The Rise of "STI" Walker

A multidisciplinary approach to common primary care infectious diseases and epidemiologic concerns

DATE: February 2020 PRESENTED BY: Erin Bonura MD, MCR & James Lewis PharmD

Objectives

- State the recommended treatment for Ocular Syphilis
- Describe the treatment issues with
- State the indications for PrEP
- State the rationale and current uptake of the HPV vaccine
- State the treatment options for UTIs
- Describe the impact of seasonal Influenza infections
- State current best practices for the nCov

Case 1: Poe

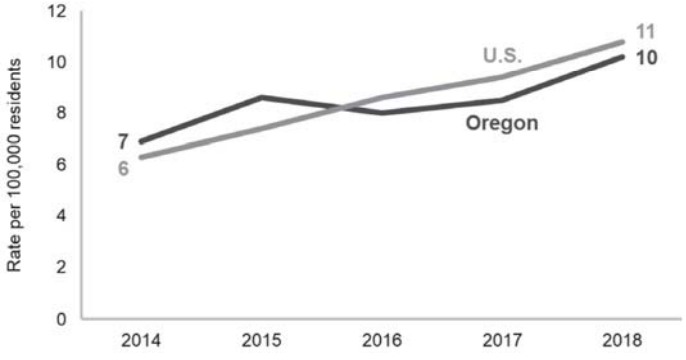
A 32 year old pilot who has been noticing worsening visual acuity when looking at his flight instruments for the past month. He is now noticing an intermittent worsening in his distance vision with increased floaters in his visual field and has been suffering from left eye redness and mild discomfort for the past week. He has been sexually active with 1 partner during the past 12 months and uses condoms inconsistently. What is the most correct statement?

A. Poe should receive an IM injection of Ceftriaxone
B. Poe should receive an IM injection of procaine penicillin
C. Poe should receive 3 weekly doses of benzathine penicillin
D. Poe should receive 14 days of IV Penicillin G

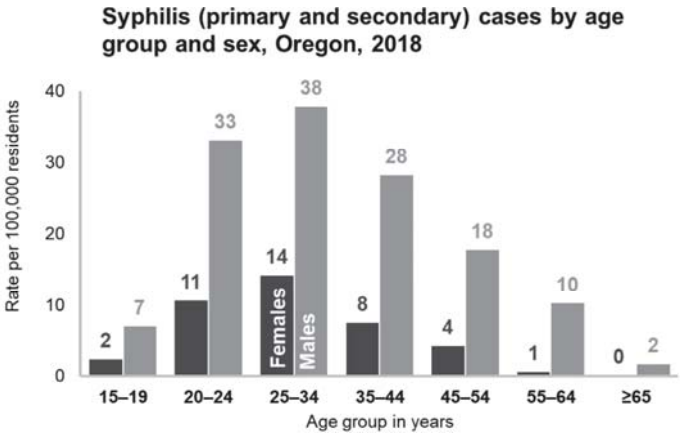
Portland known for bicycles, beer and ... syphilis

https://www.oregonlive.com/health/2015/11/portland_known_for_bicycles_be.html

Syphilis (primary and secondary) by year, Oregon & U.S.



https://www.oregon.gov/OHA/PH/ABOUT/Documents/indicators/syphilis.pdf



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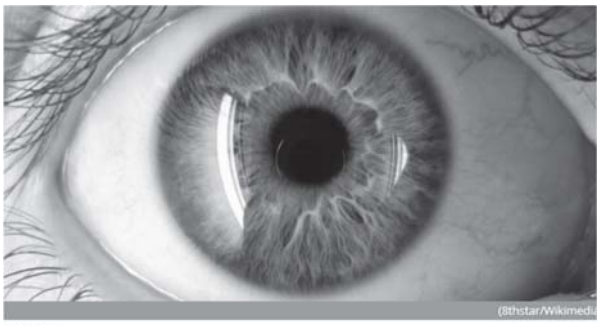


HEALTH

Syphilis Is Attacking People's Eyeballs, And This Issue Is on The Rise Around The World

MICHELLE STARR 4 SEP 2018

https://www.sciencealert.com/ocular-syphilis-on-the-rise-globally-brazil-study-largest-to-date
https://www.cdc.gov/std/syphilis/clinicaladvisoryos2015.htm

SCIENTIFIC REPORTS

OPEN

Clinical Manifestations and Ophthalmic Outcomes of Ocular Syphilis at a Time of Re-Emergence of the Systemic Infection

Variable	All Patients
Bilateral Involvement	87 (68.5%)
Duration of symptom at dx	2.8 +/- 6.3 months
CSF abnormality	29 (34.1%)
Titer of serum non-treponemal test	1:64 median/ range 1:1 – 12048

Scientific Reports. 2018;8:12071 | DOI:10.1038/s41598-018-30559-7

Make sure you have the "correct" penicillin!

latimes.com

Hundreds of Syphilis Patients in L.A. Got the Wrong Drug

By Lisa Richardson

2-3 minutes

https://www.latimes.com/archives/la-xpm-2004-mar-20-me-syphilis20-story.html

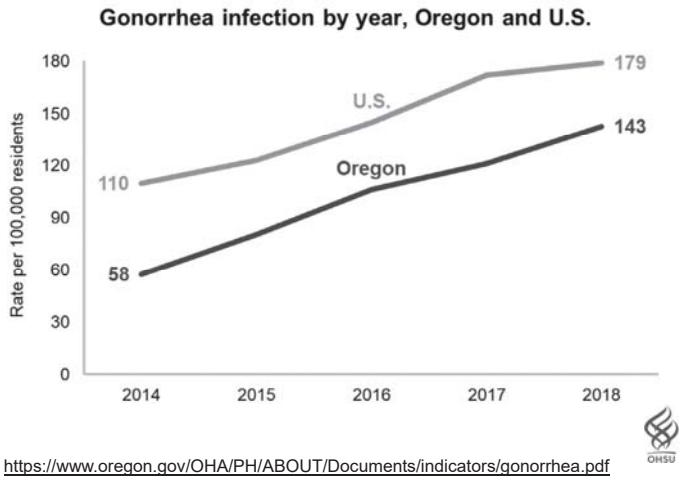
Key Points

- Syphilis can do anything!
- Think Syphilis
- Ocular often worsens with steroids alone
- Treatment is identical to neurosyphilis
- 10-14 days IV penicillin G

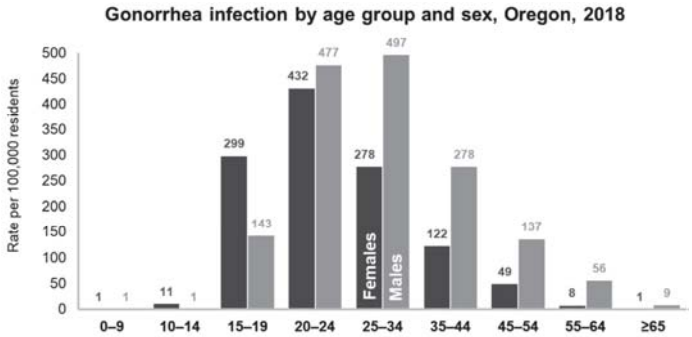
Case 2: Kylo Ren

- Mr. Ren is a 29 year old Sith who presents with testicular pain and mild swelling. He notes no penile discharge and has been sexually active with multiple partners during the past year. He reports infrequently uses condoms. Exam notes testicular tenderness with palpation and some relief with elevation of left testicle. Urethral examinations notes mild discharge. What is the best treatment course at this time?

A. Ceftriaxone 1 gram x 1
B. Azithromycin 2 grams x 1
C. Ceftriaxone 250mg x 1 plus Azithromycin 1 gram
D. Ceftriaxone 1 gram x 1 plus Azithromycin 2 grams



https://www.oregon.gov/OHA/PH/ABOUT/Documents/indicators/gonorrhea.pdf

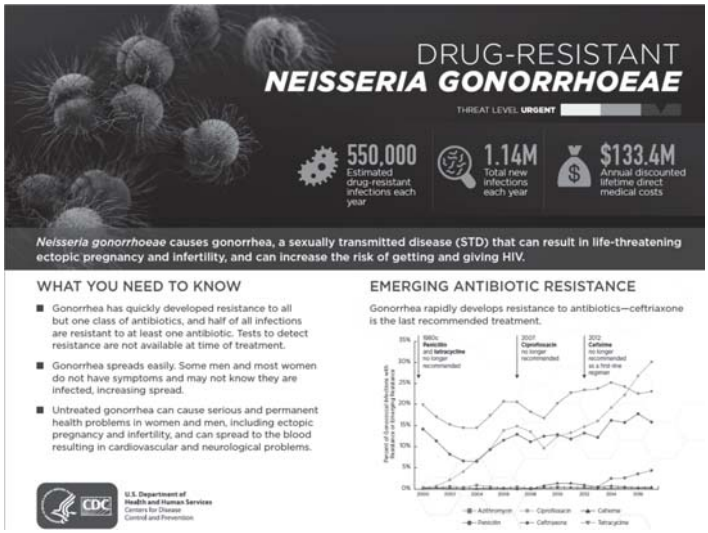


https://www.oregon.gov/OHA/PH/ABOUT/Documents/indicators/gonorrhea.pdf

The CDC's Top Antibiotic Resistance Threats in the U.S.

Resistant germ	Threat Estimate, 2019 report	What CDC Counted, 2019 report	What CDC Did Not Count, 2019 report	Year-to-Year Comparison Provided, 2019 report	Resistant Infection Increase/ Decrease, 2019 report
Drug-resistant *Neisseria gonorrhoeae*	550,000 infections	All infections	N/A	Resistance over time from 2000–2017	⬆ Increase
Candida auris	323 clinical cases	Clinical cases	Colonization/ screening cases	Cases over time from 2015–2018	⬆ Increase
ESBL-producing Enterobacteriaceae	197,400 cases & 9,100 deaths	Incident hospitalized positive clinical cultures, including hospital- & community-onset	Non-hospitalized cases	Cases over time from 2012–2017	⬆ Increase
Erythromycin-resistant group A *Streptococcus*	5,400 infections & 450 deaths	Invasive infections	Non-invasive infections including common upper-respiratory infections like strep throat	Invasive infection rates over time from 2010–2017	⬆ Increase
Carbapenem-resistant Enterobacteriaceae	13,100 cases & 1,100 deaths	Incident hospitalized positive clinical cultures, including hospital- & community-onset	Non-hospitalized cases	Cases over time from 2012–2017	Stable

https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf



But No Worries… We've got Ceftriaxone!

Ceftriaxone-Resistant *Neisseria gonorrhoeae*, Canada, 2017

RAPID COMMUNICATION

Multidrug-resistant *Neisseria gonorrhoeae* isolate, belonging to the internationally spreading Japanese FC428 clone, with ceftriaxone resistance and intermediate resistance to azithromycin, Ireland, August 2018

Daniel Golparian[1], Lisa Rose[2], Almida Lynam[3], Aia Mohamed[3], Beatrice Bercot[4], Makoto Ohnishi[5], Brendan Crowley[2,6,7], Magnus Unemo[6,7]

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Single-Dose Zoliflodacin (ETX0914) for Treatment of Urogenital Gonorrhea

Stephanie N. Taylor, M.D., Jeanne Marrazzo, M.D., M.P.H., Byron E. Batteiger, M.D., Edward W. Hook, III, M.D., Arlene C. Seña, M.D., M.P.H., Jill Long, M.D., M.P.H., Michael R. Wierzbicki, Ph.D., Hannah Kwak, M.H.S., Shacondra M. Johnson, B.S.P.H., Kenneth Lawrence, Pharm.D., and John Mueller, Ph.D.

Solithromycin versus ceftriaxone plus azithromycin for the treatment of uncomplicated genital gonorrhoea (SOLITAIRE-U): a randomised phase 3 non-inferiority trial

Marcus Y Chen, Anna McNulty, Ann Avery, David Whiley, Sepehr N Tabrizi, Dwight Hardy, Anita F Das, Ashley Nenninger, Christopher K Fairley, Jane S Hocking, Catriona S Bradshaw, Basil Donovan, Benjamin P Howden, David Oldach, on behalf of the Solitaire-U Team

Gentamicin compared with ceftriaxone for the treatment of gonorrhoea (G-ToG): a randomised non-inferiority trial

Jonathan D C Ross, Clare Brittain, Michelle Cole, Claire Dewsnap, Jan Harding, Trish Hepburn, Louise Jackson, Matthew Keogh, Tessa Lawrence, Alan A Montgomery, Tracy E Roberts, Kirsty Sprange, Wei Tan, Sukhwinder Thandi, John White, Janet Wilson, Lelia Duley, on behalf of the G-ToG trial team

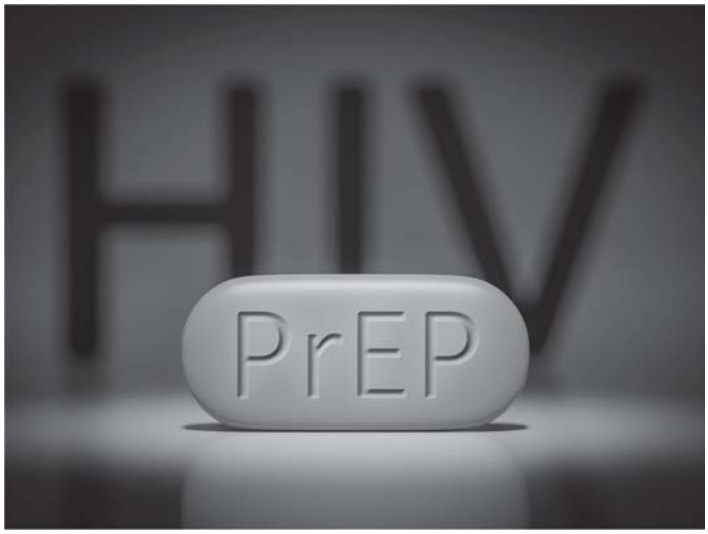
So Where Do We Stand?

- 250mg ceftriaxone + 1g azithromycin
- Rampant resistance issues & test of cure
- Higher doses of ceftriaxone likely forthcoming
- Other options when ceftriaxone not available
- Penicillin allergy

Case 3: Zori Bliss

Zori is a 30 year old woman with no significant past medical history. She recently started a relationship with an HIV positive man who states he is "controlled". She wants to know if she is a candidate for PrEP and if so, can you prescribe the medication. Which of the following is the most correct?

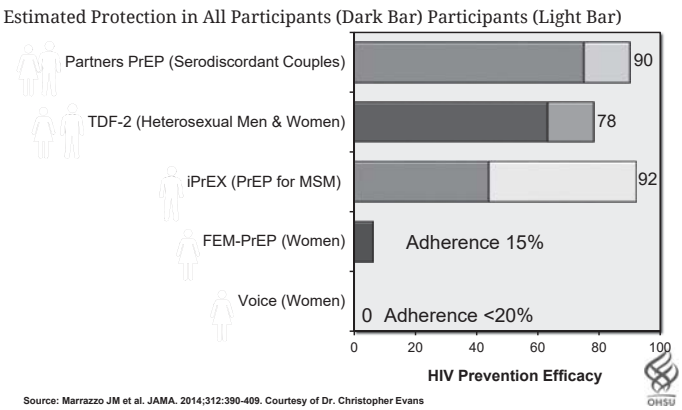
A. She is a candidate but she should see Infectious Diseases for a prescription
B. She is a candidate and you can write her a script today
C. She is not a candidate as her partner is virally suppressed
D. She is not a candidate as the studies were only performed on men who have sex with men



PrEP Regimen

Truvada®
emtricitabine 200 mg / tenofovir disoproxil fumarate 300 mg tablets
for PrEP pre-exposure prophylaxis

Tenofovir-Emtricitabine as Sexual PrEP for HIV Prevention
Estimated Protection in Adherent Patients



Source: Marrazzo JM et al. JAMA. 2014;312:390-409. Courtesy of Dr. Christopher Evans

Efficacy of PrEP compared to other medical interventions

	PROUD	iPrEx	ASCOT-LLA
Intervention	PrEP daily	PrEP daily	Atorvastatin for MI prevention
RRR	86%	44%	36%
NNT	13	62	94

(iPrEx) Grant RM et al., N Engl J Med. 2010;363:2587-99.
(PROUD) McCormack,S., et al., Lancet. 2016 Jan 2;387(10013):53-60
(ASCOT-LLA) Lancet 2003; 361: 1149–58

Estimated per-act risk for acquisition of HIV

Exposure Route		Risk per 10k exposures
Blood Borne	Blood transfusion	9000 (9/10)
	Needle-sharing IDU	67 (1/150)
	Percutaneous Needle stick	23 (1/435)
	Mucous membrane exposure to blood	10 (1/1000)
Sexual Exposure	Receptive anal	138 (1/72)
	Insertive anal	11 (1/900)
	Receptive penile-vaginal	8 (1/1250)
	Insertive penile-vaginal	4 (1/2500)
	Oral	0-4

Online Resources: Sexual History

https://www.lgbthealtheducation.org/publication/ready-set-go-guidelines-tips-collecting-patient-data-sexual-orientation-gender-identity/

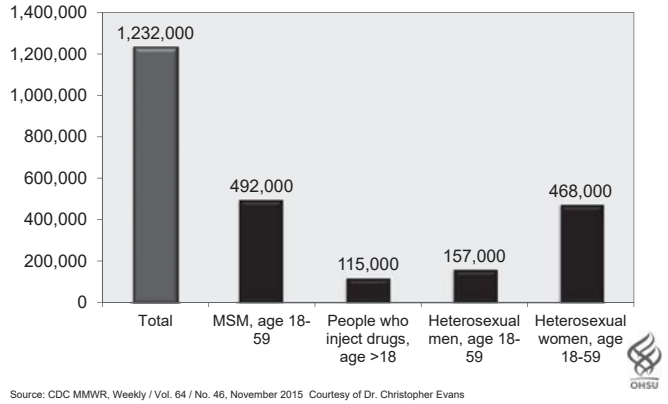
Assess Risk of Treatment

- ❑ Acute HIV
- ❑ Renal function
- ❑ HBV
- ❑ Osteoporosis
- ❑ Pregnancy

Who is a candidate for PrEP?

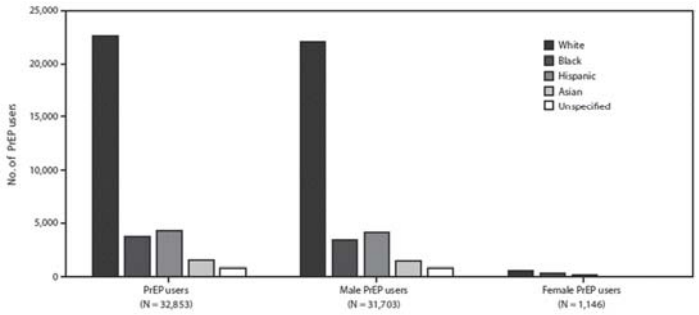
Sexually-Active Adults and Adolescents	Persons Who Inject Drugs
Intercourse in last 6 months ***plus*** HIV + partner **OR** Recent STI **OR** Inconsistent/No condom use	HIV-positive injecting partner **OR** Shares drug prep/equipment
Documented negative HIV test before prescribing PrEP; ***and*** No signs/symptoms of acute HIV; ***and*** Normal renal function; ***and*** No contraindicated medications	

Estimated number of adults with PrEP indication (2015)



Source: CDC MMWR, Weekly / Vol. 64 / No. 46, November 2015 Courtesy of Dr. Christopher Evans

PrEP users by sex and race/ethnicity 2014-2016



https://www.cdc.gov/mmwr/volumes/67/wr/mm6741a3.htm

Recommended Testing and Follow up for Patients on PrEP

Test	Baseline	Every 3 Mo	At least every 6 mo	Notes
HIV Assay	√	√		Consider need for HIV RNA PCR
HBV / HCV Ab	√			Offer vax if not immune
Serum Creatinine	√		√	CrCl decrease may require d/c
STI screening	√	√	√	Oral/rectal if MSM if risk
Pregnancy test	√	√		Safety unknown

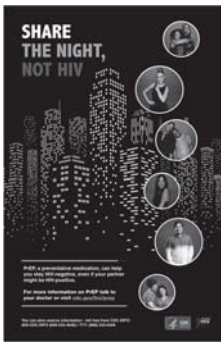
CDC. MMWR Morb Mortal Wkly Rep. 2011;60:65-68. Tenofovir/emtricitabine [package insert]. July 2012

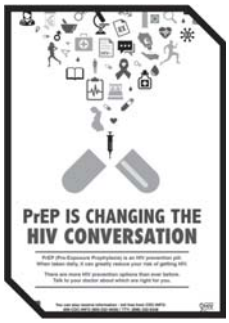
Online Resources: HIV Nexus

https://www.cdc.gov/hiv/clinicians/index.html

Online Resources: HIV Nexus

Online Resources: HIV Nexus





https://www.cdc.gov/hiv/clinicians/index.html

Key Points

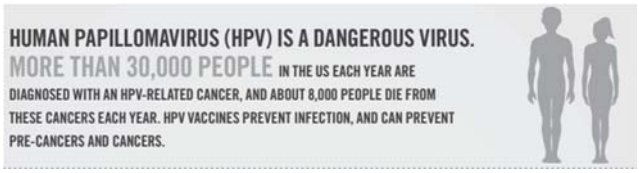
- Patients should be evaluated for PrEP use
- PrEP is effective at preventing HIV
- Patients on PrEP still need screening labs and monitoring

Case 4: Rey

Rey is an 11 year old girl who is brought to her pediatrician by her guardian for a well child check up. She has no history of medical illness though she is healing from a electrical burn after trying to fix her droid. The guardian asks about the HPV vaccination and if Rey should get it. What is the most correct statement below?

A. Rey should receive the 3 part series vaccine next year
B. Rey should receive the 2 part series vaccine today
C. Rey should not receive the vaccine until she is sexually active
D. Rey should have received the vaccine at 9 years of age and is now past the age limit

Why Give the HPV Vaccine?



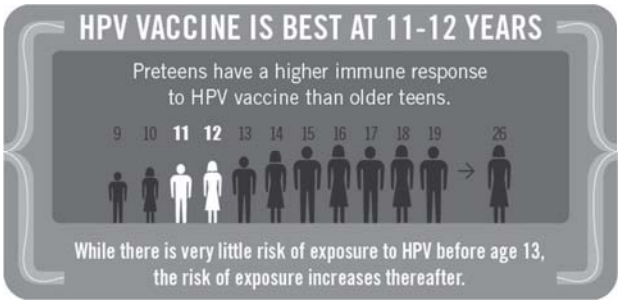
- HPV causes genital warts
- HPV causes cancer:
  - **Tongue and tonsils**: 10k-12k/year
  - **Cervix**: 10k-12k/year
  - **Anus**: 4-5k/year
  - **Vagina and vulva**: 3k/year
  - **Penis**: 700/year

https://www.aap.org/en-us/Documents/AAPFact%20Sheet_HPV%20vaccine.PDF

Types of HPV Vaccine

Bivalent	Cervarix (GlaxoSmithKline) 16, 18
Quadrivalent	Gardasil (Merck) 6, 11, 16, 18
9-valent	Gardasil 9 (Merck) 6, 11, 16, 18, 31, 33, 45, 52, 58

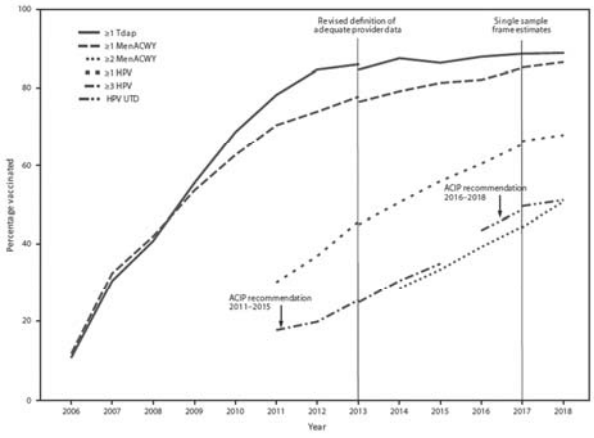
Who should get the HPV vaccine?



2 Doses (0, 6-12mo) | **3** Doses (0, 1-2, 6mo)

http://dhss.alaska.gov/dph/Epi/iz/Pages/hpv/default.aspx

What is the HPV vaccination rate?



HPV Quadrivalent Vaccine Efficacy

End Point	Vaccine Group (N=2723)			Placebo Group (N=2732)			Efficacy
	No. of Subjects	No. of Cases	Rate per 100 Person-Years at Risk	No. of Subjects	No. of Cases	Rate per 100 Person-Years at Risk	% (95% CI)
Lesions associated with vaccine-type HPV							
Per-protocol susceptible population†							
External anogenital and vaginal lesions	2261	0	0	2279	60	1.1	100 (94–100)

Garland, S.M., et al,. N Engl J Med 2007;356:1928-43.

HPV Quadrivalent Vaccine Efficacy

End Point	Vaccine Group		Placebo Group		Efficacy
	Subjects	Cases	Subjects	Cases	
CIN grade 2	5305	0	5260	28	100
CIN grade 3	5305	1	5260	29	97
AIS	5305	0	5260	1	100

The FUTURE II Study Group. N Engl J Med 2007;356:1915-27

HPV Vaccine Efficacy of 9-valent Vaccine vs 4-valent

End Point	9v no/total	4v no/total	Risk reduction
High-grade cervical, vulvar, vaginal			
31, 33, 45, 52, 58	1/6016	30/6017	96.7
6, 11, 16, 18	1/5883	3/5898	66.6
High grade CEN, AIS, cervical cancer			
31, 33, 45, 52, 58	1/5948	27/5943	96.3
6, 11, 16, 18	1/5823	1/5832	-0.4
Persistent infection >6mo			
31, 33, 45, 52, 58	35/5939	810/5953	96
6, 11, 16, 18	59/5812	80/5830	5

Joura, E.A., et. al.N Engl J Med. 2015;372(8):711-723

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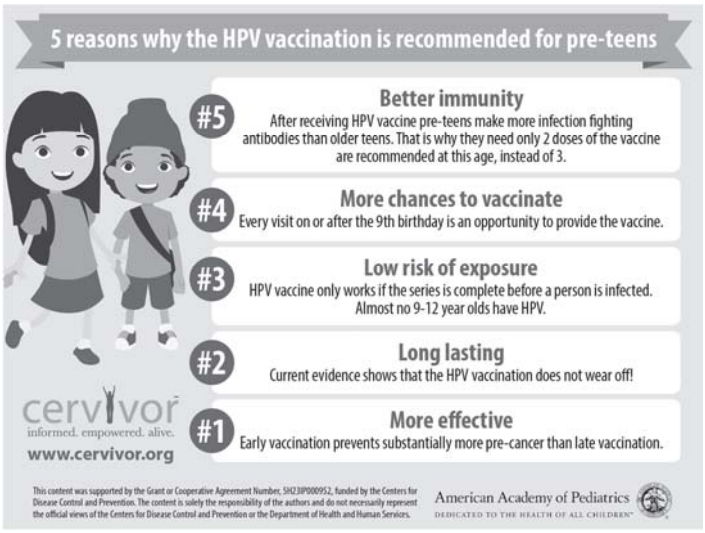


Online Resources: HPV Vaccine

https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/immunizations/HPV-Champion-Toolkit/Pages/Printable-Resources.aspx

Online Resources: HPV Vaccine

https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/immunizations/HPV-Champion-Toolkit/Pages/Printable-Resources.aspx

Key Points

- All children 11-13 should receive HPV vaccines
- Vaccination is rising but we can do better
- Current data show HPV vaccine efficacious

Case 5: Maz

Maz is a 9200 yo F with a history of kidney stones, recurrent cystitis, and several bouts of pyelonephritis during the past several years. She presents today with left flank pain, febrile to 102F, with dysuria and hematuria. Her last case of pyelonephritis was 7.5 months ago. She received a course of cefpodoxime 200mg BID for cystitis 4 months ago. Which of the following is the most correct statement?

A. She should drink more water in between UTI episodes
B. She should start cefpodoxime 200mg po BID suppression
C. She should receive fosfomycin x 1
D. She should receive nitrofurantoin.
E. She should receive ciprofloxacin x 14 days

OHSU Outpatient *E. coli* 2019

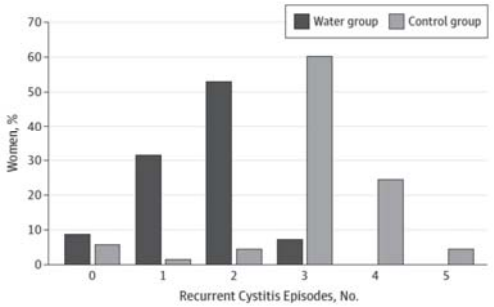
	No. Tested	Ampicillin	Amoxicillin/ Clavulanate	Cefazolin	Cefepime	Ceftriaxone	Ciprofloxacin	Ertapenem	Gentamicin	Meropenem	Nitrofurantoin (urine only)	Piperacillin/ Tazobactam	Tetracycline	Trimeth/Sulfa
Escherichia coli	**1369**	**62**	**84**	**90**	**98**	**93**	**87**	**100**	**95**	**100**	**97**	**98**	**77**	**79**

JAMA Internal Medicine | Original Investigation

Effect of Increased Daily Water Intake in Premenopausal Women With Recurrent Urinary Tract Infections
A Randomized Clinical Trial

Thomas M. Hooton, MD; Mariacristina Vecchio, PharmD; Alison Iroz, PhD; Ivan Tack, MD, PhD; Quentin Dornic, MSc; Isabelle Seksek, PhD; Yair Lotan, MD

Figure 2. Recurrent Cystitis Episodes by Study Group



Fosfomycin & UTIs: What's Missing & What is…?

Woman with acute cystitis
- No fever, flank pain, or suspicion for pyelo
- Able to take oral medications

⇩

Use one of the below if available, no allergy, and pt able to tolerate

⇩

Nitrofurantoin monohydrate/macrocrystals 100mg bid X 5d
OR
TMP-SMX 1 double strength tablet twice daily X 3 days
OR
Fosfomycin 3gm single dose
OR
Pivmecillinam 400mg bid X 5 days

Gupta K, et al. *Clin Infect Dis* 2011;52:e103

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

Angela Huttner, MD; Anna Kowalczyk, MS; Adi Turjeman, MSc; Tanya Babich, MSc; Caroline Brossier, RN; Noa Eliakim-Raz, MD; Katarzyna Kosek, MD, PhD; Begoña Martinez de Tejada, MD, PhD; Xavier Roux, MD; Shachaf Shiber, MD; Ursula Theuretzbacher, PhD; Elodie von Dach, PhD; Dafna Yahav, MD; Leonard Leibovici, MD; Maciek Godycki-Cwirko, MD, PhD; Johan W. Mouton, MD, PhD; Stephan Harbarth, MD

- 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

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	

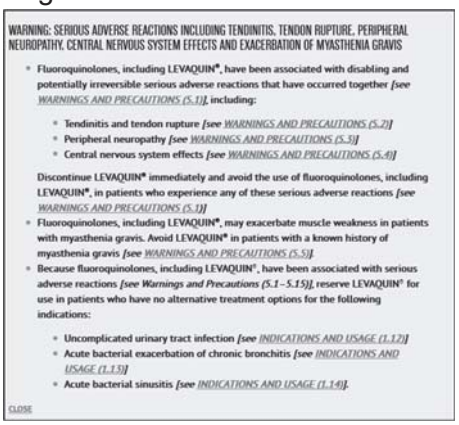
***E.coli* #2**

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	

What about the oral beta-lactams?

- Likely OK for cystitis
- NOT as effective as front line agents
  - Nitro, TMP/SMX, Fosfo
- Ampicillin & Amox likely resistant
- Cephalexin 500mg but 4 times daily
- Oral 3rd generation cephs, more studied, more expensive

The Latest on the Quinolones: Levo Package Insert 2019



WARNING: SERIOUS ADVERSE REACTIONS INCLUDING TENDINITIS, TENDON RUPTURE, PERIPHERAL NEUROPATHY, CENTRAL NERVOUS SYSTEM EFFECTS AND EXACERBATION OF MYASTHENIA GRAVIS

- Fluoroquinolones, including LEVAQUIN®, have been associated with disabling and potentially irreversible serious adverse reactions that have occurred together *[see WARNINGS AND PRECAUTIONS (5.1)]*, including:
  - Tendinitis and tendon rupture *[see WARNINGS AND PRECAUTIONS (5.2)]*
  - Peripheral neuropathy *[see WARNINGS AND PRECAUTIONS (5.3)]*
  - Central nervous system effects *[see WARNINGS AND PRECAUTIONS (5.4)]*

  Discontinue LEVAQUIN® immediately and avoid the use of fluoroquinolones, including LEVAQUIN®, in patients who experience any of these serious adverse reactions *[see WARNINGS AND PRECAUTIONS (5.1)]*
- Fluoroquinolones, including LEVAQUIN®, may exacerbate muscle weakness in patients with myasthenia gravis. Avoid LEVAQUIN® in patients with a known history of myasthenia gravis *[see WARNINGS AND PRECAUTIONS (5.5)]*.
- Because fluoroquinolones, including LEVAQUIN®, have been associated with serious adverse reactions *[see Warnings and Precautions (5.1 - 5.15)]*, reserve LEVAQUIN® for use in patients who have no alternative treatment options for the following indications:
  - Uncomplicated urinary tract infection *[see INDICATIONS AND USAGE (1.12)]*
  - Acute bacterial exacerbation of chronic bronchitis *[see INDICATIONS AND USAGE (1.13)]*
  - Acute bacterial sinusitis *[see INDICATIONS AND USAGE (1.14)]*.

CLOSE

https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a1f01e8e-97e9-11de-b91d-553856d89593

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 sypmtoms	7%	7%	-	-

- The take home: pyelo = 7 days with quinolones!
- Even bacteremic pyelo!
- Questions when using non-quinolone agents

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

TETRAPHASE ANNOUNCES TOP-LINE RESULTS FROM IGNITE3 PHASE 3 CLINICAL TRIAL OF ERAVACYCLINE IN COMPLICATED URINARY TRACT INFECTIONS (CUTI)

February 13, 2018

– *Eravacycline Did Not Achieve Co-Primary Endpoints in cUTI Trial* –

PDF Version

– *Company Continues to Prepare for Commercialization of Eravacycline as a Treatment for cIAI in the U.S. and Europe, Assuming Regulatory Approval* –

PARATEK

Paratek Announces Top Line Results of Phase 2 Clinical Studies of Omadacycline in Urinary Tract Infections

Be careful with tetracyclines in the urine…

Remember TMP/SMX!

- Still equivalent to FQs
- 1 DS tablet twice daily for 7 days
- IV = Oral
- Limited by resistance – CULTURES
- Issues with rash & potassium

About to go "Old School"?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Once-Daily Plazomicin for Complicated Urinary Tract Infections

Florian M.E. Wagenlehner, M.D., Daniel J. Cloutier, Pharm.D., Allison S. Komirenko, Pharm.D., Deborah S. Cebrik, M.S., M.P.H., Kevin M. Krause, M.B.A., Tiffany R. Keepers, Ph.D., Lynn E. Connolly, M.D., Ph.D., Loren G. Miller, M.D., M.P.H., Ian Friedland, M.D., and Jamie P. Dwyer, M.D., for the EPIC Study Group*

- Modern aminoglycoside data
- Less nephrotoxicity than expected, but still there
- Can be given IV or IM

NEJM 2019;380:729

Take Home Points

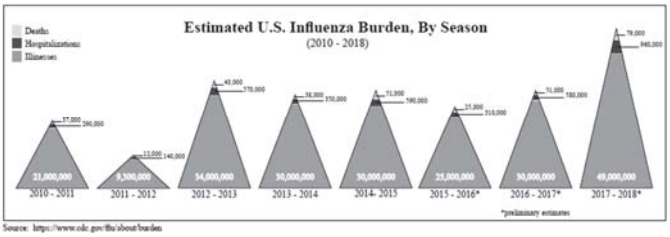
- E. coli resistance in the community is a challenge
- Hydration data is a pleasant surprise
- Recurrent UTI = more likely resistance
- Cultures are key in recurrence
- Duration of therapy for pyelo & FQ dangers

Case 6: Leia Organa

Admiral Organa presents with an acute onset of fever to 103F, chills, myalgias, and cough x 1 day after completing a winter Jedi training exercise on Hoth. Base occupants have recently been complaining of respiratory symptoms and fevers. Her advanced molecular diagnostic panel aboard the Millenium Falcon returns with an identification of Influenza A.

A. She should receive oseltamivir now
B. She should be placed on airborne precautions
C. She should receive the high dose Influenza vaccine now
D. She should be given supportive care

CDC Estimate of Influenza Burden: Deaths, Hospitalizations, Illnesses



Source: https://www.cdc.gov/flu/about/burden

Burden of influenza. CDC website. cdc.gov/flu/about/burden/index.html. Accessed September 19, 2019.

Who is at highest risk of serious complications?

- Hospitalized
- Younger age (6-59 months)
- Older age (≥50 years)
- Chronic diseases
  - Pulmonary (eg, asthma)
  - Cardiovascular (excluding isolated hypertension)
  - Renal
  - Hepatic
  - Neurologic
  - Hematologic
  - Metabolic (eg, diabetes)
- Immunocompromised
- Women who are or will be pregnant during the influenza season
- Individuals 6 months through 18 years of age receiving long-term aspirin or salicylate therapy
- Long-term care facility residents
- American Indians/Alaska Natives
- Obese patients (BMI ≥40 kg/m^2)

Grohskopf LA, et al. *MMWR Recomm Rep.* 2019; 68(3):1–21.

Make a Strong Flu Vaccine Recommendation

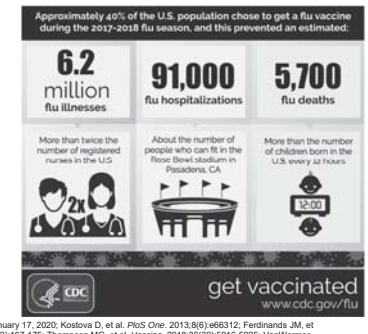
Español

As a health care professional, your strong recommendation is a critical factor that affects whether your patients get an influenza vaccine. Most adults believe vaccines are important, but they need a reminder from you to get vaccinated. Follow up with each patient during subsequent appointments to ensure the patient received an influenza vaccine. If the patient still is unvaccinated, repeat the recommendation to try to identify and address any questions or concerns.

Make a strong flu vaccine recommendation. CDC website. cdc.gov/flu/professionals/vaccination/flu-vaccine-recommendation.htm. Accessed October 23, 2019.

Influenza Vaccine

- Reduces hospitalizations
- Decreases risk of intensive care unit (ICU) admission in children
- Decreases risk of ICU admission or death among hospitalized adults
- Reduces severity among vaccinated patients who develop influenza
- **Does not give you the flu!**



CDC website. cdc.gov/flu/vaccines-work/averted-estimates.htm. Accessed January 17, 2020; Kostova D, et al. *PloS One*. 2013;8(6):e66312; Ferdinands JM, et al. *J Infect Dis*. 2014;210(5):674-683; Castilla J, et al. *Clin Infect Dis*. 2013;57(2):167-175; Thompson MG, et al. *Vaccine*. 2018;36(39):5916-5925; VanWormer JJ, et al. *BMC Inf Dis*. 2014;14(1):231; Deiss RG, et al. *Vaccine*. 2016;33(51):7160-7167.

Issues With Vaccine Waning?

- Lots of questions: studies showing varying results
- Not consistently seen
- Varying degrees of waning
- Different between different viruses?
- "Variable data… unpredictable timing of the season… prevent determination of an optimal time to vaccinate."
- Fears of missing patients versus fears of waning
- Vaccination recommended by the end of October

Morbidity and Mortality Weekly Report. CDC website. cdc.gov/mmwr/volumes/68/rr/rr6803a1.htm?s_cid=rr6803a1_w. Accessed September 16, 2019.
Ferdinands JM, et al. Clinical Infectious Diseases, ciz452, https://doi.org/10.1093/cid/ciz452

Patients With ILI at High Risk of Complications Should Receive Antiviral Therapy

- Hospitalized
- Younger age (6-59 months)
- Older age (≥50 years)
- Chronic diseases
  - Pulmonary (eg, asthma)
  - Cardiovascular (excluding isolated hypertension)
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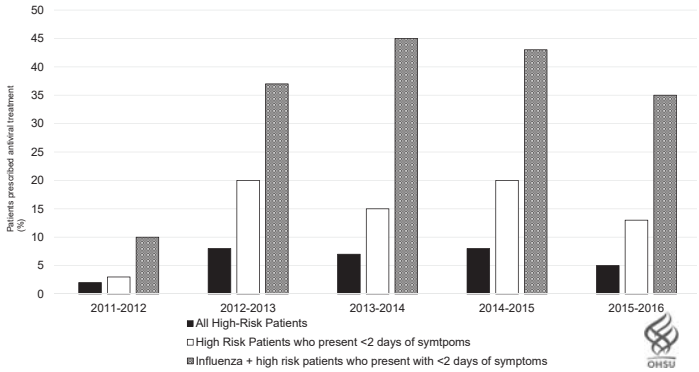
Grohskopf LA, et al. *MMWR Recomm Rep*. 2019; 68(3):1–21.

Clinical Infectious Diseases
MAJOR ARTICLE

IDSA hivma

Influenza Antiviral Prescribing for Outpatients With an Acute Respiratory Illness and at High Risk for Influenza-Associated Complications During 5 Influenza Seasons—United States, 2011–2016



Stewart RJ, et al. *Clin Infect Dis*. 2018;66:1035-1041.

Oseltamivir plus usual care versus usual care for influenza-like illness in primary care: an open-label, pragmatic, randomised controlled trial

Christopher C Butler, Alike W van der Velden, Emily Bongard, Benjamin R Saville, Jane Holmes, Samuel Coenen, Johanna Cook, Nick A Francis,

- Estimated benefit 1.02 days…
- BUT
- In patients >65yo, more severe illness, comorbidities, longer duration of illness
- Benefit of 3.20 days
- More GI effects in oseltamivir group

Lancet 2020; 395: 42–52

Veterans and Oseltamivir (OTV)

- Laboratory confirmed flu patients only
- High rates of lung disease
- 62% of patients received antivirals
- Low antibiotic prescribing
- OTV - 75% reduction in risk of hospitalization days 1-30.

Sutton S, et al. *Clin Infect Dis* 2020 epub AOP 1/24/20

Take Home Points

- If it moves… vaccinate it
- Particularly the high risk groups
- Questions about HD vaccine and vaccine waning
- Appropriate use of antivirals
- Target high risk groups with antivirals

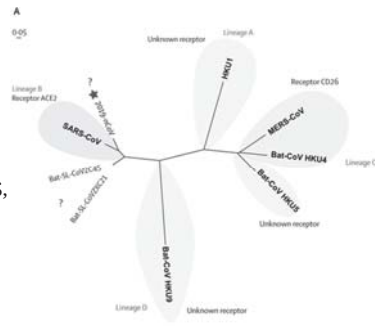
Case 7: Finn

Finn is visiting Rey on Jakku when he hears of a new respiratory viral outbreak on Bespin. Lando calls requesting help to contain the outbreak of this novel coronavirus as it has already spread to 3 other planets. Which of the following is the most correct statement?

A. Coronaviruses are typically foodborne thus Finn should ask Lando to wear contact precautions.
B. This coronavirus likely has a Ro of 1
C. Lando should hand out storm trooper helmets as airborne precautions
D. Lando should use droplet and contact precautions

Coronaviruses

- Enveloped RNA virus
- Positive sense SS
- Largest RNA genome
- Animal reservoirs: camels, cattle, cats, bats
- Rarely infect people (MERS, SARS, n-CoV)
- Spread usually with close contacts (droplet)
  - Unclear if n-CoV acquired by fomites



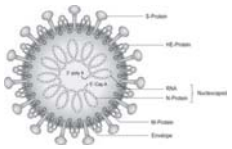
https://www.thelancet.com/action/showPdf?pii=S0140-6736%2820%2930251-8

Clinical Features of Coronaviruses SARS and MERS

	MERS	SARS
Incubation Period	2-13d	2-14d
Reproduction no.	<1	2-3
Median Age	50	39.9
Male/Female	64.5/35.5	43/57
Mortality	40%	9.6%

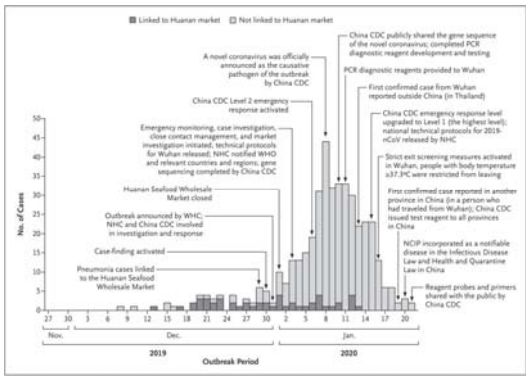
Zumla a., et al., Middle East Respiratory Syndrome. Lancet.2015;386(9997):5-11

What We Know About 2019-nCoV…



- 2019 Novel Coronavirus (2019-nCoV)
- Early link at a large seafood and animal market
- Move to person-person spread
- Incubation 2-14 days (similar to MERS)

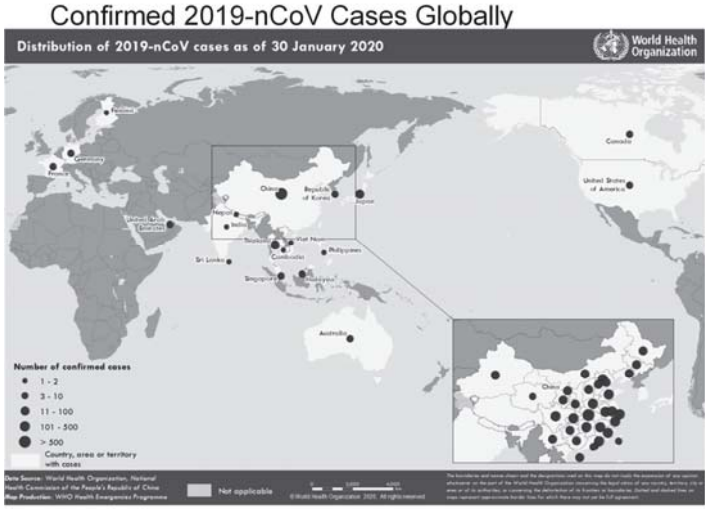
Onset of Illness among the First 425 Confirmed Cases of Novel Coronavirus (2019-nCoV)–Infected Pneumonia (NCIP) in Wuhan, China.



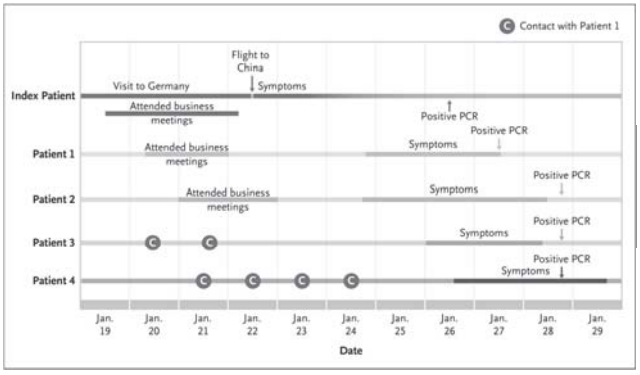
Q Li et al. N Engl J Med 2020. DOI: 10.1056/NEJMoa2001316

OHSU

Confirmed 2019-nCoV Cases Globally



Timeline of Exposure to Index Patient with ~~Asymptomatic~~ 2019-CoV Infection in Germany.



C Rothe et al. N Engl J Med 2020. DOI: 10.1056/NEJMc2001468

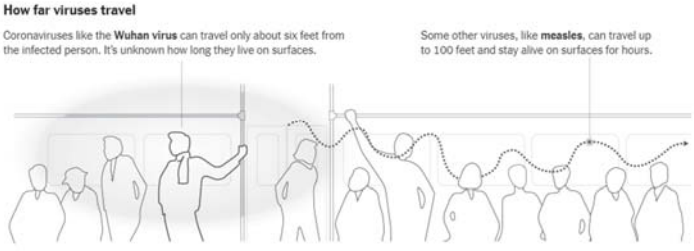
OHSU

States with confirmed 2019-nCoV cases

CDC

OHSU

Respiratory Transmission



https://www.nytimes.com/interactive/2020/world/asia/china-coronavirus-contain.html

OHSU

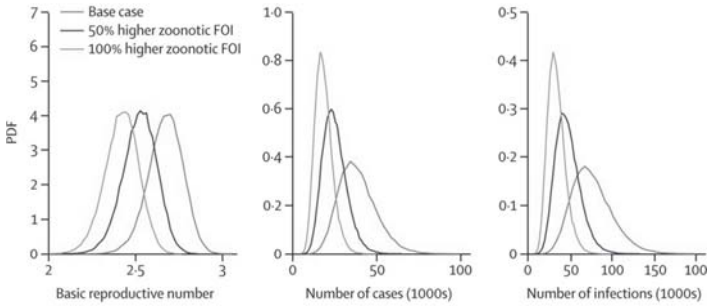
SARS Transmission

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

OHSU

Posterior Distributions of Estimated Basic Reproductive Number and Estimated Outbreak size in greater Wuhan



https://www.thelancet.com/action/showPdf?pii=S0140-6736%2820%2930260-9

TIME

HEALTH • 2019-NCOV

The Coronavirus Outbreak Is Now a Public Health Emergency of International Concern. Here's What That Means

HEALTH AND SCIENCE

CDC issues mandatory quarantine for first time in more than 50 years to Wuhan passengers in California

PUBLISHED FRI, JAN 31 2020•1:15 PM EST | UPDATED 15 MIN AGO

Clinical Features of Coronaviruses SARS and MERS

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Incubation Period	2-14d	2-13d	2-14d
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Median Age	59	50	39.9
Male/Female	56/44	64.5/35.5	43/57
Mortality	?	40%	9.6%

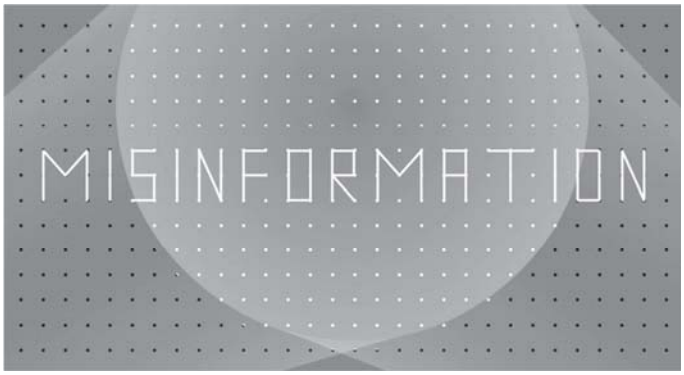
Zumla a., et al., Middle East Respiratory Syndrome. Lancet.2015;386(9997):5-11

Criteria to Guide Evaluation of Patients Under Investigation (PUI)

Clinical Features	&	Epidemiologic Risk
Fever or signs/symptoms of lower respiratory illness (cough, SOB)	**AND**	Any person, including HCW, who has had close contact with a laboratory-confirmed case in 14 days of symptoms
Fever AND signs/symptoms of lower respiratory illness (cough, SOB)	**AND**	Hx of travel from Hubei Province, China within 14d of symptom onset
Fever AND signs/symptoms of lower respiratory illness (cough, SOB) requiring hospitalization	**AND**	Hx of travel from mainland China within 14d of symptom onset

IMMEDIATELY notify infection control and the facility and health department if PUI for 2019-nCoV

https://www.cdc.gov/coronavirus/2019-nCoV/hcp/clinical-criteria.html



Online Resources: nCov

https://www.cdc.gov/coronavirus/2019-ncov/index.html

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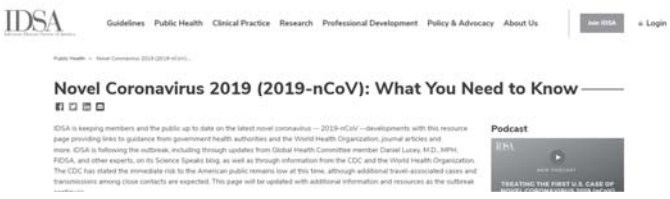


https://www.idsociety.org/public-health/novel-Coronavirus/

Key Points

- Go to reputable sources only (CDC, WHO, etc)
- Do not spread misinformation
- 2019-nCoV likely spread by droplet
- Low risk currently in the US – more risk of Flu!
- Healthcare centers and providers should implement screening processes
- Travel bans will not contain the disease

Thank You

The Geriatric Primary Care Patient

Tips to help older adults thrive

Kathleen Drago, MD
Assistant Professor, OHSU General Internal Medicine & Geriatrics
February 14, 2020

Disclosures

- I have no disclosures or conflicts of interest

Objectives

- Incorporate geriatrics specific review of systems into annual health maintenance for older adults
- Describe a framework for assessing & treating falls risk factors
- List principles of thoughtful prescribing and evidence based tools to support safe prescribing practices

Betty
80 year old retired school teacher

Lives in Arizona during the winter, Portland in the summer

Here to establish care after previous PCP retired

Medical History:
-Osteoarthritis of hands & knees
-Glaucoma
-Hypothyroidism
-Impaired bone density

Medications:
-Tylenol 650mg BID PRN
-Timolol eye drops
-Levothyroxine 88mcg daily
-Calcium-Vit D

What else should we ask about Betty?

- Functional status, social supports, personal health goals, advance directive, surrogate decision maker
- **Geriatric syndromes**

- Goal is to appraise overall risk for health issues related to normal & pathologic aging

Syndrome: from *syn* + *dromos* "a running together, tumultuous concourse; a concurrence of symptoms"

Geriatric Syndrome: Multifactorial condition of frail elderly usually due to multiple contributors. Results from interaction between patient-specific impairments and situation-specific stressors

Labella, J Hosp Med 2011

Geriatric Syndromes

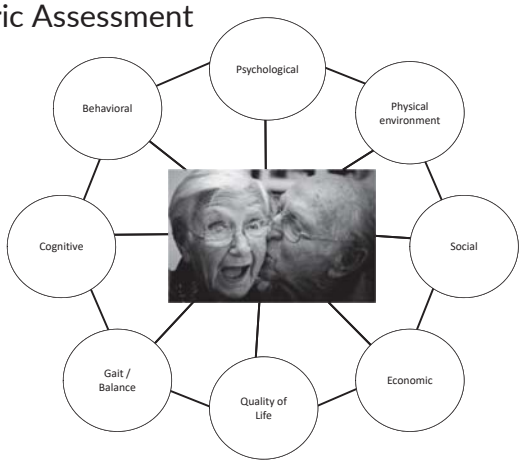
- Increasingly common with advancing age
  - ~85% of those over 80 years old have at least 1 geriatric syndrome
  - Half of those over 80 years old have 4+ geriatric syndromes
- Many go unreported, unrecognized or attributed to aging or other chronic disease

Tabue-Teguo M, et al. J Gerontol A Biol Sci Med Sci 2018;
Bulut EA, et al. Clin Interv Aging 2018

Geriatric Syndromes

- Dehydration
- Dementia
- Delirium
- Falls
- Dysphagia / Aspiration
- Pressure injuries
- Syncope/dizziness
- Pain
- Polypharmacy
- Constipation
- Depression
- Malaise / fatigue
- Functional & mobility impairment
- Speech / hearing difficulties
- Adverse drug events
- Malnutrition
- Urinary incontinence
- Sleep Disturbance

Geriatric Assessment



Geriatrics Review of Systems

- Primary care tool to screen for geriatric syndromes
- Goal to identify those conditions amenable to intervention and those who may benefit from specialty geriatric assessment

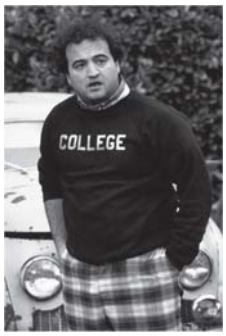
Geriatrics Review of Systems

ADL / IADL function	**"What help do you need to …"**
Falls	**"Have you fallen or come close in the last year?"**
Hearing / vision function	**"Do you have trouble seeing or hearing? Wear glasses or hearing aids?""**
Dysphagia	**"Do you have trouble swallowing food or liquid?"**
Mood disruption	**"How would you describe your mood in the last 2 weeks?"**
Memory impairment	**"What concerns do you or your family have about your memory?"**
Incontinence	**"How often have you leaked urine or stool in the last 2 weeks?**
Sleep	**"Do you have trouble falling or staying asleep? Do you feel rested when you wake up?"**

ADLs & IADLs

- Transferring
- Dressing
- Bathing
- Grooming
- Self feeding
- Continence
- Using the telephone
- Medications
- Meal preparation
- Finances
- Housecleaning
- Transportation
- Shopping, errands
- Laundry

ADLs & IADLs



Geriatrics Review of Systems

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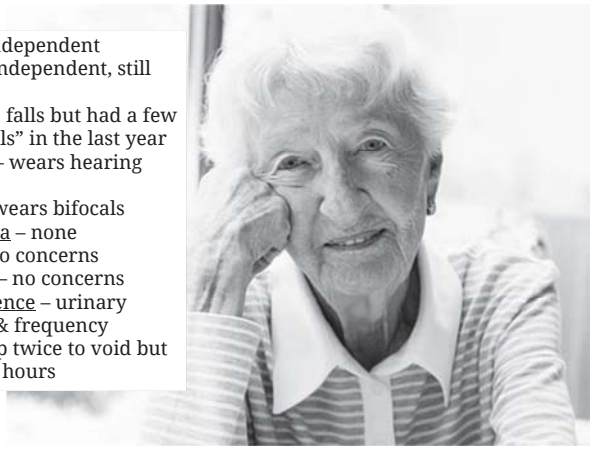
ADLs – independent
IADLs – independent, still drives
Falls – no falls but had a few "close calls" in the last year
Hearing – wears hearing aids
Vision – wears bifocals
Dysphagia – none
Mood – no concerns
Memory – no concerns
Incontinence – urinary urgency & frequency
Sleep – up twice to void but sleeps ~5 hours



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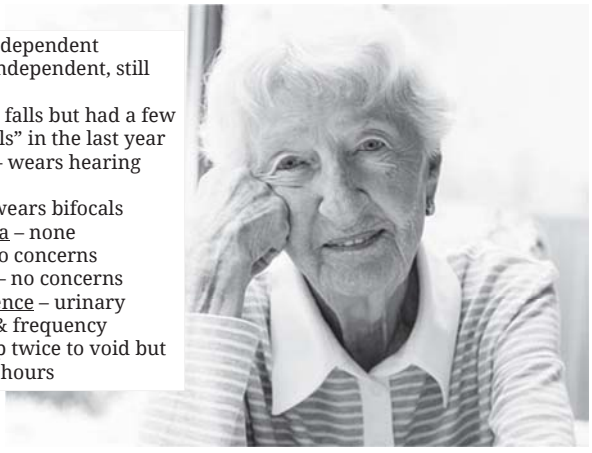


Falls

- Betty has "stumbled" 3 times in the last year
- She was always able to steady herself so didn't think it was a problem …

- Is this a problem? What can be done to help?

Falls by the numbers

600	Oregon seniors who died from a fall (2012)
8,600	Oregon seniors hospitalized due to a fall (2012)
60%	Oregon seniors discharged to long term care after falling (2012)
26x	Rate of fatal falls for seniors 85+ (vs 65-74)
1st	Falls as leading cause of injurious deaths for 65+ (CDC, 2011)

Falls are common, morbid and preventable

Multifactorial & preventable

- Cluster randomized trial of 301 older adults with at least 1 risk factor for falls found that:
- Falls are preventable → **31%** reduction with multicomponent falls prevention intervention
- Fall risk is multifactorial
  - Assess for common risk factors in everyone to craft individual falls risk profiles

Tinetti et al. NEJM 1994

Risk factors for falls

Risk Factor	OR/RR	Risk Factor	OR/RR
Muscle weakness	4.4	ADL impairment	2.3
History of falls	3.0	Depression	2.2
Gait Impairment	2.9	Cognitive impairment	1.8
Balance impairment	2.9	Age > 80	1.7
Assistive device use	2.6	Vision impairment	1.5
Arthritis	2.4	Medications	Varies

AGS/BGS 2001

Gait/strength/balance

- Ask about functional status, balance, walking & transferring
  - Weakness & poor balance are not normal parts of aging!
- Testing Gait, Strength & Balance:
  - Timed Up & Go (TUG)
  - 30 Second Sit to Stands
  - 4 Stage Balance Test
  - Tinetti Gait & Balance
- Gait/balance training → **~20%** reduction in fall risk

Frick, et al. J Amer Geriatr Soc 2010

Gait/strength/balance

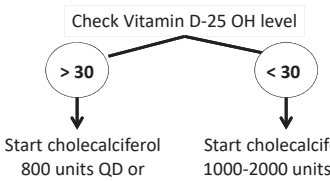
Hypothyroidism & B12 Deficiency

- Common, often overlooked
  - Vague symptoms, easily attributable to other chronic conditions
- Hypothyroidism → fatigue, muscle weakness, cognitive impairment, poor safety awareness
- B12 Deficiency → neuropathy, impaired balance

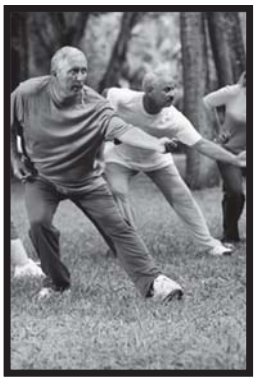
Younge, J. BMJ 2016
Rubenstein, L. Age & Ageing 2006

Vitamin D deficiency

- Vitamin D quickly increases muscle strength through calcium transport & protein synthesis
- In people with deficiency, **~26%** fall reduction can be observed within months **(NNT = 15)**



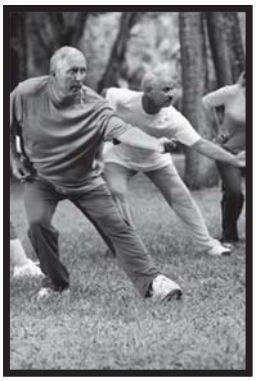
Bischoff-Ferrari et al. JAMA Int Med. 2004



TAI CHI

- RCT of 256 older Portland residents found that regular tai chi:
- Reduces fall risk by ~55%
- Reduces injurious falls (**NNT 9**)
- Reduces fear of falling
- Goal 1 hour three times a week

Li et al. J Gerontol A Biol Sci Med Sci 2005



TAI CHI

- RCT of 670 older adults found that twice weekly tai chi compared to multimodal exercise and stretching:
- Reduces falls by 58% compared to stretching (NNT 39) and 31% (NNT 200) compared to multimodal exercise
- Reduces serious injurious falls compared to stretching (p = 0.008)

Li et al. JAMA Int Med 2018

Tai Chi: Moving for Better Balance

https://public.health.oregon.gov/PreventionWellness/SafeLiving/FallPrevention/Pages/TaiChi.aspx

Home safety

- No throw rugs, mats, long cords
- Mark uneven surfaces
- Decrease clutter
- Chairs, toilet at right height
- Nightlights, grab bars, handrails
- Even, non-glare lighting
- Involving PT, OT, RNs in home safety modifications:
  - Cost effective
  - Reduces fall risk by **~34%**

Frick et al. J Amer Geriatr Soc 2010

HIGH RISK MEDICATIONS

- Oregonians over 65 take ~19 prescriptions per year
- Effect of high risk meds is additive

Antipsychotics	OR 1.6
Benzodiazepines	OR 1.5
Sedative-Hypnotics	OR 1.45
Antidepressants	OR 1.6
Antihypertensives	OR 1.24
Opioids*	OR 3.3-4.1
Anticholinergics	OR 1.3-2.1
Antiepileptics	OR 1.62

Woolcott et al. Arch Intern Med. 2009; Rolita et al. J Amer Geriatr Soc. 2013; Carbone et al. J Bone Miner Res. 2010; Rudolph et al. Arch Intern Med. 2008

Orthostatic hypotension

- Affects 18% of adults over 65
- Of those with OH (symptomatic or not):
  - HR for falls (community dwelling) = 2.5
- No association between falls and hypertension (controlled or uncontrolled) without orthostasis
- All those at risk should have orthostatic vital signs checked

Ooi et al. Am J Med. 2000
Gangavati et al. J Amer Geriatr Soc. 2011

Footwear

- Prospective 2-year study of 327 independent older adults found:
- Footwear matters …
  - Safest shoes = **athletic & canvas shoes** (others increase risk by 70%)
  - Going barefoot dramatically increases falls 10-fold (1000%)

Koepsell, JAGS 2004

Bifocals vs single focus lenses

- Randomized trial of 606 older multifocal wearers who had fallen in the past year or had Timed Up and Go > 15 seconds found:
  - Falls were prevented by downgrading bifocals/progressives to single focus lenses for community ambulators (**NNT = 2**)
  - For homebound, non-community ambulators, single focus lenses increased fall rate

Haran, BMJ, 2010

Back to Betty …

- BP 130/76, orthostatic BPs negative
- Slow gait, lost balance twice while walking
- Timed Up & Go = 16 seconds (normal < 14)
- 4 stage standing balance = made it to stage 2
- Wearing bifocals and backless shoes
- Vitamin D = 13 (low) B12 = 450 (nl)
  TSH = 1.2 (nl)

What should Betty do?

- 2-3 hours of tai chi every week
- Wear athletic or tennis shoes
- Change bifocals to a distance pair & reading pair
- Physical therapy for gait & balance training
- Add cholecalciferol 1000-2000 units daily
- Follow up in 3 months

Patient Education Materials

https://www.cdc.gov/steadi/patient.html

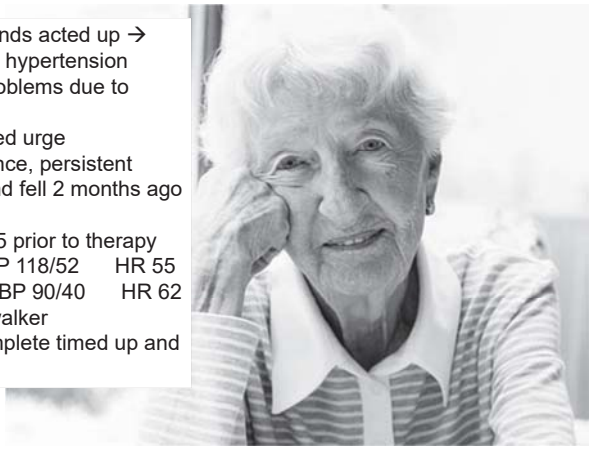
2 years later
Betty moved to Arizona to care for her sister, now back in Portland

Diagnosed with hypertension, insomnia

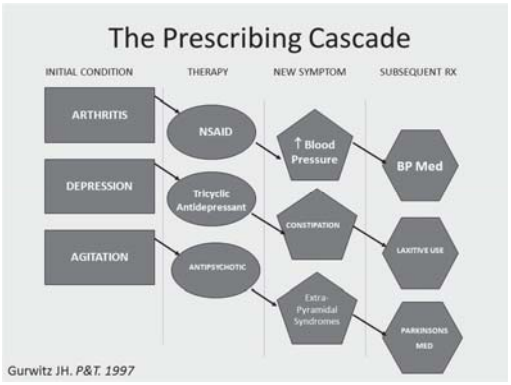
New medications: naproxen 440mg BID for arthritis, HCTZ 25mg QD, KCl 20mEq QD, amlodipine 5mg QD, metoprolol tartrate 25mg BID, Tylenol PM QHS

-OA of hands acted up → NSAID → hypertension
-Sleep problems due to nocturia
-Developed urge incontinence, persistent fatigue and fell 2 months ago

BP 155/85 prior to therapy
Seated BP 118/52 HR 55
Standing BP 90/40 HR 62
Using a walker
Can't complete timed up and go



What happened to Betty?



Prescribing Cascade

- Cycle of misdiagnosis of drug side effects as new symptoms or conditions resulting in the addition of more medication
- One of the main drivers of polypharmacy
  - Taking >4 medications (Rx or OTC) daily
  - Contributes to other geriatric syndromes, poor quality of life & higher symptom burden

Prevention is Key!

- Goal should be to avoid entering the prescription cascade, prevent polypharmacy
- Use the principles of safe prescribing and clinical references like the Beers List, START and STOPP guidelines

Thoughtful Prescribing

- What is the indication? Is it necessary?
- Think side effects
- Think renal impairment
- Think time to benefit

Think Side Effects

Drugs	Known Side Effects	Under-Appreciated Side Effects
Cholinesterase inhibitors (donepezil)	Bradycardia, AV block	GI distress, urinary incontinence, confusion
Amiodarone	Pulmonary, thyroid, ocular	Ataxia, fatigue, peripheral neuropathy
Digoxin	Multiple drug interactions	Confusion, visual changes, anorexia, weight loss
Rivaroxaban	Bleeding	Fatigue (less so with apixaban)
SSRIs/SNRIs	Hyponatremia, QT prolongation	Withdrawal syndrome-akathisia, anxiety, chills, irritability, malaise
Leviteracetam		Personality changes, irritability

Think Renal Impairment

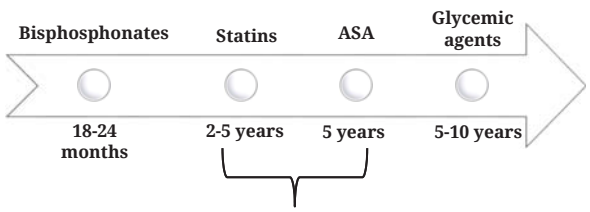
- Cockcroft-Gault
  - Underestimates renal function ~30% of time
  - Found in UptoDate or www.MDcalc.com or GFRcalc app
  - Found in Epic® at .gfrcg
- MDRD
  - Generally reported with lab results
  - Overestimates renal function ~50% of the time in patients ≥80 yo

Age	92
Weight	124 lbs
Cr	1.08
CrCl (per CG)	29.57 ml/min
CrCl (per MDRD)	48.44 m/min

Think Time to Benefit

	25th percentile		50th percentile		75th percentile	
Age	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**
75	6	7	10	12	15	17
80	4	5	8	9	11	13
85	2	3	6	7	8	10
90	1	2	4	5	6	7
Judge health status as being above 75th, at 50th, or below average (25th) for age and gender						

Think Time to Benefit



Remember the evidence for primary prevention in those over 75, with poor health is not clear …

Holmes, *Drugs and Ageing*, 2013

Tools for Thoughtful Prescribing

<u>Beers List</u>

- Evidence based list of high risk medications, drug-drug and drug-disease combinations for older adults
- 2019 latest update


TABLE 1. 2019 American Geriatrics Society Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults

Drug: System, Therapeutic Category, Drug(s)	Recommendation, Rationale, Quality of Evidence (QE), Strength of Recommendation (SR)
Anticholinergics *	
First-generation antihistamines: ■ Brompheniramine ■ Carbinoxamine ■ Chlorpheniramine ■ Clemastine ■ Cyproheptadine ■ Dexbrompheniramine ■ Dexchlorpheniramine ■ Dimenhydrinate ■ Diphenhydramine (oral) ■ Doxylamine ■ Hydroxyzine ■ Meclizine ■ Promethazine ■ Pyrilamine ■ Triprolidine	*Avoid* Highly anticholinergic; clearance reduced with advanced age, and tolerance develops when used as hypnotic; risk of confusion, dry mouth, constipation, and other anticholinergic effects or toxicity Use of diphenhydramine in situations such as acute treatment of severe allergic reaction may be appropriate *QE = Moderate; SR = Strong*

Tools for Thoughtful Prescribing


Section A: Cardiovascular System

1. Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors in the presence of chronic atrial fibrillation.
2. Aspirin (75 mg – 160 mg once daily) in the presence of chronic atrial fibrillation, where Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors are contraindicated.
3. Antiplatelet therapy (aspirin or clopidogrel or prasugrel or ticagrelor) with a documented history of coronary, cerebral or peripheral vascular disease.
4. Antihypertensive therapy where systolic blood pressure consistently > 160 mmHg and/or diastolic blood pressure consistently >90 mmHg; if systolic blood pressure > 140 mmHg and /or diastolic blood pressure > 90 mmHg, if diabetic.

Section B: Cardiovascular System

1. Digoxin for heart failure with normal systolic ventricular function (no clear evidence of benefit).
2. Verapamil or diltiazem with NYHA Class III or IV heart failure (may worsen heart failure).
3. Beta-blocker in combination with verapamil or diltiazem (risk of heart block).
4. Beta blocker with bradycardia (< 50/min), type II heart block or complete heart block (risk of complete heart block, asystole).
5. Amiodarone as first-line antiarrhythmic therapy in supraventricular tachyarrhythmias (higher risk of side-effects than beta-blockers, digoxin, verapamil or diltiazem).
6. Loop diuretic as first-line treatment for hypertension (safer, more effective alternatives available).

<u>START / STOPP criteria</u>

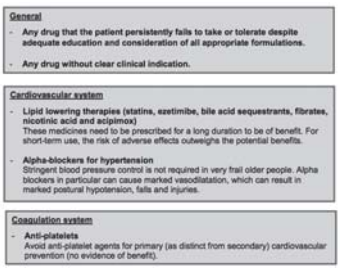
- Evidence based "do" and "don't" recommendations
- Drug-drug and drug-disease combinations
- Identify high risk combinations & omissions in ~20% of primary care patients

Ryan C, et al. Br J Clin Pharmacol 2009

Tools for Thoughtful Prescribing

<u>STOPPFrail List</u>:

- Focused list of low yield / risky treatments specific to patients with life limiting illness & poor prognosis
- Validated internally & externally (2017 & 2019)


General

- **Any drug that the patient persistently fails to take or tolerate despite adequate education and consideration of all appropriate formulations.**
- **Any drug without clear clinical indication.**

Cardiovascular system

- **Lipid lowering therapies (statins, ezetimibe, bile acid sequestrants, fibratee, nicotinic acid and acipimox)**
  These medicines need to be prescribed for a long duration to be of benefit. For short-term use, the risk of adverse effects outweighs the potential benefits.
- **Alpha-blockers for hypertension**
  Stringent blood pressure control is not required in very frail older people. Alpha blockers in particular can cause marked vasodilatation, which can result in marked postural hypotension, falls and injuries.

Coagulation system

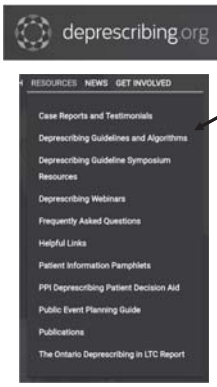
- **Anti-platelets**
  Avoid anti-platelet agents for primary (as distinct from secondary) cardiovascular prevention (no evidence of benefit).

1. Lavan AH, et al. Age and Ageing, 2017
2. Lavan AH, et al. Eur J Clin Pharmacol, 2019

What about the patient with polypharmacy?

- Use the rules & tools …
- Critically review all medications
  - Determine the indication, ask about effectiveness, review safety concerns
  - Stop those that can be discontinued, taper others, set a plan for removing 1-2 at a time
- Follow up
  - Successful med reduction is a process!

Tools for Successful De-Prescribing



Deprescrbing.org

- Evidence based deprescribing algorithms, patient materials & community support
  - PPIs, BZDs, Z-drugs, oral diabetic agents, antipsychotics, cholinesterase inhibitors
- Canadian Deprescribing Network (CADEN)

Back to Betty …

- Feeling terrible, would like to feel more energetic and walk more easily

- Discontinue HCTZ, amlodipine and KCl. Taper metoprolol over the next 1-2 weeks
  - BP goal ~140-150/80s
- Advise Betty to get 48-64oz of fluid every day
- Discontinue naproxen, increase Tylenol to 1000mg TID for arthritis
- Discontinue Tylenol PM due to anticholinergic side effects

6 months later
Betty is feeling much better

-Sleeping with melatonin, nightly bath
-Topical diclofenac & Tylenol for OA
-Started tai chi once a week
-Still dealing with urge incontinence but feels she is coping with it more easily

Traumatic Brain Injury (TBI): Neuropsychiatric Sequelae

David Mansoor, MD
Associate Professor of Psychiatry
February 2020

Overview

- Review epidemiology of TBI
- Discuss definition of TBI
- Discuss mechanisms of TBI and how severity is graded
- Review chronic cognitive, emotional, and behavioral changes that can occur after TBI
- Discuss TBI in relation to dementia
- Discuss approach to assessment and treatment

TBI Epidemiology

- 2.5 million ED visits; 282K hospitalizations; 56,000 deaths in the US in 2013[1]
  - 30% of all injury related deaths[1]
- 2% of population lives with TBI-associated disability[1]
- Economic impact in 2010: $76.5 billion[2]
  - Cardiovascular disease: $444 billion[3]

1) MWR Surveill Summ. 2017;66(9):1. Epub 2017 Mar 17
2) Coronado et al. Brain Injury Medicine, 2nd ed. Demos Medical Publishing. 2012
3) Centers for Disease Control, 2010

TBI Epidemiology

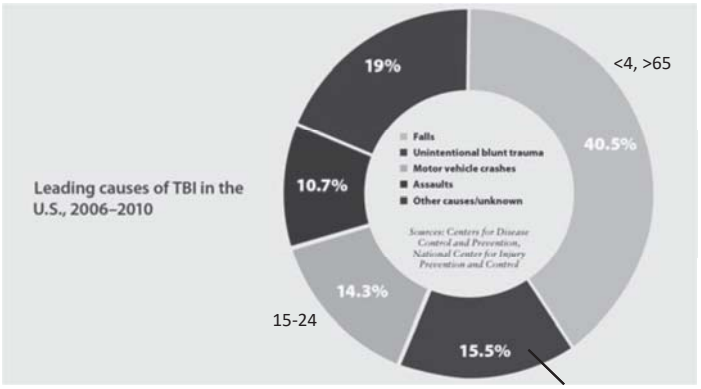
- Age: The highest rates of TBI were observed in older adults (≥75 years), very young (0 to 4 years), and young adults (15 to 24 years)
- Gender: Males had higher rates of TBI than females

MWR Surveill Summ. 2017;66(9):1. Epub 2017 Mar 17.

TBI Epidemiology

- Risk factors
  - (Age)
  - (Gender)
  - Prior TBI , particularly among athletes
  - Alcohol and drug use
  - Cognitive disorders

TBI Epidemiology



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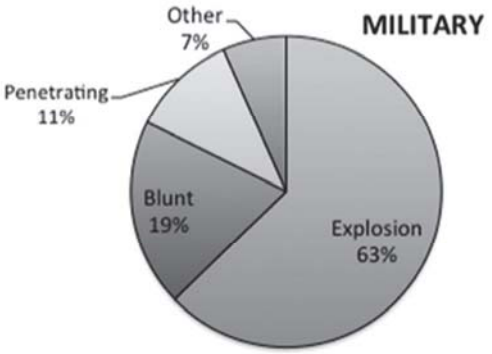

Journal of Biomechanical Engineering 136(2) · February 2014

TBI Definition

TBI Definition

Why is this important to define?

To diagnosis TBI related sequelae we need to establish that there was a traumatic brain injury

TBI Definition

- TBI is heterogeneous
- Traumatic brain injury:
  - A blow to the head that disrupts normal function of the brain

TBI Definition

- Disruption in the normal function of the brain due to an *external mechanical force*
  - that is indicated by the new onset or worsening of at least one of the following clinical signs immediately following the event:
    1. Any period of loss of consciousness (LOC)
    2. Any loss of memory for events before or after (post-traumatic amnesia (PTA))
    3. Any alteration in mental state (confusion, disorientation)
    4. Neurological deficits (including neuroimaging)

DSM 5

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DSM 5

TBI Definition

- Two categories of external mechanical forces
  - Contact/Impact
    - Brain comes into contact with some external object (includes the skull)
    - Damage to scalp, skull, and brain surface (contusions, lacerations, and hematomas)
    - Frequent sites of injury: frontal and temporal cortices
  - Inertial
    - Rapid acceleration/deceleration (velocity change) of the brain
    - Shearing forces/mechanisms
      - Axons and blood vessels, resulting in axonal injury, tissue tears, and intracerebral hematomas
      - Diffuse injury to white matter ("diffuse axonal injury")
    - Frequent sites: GM/WM junction, corpus callosum, the rostral brainstem

TBI Definition

- Two categories of external mechanical forces
  - Contact/Impact
    - Brain moves and strikes the inner surface of the skull
    - Leads to focal contusions, lacerations, and hematomas
    - Frequent sites of injury: frontal and temporal cortices
  - Inertial
    - Rapid acceleration/deceleration (velocity change) of the brain
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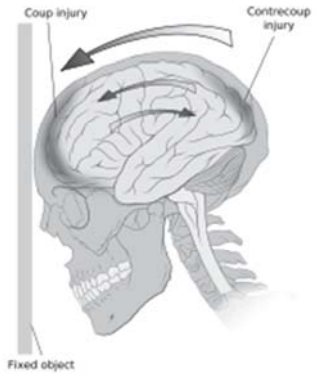
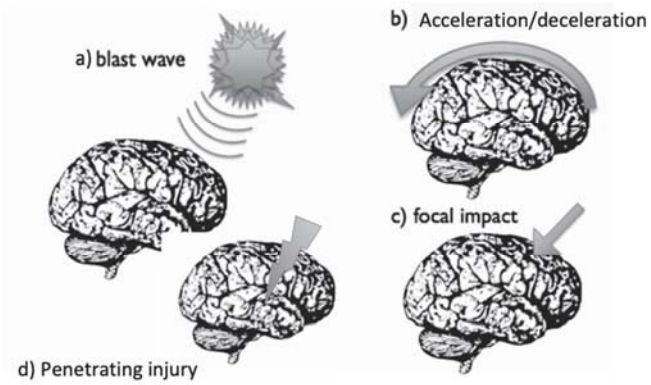


Coup-Contrecoup: moving head hits stationary object

TBI Definition



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    3. Any alteration in mental state (confusion, disorientation)
    4. Neurological deficits (including neuroimaging)

DSM 5

Loss of Consciousness

- Near or complete near lack of responsiveness to people or other environmental stimuli
- Have to investigate
  - Review records or ask patient:
    - "Did you lose consciousness?"
    - "Were you knocked out?"
    - "Did you black out?"
- Determined by duration

TBI Definition

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DSM 5

Post-Traumatic Amnesia and AMS

- State of confusion that occurs immediately after a head injury
  - Trouble forming new memories
    - Unaware of the injury, difficulty forming continuous memories
  - Disorientation to self, time, place
  - Impaired attention
  - Slow processing speed
  - Behavior change
    - Irritability, tension, anxiety, affective lability, impulsive, apathy, aggression, poor decision making
- Determined by duration

Trzepacz PT, Kennedy RE (2005)

TBI Severity Grading

Injury characteristic	Mild	Moderate	Severe
LOC	< 30 minutes	30 minutes – 24 hours	>24 hours
PTA	<24 hours	24 hours – 7 days	> 7 days
GCS	13-15	9-12	3-8

Severity is rated at the time of injury

DSM 5, 2013; Department of Veterans Affairs

GCS

BEHAVIOR	RESPONSE	SCORE
Eye opening response	Spontaneously	4
	To speech	3
	To pain	2
	No response	1
Best verbal response	Oriented to time, place, and person	5
	Confused	4
	Inappropriate words	3
	Incomprehensible sounds	2
	No response	1
Best motor response	Obeys commands	6
	Moves to localized pain	5
	Flexion withdrawal from pain	4
	Abnormal flexion (decorticate)	3
	Abnormal extension (decerebrate)	2
	No response	1

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    3. Any alteration in mental state (confusion, disorientation)
    4. Neurological deficits (including neuroimaging)

DSM 5

Neurological Signs

- Symptoms variable depending on the type and location of injury
  - Headache
  - Fatigue
  - Sleep difficulty
  - Vertigo
  - Tinnitus
  - Photosensitivity
  - Aphasia
  - Hemiparesis
  - Seizures
  - Visual disturbance

*New onset, progressive, or worsening symptoms

Neurological Signs

- Symptoms variable depending on the type and location of injury
  - Headache
  - Fatigue
  - Sleep difficulty
  - Vertigo
  - Tinnitus
  - Photosensitivity
  - Aphasia
  - Hemiparesis
  - Seizures
  - Visual disturbance
- Imaging
  - Acute: CT for GCS less than 15
    - Skull fx, hemorrhage, edema, contusion, DAI
    - Abnormal in 10% mTBI cases[1]
  - Post-acute: MRI
    - Not typically done unless atypical symptoms*
    - Encephalomalacia, gliosis, microhemorrhage (DAI)
    - Goal: further evaluate and enhance understanding of symptoms

*New onset, progressive, or worsening symptoms

1. J Rehabil Med. 2004

Neurological Signs

- The presence of neuroimaging lesions are prognostically important
  - An injury that otherwise meets criteria for mild TBI, but is associated with CT or MRI abnormalities is associated with cognitive and functional outcomes more similar to those of moderate TBI

Wortzel HS, Arciniegas DB. *Neurorehabilitation*. 2014

Activity

Grade This TBI

- 42-year old male who was in an MVA at age 24. He experienced LOC for 3 minutes, and describes a 4 day period of headache and poor attention. GCS was 15 upon assessment by first responders.
  - Mild
  - Moderate
  - Severe

Grade This TBI

- 42-year old male who was in an MVA at age 24. He experienced LOC for 3 minutes, and describes a 4 day period of headache and poor attention. GCS was 15 upon assessment by first responders.
  - Mild
  - Moderate
  - Severe

Chronic Sequelae

TBI Sequelae

- Acute disorder that can become a chronic disease
  - Cognitive and personality changes
  - Sensory and motor deficits

TBI Sequelae

- Cognitive and behavioral changes are more closely associated with long-term disability[1]
- Injury severity may help predict neuropsychiatric outcome[2]
  - Duration of PTA is the best predictor of behavior/emotional change
  - Duration of LOC is a good predictor of cognitive impairment[3]

1) NIH Concensus Development Panel on Rehabilitation of Persons with Traumatic Brain Injury. Rehabilitation of persons with traumatic brain injury. Journal of the American Medical Association. 1999; 282(10):974–83.
2)Tellier et al, 2009
3) Dikmen SS, Machamer JE, Winn HR, Temkin NR. Neuropsychological outcome at 1-year post head injury. Neuropsychology. 1995;9(1):80.

Mild TBI

Chronic Effects in **Mild TBI**

- **Postconcussion Syndrome**
  - Headache, dizziness, fatigue, irritability, anxiety, insomnia, memory loss, poor concentration, depression
- Symptoms are greatest within the first 7-10 days
- There is often full neurologic recovery after mTBI between 3-12 months
  - 15–30% of subjects develop prolonged neurocognitive and behavioral changes[1] (**persistent post-concussive syndrome**)
  - Deterioration of symptoms should trigger consideration of additional diagnoses

1. Daneshvar et al., 2011b

Chronic Effects in **Mild TBI**

- Factors associated with delayed recovery
  - Age
  - Premorbid psychiatric illness (depression, anxiety)
  - Premorbid history of brain damage (past TBI, dementia)
  - Social support
  - Pain
  - Sleep disorder
  - Substance Use
  - Compensation or litigation
  - Expectation of a poor outcome

Moderate/Severe TBI

Chronic Effects in **Moderate/Severe TBI**

- As many as 65% of moderate to severe TBI patients report long-term problems with cognitive functioning[1]
- 49% emotional and behavioral symptoms one year after the injury[2]

1. Whiteneck et al. 2004
2. Fann et al. 2004

Cognitive Changes

- Typically a mixture of deficits of varying degrees
  - Executive dysfunction (problem solving, set shifting, impulse control, self-monitoring)
  - Attention/concentration
    - Sustained, divided, selective
  - Learning and short-term memory
  - Processing speed
  - Speech and language

Personality Changes

- Emotional and behavioral disturbance are often expressed as personality change
  - Aggression
    - Risk factors: frontal lobe injury; premorbid mood, personality, or substance use disorder[1]
  - Irritability
  - Impulsivity, disinhibition (no filter)
  - Emotional lability
  - Apathy, lack of spontaneity, emotional indifference
  - Depression
    - High prevalence of MDD, up to 53% at 12 months [1]
    - Most frequent NBS of TBI
  - Anxiety
- More frequently reported after moderate to severe TBI[2]

1. Hibbard MR, Uysal S, Kepler K, Bogdany J, Silver J. Axis I psychopathology in individuals with traumatic brain injury. J Head Trauma Rehabil. 1998;13:24–39
2. Hesdorffer D, Rauch S, Tamminga C. Long term psychiatric outcomes following traumatic brain injury: a review of the literature. J Head Trauma Rehabil 2009; 24:452–9.

Diagnostic Language

Cognitive Changes: Diagnostic Language

- Case
  - 26-year old male who sustained a moderate head injury while in a MVA one year prior. He reports attention problems leading to difficulty completing tasks at work and home (particularly reading lengthy pieces of information), trouble learning new information such as telephone numbers or names, word finding difficulty, and an inability to concentrate in noisy environments.

Cognitive Changes: Diagnostic Language

- Diagnosis
  - Major or Minor Neurocognitive Disorder due to Traumatic Brain Injury
    - Minor: modest cognitive decline, no functional impairment
    - Major: significant cognitive decline, some functional impairment

Personality Changes: Diagnostic Language

- 65-year old with a history of head injury at age 40 while working as a logger. He has shown chronic irritability since then, which was not characteristic of him prior to the TBI. In addition, he has had symptoms of major depressive disorder successfully treated with antidepressant medication.

Personality Changes: Diagnostic Language

- Diagnosis
  - Psychiatric disorder due to another medical condition (TBI)
    - Depressive disorder due to TBI, with major depressive-like episode
      - (must establish that the symptoms are etiologically related to the TBI)

Physical Effects

- Headaches
  - Up to 30% experience chronic headache
    - Migraine, tension, cervicogenic (whiplash)
- Insomnia
  - Up to 83% of patients[1]
- Fatigue
- Low energy
- Dizziness
- Balance/coordination changes
- Sensory disturbance

Parcell et al, 2006

ASSESSMENT

Assessment

- TBI often a mix of localized and diffuse damage: neurocognitive effects can be very diverse, evaluation needs to be comprehensive
  - Clinical interview
    - History of present illness
    - Premorbid history and characteristics
    - Psychosocial factors
    - Collateral history
  - Cognitive testing
    - Attention, processing speed, executive function, memory
    - Matching profile of brain injury with the behavioral/cognitive circuitry this would disrupt

Assessment

- The goal of assessment is to determine the presence of cognitive, behavioral, emotional, and functional deficits
  - Clinical history
    - Determining TBI history and severity
  - Screening instruments
    - PHQ-9, GAD-7, PCL5
  - Cognitive testing
    - MMSE, MoCA, SLUMS lack sensitivity for mild TBI
  - Neurologic exam

Assessment

- Various assessment tools
  - Acute Concussion Evaluation (ACE) office version
    - Initial evaluation and diagnosis
      - Injury characteristic, symptom check list, risk factors for protracted recovery, red flags, follow-up plan
  - Neurobehavioral Symptom Inventory
    - Given serially to measure symptom change
    - 21 symptoms, none/mild/moderate/severe/v severe
  - Rancho Scale: 8 levels, from rehab through recovery
    - Typically moderate/severe TBI

Assessment

- **Neuropsych Assessment Referral Questions**
  - Track status during acute/post-acute recovery
  - Provide objective measures to track longer term recovery
  - Determine post-recovery final status (eg, "new baseline")
  - Assess independent living capacity (ADLs & IADLs)
  - Caregiver guidance
  - Guidance for placement decisions
  - Assess social adaptive functioning
  - Vocational and educational capacity

Assessment

- Enhanced sensitivity and specificity - enables multifactorial evaluation
  - Baseline ability
  - Psychiatric comorbidity
  - Motivation
  - Effects of fatigue, meds, etc.
- Better estimation of functional capacity
- Objective basis for longitudinal assessment

TREATMENT

Treatment

- Appreciation of slow recovery is important
- Physical and cognitive rest**
- Susceptible to periodic impairments with physical or psychological stress
  - Alcohol, sleep deprivation, lengthy travel, workload
  - Most notable in elderly and those with demanding work/school requirements

Treatment

- Psychoeducation / support (mild TBI)
  - Acute
    - Education on post-concussive symptoms
    - Reassurance and education on the expectation for complete recovery
    - Guidance regarding rest and gradual resumption of typical activities
  - Post-acute
    - Cognitive rehabilitation for attention deficits
      - Rote practice of basic skills, functional skill development
      - Metacognitive skills for self-management of cog difficulties
        - » Internal: self-monitoring, self-regulation
        - » External: reminders, organizational systems
    - Cognitive behavioral therapy for symptoms of depression and anxiety

Treatment

- Pharmacotherapy – symptom oriented
  - Antidepressants: depression, anxiety, mood lability, apathy
    - SSRIs/SNRIs > TCAs
  - Anticonvulsants: mood lability, impulsivity, severe aggression
  - Psychostimulants: inattention and other cognitive symptoms
  - Cholinesterase inhibitors: cognitive symptoms

Treatment

- Pharmacotherapy, continued
  - Antipsychotics: for extreme agitation or psychotic symptoms
  - Insomnia: trazodone, melatonin, mirtazapine (if mood symptoms), z-drugs (though we try to avoid them)
  - Medicines to avoid: anticholinergic, benzodiazepines
    - Interfere with functional recovery, prolong PTA

Association with Dementia

Dementia and TBI

- TBI may increase risk for Alzheimer's disease and other dementias
  - Linked to number and severity of head injuries
    - 17% increase in risk for mild TBI
    - 35% increase in risk for severe TBI[1]
    - 33% for 2 or 3 TBIs
    - 61% for 4 TbIs
    - 183% for 5 or more TBIs
- Important to control for other dementia risk factors: smoking, HTN, diabetes, etc.
  - Also try to prevent further TBIs!

Fann et al, Lancet Psychiatry, April 2018

Dementia and TBI

- **Chronic traumatic encephalopathy** is an emerging concept
  - Repeated head injuries
  - Tauopathy, preference for superficial cortical layers distributed around small blood vessels
  - No specific clinical syndrome, imaging feature, or other biomarker
  - Clinical features:
    - Cognitive impairment: memory and executive function
    - Behavior change: aggression, paranoia, impulsivity
    - Mood disorders: depression, anxiety, suicidality
    - Neurologic change: parkinsonism

Summary

- A bump on the head may have variable consequences depending on previous vulnerabilities (eg, age), what kind of injury was sustained, and how the brain reacted to it
- TBI can present with persistent cognitive and behavioral symptoms
  - This can be assessed and symptomatically treated

The End

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