'S.

PROSTATITIS: A MAJOR CLINICAL PROBLEM

INCIDENCE/PREVALENCE: 4% -11%

8-12% OF UROLOGIST OFFICE VISITS

LIFE TIME PREVALENCE 14.8%

MOST COMMON UROLOGICAL DIAGNOSIS IN MEN > 50

QUALITY OF LIFE IS DISMAL (DEPRESSING) !

ETIOLOGY

- GRAM NEGATIVE ENTEROBACTERIA ACCOUNT FOR 90% OF ACUTE BACTERIAL PROSTATITIS. (*E. COLI, KLEBSIELLA, SERRATIA, PSEUDOMONAS)*
- *ENTEROCOCCUS (*GRAM +VE) 5 – 10%, AND *S. AUREUS* 1%
- ROLE OF ANAEROBES ARE UNKNOWN.
- ANTI-CHLAMYDIAL ANTIBODIES IN 30% OF CHRONIC PROSTATITIS, BUT < 1% CULTURE ORGANISM.
- UNDER-REPORTED OR UNKNOWN – *UREOPLASMA UROLYTICUM*, *MYCOPLASMA GENITALIUM*

INVESTIGATION

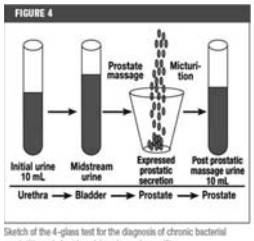
- PHYSICAL – SIGNS OF INFECTION, LOWER ABDOMINAL TENDERNESS, DRE (ANAL TONE, PROSTATE, PAIN).
  - PROSTATE BOGGINESS VERY INSENSITIVE
- EXAMINATION OF URINE.
- URODYNAMICS (VIDEO)
  - RULE OUT OTHER CAUSE – OBSTRUCTION, OAB, DYSSYNERGIA.
- CYSTOSCOPY?
- TRANSRECTAL ULTRA-SOUND (TRUS)
  - ABSCESS, MEDIAL CYSTS, SV OBSTRUCTION.
  - NOT DIAGNOSTIC FOR CHRONIC PROSTATITIS.
  - BIOPSY OF NO CLINICAL BENEFIT TO MANAGEMENT.

EXAMINATION OF URINE

- 1968 MEARES AND STAMEY - 4 GLASS TEST.
- FOR CHRONIC PROSTATITIS ONLY.
- SIMPLIFIED 2 GLASS TEST SIMILAR SENSITIVITY AND SPECIFICITY TO 4 GLASS TEST.
- 10 WBC'S PER HPF IS CUT OFF FOR INFLAMMATORY AND NON-INFLAMMATORY CATEGORY III PROSTATITIS.

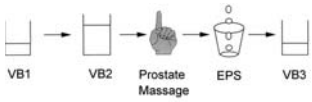
EXAMINATION OF URINE

CLASSIC STAMEY 4 GLASS TEST



Sketch of the 4-glass test for the diagnosis of chronic bacterial prostatitis and chronic pelvic pain syndrome (9)

Wagenlehner, F M E; Naber, K G; Bschleipfer, T; Brähler, E; Weidner, W
Prostatitis and Male Pelvic Pain Syndrome: Diagnosis and Treatment
Dtsch Arztebl Int 2009; 106(11): 175-83; DOI: 10.3238/arztebl.2009.0175



4-Glass Test (Meares-Stamey Test)

Classification	Specimen	VB_1	VB_2	EPS	VB_3
CAT II	WBC	-	+/-	+	+
	Culture	-	+/- *	+	+
CAT IIIA	WBC	-	-	+	+
	Culture	-	-	-	-
CAT IIIB	WBC	-	-	-	-
	Culture	-	-	-	-

PROSTATITIS DIAGNOSIS

DONNA R. COFFMAN, MD

COMPARISON OF FOUR-GLASS AND TWO-GLASS PREMASSAGE AND POSTMASSAGE TEST

Nickel JC, Shoskes D, Wang Y, et al: How does the pre-massage and post-massage 2-glass test compare to the Meares-Stamey 4-glass test in men with chronic prostatitis/chronic pelvic pain syndrome? J Urol 176(1):119-124, 2006 .

The Premassage postmassage test (PPMT) may offer an adequate screening test as an alternative that is simpler, faster, and less expensive than the four-glass test .

VB= voiding bladder
CP = chronic prostatitis
EPS=expressed prostate secretion

Interpretation of Meares-Stamey Testing (after Nickel, AUA Update 2006)

Types	VB1		VB 2		EPS		VB 3	
	WBC	Bact	WBC	Bact	WBC	Bact	WBC	Bact
CP/CPPS II	-	-	-	-	+	+	+	+
CP/CPPS IIIA	-	-	-	-	+	-	+	-
CP/CPPS IIIB	-	-	-	-	-	-	-	-

CLASSIFICATION

Table 15–1. CLASSIFICATION SYSTEM FOR THE PROSTATITIS SYNDROMES

Traditional	National Institutes of Health	Description
Acute bacterial prostatitis	Category I	Acute infection of the prostate gland
Chronic bacterial prostatitis	Category II	Chronic infection of the prostate gland
N/A	Category III chronic pelvic pain syndrome (CPPS)	Chronic genitourinary pain in the absence of uropathogenic bacteria localized to the prostate gland with standard methodology
Nonbacterial prostatitis	Category IIIA (inflammatory CPPS)	Significant number of white blood cells in expressed prostatic secretions, postprostatic massage urine sediment (VB3), or semen
Prostatodynia	Category IIIB (noninflammatory CPPS)	Insignificant number of white blood cells in expressed prostatic secretions, postprostatic massage urine sediment (VB3), or semen
N/A	Category IV asymptomatic inflammatory prostatitis (AIP)	White blood cells (and/or bacteria) in expressed prostatic secretions, postprostatic massage urine sediment (VB3), semen, or histologic specimens of prostate gland

N/A, not applicable.

Table 1. Classification of Prostatitis According to Classical and Newer National Institutes of Health (NIH) Categories Based on Prostatic Localization Studies for White Blood Cells (WBC) and Bacteria

Classical classification (NIH category)	Prostatitis cases, %	Mid-stream urine specimen (VB2)		Prostatic specimen (EPS or VB3)	
		WBC	Culture	WBC	Culture
ABP (I)	<1	++	+	++	+
CBP (II)	5–10	+	+	+	+
CP/CPPS (III)	80–90				
Inflammatory (IIIA)		–	–	+	–
Noninflammatory (IIIB)		–	–	–	–
AIP (IV)	10	+	–	–	–

NOTE. Adapted from Doble [4]. +, present or positive; ++, present in large numbers or strongly positive; –, negative; ABP, acute bacterial prostatitis; AIP, asymptomatic inflammatory prostatitis; CBP, chronic bacterial prostatitis; CP/CPPS, chronic prostatitis/chronic pelvic pain syndrome; EPS, expressed prostatic secretions; VB2, voided bladder second specimen (a clean-catch mid-stream urine specimen); VB3, voided bladder third specimen (a post–prostatic massage urine specimen).

Lipsky et al, Clin Infect Dis. 2010;50;1641-52

CATEGORY I – ACUTE BACTERIAL

THE PATIENT TYPICALLY COMPLAINS OF :

- URINARY FREQUENCY, URGENCY, AND DYSURIA.
- OBSTRUCTIVE VOIDING COMPLAINTS INCLUDING HESITANCY, POOR INTERRUPTED STREAM, STRANGURY, AND EVEN ACUTE URINARY RETENTION ARE COMMON. TENESMUS.
- PERINEAL AND SUPRAPUBIC PAIN
- ASSOCIATED PAIN OR DISCOMFORT OF THE EXTERNAL GENITALIA.
- SIGNIFICANT SYSTEMIC SYMPTOMS INCLUDING FEVER, CHILLS, MALAISE, NAUSEA AND VOMITING, AND EVEN FRANK SEPTICEMIA WITH HYPOTENSION

NOT COMMON

APPROXIMATELY 5% OF PATIENTS WITH ACUTE BACTERIAL PROSTATITIS MAY PROGRESS TO CHRONIC BACTERIAL PROSTATITIS) CHO ET AL., 2005

CATEGORY I – ACUTE BACTERIAL

- SEND MSSU (MID STREAM SPECIMEN OF URINE) / BLOOD CULTURES.
- CT PELVIS
  - MAY SHOW PROSTATIC ABSCESS
- ANTIBIOTICS
  - I.V. IF EVIDENCE OF SEPSIS
  - CEPHALOSPORINS, OR FLUOROQUINOLONES.
  - 4 WEEKS TREATMENT.
- SURGERY
  - SP CATHETER
  - TRUSS OR CT TO EXCLUDE ABSCESS.
  - ABSCESS BEST DRAINED BY TUR.

CATEGORY II – CHRONIC BACTERIAL PROSTATITIS.

- 10% OF ALL PROSTATITIS
- RECURRENT UTI'S IN 25 – 40%
- MAY BE ASYMPTOMATIC BETWEEN EPISODES OR HAVE A LONG HISTORY OF CPPS.
- TREAT WITH ANTIBIOTICS
  - FLUOROQUINOLONES (CIPRO AND LEVOFLOXACIN) MOST EFFECTIVE, BACTRIM NEXT ALTERNATIVE.
  - 6-12 WEEKS OF TREATMENT.
  - 60 – 85% BACTERIOLOGICAL CURE.
  - 40% SYMPTOM CURE.

PREVENTATIVE ISSUES?

Table 2. Antibiotics with Pharmacological Data, Clinical Case Report(s), or a License to Support Their Use for Treatment of Bacterial Prostatitis

Drugs[a]	Prostate tissue or fluid concentration	FDA approval	References
Amoxicillin-clavulanate	Tissue, 3.8–7.2 μg/g amoxicillin	UTI	[55, 56]
Ampicillin-sulbactam	Tissue, 0.42–548.33 μg/g ampicillin	No	[57]
Piperacillin	Tissue, 70.7 μg/g	UTI	[42, 58]
Piperacillin-tazobactam		No	
Cephalexin	Tissue, 0.5–10 μg/g	UTI, ABP	[42, 59, 60]
Cefazolin	Fluid, <10 μg/mL	UTI, BP	[42, 60]
Cefaclor	Tissue, 0.74 μg/g	C-UTI, UC-UTI	[42, 61]
Cefuroxime	Tissue, 7.6–29.2 μg/g	UTI	[62–64]
Cefotetan	Tissue, 36 μg/g; Fluid, 0.8 μg/mL	UTI	[42, 65]
Cefotaxime	Tissue, 6.8–22.5 μg/g	UTI	[42, 66–68]
Ceftriaxone	Tissue, 12.9–73.7 μg/g	UTI	[42, 69]
Ceftazidime	Tissue, 23.4 μg/g	UTI	[70]
Cefepime		C-UTI, UC-UTI	
Cefixime	Tissue, 1.06 μg/g	UC-UTI	[71]
Cefpodoxime	Tissue, 0.5 μg/g	UC-UTI	[72]
Aztreonam	Tissue, 6–10 μg/g	C-UTI, UC-UTI	[73, 74]
Imipenem[b]	Tissue, 5.3 μg/g	C-UTI, UC-UTI	[21, 42]
Doripenem		C-UTI	
Ertapenem[b]		C-UTI	[75]
Vancomycin[b]		No	[76, 77]
Trimethoprim-sulfamethoxazole	Tissue, 7.1 μg/g for trimethoprim, 24 μg/g for sulfamethoxazole	UTI	[78]
Nitrofurantoin		UTI	
Ciprofloxacin	Tissue, 0.6–4.18 μg/g	UTI, CBP	[79]
Gatifloxacin	Fluid, 1.72–3.1 μg/mL	UTI	[80]
Levofloxacin	Tissue level greater than corresponding plasma level	C-UTI, UC-UTI	[81]
Moxifloxacin	Fluid, 3.8–8.5 μg/mL	No	[82, 83]
Ofloxacin	Tissue, 4.1 μg/g; fluid, 4.9 μg/mL	C-UTI, UC-UTI, BP	[84]
Prulifloxacin	Tissue, 1.9–5.5 μg/g	No	[85]
Clindamycin	Tissue level greater than corresponding plasma level	No	[42]

Lipsky et al, Clin Infect Dis. 2010;50;1641-52

ANTIBIOTIC SUMMARY

- QUINOLONES AND TRIMETHROPRIM/SULFA ARE BEST ORAL ANTIBIOTICS
  - WATCH DRUG INTERACTIONS AND TOXICITIES
- DOXYCYLINE GETS 40% INTO PROSTATE
- INTRAVENOUS CEPHALOSPORINS ARE SUPERIOR THAN ORAL AS THEY ACHIEVE HIGH LEVELS AND OVERCOME ALKALIZATION WITHIN THE PROSTATE
- IV ERTAPENEM AND PIP/TAZO ARE ALSO EFFECTIVE
- AVOID NITROFURANTOIN, FOSFOMYCIN AND MACROLIDES
  - HOWEVER MAY NEED A MACROLIDE FOR NGU
- USE YOUR CULTURE DATA AND RESISTANCE PATTERNS

CATEGORY IIIA – CHRONIC PELVIC PAIN SYNDROM (CPPS INFLAMMATORY)

- PAIN – PERINEUM, SUPRAPUBIC AND PENILE BUT CAN BE TESTES, GROIN AND LOWER BACK.
- PAIN DURING OR AFTER EJACULATION.
- LUTS (STORAGE AND VOIDING SYMPTOMS)
- ERECTILE DYSFUNCTION IS INCREASED.
- SYMPTOMS PRESENT FOR > 3 MONTHS.
- FREQUENTLY NON-BACTERIAL
- SICKNESS IMPACT PROFILE – QL SCORES SIMILAR TO MI, ANGINA AND CROHN'S.

CATEGORY IIIB – CHRONIC PELVIC PAIN SYNDROM (CPPS NON-BACTERIAL)

- SAME PRESENTING FEATURES AS IIIA, BUT < 10 WBC'S PER HIGH POWER FIELD ON EXPRESSED PROSTATIC SECRETION AND VB3.
- MAY HAVE ELEVATED PSA
  - REFLECTS CHRONIC INFLAMMATION
- NIH – CHRONIC PROSTATITIS SYMPTOM INDEX.

CATEGORY IV – ASYMPTOMATIC INFLAMMATORY PROSTATITIS

- AS NAME SUGGESTS!!
- WBC'S OR BACTERIA IN EPS OR VB3 OR HISTOLOGICAL EXAMINATION OF GLAND.
- PRESENT WITH OBSTRUCTION, RAISED PSA, INFERTILITY.

CPPS TREATMENT

- α-BLOCKERS
  - MEHIK ET AL UROLOGY. 2003 SEP;62(3):425-9. RCT OF XATRAL (ALFUZOSIN) V PLACEBO FOR 6 MONTHS. MODEST BUT SIGNIFICANT REDUCTION IN PAIN AND SYMPTOM SCORE.
  - WANG ET AL. INT UROL NEPH 2016 48: 8-13. RCT LEVOFLOXACIN +/- TERAZOSIN. 115 PATIENTS, THE ADDITION INCREASED RESPONSE BY 5%. NO ROLE FOR TERAZOSIN ALONE
  - COHEN ET AL. PLOS ONE 2012 :7 META-ANALYSIS OF MULTIMODALITY TREATMENTS IN CPPS. NO CLEAR EVIDENCE THAT ANY WORK.

Alpha blockers for CP/CPPS

- Systematic review of eight trials (Cohen 2012)
- Among 7/8 RCTs (n= 770) comparing alpha-blockers to placebo:
  - Average NIH-CPSI **total** reduction of 4.8 (95% CI: -7.1 to -2.6)
  - Average NIH-CPSI **pain** reduction of 2.1 (95% CI: -3.1 to -1.2
  - Average NIH-CPSI **voiding** reduction of 1.1 (95% CI: -1.7 to -0.4 [7 RCTs]
  - Average NIH-CPSI **QoL** reduction of 1.4 (95% CI: -2.3 to -0.4) [7 RCTs]
- EAU guidelines for chronic pelvic pain (Feb 2012):
  - α–blockers have moderate treatment effect regarding total, pain, voiding, and QoL scores in PPS (1a) and are recommended for patients with a duration of PPS < 1 year

ALPHA-BLOCKERS

- ALFUZOSIN, TERAZOSIN, TAMSULOSIN
- *N ENGL J MED. 2008 DEC 18;359(25):2663-73. ALFUZOSIN AND SYMPTOMS OF CHRONIC PROSTATITIS-CHRONIC PELVIC PAIN SYNDROME NICKEL JC ET AL.*
- MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF ALFUZOSIN.
- 272 MEN WERE RANDOMLY ASSIGNED TO TREATMENT FOR 12 WEEKS WITH EITHER 10 MG OF ALFUZOSIN/DAY OR PLACEBO.
- THE PRIMARY OUTCOME WAS A REDUCTION OF AT LEAST 4 POINTS IN THE CPSI SCORE.

	Placebo N=134	Alfuzosin N=138
CPSI responders	66(49%)	68(49%)

CPPS TREATMENT

- ANTI-INFLAMMATORY AGENTS
  - NSAID'S IMPROVE PAIN AND SYMPTOMS.
  - NICKEL ET AL J UROL. 2005 APR;173(4):1252-5. RCT OF PENTOSAN POLYSULFATE SODIUM (USED FOR INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME) VERSUS PLACEBO IN CPPS. 300MG TDS FOR 16 WEEKS. SLIGHT IMPROVEMENT OVER PLACEBO, ONLY SIGNIFICANT IN QOL SCORE.

ANTI-INFLAMMATORIES

- CELECOXIB, ROFECOXIB
- *J UROL. 2003 APR;169(4):1401-5. A RANDOMIZED, PLACEBO CONTROLLED, MULTICENTER STUDY TO EVALUATE THE SAFETY AND EFFICACY OF ROFECOXIB IN THE TREATMENT OF CHRONIC NONBACTERIAL PROSTATITIS. NICKEL JC ET AL.*
- MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF ROFECOXIB.
- 161 MEN WERE RANDOMLY ASSIGNED TO TREATMENT WITH EITHER 25-50 MG OF ROFECOXIB/DAY OR PLACEBO.
- OF THE PATIENTS, 79% ON 50 MG ROFECOXIB VERSUS 59% ON PLACEBO REPORTED NO OR MILD PAIN. BUT NOT STATISTICALLY SIGNIFICANT.

CPPS TREATMENTS???

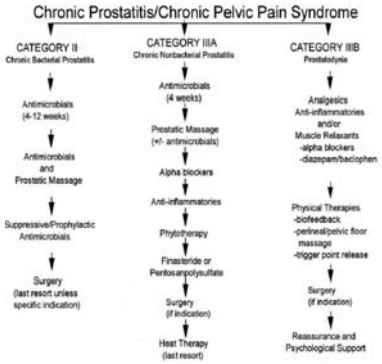
- PROSTATE MASSAGE
  - CAMPBELL'S NO GOOD EVIDENCE TO SUPPORT USE.
- PHYTOTHERAPY
  - SAW PALMETTO – NO EFFECT
  - BEE POLLEN EXTRACT (A BIOFLAVONOID) SHOWED SLIGHT IMPROVEMENTS.
- HORMONE THERAPY
  - NICKEL ET AL BJU INT. 2004 MAY;93(7):991-5. RCT OF FINASTERIDE V PLACEBO SLIGHT IMPROVEMENT BUT NOT PROPERLY POWERED.
- PERINEAL OR PELVIC FLOOR MASSAGE OR MYOFASCIAL TRIGGER POINT RELEASE
  - WHAT?
  - CORNEL ET AL EUR UROL. 2005 MAY;47(5):607-11. EPUB 2005 JAN 22. RCT OF BIOFEEDBACK SHOWED SIGNIFICANT REDUCTION IN NIH-CPSI SCORES.
  - OTHER SMALLER STUDIES GIVE SIMILAR RESULTS.

CPPS TREATMENT

- SURGERY
  - TURP/BNI ONLY IF EVIDENCE OF OBSTRUCTION.
  - TURP IN REFRACTORY CAT. II REPORTED.
  - TURP IN CPPS – NO EVIDENCE
  - RADICAL PROSTATECTOMY – ONE CASE REPORTED

    'NO DEFINITIVE CLINICAL SERIES OR LONG-TERM FOLLOW-UP HAS EVER BEEN PRESENTED, AND THIS TYPE OF SURGERY SHOULD NOT BE ENCOURAGED OR RECOMMENDED AT THIS TIME'.

ALGORITHM OR TREATMENT OF CPPS



CONCLUSION

- BACTERIAL CAUSES FOR PROSTATITIS IS RESPONSIBLE FOR 10% OF CASES
- PROVEN BACTERIAL CASES SHOULD BE TREATED WITH ORAL FLUOROQUINOLONE, TRIMETHOPRIM/SULPHA OR IV ANTIBIOTIC
- NON-BACTERIAL CAUSES REQUIRE SYMPTOMATIC HELP WITH NO GOOD DATA SUPPORTING NSAID'S, ALPHA BLOCKERS OR HORMONE THERAPY, HOWEVER CAN BE TRIED ON CASE BY CASE BASIS

Hepatitis B and Hepatitis C for the Non-specialist

Janice Jou, MD MHS
Associate Professor
Division of Gastroenterology and Hepatology
Oregon Health and Science University
Portland VA Medical Center

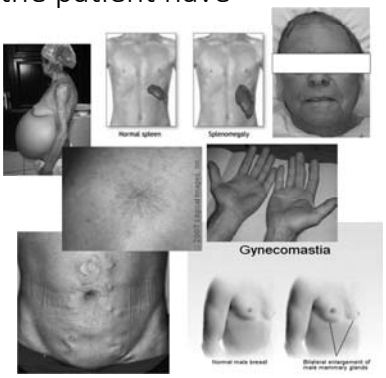
May 31, 2019

Case #1

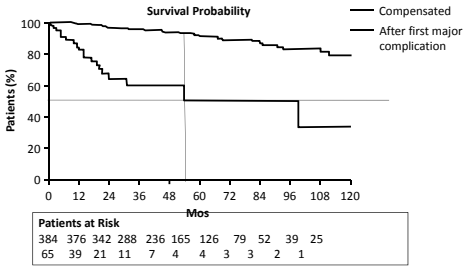
- You are seeing a 55yo male as a new patient in your clinic
- He has a history of hepatitis C
- No current EtOH, quit 2 years ago
  - Prior to that he was drinking 6 beers a day
- He also reports that he was once told he might have had hepatitis B
- Next steps?

First things first…Does the patient have cirrhosis?

- Exam- muscle wasting, spider angiomata, palmar erythema, hyperestrogenemic findings
- Laboratory Data- PLT, INR, **flip-flop in the AST/ALT ratio**
- Imaging (U/S, CT)- nodular liver, caudate hypertrophy, splenomegaly, signs of portal hypertension (varices)
- This hepatologist's approach, choice of 1st imaging test
  - Mild disease suspected → U/S liver
  - Cirrhosis suspected → Multiphase CT of the liver (liver morphology and evaluate for HCC at time of diagnosis of cirrhosis)



First decompensation of liver disease is a poor prognosticator



Fattovich G, et al. Gastro1997; 112: 463-472

Fibrosis Assessment: Liver Biopsy

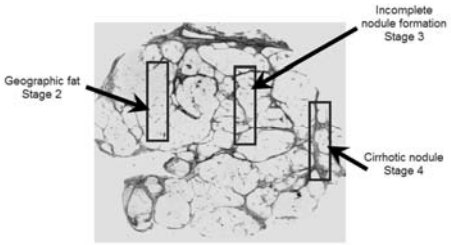
PRO

- Provides greatest amount of information compared to other methods of assessment
- Can assist in
  - Defining etiology of liver disease
  - Fibrosis stage
  - Inflammatory grade
- May assist in determining prognosis (disease activity, recovery from injury)

CON

- Risk
  - 1:1000 risk of bleeding
  - 1:2000 risk of infection
  - 1:2000 risk of injury to adjacent organ
  - 1:10,000 chance of death
- Sampling Error
  - Geographic variation in fibrosis and fat
  - Up to a 30% chance of sampling error
  - "Inter-observer" variation
- Result is often descriptive rather than clearly diagnostic

Potential for Sampling Error in Liver Biopsies



Bedossa P, et al. Hepatology. 2003;38:1449-1457.

Fibroscan (Transient Elastography)

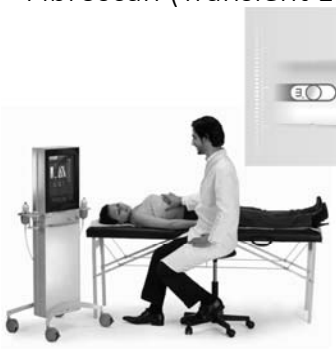


Table 1 Recommended values for different stage of fibrosis

Disease	F0–F1 (Kpa)	F2 (Kpa)	F3 (kpa)	F4 (kpa)
Hepatitis B	≤6.0	≥6.0	≥9.0	≥12.0
Hepatitis C	≤7.0	≥7.0	≥9.5	≥12.0
HCV–HIV coinfection	≤7.0	≤10	≥11.0	≥14.0
Cholestatic liver disease	≤7.0	≥7.5	≥10.0	≥17.0
NAFLD/NASH	≤7.0	≥7.5	≤10	≥14.0

Bonder A, Afdhal N, Curr Gastroenterol Rep (2014) 16:372

FIB-4 (Fibrosis-4)

- **Formula :**

  (Age x AST) / (Platelets x (sqr (ALT))
- **Explanation of Result**
  - **NASH :**
    - Fib4 score < 1.30 = F0-F1
    - Fib4 score > 2.67 = F3-F4
  - **HCV :**
    - Fib4 score < 1.45 = F0-F1
    - Fib4 score > 3.25 = F3-F4

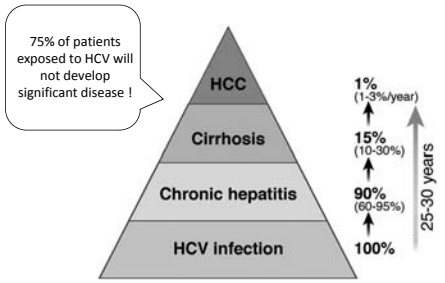
Martínez SM1et al. Noninvasive assessment of liver fibrosis. Hepatology. 2011

Bottom Lines…

- Clinical/Lab/Imaging all support diagnosis of cirrhosis
  - Diagnosis made!
  - HCC surveillance- regardless of etiology of liver disease
    - U/S of the liver with or without AFP every 6 months
  - EGD for variceal screening
- Making the diagnosis of cirrhosis is potentially the most important component of the initial evaluation of a patient with chronic liver disease
- If no evidence of cirrhosis with clinical data/labs/imaging, risk stratify by assessing degree of fibrosis:
  - Fibroscan
  - Fib-4
  - (Liver biopsy)

Hepatitis C

Natural History



El Serag, Gastro 2007

HCV Screening Guidelines

HCV Screening Guidelines From AASLD/IDSA/IAS-USA, CDC, and USPSTF

Age-based	• One-time screening for adults born between 1945 and 1965[1-3]
Risk-based	• Past or current injection drug use[1-3] or intranasal drug use[1,3]
	• Long-term kidney dialysis[1-3]
	• Recipients of: transfusion of blood or blood component, organ transplant before July 1992,[1-3] clotting factor concentrate before 1987;[1,2] blood from a donor who later tested HCV-positive[1,2]
	• Healthcare worker exposed to HCV-infected blood[1-3]
	• Receipt of an unsterile/unregulated tattoo[1,3]
	• Children born to HCV-infected mothers[1-3]
	• Incarceration[1,3]
Other medical conditions	• HIV infection[1,2]
	• Unexplained chronic liver disease, including persistently elevated ALT[1,2]

ALT = alanine aminotransferase; AASLD, IDSA, IAS-USA = The American Association for the Study of Liver Diseases, the Infectious Diseases Society of America, and the International Antiviral Society-USA; CDC = Centers for Disease Control and Prevention; HIV = human immunodeficiency virus; USPSTF = US Preventive Services Task Force.

1. AASLD, IDSA, IAS-USA. Recommendations for testing, managing, and treating hepatitis C. 2014. www.hcvguidelines.org. Accessed May 27, 2014; 2. CDC Testing Recommendations for Chronic Hepatitis C Virus Infection. January 17, 2012. www.cdc.gov/hepatitis/hcv/guidelinesc.htm. Accessed April 22, 2014; 3. Moyer VA, et al. *Ann Intern Med*. 2013;159:349-357.

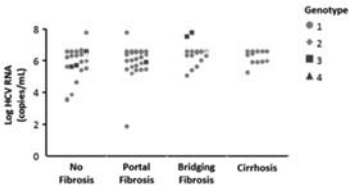
HCV Tests: What the Results Mean

TEST	NOTES
HCV Antibody	Exposure to virus Does not confer immunity
HCV RNA PCR (QUANT)	Amount of virus in the blood Confirms presence of infection
HCV QUAL	Mostly an antiquated test Detectable virus below the limit of detection
HCV genotype	Impacts treatment regimen

Anti-HCV	HCV RNA	Interpretation
+	+	Acute or chronic HCV depending on the clinical context
+	–	False positive HCV antibody Resolved infection (Low-level intermittent viremia)
–	+	Early acute HCV infection Chronic HCV in setting of immunosuppressed state False positive HCV RNA test
–	–	Absence of HCV infection

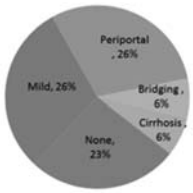
Ghany MG, et al. *Hepatology*. 2009;49:1335-1374.

HCV viral load does *not* predict fibrosis



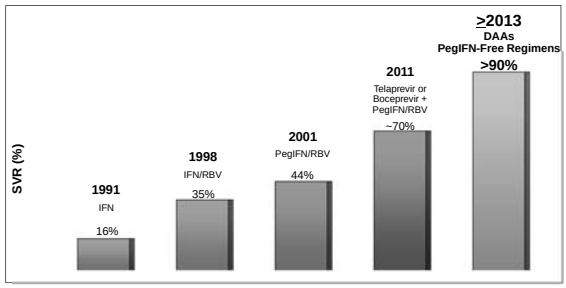
Ferreira-Gonzalez A, et al. Semin Liver Dis. 2004;24(Suppl 2):9-18.

Fibrosis can be present despite normal liver tests



Schiffman et al. J Infect Dis. 2000; 182: 1595-1601

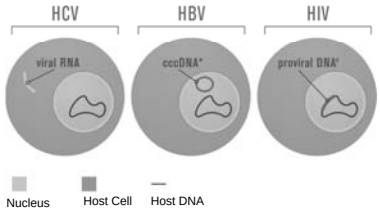
Chronic HCV Therapy: Presently High Cure Rates with Direct Acting Antivirals



Schaefer EA, et al. *Gastroenterology.* 2012;142:1340-1350.
Ghany MG, et al. *Hepatology.* 2009;49:1335-1374.
Ghany MG, et al. *Hepatology.* 2011;54:1433-1444.

Why Is Cure Possible?

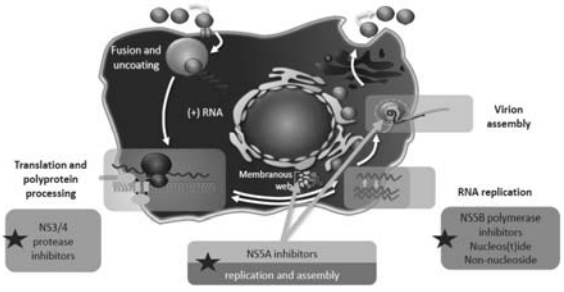
- HCV does not integrate into the nuclei of infected cells, while HBV and HIV DNA are incorporated into the nucleus of the cell



*HBV cccDNA (covalently closed circular DNA): accumulates in hepatocyte nuclei, acting as a template for viral messenger RNA transcription.
†HIV proviral DNA: integrates into the chromatin of infected cells, acting as the template for the transcription of viral genes.

Soriano V et al. J *Antimicrob Chemother.* 2008;62(1):1-4.

Current Treatments for HCV

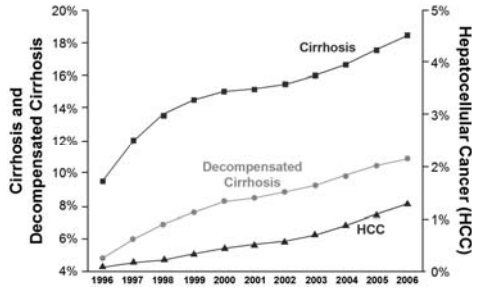


HCV Treatment

- Sustained Virologic Response (SVR)
  - Durable- 99% stay HCV negative for >10 years
  - SVR = undetectable HCV RNA in patient's blood 3-6 months after stopping treatment
- Benefits of achieving SVR
  - Delays liver disease progression
  - Decreases risk of liver cancer
  - Reduces need for liver transplant
  - Reduces transmission

Progressive Increase in Incidence of HCV-Related Cirrhosis and HCC in US

Annual Prevalence Rates Between 1996 and 2006 Among HCV-Infected Veterans



El-Serag HB. *Gastroenterology* 2012;142:1264–1273.

Treatment of Hepatitis C

- No more interferon! (And practically no ribavirin)
- Regimen choice often made in conjunction with gastroenterologist/hepatologist
- ECHO program

Current Treatment Options- Comparisons

	Mavyret™[1] (glecaprevir/pibrentasvir)	Zepatier®[2] (elbasvir/grazoprevir)	Harvoni®[3] (ledipasvir/sofosbuvir)	Epclusa®[4] (sofosbuvir/velpatasvir)	Vosevi®[5,a] (sofosbuvir/velpatasvir/voxilaprevir)
Manufacturer	AbbVie	Merck	Gilead	Gilead	Gilead
MOA	PI + NS5A	NS5A + PI	NS5A + NS5B	NS5B + NS5A	NS5B + NS5A + PI
Genotype coverage	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6
Dosing of DAAs	Once daily (3-pill blister pack)	Once daily (1 pill)	Once daily (1 pill)	Once daily (1 pill)	Once daily (1 pill)
8-week duration	1 2 3 4 5 6	1 2 3 4 5 6	1[b] 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6
Data in NS5A-inhibitor failures	Yes[c]	No	No	No	Yes
Concomitant ribavirin	Not indicated for any populations	GT1a with resistance and GT1 and 4 P/R-experienced	Treatment- experienced cirrhotics, decompensated cirrhosis	Decompensated cirrhosis	Not indicated for any populations
Use in decompensated cirrhosis	No	No	Yes	Yes	No
Use in severe renal impairment	Yes	Yes	No dose recommendation in severe CKD	No dose recommendation in severe CKD	No dose recommendation in severe CKD

Cost of HCV Medications

Estimated Wholesale Acquisition Cost (WAC)	
Recommended Regimens for GT1a HCV, without Cirrhosis	
Regimens and Duration of Therapy	Cost of Regimen
*Elbasvir-Grazoprevir x 12 weeks	$54,600
Glecaprevir-Pibrentasvir x 8 weeks	$26,400
^Ledipasvir-Sofosbuvir x 8 weeks	$63,000
Ledipasvir-Sofosbuvir x 12 weeks	$94,500
Sofosbuvir-Velpatasvir x 12 weeks	$74,760

*This 12-week regimen is for patients without baseline NS5A resistance-associated substitutions (at amino acid positions 28, 30, 31, or 93) for elbasvir
^This 8-week regimen is appropriate only for patients who are non-black, HIV-uninfected, and whose HCV RNA level is <6 million IU/mL

http://www.hepatitisc.uw.edu

Current Treatment Options- Comparisons

	Mavyret™[1] (glecaprevir/pibrentasvir)	Zepatier®[2] (elbasvir/grazoprevir)	Harvoni®[3] (ledipasvir/sofosbuvir)	Epclusa®[4] (sofosbuvir/velpatasvir)	Vosevi®[5,a] (sofosbuvir/velpatasvir/voxilaprevir)
Manufacturer	AbbVie	Merck	Gilead	Gilead	Gilead
MOA	PI + NS5A	NS5A + PI	NS5A + NS5B	NS5B + NS5A	NS5B + NS5A + PI
Genotype coverage	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6
Dosing of DAAs	Once daily (3-pill blister pack)	Once daily (1 pill)	Once daily (1 pill)	Once daily (1 pill)	Once daily (1 pill)
8-week duration	1 2 3 4 5 6	1 2 3 4 5 6	1[b] 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6
Data in NS5A-inhibitor failures	Yes[c]	No	No	No	Yes
Concomitant ribavirin	Not indicated for any populations	GT1a with resistance and GT1 and 4 P/R-experienced	Treatment- experienced cirrhotics, decompensated cirrhosis	Decompensated cirrhosis	Not indicated for any populations
Use in decompensated cirrhosis	No	No	Yes	Yes	No
Use in severe renal impairment	Yes	Yes	No dose recommendation in severe CKD	No dose recommendation in severe CKD	No dose recommendation in severe CKD

Harvoni (LED/SOF)

- High cure rate across many previously difficult to treat population
  - Decompensated cirrhosis
  - HIV
  - Post liver transplant
  - Treatment experienced
- Duration of treatment: 8*, 12, or 24 weeks
- Very well tolerated: headaches, nausea, fatigue

*Must be HCV treatment naïve, non-cirrhotic, with baseline viral load <6 million IU/mL

Epclusa (VEL/SOF)

- More "potent" version of Harvoni
  - Works on all genotypes
  - More resistant to NS5A mutations
- Duration of treatment: 12 weeks
- Very well tolerated: Headaches, nausea, fatigue

Current Treatment Options- Comparisons

	Mavyret™[1] (glecaprevir/pibrentasvir)	Zepatier®[2] (elbasvir/grazoprevir)	Harvoni®[3] (ledipasvir/sofosbuvir)	Epclusa®[4] (sofosbuvir/velpatasvir)	Vosevi®[5,6] (sofosbuvir/velpatasvir/voxilaprevir)
Manufacturer	AbbVie	Merck	Gilead	Gilead	Gilead
MOA	PI + NS5A	NS5A + PI	NS5A + NS5B	NS5B + NS5A	NS5B + NS5A + PI
Genotype coverage	1 2 3 4 5 6	1 4	1 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6
Dosing of DAAs	Once daily (3-pill blister pack)	Once daily (1 pill)	Once daily (1 pill)	Once daily (1 pill)	Once daily (1 pill)
8-week duration	1 2 3 4 5 6	1 2 3 4 5 6	1[7] 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6
Data in NS5A-inhibitor failures	Yes[1]	No	No	No	Yes
Concomitant ribavirin	Not indicated for any populations	GT1a with resistance and GT1 and 4 P/R-experienced	Treatment- experienced cirrhotics, decompensated cirrhosis	Decompensated cirrhosis	Not indicated for any populations
Use in decompensated cirrhosis	No	No	Yes	Yes	No
Use in severe renal impairment	Yes	Yes	No dose recommendation in severe CKD	No dose recommendation in severe CKD	No dose recommendation in severe CKD

Mavyret (GLE/PIB)

Next Generation Direct-Acting Antivirals

Glecaprevir (formerly ABT-493) pangenotypic NS3/4A protease inhibitor

GLE PIB

Collectively: G/P

Pibrentasvir (formerly ABT-530) pangenotypic NS5A inhibitor

In vitro:[1,2]
- High barrier to resistance
- Potent against common NS3 polymorphisms (e.g., positions 80, 155, and 168) and NS5A polymorphisms (e.g., positions 28, 30, 31 and 93)
- Additive/synergistic antiviral activity

Clinical PK & metabolism:
- Once-daily oral dosing
- Minimal metabolism and primary biliary excretion
- Negligible renal excretion (<1%)

G/P is co-formulated and dosed once daily as three 100 mg/40 mg pills for a total dose of 300 mg/120 mg
Glecaprevir was identified by AbbVie and Enanta.

1. Ng TI, et al. Abstract 636. CROI; 2014. 2. Ng TI, et al. Abstract 639. CROI, 2014.

Mavyret (GLE/PIB)

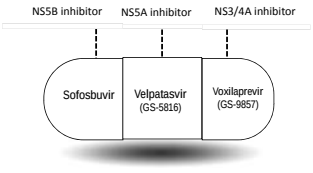
- FDA indications:
  - Treatment of chronic HCV in GT 1-6
  - Treatment of GT 1 patients who previously failed a regimen containing an HCV NS5A inhibitor OR an NS3/4A PI, BUT NOT BOTH
- Dosing
  - 3 tablets (100mg/40mg) daily X 8 to 16 weeks
  - Comes in 4 or 8 weeks package

Mavyret Prescribing Information 2017

Current Treatment Options- Comparisons

	Mavyret™[1] (glecaprevir/pibrentasvir)	Zepatier®[2] (elbasvir/grazoprevir)	Harvoni®[3] (ledipasvir/sofosbuvir)	Epclusa®[4] (sofosbuvir/velpatasvir)	Vosevi®[5,6] (sofosbuvir/velpatasvir/voxilaprevir)
Manufacturer	AbbVie	Merck	Gilead	Gilead	Gilead
MOA	PI + NS5A	NS5A + PI	NS5A + NS5B	NS5B + NS5A	NS5B + NS5A + PI
Genotype coverage	1 2 3 4 5 6	1 4	1 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6
Dosing of DAAs	Once daily (3-pill blister pack)	Once daily (1 pill)	Once daily (1 pill)	Once daily (1 pill)	Once daily (1 pill)
8-week duration	1 2 3 4 5 6	1 2 3 4 5 6	1[7] 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6
Data in NS5A-inhibitor failures	Yes[1]	No	No	No	Yes
Concomitant ribavirin	Not indicated for any populations	GT1a with resistance and GT1 and 4 P/R-experienced	Treatment- experienced cirrhotics, decompensated cirrhosis	Decompensated cirrhosis	Not indicated for any populations
Use in decompensated cirrhosis	No	No	Yes	Yes	No
Use in severe renal impairment	Yes	Yes	No dose recommendation in severe CKD	No dose recommendation in severe CKD	No dose recommendation in severe CKD

Vosevi (SOF/VEL/VOX)



- Broad genotypic activity
- Retains activity against almost all clinically relevant resistance associated substitutions (RAS)
- All-oral, once-daily regimen with food

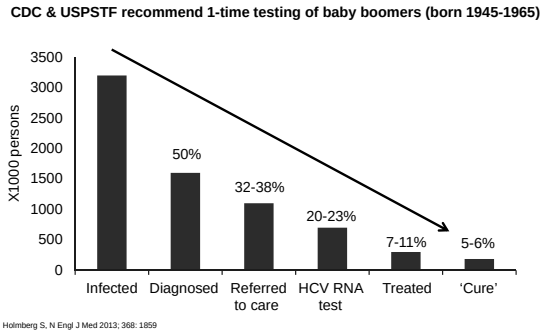
FDA indications:
-Genotype 1-6 who have previously been treated with an HCV regimen containing an NS5A inhibitor
-GT 1a or 3 who have previously been treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor

HCV Treatment: Drug Interactions

Liverpool Hep C Interactions

- Common Drug Interactions:
  - Acid Reducers
  - Statins
  - Amiodarone
  - CYP and PGP inducers
  - CYP inhibitors

HCV-Infected Persons in the US: Estimated Rates of Detection, Referral to Care and Cure



Holmberg S, N Engl J Med 2013; 368: 1859

Case #1

- You are seeing a 55yo male as a new patient in your clinic
- He has a history of hepatitis C
- No current EtOH, quit 2 years ago
  - Prior to that he was drinking 6 beers a day
- He also reports that he was once told he might have had hepatitis B
- Next steps?
  - Liver panel, INR, CBC
  - Fibrosis assessment- Fibroscan
  - Treat HCV
  - History of HBV….stay tuned

Resources

- HCV guidelines
  - http://www.hcvguidelines.org/
- HCV resources
  - www.**hepatitisc.uw**.edu/
- AASLD website
  - www.aasld.org
- Liverpool HCV Interactions
  - https://www.hep-druginteractions.org/

- OHSU Consult Line 503-494-4567

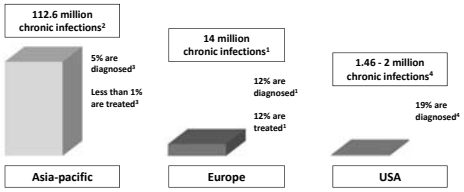
Take home points: HCV treatment

- Revolutionary!
- Need to be aware of drug-drug interactions- close partnership with pharmacy
- For those on the front lines
  - Identify chronic HCV- Birth cohort screening
  - Identify HCV cirrhosis, refer if needed
  - Those without cirrhosis or prior DAA failure can be treated safely in the primary care setting
  - More and more HCV being treated by PCP's
- All patients with HCV should be considered for treatment
  - Underinsured
  - Insurance pre-authorization *
- Compensated cirrhosis
  - Ensure that there is no evidence of HCC with multiphase CT scan
  - Child's A cirrhosis patients tolerate treatment well

Hepatitis B

Hepatitis B- An Unmet Medical Need

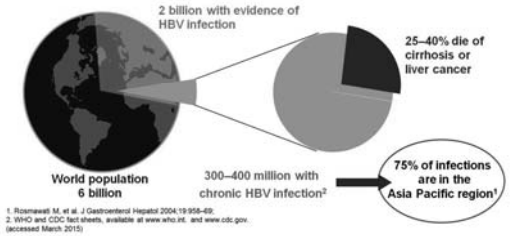
- Under-diagnosed
- Under-treated



1. BMS Market Research. Information available upon request from Bristol-Myers Squibb;
2. Mohamed R, et al. J Gastroenterol Hepatol 2004;19:958-69;
3. Decision Resources. Hepatitis B virus in China – Emerging markets study #5; 4. BMS Market Research.

Global Impact of HBV

- Due to its high incidence and risk of liver injury, CHB constitutes a significant health and economic burden within the Asia Pacific region[1]

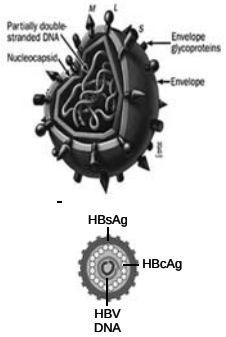


1. Rosmawati M, et al. J Gastroenterol Hepatol 2004;19:958–69;
2. WHO and CDC fact sheets, available at www.who.int. and www.cdc.gov. (accessed March 2015)

HBV Virology

Spherical particle comprised of:
- Outer Envelope (**HBsAg**) protein
- Inner Nucleocapsid (**HBcAg**) protein
- Within nucleocapsid is the partially double stranded circular molecule of **HBV DNA**

cccDNA = viral RNA template
- Stable
- Resistant to host immune response
- Resistant to antiviral therapy
- Stuck in hepatocyte DNA permanently
- Stimulates oncogenesis



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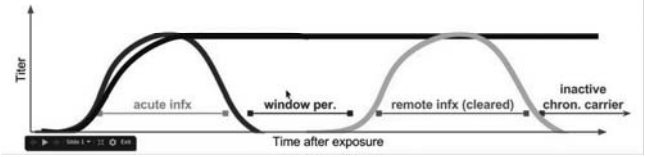
Hepatitis B serologies

Screencastify Lite

Marker	Meaning	Acute infection	Window period	Chronic infection	Remote infection (cleared)	Immun-ization	Inactive chronic carrier
HBcAb	Exposure	+	+	+	+	-	+
HBsAg	Infection	+	-	+	-	-	-
HBsAb	Immunity	-	-	-	+	+	-

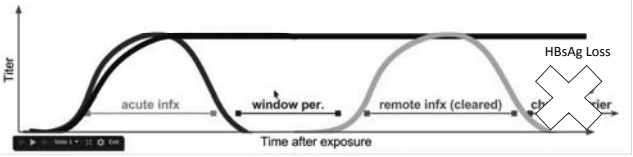


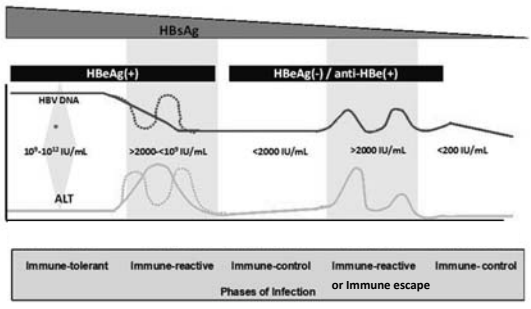
Hepatitis B serologies

Screencastify Lite

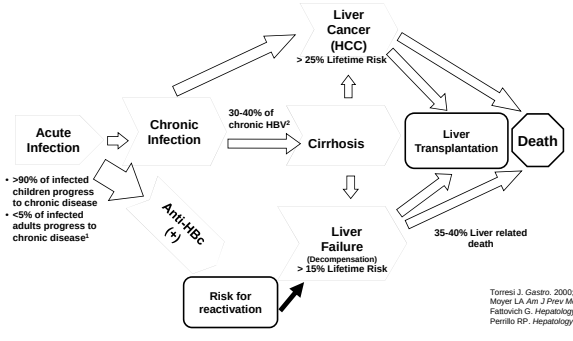
HBsAg Loss

Marker	Meaning	Acute infection	Window period	Chronic infection	Remote infection (cleared)	Immun-ization	
HBcAb	Exposure	+	+	+	+	-	+
HBsAg	Infection	+	-	+	-	-	-
HBsAb	Immunity	-	-	-	+	+	-





Natural History of HBV



Torresi J. *Gastro.* 2000;118:S83-103[3]; Moyer LA *Am J Prev Med.* 1994;10:45-55[5]; Fattovich G. *Hepatology.* 1995;1:77-82[2]; Perrillo RP. *Hepatology.* 2001;33:424-432.[4]

Surveillance for HCC in HBV

- Who should receive HCC surveillance?
  - Chronic HBV with or without cirrhosis
- How?

AASLD Guidelines:

- Liver ultrasound with or without Alpha-fetoprotein (AFP) every 6 months
- CT/MRI not recommended for HCC surveillance

AASLD Guidelines for HCC 2017

Take home points: HBV Epidemiology and Testing

- Remains a globally important disease
- This hepatologists' view: avoid using terminology for the phases of HBV without specifically documenting the patient's serologic status
  - HBsAg
  - HBcAb
  - HBsAb
- "Chronic carrier", "inactive carrier" can be ambiguous and confusing
- Risk for HCC in patients with and without cirrhosis in HBV

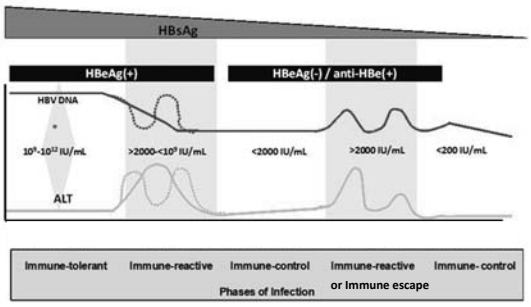
Case #2

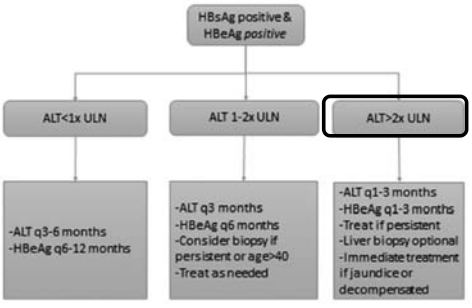
- 32yo male presents with a new diagnosis of chronic HBV after giving blood
- He mentions he was once told that he had family members with liver disease
- You check liver tests and ALT 25, AST 22
- HBeAg pos
- HBV DNA 2,000,000 IU/mL
- Should this patient be treated for HCV?

Who should be treated for HBV?

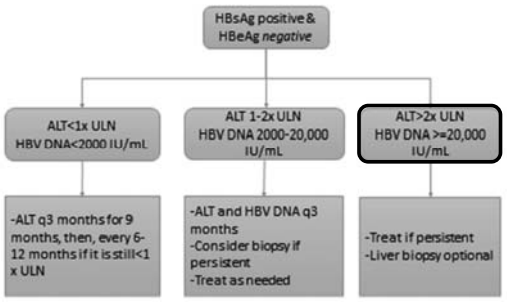
- HBeAg +, ALT >2x ULN, HBV DNA >20,000 IU/ml
- HBeAg -, ALT >2x ULN, HBV DNA>2,000 IU/ml
- Compensated/decompensated cirrhosis
- Prevention of reactivation of HBV in those receiving immune suppression or cytotoxic therapy

Rajbhandari R et al. Clin and Transl Gastro 2016





Rajbhandari R et al. Clin and Transl Gastro 2016



Rajbhandari R et al. Clin and Transl Gastro 2016

FDA-Approved Treatments for HBV

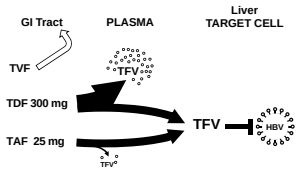
Nucleosides/Nucleotides			
Tenofovir AF	VEMLIDY™	Gilead Sciences	2017
Tenofovir DF	VIREAD®	Gilead Sciences	2008
Telbivudine	TYZEKA™	Idenix / Novartis	2006
Entecavir	BARACLUDE™	Bristol-Myers Squibb	2005
Adefovir dipivoxil	HEPSERA™	Gilead Sciences	2002
Lamivudine	EPIVIR-HBV®	GlaxoSmithKline	1998
Interferons			
Peginterferon alfa-2a	PEGASYS®	Roche	2005
Interferon alfa-2b, recombinant	INTRON® A	Schering / Merck	1992

Preferred regimens

	Potency	Resistance	Disadvantages	Notes
Tenofovir disoproxil fumarate	++	None Effective against LAM, telbivudine and entecavir resistance	Nephrotoxicity with Fanconi's syndrome	Treatment of choice in patients with HBV/HIV co-infection
Entecavir	+	Low Effective against adefovir resistant strains	Can lead to HIV resistance Increased risk of resistance in those who are LAM resistant	Less nephrotoxic than TDF

Tenofovir Alafenamide (TAF)

- Prodrug of tenofovir DF
- Tenofovir AF is more stable in plasma/tissues than tenofovir DF
  - Higher levels in target cells
- Tenofovir DF (but not tenofovir AF) actively enters renal tubular cells via organic anion transporters 1 and 3
- Tenofovir AF has a lesser effect on the proximal renal tubule



90% Lower TFV Levels in Plasma
Minimizes Renal and Bone Effects While Maintaining High Potency in target cells

DHHS. http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Revision July 14, 2016.

Case #2

- 32yo male presents with a new diagnosis of chronic HBV after giving blood
- He mentions he was once told that he had family members with liver disease
- You check liver tests and ALT 25, AST 22
- HBeAg pos
- HBV DNA 2,000,000 IU/mL
- Should this patient be treated for HCV?

Goals of Treatment for HBV

Primary Goals

- Reduction in fibrosis/cirrhosis
- Reduce risk of hepatocellular carcinoma
- Decrease mortality

Surrogate Goals

- Improvement in hepatic inflammation, fibrosis
- Virologic suppression:
  - Undetectable or low HBV DNA level
  - eAg loss/eAb development
- Normalization of serum ALT
- Loss of HBsAg +, appearance of HBsAb (rare but optimal)

Lok ASF. *Hepatology*. 2004;39:857-861.
Keeffe EB. *Clin Gastroenterol Hepatol*. 2006;4:936-962.

Other considerations for HBV treatment

- Liver biopsy to distinguish between immune control and immune reactive/escape phases in HBeAg neg CHB
- Fibroscan can to assess for advanced fibrosis but not inflammation
- Test all "at risk" patients for delta hepatitis (HDV)
  - Advanced liver disease
  - IVDU or sexual transmission as risk for HBV
- Test for HBV mutations if viral breakthrough with treatment
- Entecavir or TAF in renal insufficiency
- Lactic acidosis: class warning with nucleot(s)ide analogues

Take home points: HBV Treatment Overview

- Is not "curable"
- Loss of HBsAg is a "functional cure"
  - Very uncommon
- In those with an indication for treatment: ETV and TDF preferred
- Counsel patients that indefinite treatment likely

Case #2

- You are seeing the following patient in consultation:

- 65yo female with hx. multiple sclerosis
- Would like to start Ocrelizumab
- HBsAg neg, HBcAb pos, HBsAb neg

- What are your next steps?

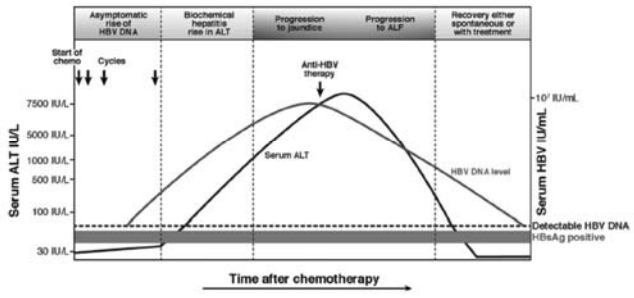
Reactivation of HBV with Immune Suppression and Biologic Therapies

2 categories

- HBV reactivation - patients with HBsAg+ with or without detectable HBV-DNA viremia in the blood
- Reverse seroconversion - reappearance of HBsAg and HBV DNA in individuals who initially are negative for HBsAg and HBV DNA in the serum before immunosuppression and then become positive after exposure to immunosuppressive therapies.
  - Occult HBV
- 25-50% of reactivation can result in severe liver injury/liver failure

Loomba R, Liang JT. Gastroenterology 2017;152:1297-1309

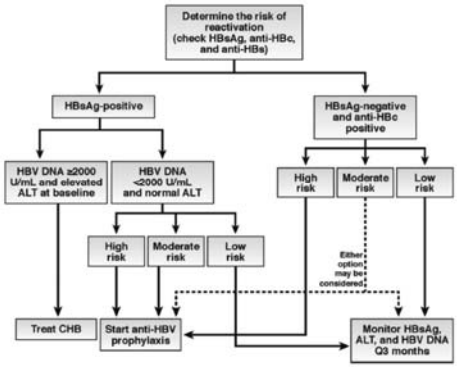
Example course of HBV reactivation



Loomba R, Liang JT. Gastroenterology 2017;152:1297-1309

RISK OF HBV REACTIVATION	**HBsAb +, HBcAb +**	**HBsAb neg, HBcAb +**
Anti-CD 20 (rituximab, ofatumumab, Obinutuzumab)	VERY HIGH (>20% risk)	MODERATE
Hematopoietic stem cell transplantation	VERY HIGH	Low
High dose corticosteroids (>20mg for 4 weeks)	HIGH (11-20% risk)	Low
Other Cytokine Inhibitors (e.g. anti-CD52)	HIGH	Low
Combination Cytotoxic Chemo without corticosteroids (cyclophosphamide, adriamycin, vincristine)	MODERATE (1-10%)	Rare
Anti-TNF inhibitors	MODERATE	Rare
Anti-rejection therapy for solid organ transplant	MODERATE	Rare
Methotrexate, Azathioprine, 6-MP	Low (<1%)	Rare

Di Bisceglie AM et al. Hepatology 2014



Loomba R, Liang JT. Gastroenterology 2017;152:1297-1309

Treatment to prevent HBV reactivation

- Most experience with LAM
- Shift to ETV and TDF
- Can start prophylaxis concurrently with immune suppressive medication
- If viral load is high, could consider starting treatment and then initiating medication if able to wait
- Medications are continued for 6 months post cessation of immune suppression with non B-cell depleting agents
- With B-cell depleting agents, continue for 12 months

Case #2

- 65yo female with hx multiple sclerosis
- Would like to start Ocrelizumab
- HBsAg neg, HBcAb pos, HBsAb neg

- High risk for reactivation → treat with TDF or ETV

Case #1

- You are seeing a 55yo male as a new patient in your clinic
- He has a history of hepatitis C
- No current EtOH, quit 2 years ago
  - Prior to that he was drinking 6 beers a day
- He also reports that he was once told he might have had hepatitis B
- Next steps?
  - Liver panel, INR, CBC
  - Fibrosis assessment- Fibroscan
  - Treat HCV
  - History of HBV….

ORIGINAL RESEARCH

Annals of Internal Medicine

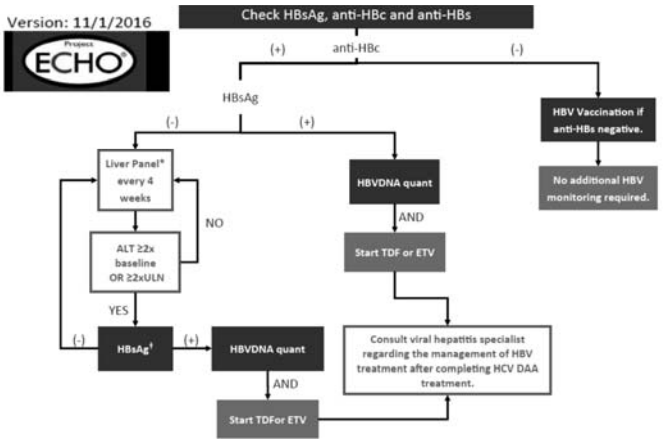
Hepatitis B Virus Reactivation Associated With Direct-Acting Antiviral Therapy for Chronic Hepatitis C Virus: A Review of Cases Reported to the U.S. Food and Drug Administration Adverse Event Reporting System

- N=29 reported to the FDA
- 2 Died and 1 received liver transplantation
- 5 patients hospitalized

Baseline HBV viral characteristics, *n*	
HBsAg	
Positive	13
Negative	4
Not reported	12
HBcAb	
Positive	6
Not reported	23
HBsAb	
Negative	3
Not reported	26
HBV DNA	
Undetectable	16
Detectable	9
Baseline not reported or detectability status unclear	4

AASLD Guidance on HBV Reactivation in Pts Receiving HCV DAA Therapy

- HBV vaccination for all susceptible individuals
- Test for HBV DNA prior to DAA therapy if HBsAg +
- Treatment of active HBV infection at the same time — or before — HCV DAA therapy is started
- Monitoring patients with low or undetectable HBV DNA levels at regular intervals (usually not more frequently than every four weeks) for HBV reactivation during treatment
- Insufficient data to provide recommendations for pts who are HBsAg- and anti-HBc+ or anti-HBs+/anti-HBc+



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- He also reports that he was once told he might have had hepatitis B
- Next steps?
  - Liver panel, INR, CBC
  - Fibrosis assessment- Fibroscan
  - Treat HCV
  - History of HBV….need to check Hepatitis B serologies and treated based on algorithm

Summary: Who to treat for HBV?

- HBeAg +, ALT >2x ULN, HBV DNA >20,000 IU/ml
- HBeAg -, ALT >2x ULN, HBV DNA>2,000 IU/ml
- Compensated/decompensated cirrhosis
- Prevention of reactivation of HBV in those receiving immune suppression or cytotoxic therapy

Rajbhandari R et al. Clin and Transl Gastro 2016

Summary: HBV in Special Populations

- HBV is never truly cleared even if HBsAg negative
- HBV genome incorporated into the hepatocyte
  - ccc DNA
  - Difficult to quantify risk in occult HBV
- 4 phases of chronic HBV
- Avoid using “carrier” as a descriptor
- Reactivation of HBV
  - Risk stratify based on medication being used and serologic status of patient
  - High risk/Moderate risk → TREAT
  - Low risk→ Observe
  - Steroids!

Questions?

- OHSU Consult Line 503-494-4567

Molecular Diagnostics in ID

May 31, 2019 Ellie Sukerman, MD MS

Disclosures

- I have no disclosures

Objectives

- Explain the pros and cons of traditional vs. molecular (culture-independent) testing
- Utilize molecular testing in the work-up of common infectious syndromes
- Understand the role of diagnostic and antimicrobial stewardship in molecular diagnostics

Background

- The ultimate goal in ID is obtaining an accurate diagnosis in a timely manner
- Inadequate empiric antimicrobial therapy associated with increased mortality
- Growing interest in and development of rapid molecular diagnostics

Retamar, et al. AAC. 2012.

Culture vs. Molecular Testing

	Culture-Dependent Testing	Molecular Testing
Requires patient specimens	✓	✓
Accuracy	High	Variable
Time to Results	Slow	Rapid
Requires special knowledge to perform	✓	✕
Produces culture for subtyping and susceptibility testing	✓	✕*
May test for bacterial, viral and parasitic infections simultaneously	✕	✓

*Susceptibility testing available for some molecular methods

What Molecular Assays are Available?

- Polymerase chain reaction (PCR)
- Microarrays 
- Matrix-Assisted Laser Desorption Ionization Time-of-Flight (MALDI-TOF)/MS
- Traditional and next-generation sequencing*

*routine use in the clinical laboratory is currently impractical

PCR Testing

- Sexually transmitted infections
- Mycobacterium tuberculosis (MTB)
- Methicillin resistant *Staphylococcus aureus*
- *C. difficile*
- Broad range PCR (16s, 18s)

A common clinical scenario

An 80yo woman presents with confusion and AKI. A BCx is included in her work-up. The following day, the BCx turns positive for GPCs.

What would you do next?

A. Start IV vancomycin pending GPC identification
B. Hold on starting antibiotic targeted at GPC bacteremia pending GPC identification
C. Start daptomycin pending GPC identification
D. Start cefazolin pending GPC identification

Microarray Examples – Bloodstream Infection (BSI)

Organism/Resistance Gene	Verigene®	BioFire® FilmArray®
Enterococcus		x
Enterococcus faecalis	x	
Enterococcus faecium	x	
Listeria spp	x	
Listeria monocytogenes		x
Staphylococcus spp	x	x
Staphylococcus aureus	x	x
Streptococcus spp	x	x
Streptococcus agalactiae	x	x
Streptococcus pneumoniae	x	x
Streptococcus pyogenes	x	x
mecA	x	x
vanA/B	x	x

https://www.luminexcorp.com/gram-positive-blood-culture/
https://www.luminexcorp.com/gram-negative-blood-culture/
https://www.biofiredx.com/products/the-filmarray-panels/filmarraybcid/

Microarray Examples – BSI

Organism/Resistance Gene	Verigene®	BioFire® FilmArray®
Acinetobacter spp	x	
Acinetobacter baumanii		x
Citrobacter spp	x	
Enterobacteriaceae		x
Enterobacter cloacae complex	x	x
Escherichia coli	x	x
Haemophilus influenzae		x
Neisseria meningitidis		x
Proteus spp	x	x
Pseudomonas aeruginosa	x	x
Serratia marcesans		x
CTX-M (ESBL)	x	
KPC (carbapenemase)	x	x
IMP, NDM, OXA, VIM (carbapenemase)	x	

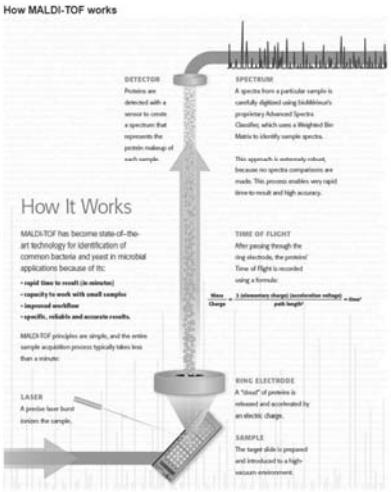
https://www.luminexcorp.com/gram-positive-blood-culture/
https://www.luminexcorp.com/gram-negative-blood-culture/
https://www.biofiredx.com/products/the-filmarray-panels/filmarraybcid/

Syndrome-Based Microarray Assays

Image: https://www.biofiredx.com/products/the-filmarray-panels/filmarraybcid/

	BioFire® FilmArray®	Verigene® Enteric Pathogens Test	xTAG® GPP	BD MAX™	Hologic® Prodesse
Campylobacter	X	x	x	x	x
Clostridium difficile (toxin A/B)	X		x		
Plesiomonas shigelloides	X				
Salmonella	X	x	x	x	x
Yersinia enterocolitica	X	x	x		
Vibrio	X	x			
Vibrio cholerae	X		x		
Enteroaggregative E. coli (EAEC)	X				
Enteropathogenic E. coli (EPEC)	X				
Enterotoxigenic E. coli (ETEC)	X		x		
Shiga-like toxin-producing E. coli (STEC)	X		x	x	x
E. Coli O157	X		x		
Shigella/Enteroinvasive E. coli (EIEC)	X	x	x	x	x
Cryptosporidium	X		x		
Cyclospora cayetanensis	X				
Entamoeba histolytica	X		x		
Giardia lamblia	X		x		
Adenovirus	X		x		
Astrovirus	X				
Norovirus GI/GII	X	x	x		
Rotavirus	X	x	x		
Sapovirus (I, II, IV and V)	X				
Shiga toxin 1, 2		x	x		x

MALDI-TOF MS



Accuracy in BSI

- Accuracy is good with monomicrobial BSI
- Targets included are not exhaustive
- Accuracy is decreased with polymicrobial BSI

Interpretation of Molecular Testing

Follow-up Case

Back to BSI…now your patient is a 32yo man with injection drug abuse who presents with fever and soft tissue infection. BCxs grow GPCs in clusters. He is started on empiric vancomycin. You have molecular testing available and you get this result:

Staphylococcus aureus, no mecA detected!!

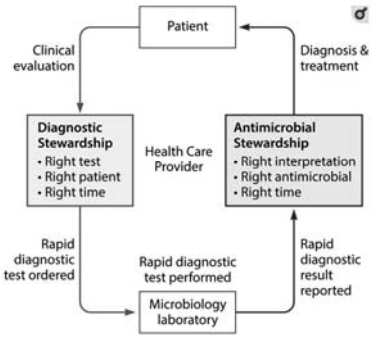
Your next best step is to:

A. Switch vancomycin to cefazolin
B. Continue vancomycin until you have susceptibility testing back
C. Stop antibiotics, this is likely a contaminant

Does that information help you?

Stewardship of Molecular Testing

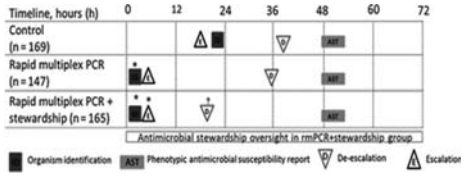
Right test for the right patient at the right time



Messacar, et al. J Clin Microbiol. 2017.

Impact of Molecular Testing

Randomized Trial of Rapid Multiplex Polymerase Chain Reaction-Based Blood Culture Identification and Susceptibility Testing



Banerjee, et al. CID. 2015.

Meningitis/Encephalitis (ME) Example

- FilmArray ME panel FDA approved 2015
- Expected turnaround 4h
- Adopted at OHSU in 2017

Bacteria	Viruses
Escherichia coli K1	CMV
Haemophilus influenzae	Enterovirus
Listeria monocytogenes	HSV-1
Neisseria meningitidis	HSV-2
Streptococcus agalactiae (GBS)	HHV-6
Streptococcus pneumoniae	Human parechovirus
	Varicella zoster virus
Yeast	
Cryptococcus neoformans/gattii	

Cost

Pathogen	Turnaround Time	Cost (Patient Charge)
Gram stain	1 hour	Approx $60
Bacterial culture	2-5 days	Approx $340
HSV PCR	2-3 days	Approx $270
Enterovirus PCR	24 hours	Approx $270
Cryptococcal Ag	1 hour (M-F 7a-330p)	Approx $85
M/E PCR Panel	4 hours	Approx $1,800

Data courtesy of Dawn Nolt, MD MPH

Audit of Test Utilization

- 254 tests run over a 14 month period
- 27/254 (11%) tests positive
- Approx 50% of tests being sent from samples without CSF pleocytosis

Data courtesy of Dawn Nolt, MD MPH

Additional Concerns

ME Panel and serum Cryptococcal Ag: 61 specimens (prior to tx)

	+Disease (+CrAg)	-Disease (-CrAg)	
+ Test (+M/E)	3 (TP)	0 (FP)	(3/3) PPV 100%
- Test (-M/E)	2 (FN)	56 (TN)	(56/58) NPV 97%
	(3/5) Sensitivity 60%	(56/56) Specificity 98%	

Data courtesy of Dawn Nolt, MD MPH

Evaluation of ME Panel

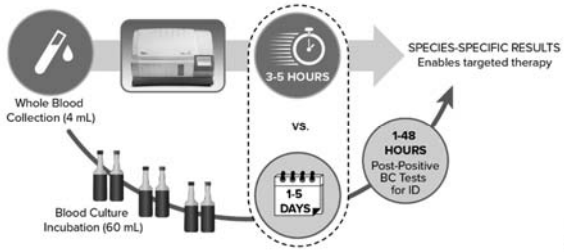
- Recent retrospective study evaluated performance of ME panel on known positive CSF samples
- The percent positive agreement was:
  - 97.5% for bacterial pathogens
  - 90.1% for viral pathogens
  - 52% for *Cryptococcus neoformans/C. gattii* (cryptococcal antigen was the comparator)

Liesman, et al. J Clin Microbiol. 2018.

New Tools in Molecular Diagnostics

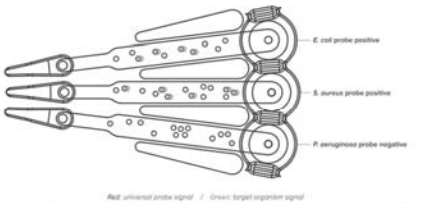
T2MR®

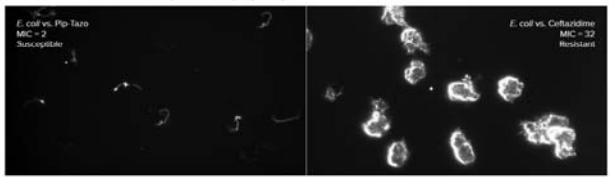
- Can identify molecular targets direct from whole blood
- Lower limit of detection 1 cfu/mL



https://www.t2biosystems.com/products-technology/t2mr-technology/
https://www.t2biosystems.com/products-technology/t2dx-instrument/

Accelerate Pheno™ System





http://acceleratediagnostics.com/products/accelerate-pheno-system/

Case

A 66yo man with T-cell prolymphocytic leukemia, hx of pulmonary nocardiosis and DM is admitted with meningoencephalitis. He undergoes LP x 2 with the following results:

2384 WBCs (85%N) -> 406 WBCs (76%N)
488 RBCs -> 594
Glucose 69 -> 21
Protein 687 -> 966
Gram stain neg, cx neg
M/E panel negative
CSF Crypto Ag neg
AFB cx neg
Fungal cx neg
HSV PCR neg
CMV PCR neg
Tb PCR neg
Broad range PCR neg
Bartonella PCR neg
Cytology neg
Quantiferon neg
Serum Crypto Ag neg
Fungal Ab panel neg
Coccidioides Ab neg
BCxs neg
Fungal BCx neg
RMSF Abs neg

What to do next?

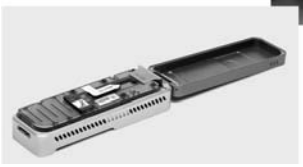
Next-Generation Sequencing (NGS)

- Unbiased sequencing analysis
- Increased use in diagnosis, antibiotic resistance, epidemiologic tracking is likely
- Current barriers include cost, availability, bioinformatics requirements

Das, et al. AJIC. 2017.

NGS Platforms

Sequencing by synthesis

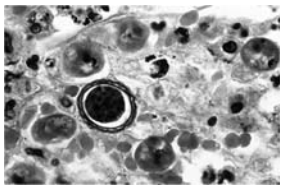


Sequencing by electrical current disruptions
Portable!!

Gu, et al. Annu Rev Pathol. 2019.

Back to our patient…

- NGS performed on residual CSF and positive for Acanthamoeba
- Targeted PCR for Acanthamoeba from post-mortem brain tissue also positive



Summary

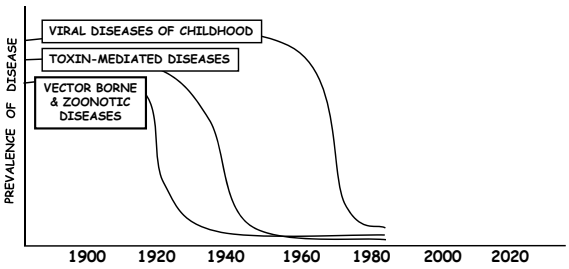
- Molecular diagnostics aid in more rapid diagnosis and are less labor intensive
- Determine what molecular diagnostics may be appropriate in your clinical practice setting
- Most valuable when combined with careful stewardship of testing and guidance in interpretation
- Monitor usage and impact after implementation

Thank You

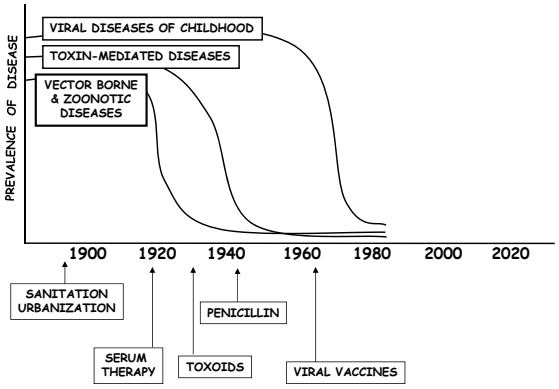
Emerging Infectious Diseases

George C. Mejicano, MD, MS
Professor and Senior Associate Dean
School of Medicine
Oregon Health & Science University

Emerging Infectious Diseases



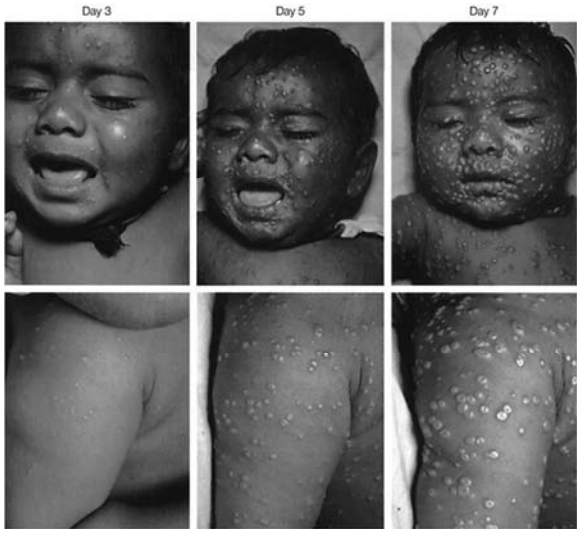
Emerging Infectious Diseases



Optimism of the 1960's ...

"One can think of the middle of the 20th century as the end of the most important social revolutions in history – the virtual elimination of infectious disease as a significant factor in social life."

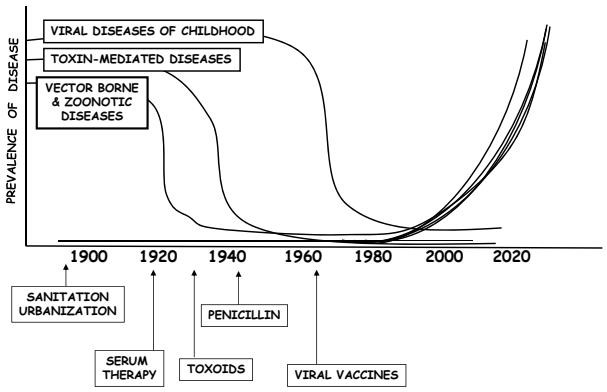
Sir M. Burnet, 1962
Nobel Laureate



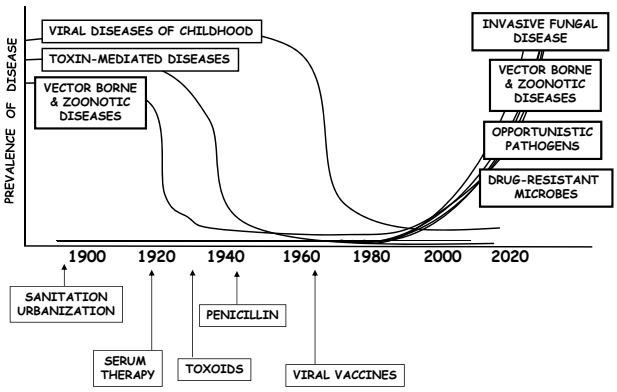
"In 1967, the surgeon general declared that the United States was ready to 'close the book' on infectious disease..."

ASM New and Reemerging Infectious Diseases, 1997

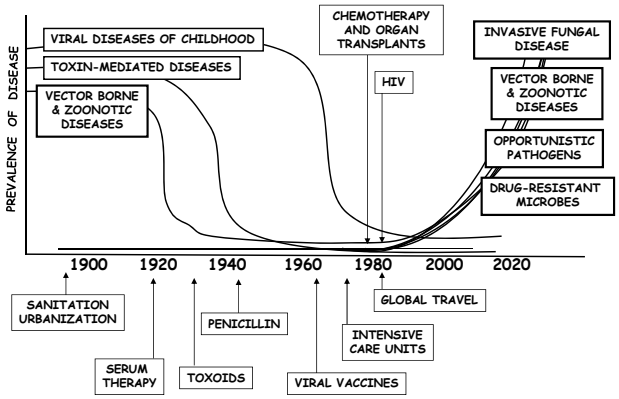
Emerging Infectious Diseases



Emerging Infectious Diseases



Emerging Infectious Diseases



...has yielded to the present situation

"The war against pathogenic micro-organisms is far from over. We live in a restless equilibrium and share the planet with countless microscopic creatures."

ASM New and Reemerging Infectious Diseases, 1997

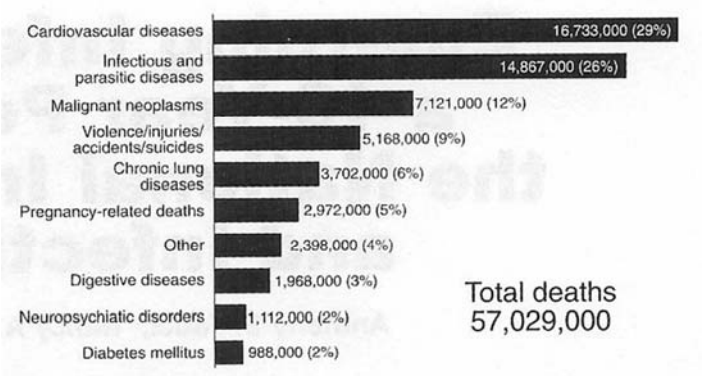


Figure 1. Leading causes of death worldwide (estimates for 2002). Nearly 15 million (>25%) of the 57 million annual deaths worldwide are caused by infectious disease (6). [EID 2005; 11:520]

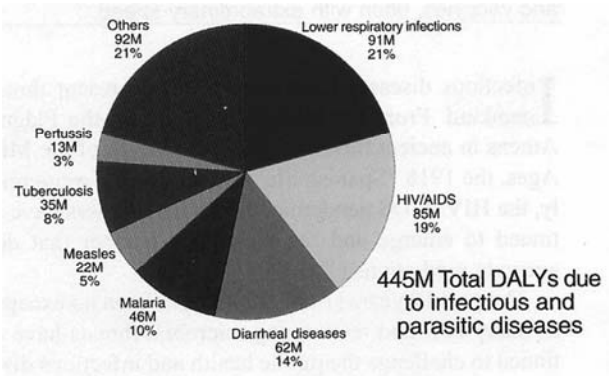
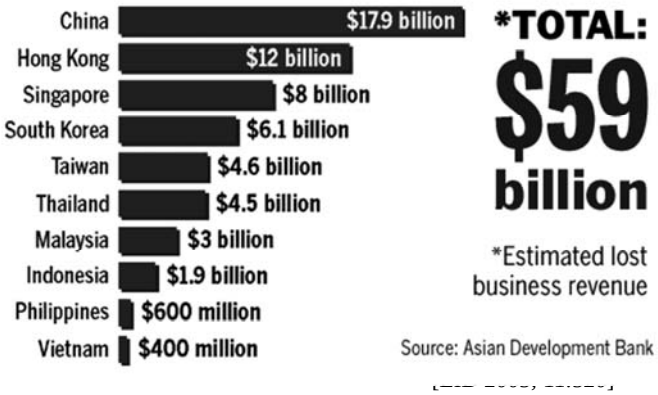


Figure 2. Leading causes of disability life years (DALYs) due to infectious and parasitic diseases (2002 estimates). Lower respiratory infections, HIV/AIDS, diarrheal diseases, and malaria are among the infectious diseases that contribute to the most DALYs lost each year throughout the world (6). [EID 2005; 11:520]

Cost of Avian Influenza (2004-5)

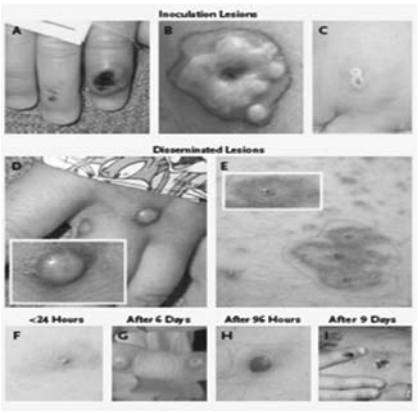


Definition of Emerging Infections

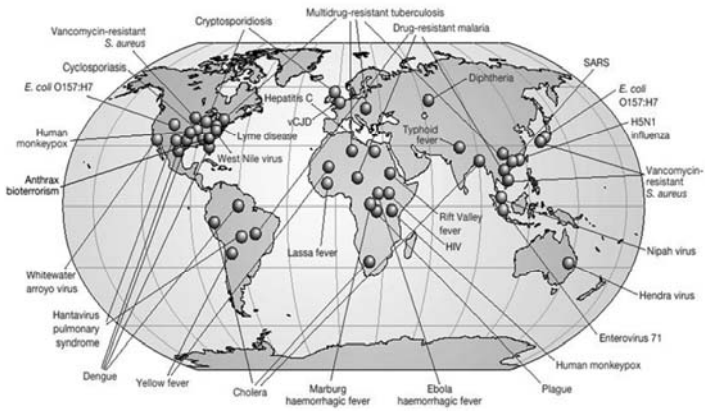
"New, re-emerging or drug-resistant infections whose incidence in humans has increased within the past two decades or threatens to increase in the near future."

Institute of Medicine Report, 1992

A "New" Infectious Disease in North America



[NEJM 2004: 350, 4]



A Subtle but Important Point

- Emerging Disease
  - Focuses on specific organisms, syndromes and outbreaks
- Disease Emergence
  - Focuses on the driving forces that are pushing the incidence of many (perhaps most) infectious diseases upward

Major Factors Contributing to the Emergence of Infectious Diseases

1. Human demographics and behavior
2. Industry and commerce
3. Economic development and land use
4. International travel
5. Microbial adaptation and change
6. Breakdown of public health measures

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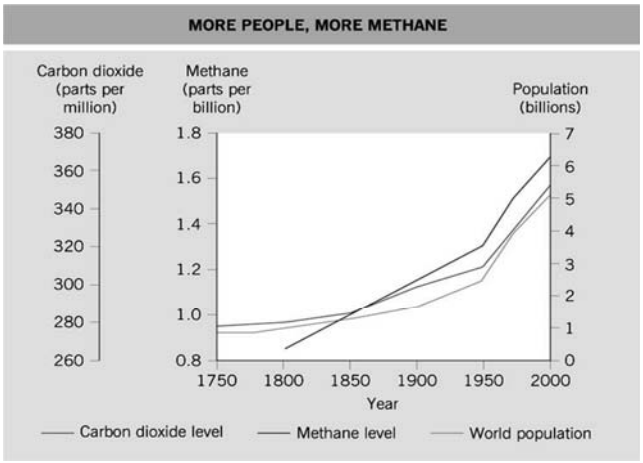

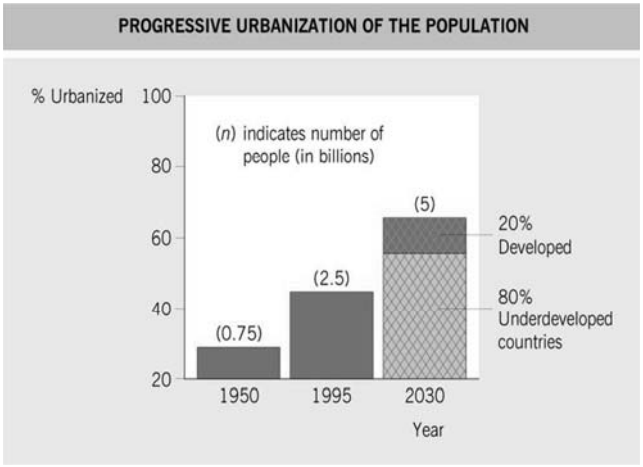

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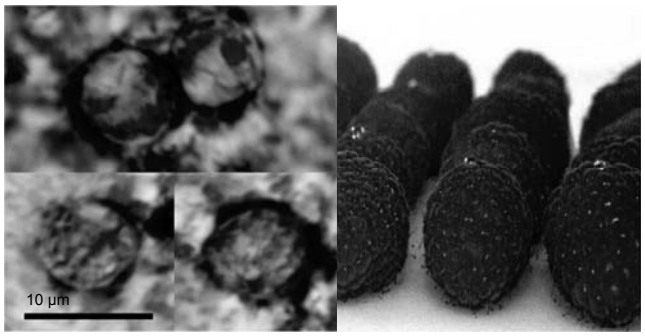
Cyclospora



Immature oocysts

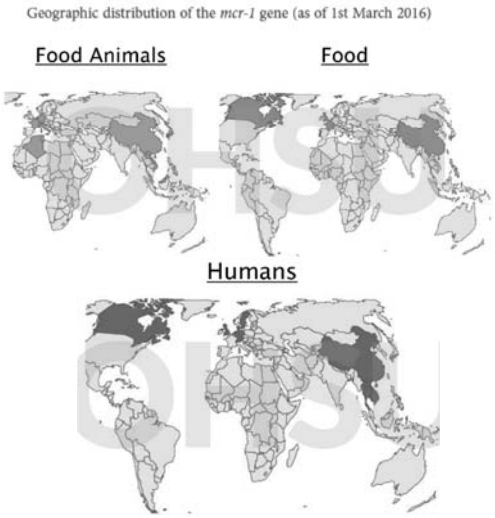
Contaminated raspberries

Drug Resistance due to Misuse in Agriculture and Farming

- Immediate cause
  - Antibiotics are used as growth promoters
  - Example: chickens and pigs fed avoparcin
- Underlying cause
  - "Economic necessity" .... Greed?
- In Denmark (1994), 24 kg of vancomycin used for humans versus 24,000 kg avoparcin
  - About this time, VRE that had first appeared in animals was transferred to humans

Size of Animal Herds and Flocks

- Poultry flocks of 75,000 birds
  - ~8,600,000,000 chickens
  - 290,000,000 turkeys/year
  - 84,400,000,000 eggs/year (2000)
- Beef cattle feedlots of 125,000 animals
  - 36,200,000 animals/year (2000)
- Swine farms of 4,800 sows
  - 98,000,000 animals/year (2000)



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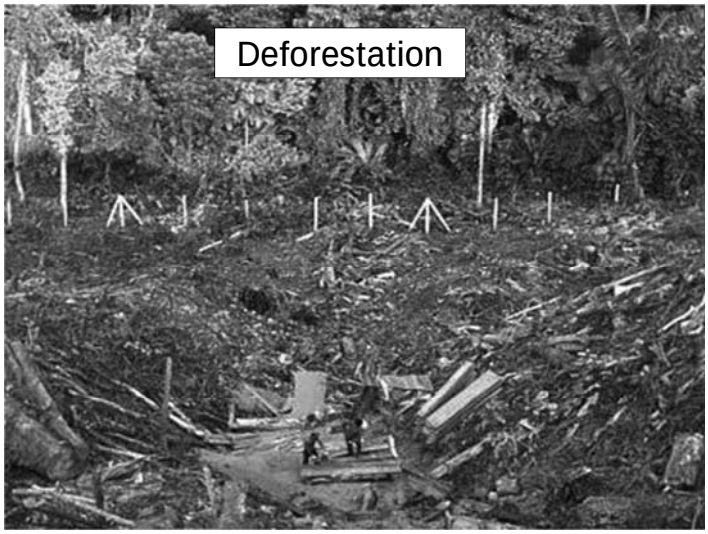

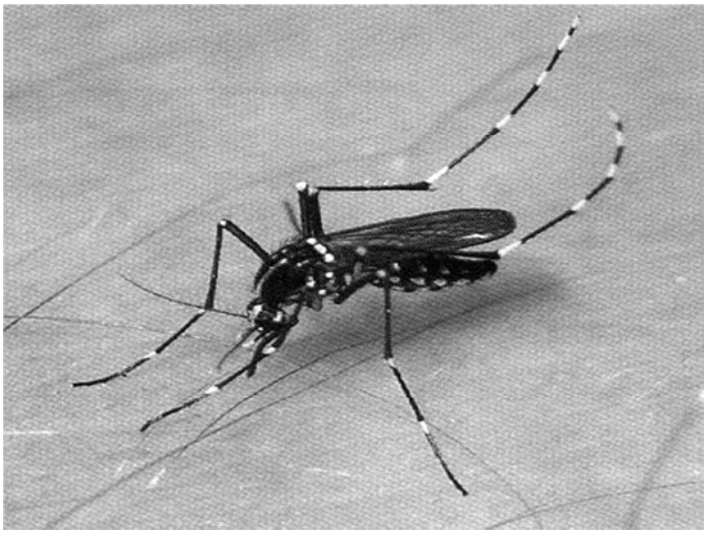

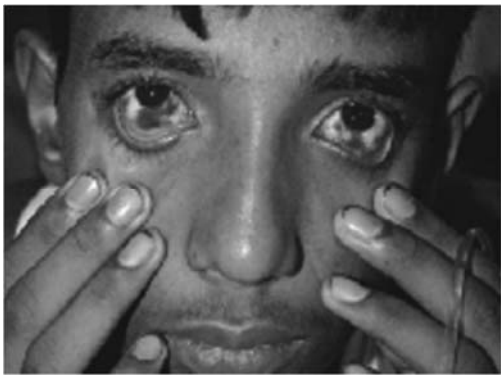

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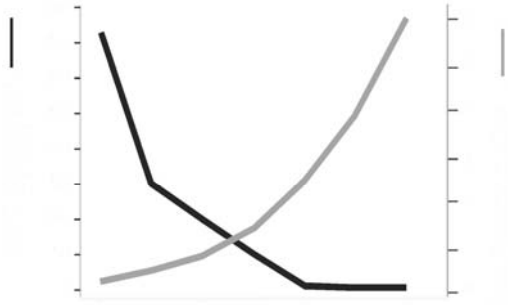
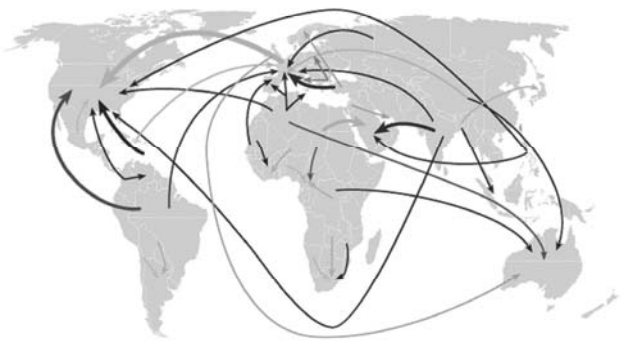
International Travel and Infectious Diseases

Speed of Global Travel in Relation to World Population Growth



Major Migration Flows: 1960-75



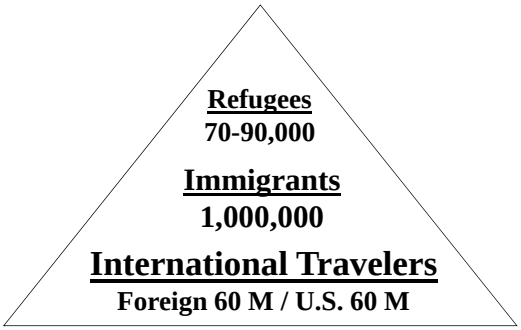
Source: Population Action International 1994

Major Migration Flows: 1990s

4 x increase in volume as compared to 1960-75

Source: Population Action International 1994

Estimated Annual International Arrivals in the United States



U.S.-Mexico Border Crossings 400M?

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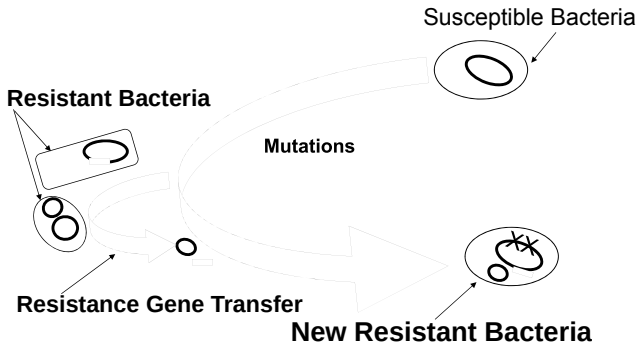
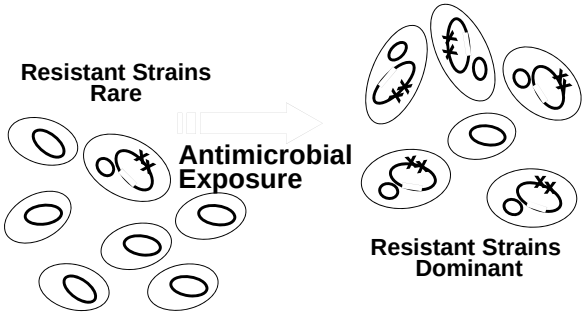
Emergence of Antimicrobial Resistance



Selection for Strains that are Resistant to Antimicrobials



Pan-resistant New Delhi Metallo-Beta-Lactamase *K. pneumoniae*

- 70 year old woman who lives in Reno
- Travelled to India and broke her hip
- Drainage from hip started 7 days later
- Organism resistant to everything:
  - ampicillin-sulbactam, ciprofloxacin, tigecyline, ceftazidime-avibactam, gentamicin, amikacin, piperacillin-tazobactam, ceftriaxone, colistin, meropenem and ceftolazone-tazobactam

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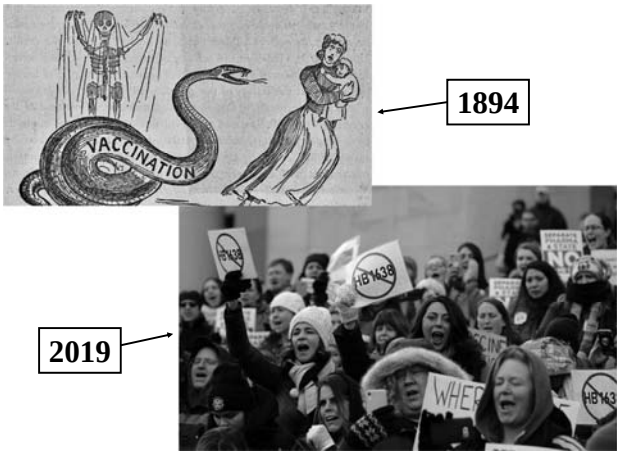
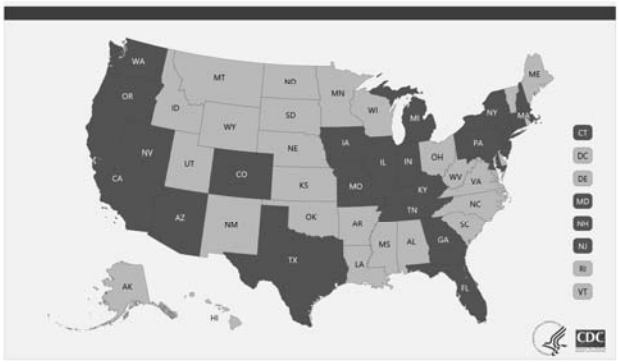
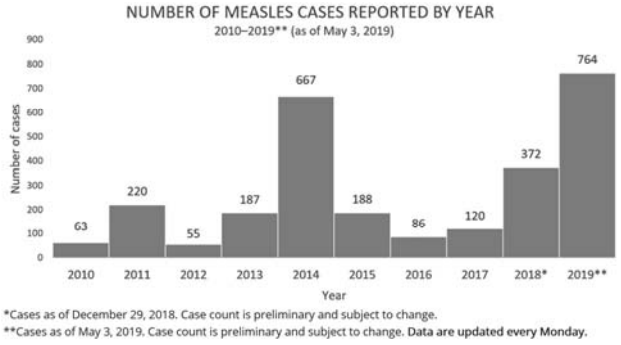




https://www.cdc.gov/measles/cases-outbreaks.html



https://www.cdc.gov/measles/cases-outbreaks.html

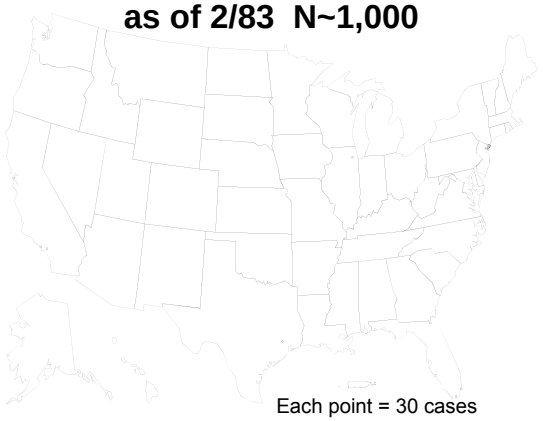
Categories of Emerging Diseases

- New Agents
- Antimicrobial Drug-Resistant Agents
- Resurgent Agents

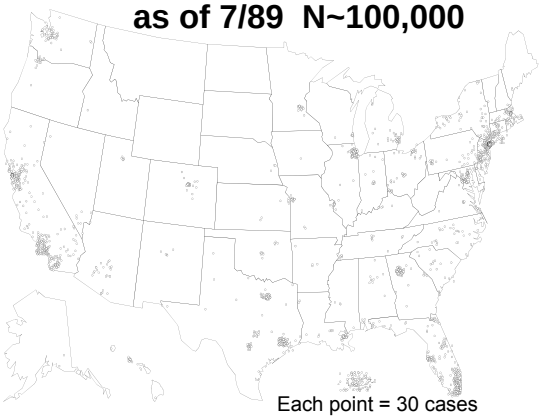
New Agents

- Does not usually mean a totally new genome has emerged "de novo"
- More often a "new" agent is an old foe that has either:
  - acquired some new virulence factor, or
  - expanded its geographic range, or
  - expanded its host species range
- Examples: HIV (geographic range & host species), *El Tor* Cholera and West Nile virus (both geographic range)

Cumulative U.S. AIDS Cases as of 2/83 N~1,000



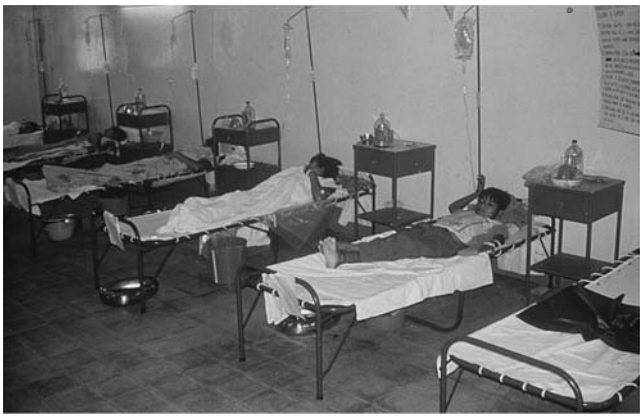
Cumulative U.S. AIDS Cases as of 7/89 N~100,000

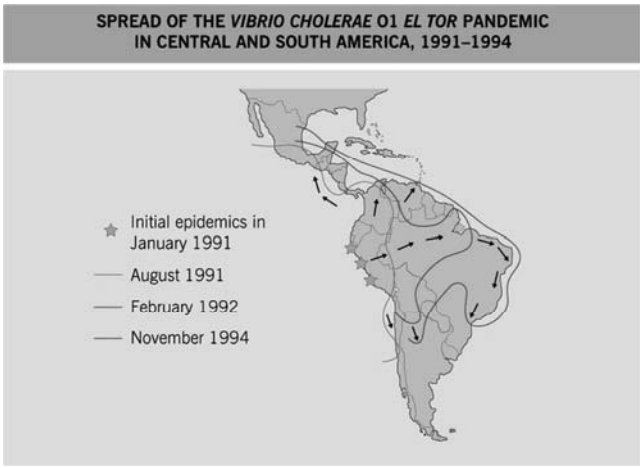


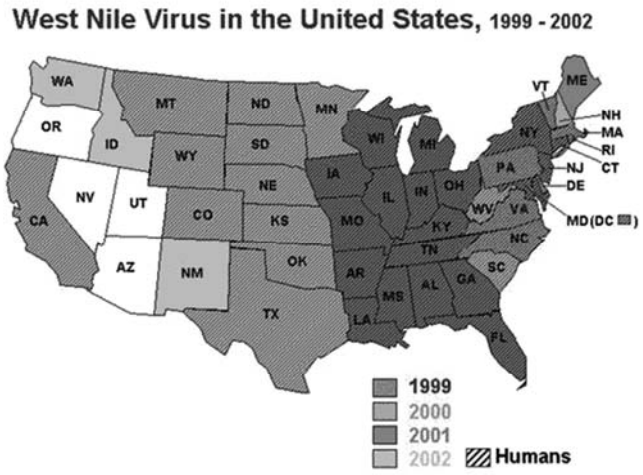
Each point = 30 cases

Dehydration from Cholera

Cholera Cots in Peru







Antimicrobial Drug-Resistant Agents

- Agent is familiar, but drug resistance creates a whole new set of problems
- Note that the incidence may not change, but containment of the agent is often dramatically affected
- Examples: VRE, CA-MRSA, CRE and MDR-TB

Clinical and Economic Outcomes of *S. Aureus* Surgical Site Infection

	MSSA SSI	MRSA SSI	Uninfected Control
No. patients	165	121	193
Mean age (yrs)	55.1	63.9	57.3
Diabetes %	34.6	48.8	34.2
Renal disease %	7.9	15.7	4.7
Hospitalization before infection (D)	5	8	----
Mortality in 90 D (%)	11 (6.7)	25 (20.7)	4 (2.1%)
Hospital days after surgery (median)	14	23	5
Hospital charges (mean)	$73,165	$118,415	$34,395

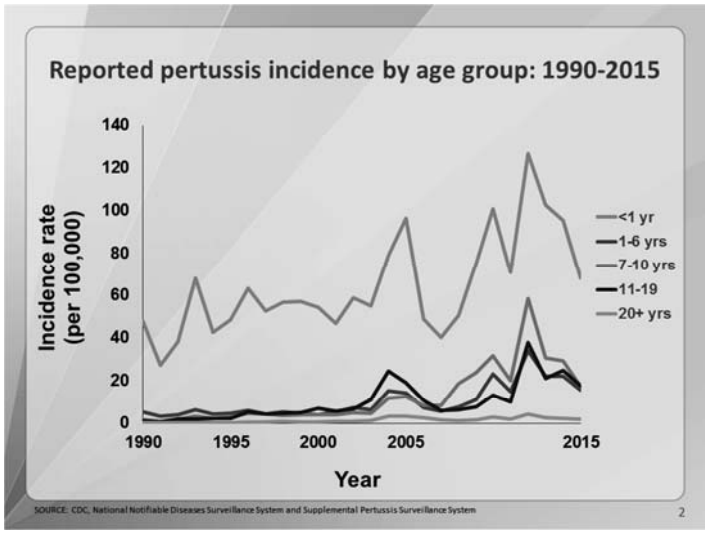
[Engemann, et al., CID 2003; 36:592]

Resurgent Agents

1. Established human disease agents
2. Agents not previously recognized as human disease agents

1. Established Human Disease Agents

- Usually spotted by clinical signs and symptoms, followed by microbiologic or serologic evidence
- Sometimes expected: diphtheria after vaccination program is disrupted
- Sometimes unexpected: *Bordatella pertussis* in adults



2. Agents Not Previously Recognized as Causes of Human Disease

a. Agents that are difficult to culture, stain, and/or identify serologically
b. Agents that were simply not suspected and so not sought

Agents That Are Difficult to Culture, Stain and/or Identify Serologically

- Campylobacter
  - Obligate microaerophile easily overgrown by normal flora... emerged in 1970's and now is the #1 cause of bacterial diarrhea
- Cyclospora
  - Protozoan emerged in 1996-97 and is hard to stain and can't be cultured
- *Legionella pneumophila*
  - Cause of 1976 pneumonia outbreak is difficult to stain and grow

Agents That Were Simply Not Suspected and so Not Sought

- *Helicobacter pylori*
  - No one suspected it to cause GI ulcers
- *Giardia lamblia*
  - Took 300 years from discovery of organism to recognize it as a significant pathogen
- *Cryptosporidium parvum*
  - First recognized in 1907; linked with diarrhea in turkeys in 1955; human diarrhea only in 1976

Underlying Causes of Pathogen Emergence

- New agents
  - Due to microbial genetic evolution
- Antimicrobial drug-resistant agents
  - Due to antimicrobial misuse
  - Due to genetic recombination
- Resurgent agents
  - Largest category of emerging diseases
  - Generally related to economic conditions

New Agents due to Microbial Genetic Evolution

Immediate Cause	Example	Underlying Cause
Species jumping (followed by modification)	*M. bovis* (cattle) → *M. tuberculosis* (human)	Cattle domestication
Species jumping (followed by modification)	Measles (human) → distemper (dogs)	Dog domestication
Genetic mixing (recombination)	SIV + ? human retrovirus ? → HIV	Increased human population, land encroachment

Drug Resistance due to Human Misuse

Immediate Cause	Example	Underlying Cause
Over-prescribing	MRSA	Fear of infection, ignorance
Over-prescribing	*H. influenzae*	Convenience (working parents)
Under-prescribing (single drug Rx)	MDR-TB	Poverty/ignorance
Non-adherence (unsupervised Rx)	MDR-TB	Ignorance/fear

Drug Resistance due to Misuse in Veterinary Medical Practice

- Same problem seen in human medicine
- Economic factors
  - High cost of cultures often preclude use, thus forcing empiric drug therapy
  - High cost of certain drugs reduces their appropriate use (so older and cheaper drugs are sometimes used when they perhaps should not be used)

Drug Resistance due to Genetic Recombination in Dual Infection

- Recombination of two strains of HIV infecting the same person may result in the formation of new strains that exhibit high level and multi-drug resistance
- This is the only factor that is due to microbial function rather than human miscalculation

Economic Conditions That Cause Agents to Resurge

	Population Movement	Food Habits	Housing	Plumbing & Sanitation
Poverty	Refugeeism (impetigo)	Malnutrition (cholera)	Rodents in house (hantavirus)	No indoor plumbing (shigellosis)
Affluence	Exotic travel (malaria)	Imported foods out-of-season (cyclospora)	"Cabin in the woods" (Lyme disease)	Showers and drinking fountains (legionellosis)

"…complacency towards infectious diseases has weakened the ability of our public health infrastructure to either prevent or control microbial diseases."

ASM New and Reemerging Infectious Diseases, 1997

Prevention of Emerging Infectious Diseases Will Require Action in Each of These Areas

- Surveillance and Response
- Applied Research
- Infrastructure and Training
- Prevention and Control

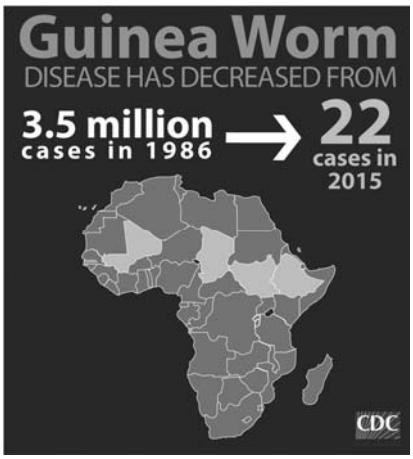
"… we must renew our commitment to the prevention and control of infectious diseases, recognizing that the competition between humans and microbes will continue long past our lifetimes and those of our children."

Jeffrey P. Koplan, Former Director, CDC

Thanks to the global eradication program, GWD now found only in four countries: Chad, Mali, Ethiopia and South Sudan.

GWD is poised to be the first disease to be eradicated using core public health practices and without vaccines or medication:
- **Surveillance,**
- **Case containment**
- **Simple interventions**

Many believe that the symbol of medicine, the Staff of Asclepius, may actually represent a Guinea worm. In the future, medicine's very symbol will have a new significance!

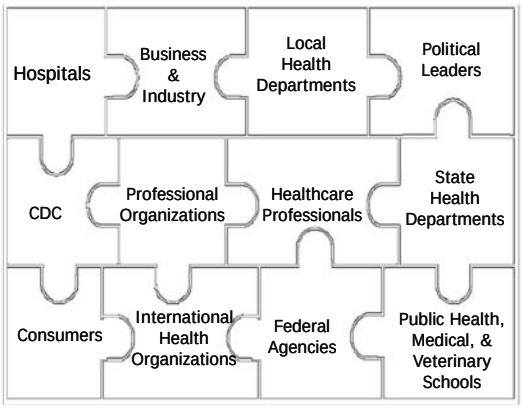


https://www.cdc.gov/parasites/guineaworm/gwep.html

Infectious Disease Information

https://www.cdc.gov/ncezid/index.html

Prevention Partners



CDC Emerging Infections
Priority Issues

- Bioterrorism
- Antimicrobial resistance
- Food and water safety
- Vectors and animal health
- Blood safety
- Infections that cause chronic diseases
- Opportunistic infections
- Maternal and child health
- Health of travelers and refugees
- Vaccines

"Pathogenic microbes can be resilient, dangerous foes. Although it is impossible to predict their individual emergence in time and place, we can be confident that new microbial diseases will emerge."

Institute of Medicine Report, 1992

Conclusions

- Be alert for unusual infections in your area and ask/tell others about them
- Think globally, act locally
  - Promote hand hygiene
  - Preferentially eat locally produced food
  - Keep immunizations up to date
  - Use antibiotics wisely
  - Counsel and advise each other

"Pitted against microbial genes, we have mainly our wits."

Joshua Lederberg
Nobel Laureate

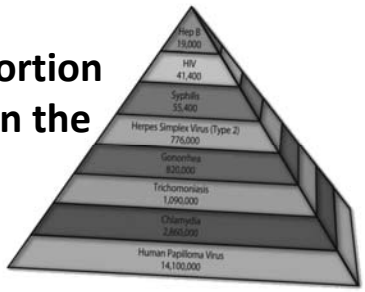
Thank you!!

OHSU

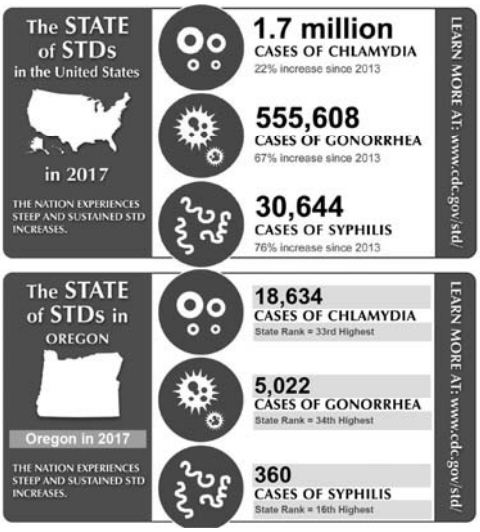
Update on Syphilis

George C. Mejicano, MD, MS, FACP
Professor of Medicine
Oregon Health & Science University

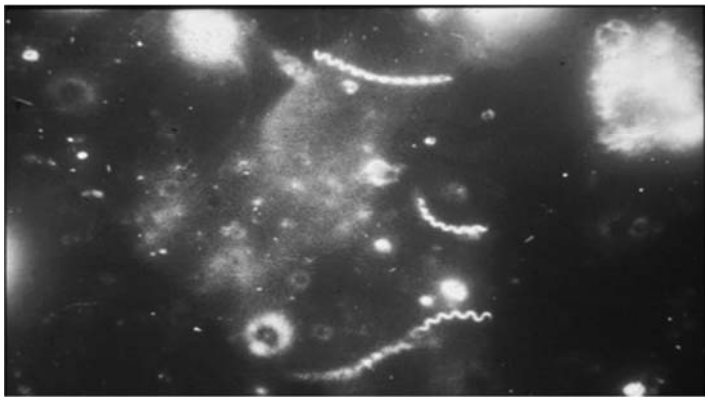
Relative Proportion of STD Rates in the United States



https://sexualhealthinyoungpeople1.weebly.com/prevalence-and-incidence.html



CDC

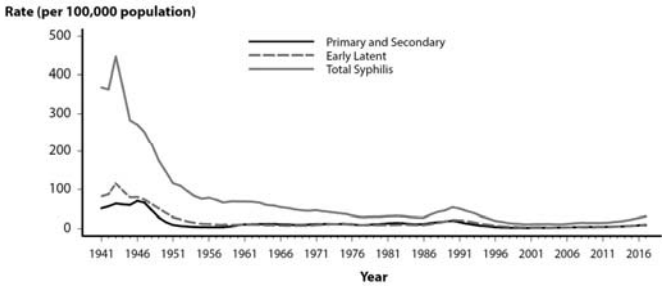


Syphilis: *Treponema pallidum*

- Rates have been increasing since 2001
- 30,644 cases reported in 2017 (10.5% increase)
- Can diagnose by sending ulcer scraping for direct fluorescent antibody (DFA)
- Screen with non-treponemal tests
  - RPR or VDRL titer used to follow response to therapy
- Confirm diagnosis with treponemal test
  - FTA-Abs and TPPA are typically positive for life

Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance, 2017. Atlanta, GA: U.S. Department of Health and Human Services; 2018.*

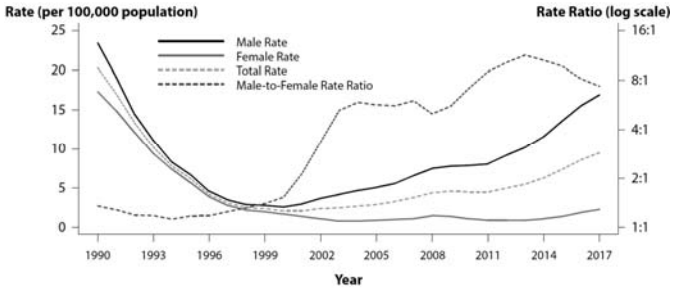
Syphilis — Rates of Reported Cases by Stage of Infection, United States, 1941–2017



NOTE: Data collection for syphilis began in 1941; however, syphilis became nationally notifiable in 1944. Refer to the National Notifiable Disease Surveillance System (NNDSS) website for more information: https://wwwn.cdc.gov/nndss/conditions/syphilis/.

CDC

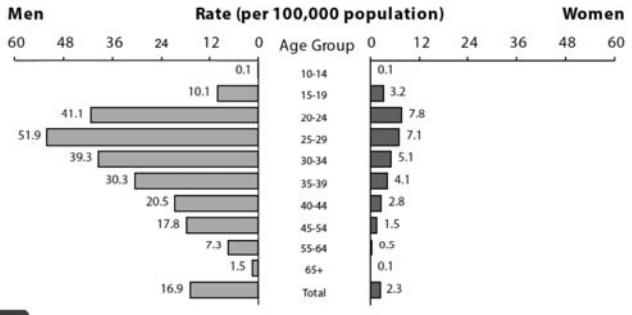
Primary and Secondary Syphilis — Rates of Reported Cases by Sex and Male-to-Female Rate Ratios, United States, 1990–2017



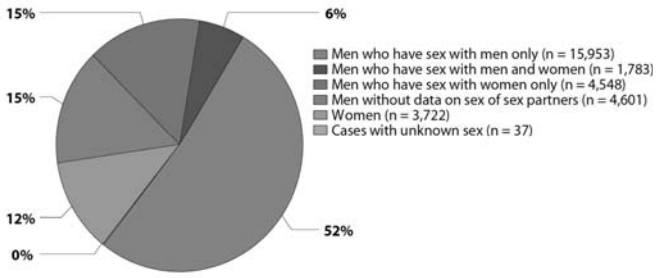
Primary and Secondary Syphilis — Rates of Reported Cases by County, United States, 2017

* In 2017, 1,562 (49.7%) of 3,140 counties in the United States reported no cases of primary and secondary syphilis. Refer to the NCHHSTP AtlasPlus for further county-level rate information: https://www.cdc.gov/nchhstp/atlas/

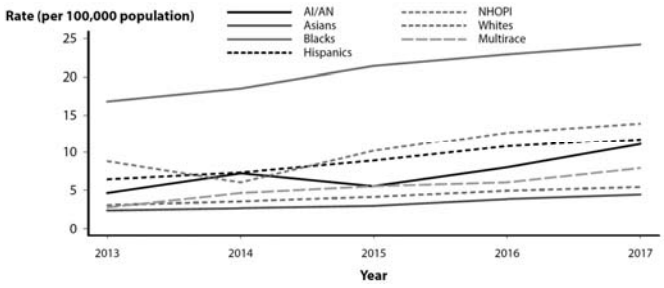
Primary and Secondary Syphilis — Rates of Reported Cases by Age Group and Sex, United States, 2017



Primary and Secondary Syphilis — Distribution of Cases by Sex and Sexual Behavior, United States, 2017

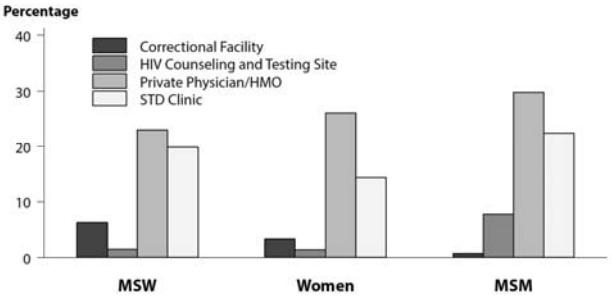


Primary and Secondary Syphilis — Rates of Reported Cases by Race and Hispanic Ethnicity, United States, 2013–2017



NOTE: Not all US jurisdictions reported cases in OMB-compliant Race categories in 2017. This may minimally under- or overestimate rates for Asians, NHOPI, or Multirace individuals. For completeness, data in this figure include cases reported from all jurisdictions. See Section A1.5 in the Appendix for information on reporting STD case data for race and Hispanic ethnicity.
ACRONYMS: AI/AN = American Indians/Alaska Natives; NHOPI = Native Hawaiians/Other Pacific Islanders; OMB = Office of Management and Budget.

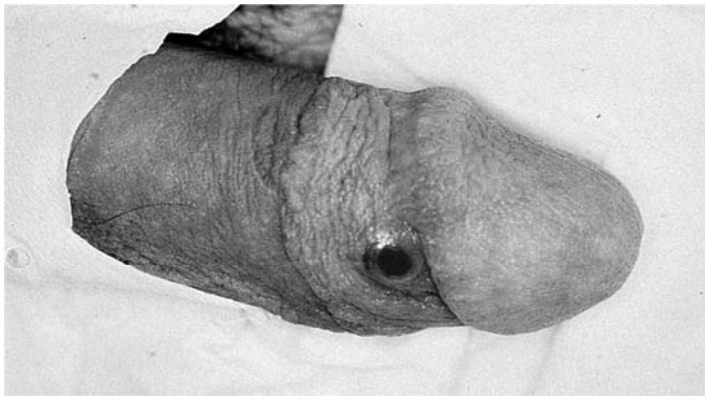
Primary and Secondary Syphilis — Percentage of Reported Cases* by Sex, Sexual Behavior, and Selected Reporting Sources, United States, 2017

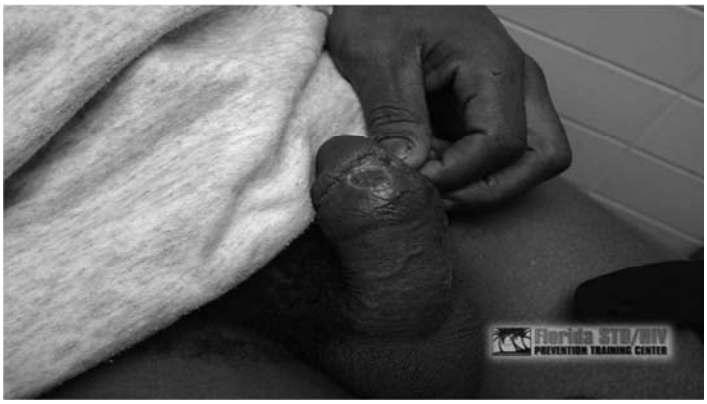


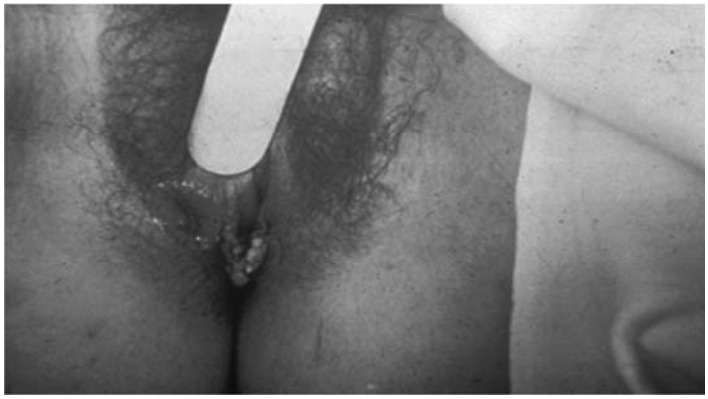
* Of all primary and secondary cases, 11.4% had a missing or unknown reporting source. Among all cases with a known reporting source, the reporting source categories presented represent 56.4% of cases; 43.6% were reported from sources other than those shown.
ACRONYMS: HMO = health maintenance organization; MSM = Gay, bisexual, and other men who have sex with men (collectively referred to as MSM); MSW = Men who have sex with women only.

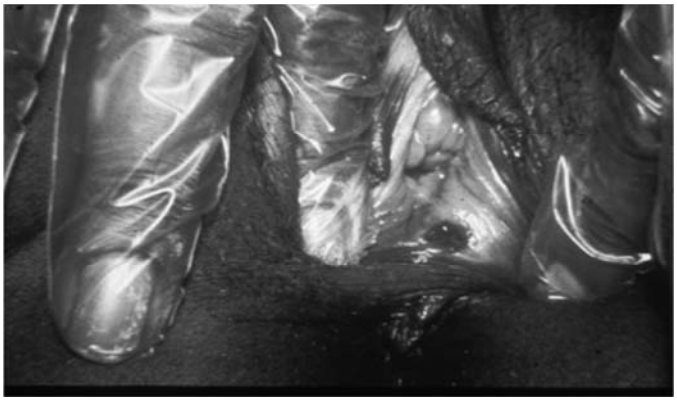
Syphilis: *Treponema pallidum*

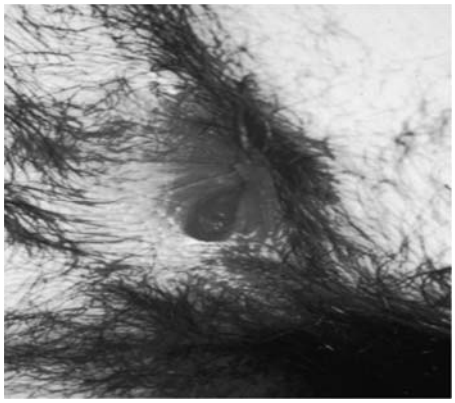
- **Primary syphilis**: painless, solitary chancre occurs 10-90 days after infection & heals within 6 weeks
- **Secondary syphilis**: 2 - 8 weeks after chancre heals
  - Infectious skin lesions are maculo-papular; hands and soles
  - May have fever, malaise, pharyngitis, wt loss, & nodes
- **Latent syphilis**: asymptomatic
  - Early latent: infected < 1 year, infectious
  - Late latent: infected > 1 year, non-infectious
- **Tertiary Syphilis**: aortitis, vasculitis, gumma, etc.
- **Neurosyphilis**: dementia, tabes dorsalis, etc.

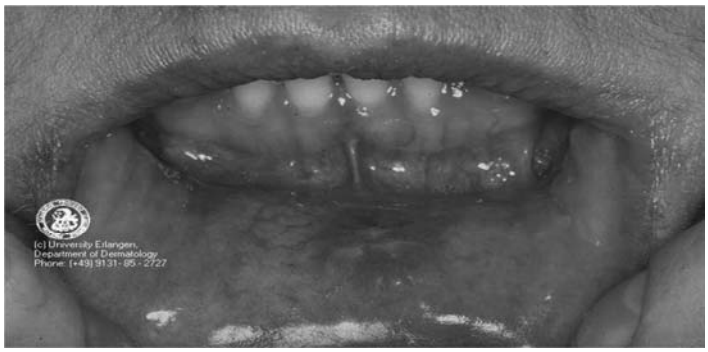


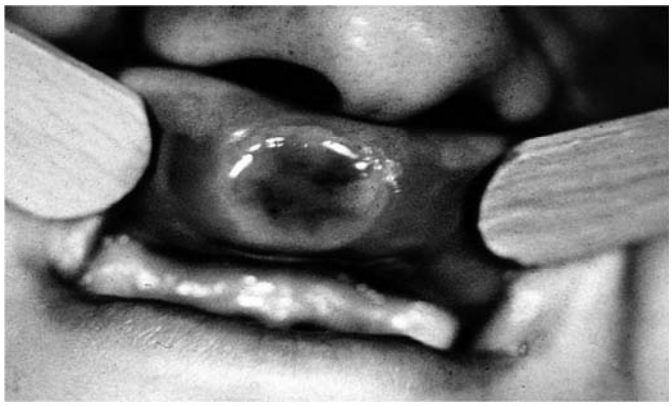


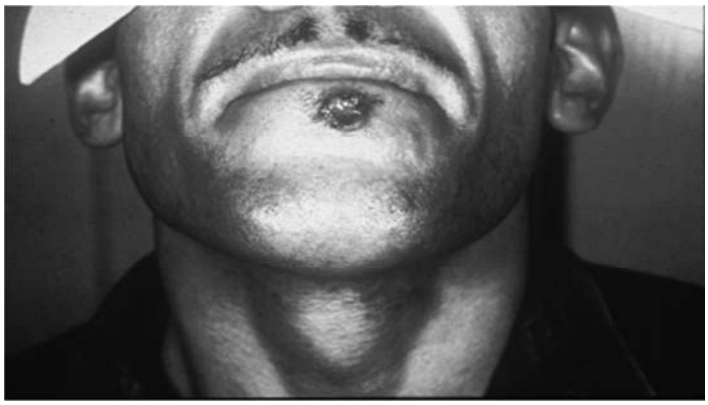


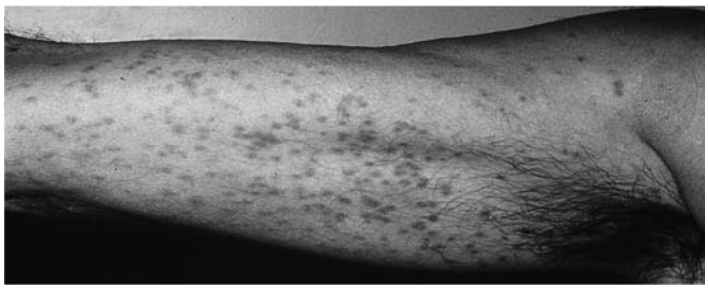


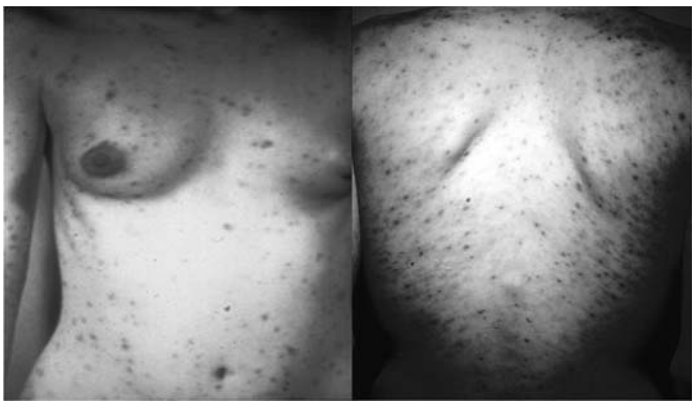


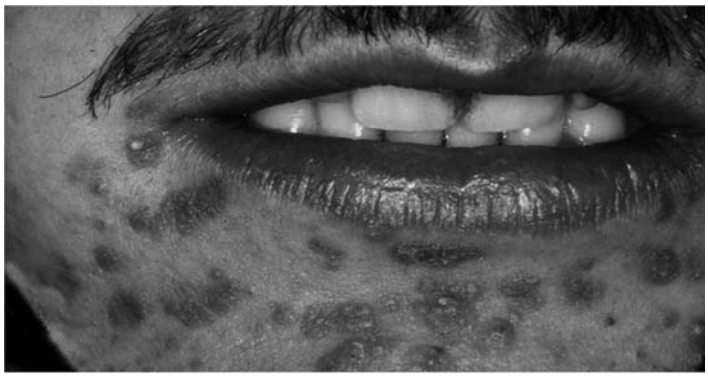

(c) University Erlangen,
Department of Dermatology
Phone: (+49) 9131 - 85 - 2727

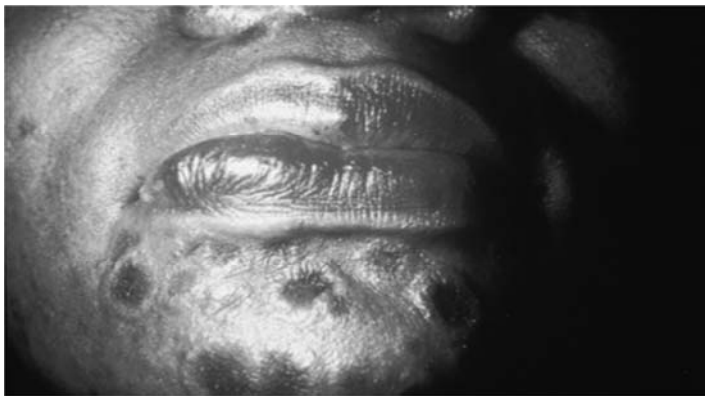


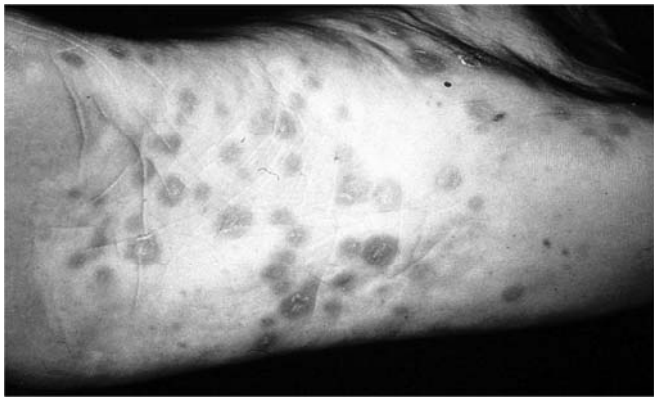


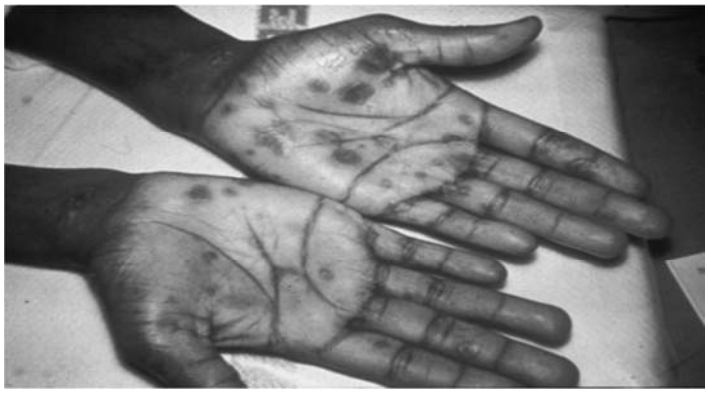


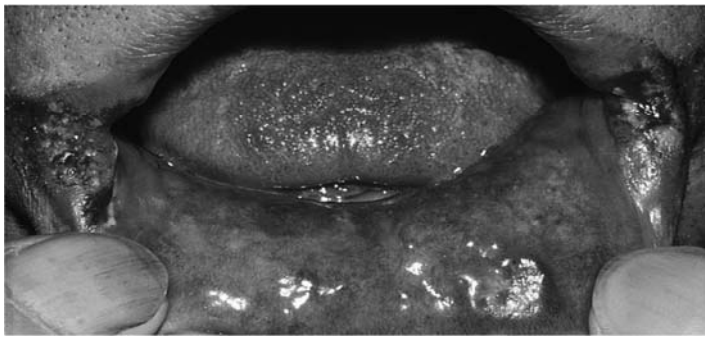


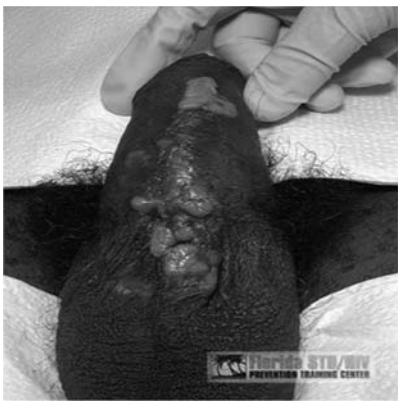


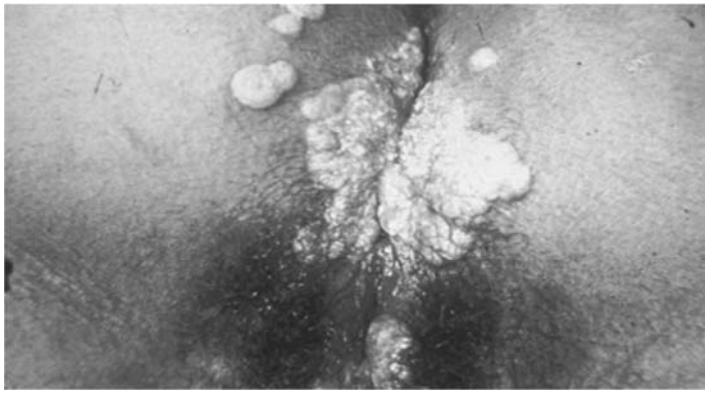


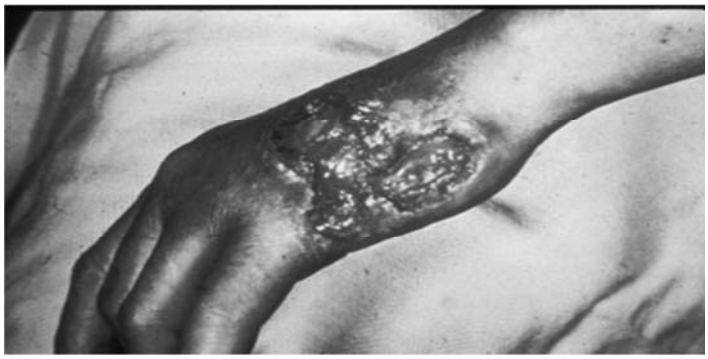







Florida STD/HIV
PREVENTION TRAINING CENTER





Syphilis: *Treponema pallidum*

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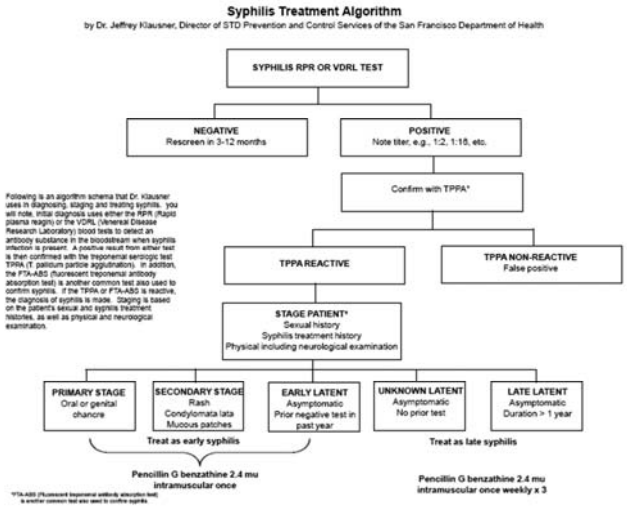
  - may have fever, malaise, pharyngitis, wt loss, & nodes
- **Latent syphilis**: asymptomatic
  - Early latent: infected < 1 year, infectious
  - Late latent: infected > 1 year, non-infectious
- **Tertiary Syphilis**: aortitis, vasculitis, gumma, etc.

Treatment of Syphilis

- Primary, Secondary or Early Latent Syphilis
  - Benzathine penicillin G 2.4 million units IM x one
  - If penicillin allergic, doxycycline 100 mg po bid x 14 d
- Late Latent Syphilis (or of unknown duration)
  - Benzathine penicillin G 2.4 million units IM q week x three (total of 7.2 million units)
- Evaluate clinically & serologically at 6 and 12 months
  - If Rx failure, check HIV test, perform LP, & retreat
- Neurosyphilis requires IV penicillin for 10-14 days



Thank you!!

Ten Cases of Fever – Ten Lessons Learned

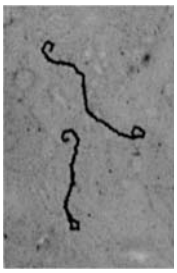
George C. Mejicano, MD, MS, FACP
Professor of Medicine
Oregon Health & Science University

Case One:

A 32 year old woman presents in July with fever, severe headache, muscle aches, conjunctivitis and nausea. No one she knows has similar symptoms. Ten days before symptom onset, she did kayak drills in a road side pond.

Leptospirosis

- *Leptospira interrogans*
  - Spirochete with over 200 serovars
- Animal reservoirs
  - Persistent infection in renal tubules
  - Prolonged excretion in the urine
  - Water contamination
  - Rats, but in the United States dogs and livestock (cattle, horses and pigs) cause more disease



Risk Factors for Leptospirosis

- Occupational Groups
  - Farmers & ranchers
  - Abattoir workers
  - Trappers
  - Veterinarians
  - Loggers
  - Sewer workers
  - Rice field workers
  - Military personnel
- Recreational Activities
  - Freshwater swimming
  - Canoeing & kayaking
  - Trail biking
  - Hunting
- Household Environment
  - Pet dogs
  - Domestic livestock
  - Rainwater catchment
  - Rodent infestation

Clinical Disease in Humans

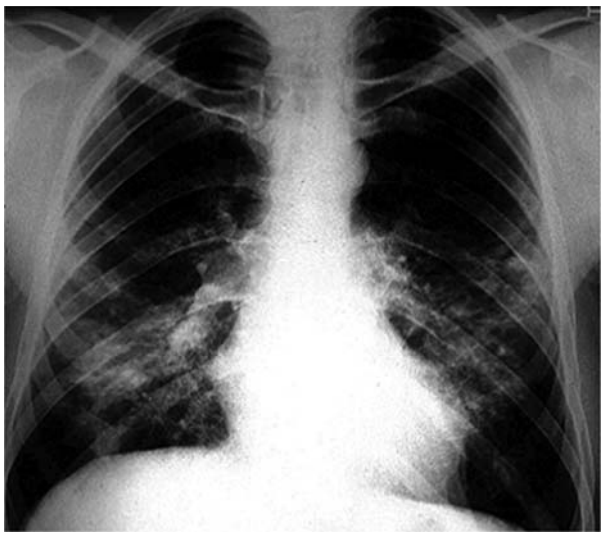
- Wide spectrum of manifestations: from subclinical to death
- Incubation period ranges from 2-20 days
- Two recognizable syndromes, each with 2 classic phases (biphasic febrile illness)
  - Icteric form (Weil Syndrome)
  - Influenza-like illness (90% of cases)

Treatment and Prevention

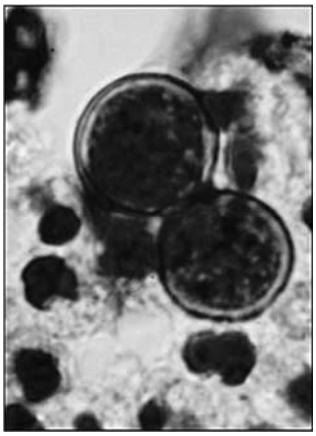
- Treatment
  - Doxycycline 100 mg BID x 7 days
  - Amoxicillin 500 mg po QID x 7days
- Prevention
  - Vaccination of domestic livestock & pet dogs
    - Animals may still excrete live organisms in urine
  - Oral doxycycline 200 mg weekly
  - Protective clothing for occupations at risk
  - Rodent control measures
  - Avoid swimming in freshwater bodies of water

Case Two:

A 44 year old man presents with both fever and shortness of breath. He has had a dry cough for two months. He has lost 15 pounds and feels week. He is an avid sportsman and likes to camp in Northern Wisconsin. His dog died a few weeks ago. His CXR shows:



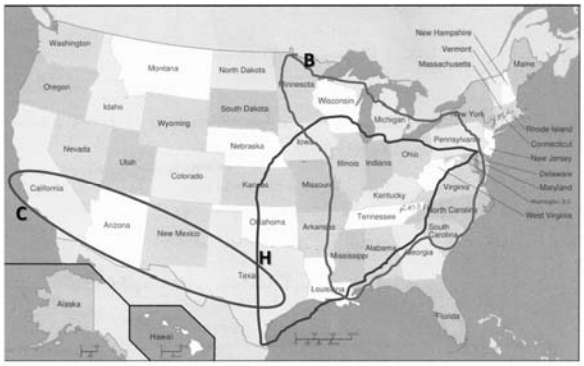
Blastomyces dermatitidis



Blastomycosis

- Presentation can mimic TB and cancer
- Organism readily isolated
  - 86% of sputum; 100% of bronchial washings
- Urinary antigen assay
  - Shows cross-reactivity with other fungi, particularly *Histoplasma capsulatum*
  - Role in diagnosis has not been established

[Clinical Infect Diseases 2008; 46: 1801-1812.]



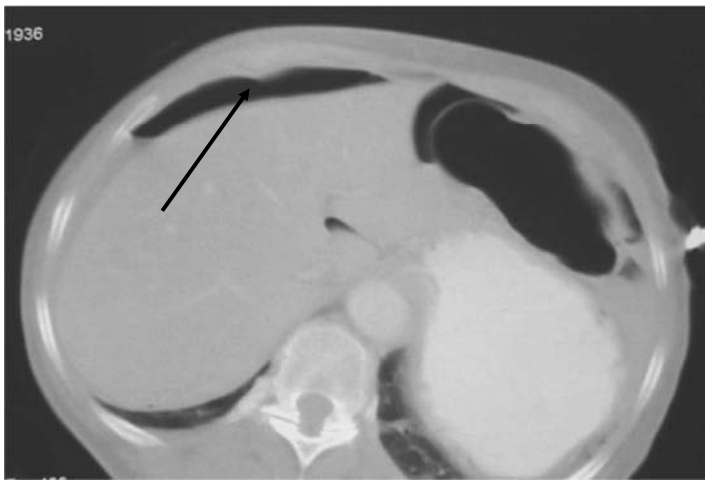
http://countdown2ck.blogspot.com/2012/05/histo-blasto-coccidiomycosis.html

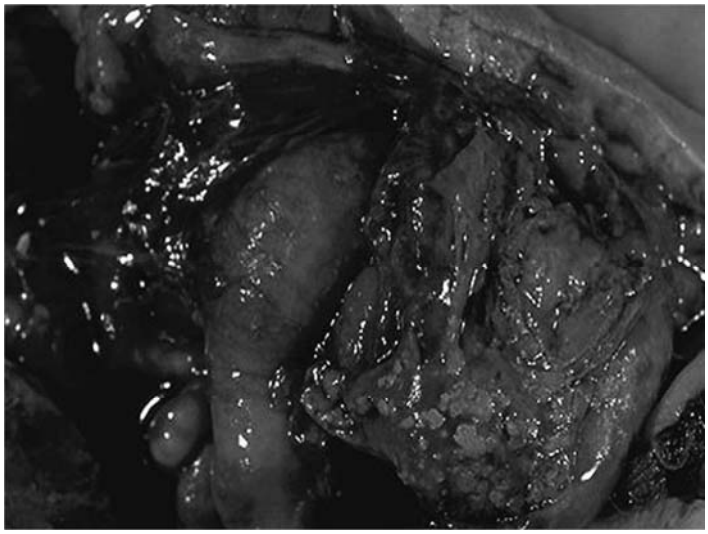
Case Three:

A 53 year old man presents to the emergency department with a 5 day history of sharp left lower quadrant pain and constipation. One day prior to presentation, he developed fevers and chills. CT imaging reveals a large bowel obstruction and diverticulitis. He is admitted for bowel rest and started on IV antibiotics (ciprofloxacin and metronidazole).

Clinical Course

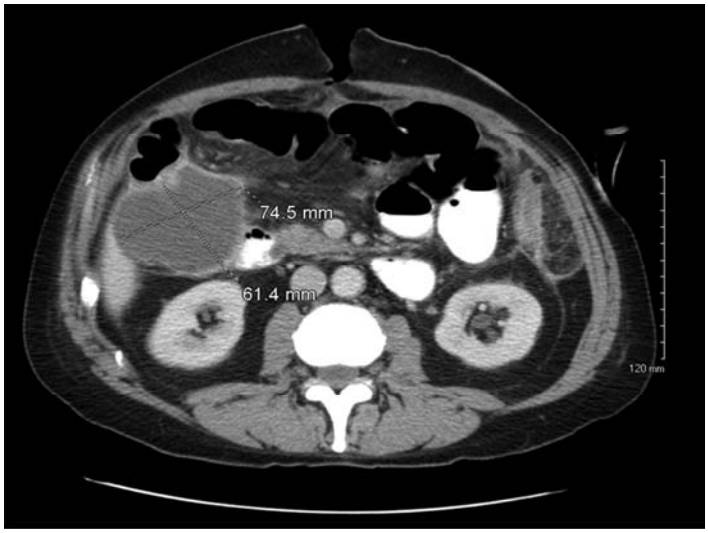
- Overnight, the abdominal pain acutely worsens and he develops peritoneal signs
- Repeat CT scan → free air in the abdomen with signs of a bowel perforation
- Taken to the operating room for emergent exploratory laparotomy
  - Cecal and sigmoid diverticuli with perforations
  - Right hemicolectomy, sigmoidectomy, end ileostomy with a Hartmann's pouch





Case Three Continues…

- Antibiotic treatment continued in the post-operative period with both ciprofloxacin and metronidazole
- Despite source control, the patient remained febrile with WBC ~16K for four days
- No localizing symptoms
- Surgical wound clean and abdominal examination is benign



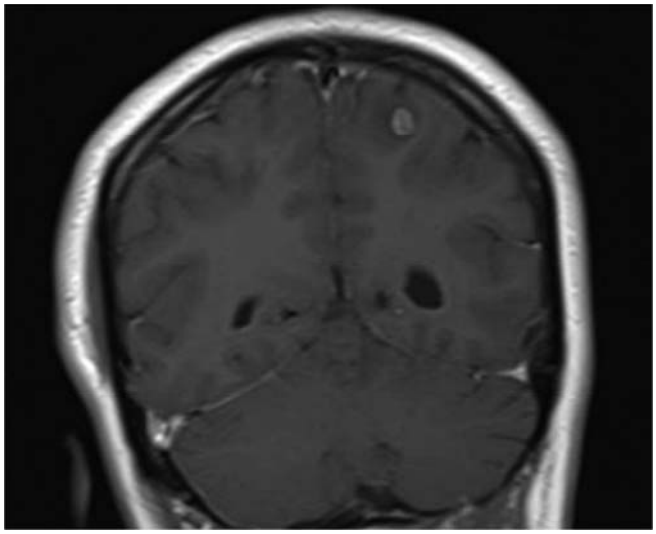
Suspected Treatment Failure

- Persistent or recurrent clinical evidence of intra-abdominal infection after 4-7 days of therapy → re-image the abdomen & pelvis
- For patients who do not respond and the focus of infection remains
  - Need repeat cultures (aerobic and anaerobic)
  - Inoculation of anaerobic blood culture bottle may improve yield

[Clinical Infectious Diseases 2010; 50:133–64]

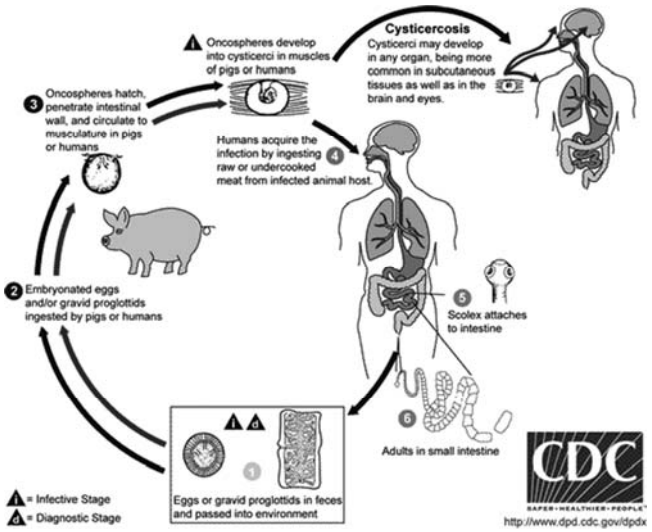
Case Four:

A 41 year old immigrant from Peru presents with new onset of tonic-clonic seizures. She denies any other medical problems and was on no medications prior to presentation. She denies headache, motor weakness, weight loss, GI symptoms or HIV risk factors. She has had subjective fevers. A head CT reveals:



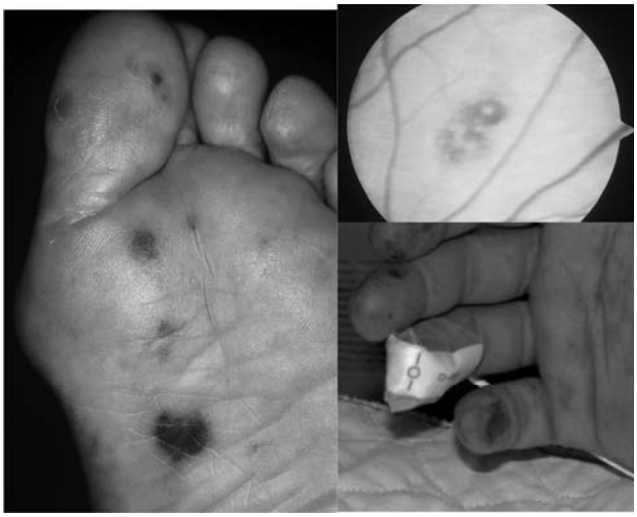
Cysticercosis

- Caused by the larval form of the pork tapeworm: *Teania soleum*
- Adult worm found in human GI tract and passes thousands of eggs daily
- Pigs or humans eat food contaminated with human waste and ingest the eggs
- Larva from eggs make their way via the bloodstream to distant sites & form cysts
- Humans eat undercooked pork and ingest encysted larva (which mature into adults)



Case Five:

A 54 year old homeless man develops severe fatigue over a three month period. He then develops shortness of breath and painful spots on her hands and feet. He seeks medical attention in your urgent care. The exam reveals a loud murmur and an echo reveals vegetations on the mitral valve. Off antibiotics, all blood cultures are negative.



Changing Microbiology of IE

- *Staphylococcus aureus* now the most common cause worldwide, 31% of patients
- Other Gram positive organisms important
  - Viridans streptococcus, coagulase-negative staphylococcus and *Enterococcus* species
- 10% → culture negative endocarditis
- Fastidious organisms
  - HACEK 2% (0.3% in North America)
    - *Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella* and *Kingella* species
  - Fungi and yeast 2%

[Arch Intern Medicine 2009;169]

Most Common Identified Causes of Culture Negative Endocarditis

Coxiella burnetii	3-48%
Bartonella species	10-28%
Staphylococcus species	2-11%
Streptococcus species	1-6%
HACEK	0.5-3%
Fungi	1-6%
Candida, Aspergillus, Cryptococcus, endemic fungi, others	
Tropheryma whipplei	0.3-3%
Others: *Legionella, Chlamydia* and *Brucella*	

[Clinical Infect Diseases 2010;96]

Bartonella species

- Endocarditis linked to *B. henselae* as well as *B. quintana*
- Both species globally endemic
- *B. henselae* transmission via cats
  - Etiology of cat scratch disease
- *B. quintana* causes trench fever
  - Vector is the human body louse

Bartonella Endocarditis

- *B. quintana* associated with alcohol dependence and homelessness
- Significant proportion are afebrile but have advanced valvular disease as well as embolic phenomenon
- Diagnosed with culture; serologic assay IgG > 1:800; PCR testing; or histology and immunohistochemistry of valve

[Arch Int Med. 2003;163]

Five Lessons Learned So Far

Case	Lesson
Leptospirosis	People do strange things
Blastomycosis	History really does matter
Intra-abdominal Abscess	If they're not getting better, keep looking for an answer
Neurocysticercosis	Think about infections even when they are not likely
Bartonella Endocarditis	Unusual bugs may cause common/typical diseases

Case Six:

A 27 year old public health nurse was referred to the outpatient infectious disease clinic because of a four week history of malaise, fatigue and daily fevers. Except for a broken ankle, her past medical history was unremarkable. She denied having any other symptoms.

Case Six (continued):

The workup included a normal CBC, RF, ANA, electrolytes, creatinine and UA. The ALT was 85 and AST was 91. The ESR was 48 and CRP was 3. An HIV ELISA, monospot test, and the serologic assays negative for Hepatitis A, Hepatitis B and Hepatitis C Viruses.

Case Six (continued):

A CT scan of the chest, abdomen, and pelvis showed only a simple cyst in the liver. A TTE showed no vegetations. A urine culture and three blood cultures were negative. When she came to the ID clinic, the patient appeared tired and had normal vital signs and normal exam.

Fever of Unknown Origin

- Temperature over 101° F on several occasions
- Duration is longer than 3 weeks
- Extensive work up unrevealing (one week hospital stay no longer needed)

Fever of Unknown Origin

- Infections (30-40%)
- Neoplasms (20-30%)
- Collagen vascular diseases (10-20%)
- Miscellaneous conditions
  e.g., drug fever (15-20%)
- Unknown (5-15%)

EBV Serologic Profiles

Heterophile Antibodies	VCA IgG	VCA IgM	EBNA	Interpretation
+/-	+	+	-	Acute infection
-	+	-	+	Past infection
-	-	-	-	No infection
+/-	+	-	-	Indeterminate
-	+	+	+	Indeterminate
-	-	+	-	Indeterminate

[Journal of Clinical Microbiology 2004; 42(8): 3381-3387]

Case Seven:

A 43 year old woman returns from Costa Rica to see the birds in the rain forest. She took malaria prophylaxis but did not use insect repellent because she doesn't like "chemicals" on her body. She reports pain behind her eyes, headache, myalgia, fevers and chills since returning home 3 days ago.

Dengue Distribution

http://www.healthmap.org/dengue/index.php

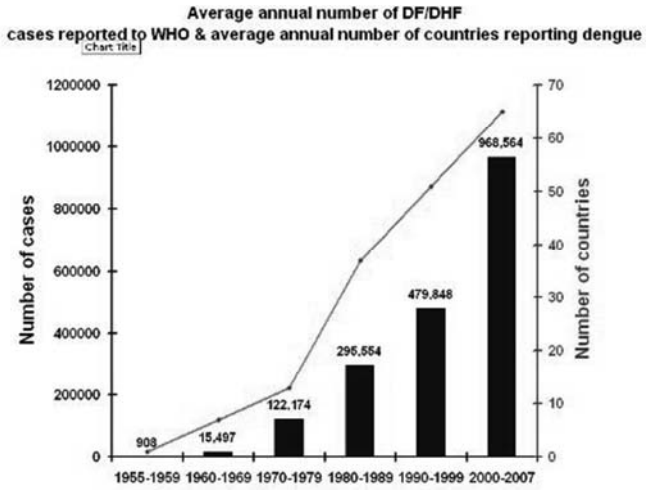


Table 5-02. Common causes of fever, by geographic area

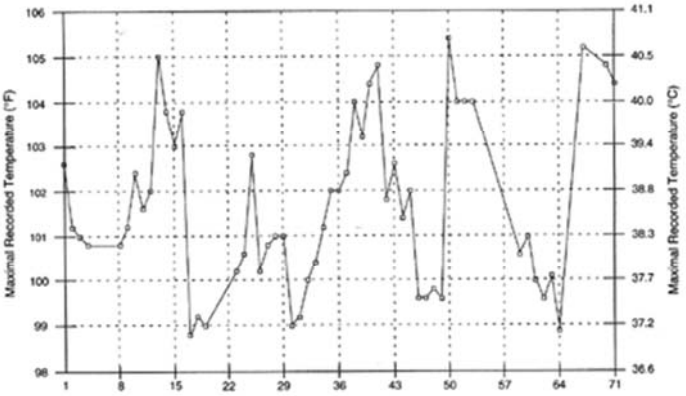
GEOGRAPHIC AREA	COMMON TROPICAL DISEASE CAUSING FEVER	OTHER INFECTIONS CAUSING OUTBREAKS OR CLUSTERS IN TRAVELERS
Caribbean	Dengue, malaria (Haiti)	Acute histoplasmosis, leptospirosis
Central America	Dengue, malaria (primarily *Plasmodium vivax*)	Leptospirosis, histoplasmosis, coccidioidomycosis
South America	Dengue, malaria (primarily *P. vivax*)	Bartonellosis, leptospirosis, histoplasmosis
South-central Asia	Dengue, enteric fever, malaria (primarily non-falciparum)	Chikungunya virus infection
Southeast Asia	Dengue, malaria (primarily non-falciparum)	Chikungunya virus infection, leptospirosis
Sub-Saharan Africa	Malaria (primarily *P. falciparum*), tickborne rickettsiae, acute schistosomiasis, filariasis	African trypanosomiasis

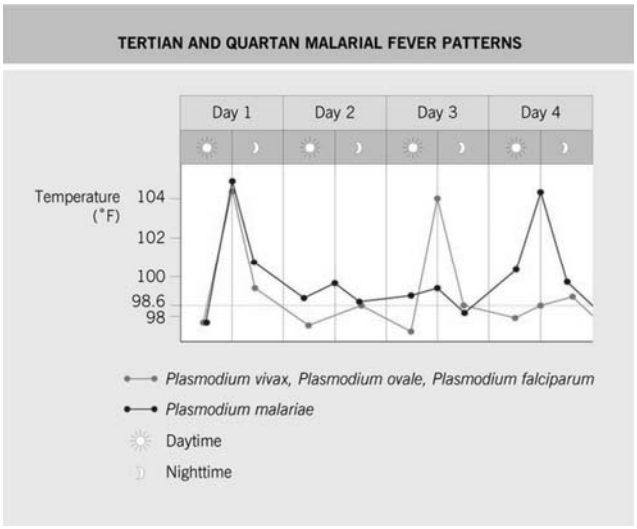
http://wwwnc.cdc.gov/travel/yellowbook/2014/chapter-5-post-travel-evaluation/fever-in-returned-travelers

Case Eight:

A 34 year old truck driver seeks medical attention because of an intermittent fever. He has lost his appetite and has lost 10 pounds. He also has fatigue. He denies cough, dyspnea, muscle aches, vomiting, diarrhea, abdominal pain or rash. The fevers wax and wane every 1-2 weeks.

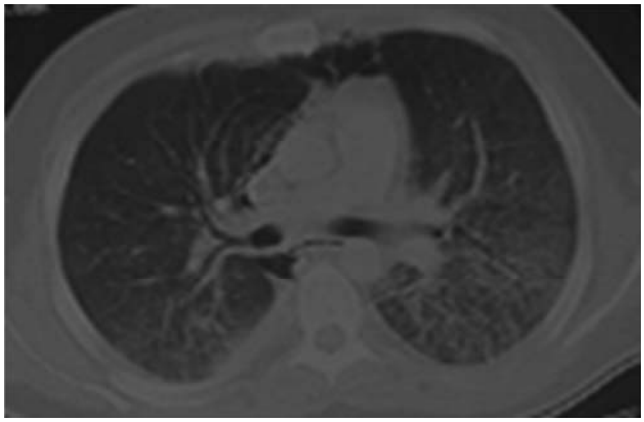
Pel Ebstein Fever





Case Nine:

A 34 year old male presents with a one week history of cough, fever and mild confusion. Exam is normal except for temperature of 104, pulse = 108, RR = 24 and rales in both bases. Room air pO_2 is 66 mm Hg, HCT = 32, WBC = 6.4 (15% L), LFT's normal. Chest CT shows:



Case Nine (continued):

The patient is found to be seropositive for HIV with a CD_4 count = 6 cells. The TBO stain is positive for *P. jiroveci* but the patient does not improve after adding trimethoprim-sulfamethoxazole and prednisone.

Case Nine (continued):

After intubation, a BAL is done which reveals a CMV DNA capture of 480. The patient slowly improves after ganciclovir is added to the regimen. The patient fails highly active antiretroviral therapy but does well with long term secondary prophylaxis against *P. jiroveci* and CMV.

Pneumocystis jiroveci Infections in Transplant Recipients Who Did Not Receive Prophylaxis

Incidence	5-10% for most types but > 25% for lung transplant recipients
Clinical Presentation	Prodrome < 5 days; pO_2 often < 60 mm Hg
Survival Rates	90% in renal transplant recipients
Preventive Measures	Allo BMT recipients during months 2-6, longer if there is chronic GVHD; consider in auto BMT recipients with intense conditioning; solid organ transplant recipients for 6-12 months; lung transplant recipients for > 12 months

[Clinical Infect Diseases 2002; 34:1098-107]

Importance of a Specific Diagnosis

- Patients may have more than one diagnosis
- Optimal treatment of each agent is unique
- Clinical presentation of diseases due to noninfectious causes as well as infectious causes may be identical
- Early treatment of some infections improves outcome (example: *Aspergillus* species)

Case Ten:

A patient presents with fever, abdominal pain, nausea and vomiting. She has a long history of alcohol dependence. An amylase and lipase are obtained and the results confirm pancreatitis.

Non-Infectious Causes of Fever

- Malignancy
  - Lymphoma and renal cell carcinoma
- Collagen Vascular Disease
  - Lupus, RA, temporal arteritis, etc.
- Granulomatous diseases
  - Sarcoid, granulomatous hepatitis, etc.
- Drug (e.g., phenytoin)
- Factitious

Five More Lessons Learned

Case	Lesson
Mononucleosis & FUO	Common things are common
Dengue Fever	Fever in a traveler → think first of Dengue and malaria
Hodgkin's Lymphoma	Pay attention to the pattern
CMV and Pneumocystis	Decreased immunity should make you throw out the Razor
Pancreatitis	Not all fevers signify infection

Thank you!!