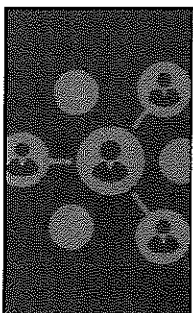


Reconnect & Rediscover:
A Convening Pediatric Experts
and Advocates
Oct. 2-4, 2021

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Experts in pediatrics, Advocates for children. 1

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**Preventing and Treating
Viral Infections in Children
and Adolescents in 2021**

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Speaker Disclosure

- No financial disclosures

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Objectives

1. Explore the intracellular life cycle of viral pathogens.
2. Review Immunizations that prevent or mitigate viral infections including influenza, polio, rotavirus, hepatitis A, hepatitis B and human papillomavirus.
3. Discuss prescribing and monitoring antiviral treatment for influenza, varicella, herpesvirus, HIV, and Hepatitis C, including emerging therapies

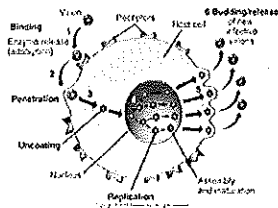


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Stages of Viral Infection of a Host Cell

- Obligate intracellular parasites
 - Dependent on host cells
 - No metabolism or incapable of independent reproduction
- Permissive host cell
 - Viron binds to receptors on the plasma membrane
 - Penetrates the cell wall
 - Replicates and matures
 - Buds and releases from the plasma membrane



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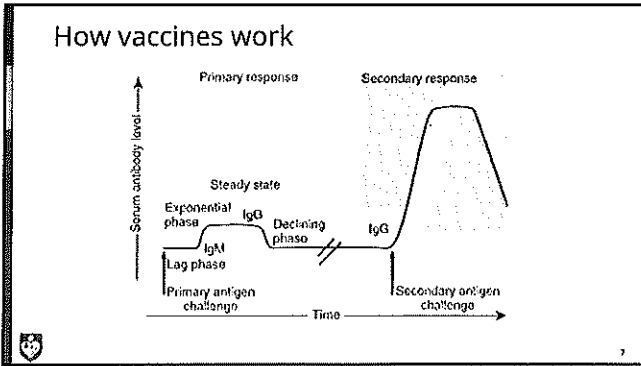
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Treatment of Viral Infections

- Prevention
- Prevention of viral replication
- Treatment to assist host response



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- ### Vaccines to Prevent Viral Infections
- Polio
 - MMR
 - Varicella
 - Rotavirus
 - Influenza
 - Hepatitis A
 - Hepatitis B
 - Human papillomavirus
 - COVID-19
 - Ebola
 - Small pox
 - Yellow fever
 - Zoster (shingles)
 - Rabies
 - Japanese Encephalitis virus

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- ### Vaccine Effectiveness
- Polio (IPV)
 - Trivalent vaccine
 - 90-100% after 2 doses, 99-100% after three doses
 - MMR
 - Measles: 94% after 1st dose if given at 12 months, ≥ 99% after 2nd dose
 - Mumps: 78% after 1st dose, 88% after 2nd dose, 88% after 3rd dose
 - Rubella: 95% after 1st dose, 99% after 2nd dose
 - Varicella
 - 70-90% after first dose, 98.3% after second dose
 - Immunity may wane, in Italian study 34% of fully vaccinated young adults had inadequate titers
 - Rotavirus
 - 74% against G1-G4 rotavirus gastroenteritis, 98% effective against severe disease
- Marin et al, 2018; McLean et al, 2013; Bianchi et al, 2021

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Vaccine Effectiveness

- Hepatitis A
 - 97-100% after 1st dose, 100% after 2nd dose
- Hepatitis B
 - HBV birth dose 75% effective in preventing perinatal HBV transmission
 - Combined with HBIG 94% effective
 - Infants and children: > 95% after 3-dose series
 - Adolescents: > 95% after 3 doses
 - Immune Memory: 15% to 50% have low or undetectable anti-HBs 5 to 15 years after vaccination
- Human papillomavirus (HPV9)
 - 2 doses (age 9 to 14 yrs): > 97.9%

Meltes et al, 2016; Nelson et al, 2020; Shillie et al, 2018

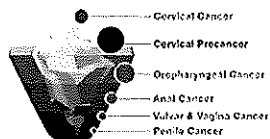


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Vaccine Effectiveness

- Human papillomavirus (HPV9)
 - 2 doses (age 9 to 14 yrs): > 97.9%
 - 3 doses: 93-100%



Meltes et al, 2016:

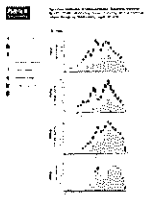


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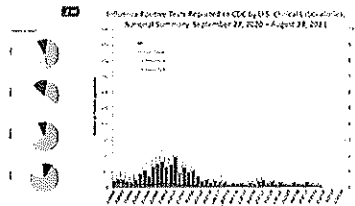
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Influenza

2019-2020



2020-2021

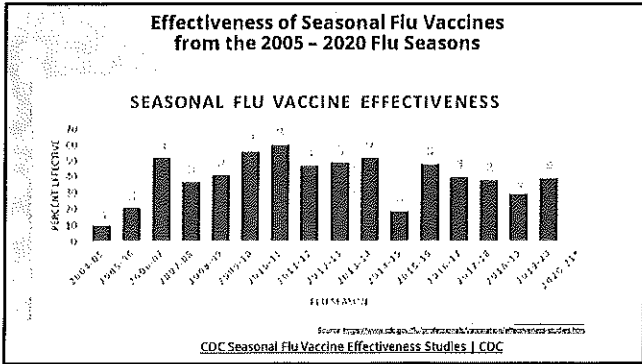


Influenza Activity from Reportable to CDC by U.S. City - Fall (October 2020 - November 2020) - Weekly

National Center for Immunization and Control

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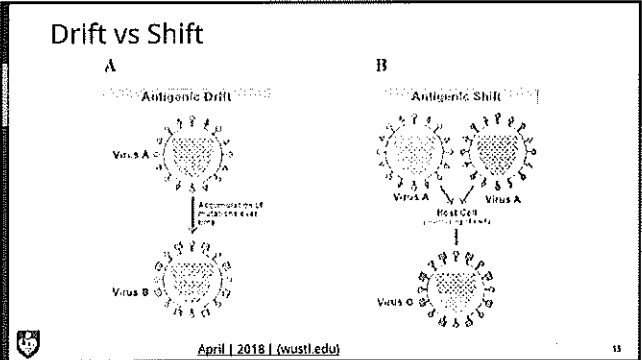


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Antigenic "Drift"

- "Good match" is 50% to 60% effective
 - Range since 2003 has been 10% to 60% effective
 - Influenza A genetically "drifts" from season to season
- 2017-2018 Vaccine was overall 36% effective
- 2018-2019 vaccine was overall 47% effective
- 2019-2020 was overall 39% effective

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Influenza Vaccine effectiveness 2019-2020

- All vaccine types, against influenza A or B viruses
 - All ages 39% effective
 - 6 mo to 8 yrs – 33% effective
 - 9yr to 17 yr – 37% effective
- Effectiveness against influenza A(H1N1)pdm09 viruses
 - All ages 31%
 - 6 mo to 8 yrs – 22%
 - 9 yrs to 17 yrs – 29%
- Effectiveness against influenza B/Victoria viruses
 - All 44%
 - 6m to 8 yrs – 38%
 - 9 yrs to 17 yrs – 39%



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2021-2022 Influenza vaccine

Composition

Vaccine	Approved Ages	Dose volume
Flucelvax Quadrivalent	6 months to 15 months 18 years	0.25 mL 0.5 mL
Flucelvax Quadrivalent	16 months to 17 years	0.5 mL
Flucelvax Quadrivalent	18 months to 15 months 18 years	0.25 mL or 0.5 mL 0.5 mL
Flucelvax Quadrivalent	16 years	0.5 mL
Flucelvax Quadrivalent	18 years	0.5 mL
Flucelvax Quadrivalent	16 years	0.7 mL
Flucelvax Quadrivalent	16 years	0.5 mL

- A/Victoria/2570/2019 (H1N1)pdm09-like virus (for egg-based vaccines) OR an A/Wisconsin/588/2019 (H1N1)pdm09-like virus (for cell culture-based and recombinant vaccines)
- A/Cambodia/e0826360/2020 (H3N2)-like virus
- B/Washington/02/2019 (Victoria lineage)-like
- B/Phuket/3073/2013 (Yamagata lineage)-like virus



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Flu Surveillance

- www.cdc.gov/flu
- Weekly flu activity surveillance
- Virologic surveillance
 - Prevalence of Type A or B, plus subtypes
- Resistance patterns



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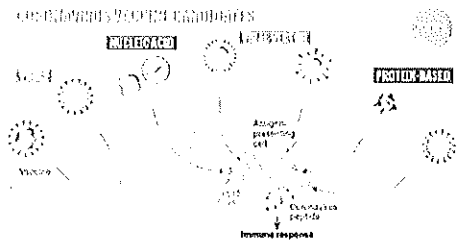
Flu Surveillance

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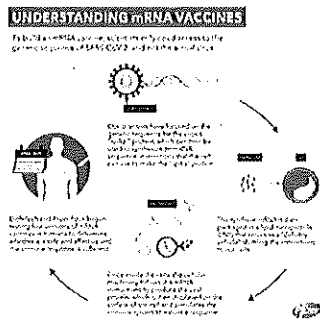
COVID19 vaccine



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mRNA vaccines



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mRNA vaccines

- Lipid nanoparticle-encapsulated, nucleoside-modified mRNA vaccine encoding the stabilized prefusion spike glycoprotein of SARS-CoV-2
- Pfizer vaccine
 - 92% efficacy after 2 doses
- Moderna vaccine
 - 94% efficacy after 2 doses



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Success
The mRNA COVID-19 vaccines are the first to be authorized for use in the United States.

1 mRNA Vaccines
The mRNA vaccines are made of a synthetic mRNA molecule that encodes the genetic instructions for making the spike protein.

2 Falling forward
The mRNA vaccines are made of a synthetic mRNA molecule that encodes the genetic instructions for making the spike protein.

3 Love these lipids
The mRNA vaccines are made of a synthetic mRNA molecule that encodes the genetic instructions for making the spike protein.

How mRNA COVID-19 Vaccines Work

The mRNA vaccine is made of a synthetic mRNA molecule that encodes the genetic instructions for making the spike protein.

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For more information about the mRNA COVID-19 vaccines, visit <https://www.fda.gov/vaccines-blood-biologics/sars-cov-2-vaccines>

1-800-368-5938

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Johnson & Johnson Janssen Pharmaceuticals

- Application submitted to FDA
- Recombinant vector vaccine that uses a human adenovirus to express the SARS-CoV-2 spike protein
- Pros
 - highly specific delivery of antigens to target cells and high expression of antigen after vaccination
 - often a single dose is enough to stimulate long-term protection



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COVID19 vaccine for children

- Potential approval of Pfizer for 5 to 11 yr olds by end of October
 - Currently in phase III trials
 - 6mo to 11 yrs being studied
- Moderna
 - Currently studying age 6 mo to 11 yrs
 - Phase II/III trials
- Johnson & Johnson
 - Adolescent trials in process

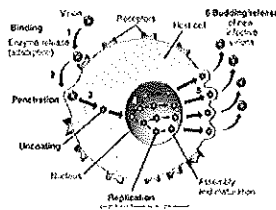


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Challenges in Developing Antivirals

- Viruses are parasites
- Antivirals either block entry or work inside the cell
- Many antivirals nonselective
- Peak replication may happen before symptoms present
- Viruses quickly mutate

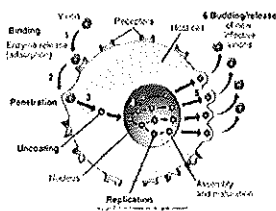


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Challenges in Developing Antivirals

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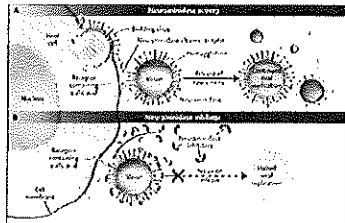


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Antivirals for Influenza: Neuraminidase Inhibitors

- Osetamivir (Tamiflu®)
 - PO age 1 year or older
 - Unlabeled 3 mo to 1 yr
 - BID for 5 days
- Zanamivir (Relenza®)
 - Inhaled age ≥ 7 yrs
 - BID for 5 days
- Peramivir (Rapivab®)
 - IV age ≥ 2 yrs
 - One dose



CDC.gov/flu

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Neuraminidase Inhibitors: Adverse effects

- Osetamivir
 - Nausea and Vomiting
- Zanamivir
 - Bronchitis, cough, and shortness of breath
- Peramivir
 - Diarrhea (8%)
 - Vomiting (3% in children)
 - Rash, EM, SJS
- Breastfeeding:
 - Osetamivir is poorly excreted in breast milk

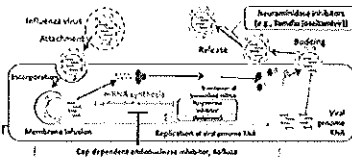


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Antivirals for Influenza: Endonuclease Inhibitor

- Baloxavir marboxil (Xofluza)
 - ≥ 12 yrs one PO dose
- Dose by weight:
 - 40 kg to 80 kg: 40 mg
 - > 80 kg: 80 mg
- Avoid co-administration with dairy products, calcium-fortified beverages, antacids, or oral supplements (e.g., calcium, iron, magnesium, selenium, or zinc).
- Safety and efficacy in patients less than 12 years of age or weighing less than 40 kg have not been established
- Adverse effects:
 - Diarrhea



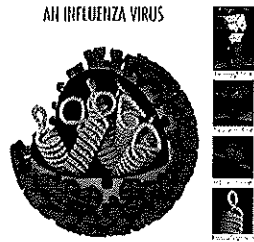
CDC.gov/flu

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Antivirals for Influenza: Adamantanes

- Amantadine
- Rimantadine (Flumadine)
- Adverse effects:
 - Orthostatic hypotension, syncope
 - Dizziness, delusions, hallucinations, paranoia



CDC.gov/flu

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Antivirals for Influenza Prophylaxis

- Oseltamivir (Tamiflu®)
 - PO age 1 year or older
 - Once a day for 5 days
- Zanamivir (Relenza®)
 - Inhaled age \geq 7 yrs
 - Once a for 5 days
- Peramivir (Rapivab®)
 - Not recommended
- Baloxavir marboxil (Xofluza)
 - One dose, same as treatment dose



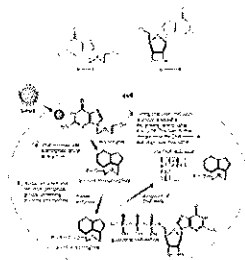
CDC.gov/flu

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Antivirals for Varicella

- Acyclovir
 - Start within 24h of onset
 - Immunocompetent host:
 - PO 20 mg/kg/dose 4 times daily X 5 days
 - Immunocompromised host:
 - IV 10 mg/kg/dose q 8 h x 7 to 14 days
- Valacyclovir
 - 20 mg/kg/dose TID x 5 days
- ADRs
 - Nephrotoxic



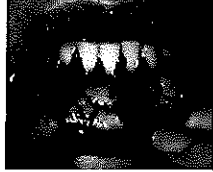
CDC.gov/chickenpox; Albrecht, 2020

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Antivirals for Herpesvirus (HSV1)

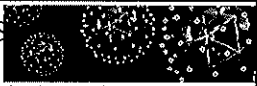
- Gingivostomatitis
 - Acyclovir
 - 20 mg/kg/dose QID x 5 to 7 days
 - 400 mg 5 times a day x 7 days
 - 200 mg five times a day x 7 days
 - Valacyclovir 1 gm BID x 7 days
 - Famcyclovir 250 mg TID x 7 d
- Cold sores
 - No therapy
 - Episodic therapy
 - Acyclovir 400 mg TID x 5 days
 - Valacyclovir 2 gm BID x 1 day
 - Famcyclovir 750 mg BID x 1 day



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Antivirals for Herpesvirus (HS

- First clinical episode
 - Acyclovir
 - 400 mg TID x 7-10 days
 - 200 mg five times a day x 7-10 days
 - Valacyclovir 1 gm BID x 7-10 days
 - Famciclovir 250 mg TID x 7-10 d
- Suppressive therapy
 - Acyclovir 400 mg BID
 - Valacyclovir 500 mg daily or 1 gm daily
 - Famciclovir 250 mg BID
- Episodic therapy for Recurrent Infections
 - Acyclovir
 - 400 mg TID x 5 days
 - 800 mg BID x 5 days
 - 800 mg TID x 2 days
 - Valacyclovir
 - 500 mg BID x 3 days
 - 1 gm daily x 5 days
 - Famciclovir
 - 125 mg BID x 5 d
 - 1 gm BID x 1 day
 - 500 mg once, followed by 250 mg BID x 2 days



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Preexposure prophylaxis (PrEP) for HIV

- PrEP reduces risk of getting HIV from sex by 99%
- PrEP approved for adolescents in 2018 (Descovy, Truvada)
- PrEP reaches maximum protection from HIV for receptive anal sex at about 7 days of daily use.
- For receptive vaginal sex and injection drug use, PrEP reaches maximum protection at about 21 days of daily use.



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Prescribing PrEP for Adolescents

- Considerations when prescribing for adolescents
 - PrEP is safe in adolescents
 - Screen for barriers related to medication and care costs
 - Medication adherence is required
 - Monthly clinic visits initially, then quarterly
 - Continue to screen for barriers to help them persist with treatment
- Who should be offered PrEP?
 - Sexually active gay and bisexual men without HIV
 - Sexually active heterosexual men and women without HIV
 - Sexually active transgender persons without HIV
 - Persons without HIV who inject drugs
- Follow state laws about consent in adolescents



Tanner et al, 2020, *Learn About PrEP | Preventing New HIV Infections | Clinicians*

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Prescribing PrEP for Adolescents

- Baseline assessment before prescribing PrEP
 - HIV testing
 - Renal function
 - Hepatitis B serology
- Approved medications (weight > 35 kg)
- emtricitabine and tenofovir disoproxil fumarate (Truvada)
 - One tablet (200 mg/300 mg) once daily with or without food
- emtricitabine and tenofovir alafenamide (Descovy)
 - One tablet (200 mg/ 25 mg) daily with or without food
- ADRs
 - GI: nausea, abdominal pain, diarrhea
 - HA



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Prescribing PrEP for Adolescents: Monitoring

Time Interval	Services at Each Visit
At 3 months after PrEP initiation:	<ul style="list-style-type: none"> • Test for HIV. • Measure serum Cr and CrCl. • Provide medication adherence and behavioral risk reduction support. • Additionally, for <ul style="list-style-type: none"> • MSM: screen for bacterial STIs*; • Women with reproductive potential: test for pregnancy; and • PWID: assess access to sterile needles/syringes and to drug treatment services.
Every 3 months after the first 3-month follow-up	<ul style="list-style-type: none"> • Test for HIV. • Provide medication adherence and behavioral risk reduction support. • Additionally, for <ul style="list-style-type: none"> • MSM: screen for bacterial STIs*; • Women with reproductive potential: test for pregnancy; and • PWID: assess access to sterile needles/syringes and to substance use disorder treatment services.



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Hepatitis C

- 2.4 million with Hep C in US
- Genotypes 1a, 1b, 2, and 3 most common in US
- Children/adolescents get infected by:
 - Maternal transmission at birth
 - IV drug use

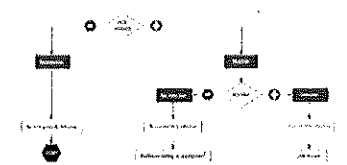


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Testing for Hepatitis C

Supplemental Testing Algorithm for Identifying
Chronic Hepatitis C Virus (HCV) Infection



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Hepatitis C Treatment: Expanded Age Range in Pediatric Patients

- glecaprevir and pibrentasvir (**Mavyret**) for chronic hepatitis C genotype 1, 2, 3, 4, 5 or 6 infection
 - Expanded the Indication to adolescents 12 years and older or weighing at least 45 kilograms (kg); previously approved in adults
- Sofosbuvir (**Solvadi**) for chronic hepatitis C genotype 1 or 4 infection
 - Expanded age range to patients age 3 to 11 years
- ledipasvir and sofosbuvir (**Harvoni**) for chronic hepatitis C genotype 1, 4, 5 or 6 infection
 - Expanded age range to patients age 3 to 11 years; and at least 17 kg
- Sofosbuvir and velpatasvir (**Eplclusa**) for chronic hepatitis C genotypes 1, 2, 3, 4, 5 & 6
 - Expands age range to age 6 yrs or older, weighing at least 37 lbs



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Antiviral Therapy for Hepatitis C infection

- Goal eradicate HCV RNA
 - Undetectable RNA level at 12 weeks completion of therapy
- Regimen selection
 - Based on genotype
 - Rapidly evolving guidelines
 - www.hcvguidelines.org
- Monitoring
 - Viral monitoring throughout therapy
 - Toxicity is rare
 - CBC, Cr, liver enzymes, bilirubin
 - Recheck viral load 12 weeks after completing therapy



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Immune Globulins for Viral Infections

- Passive immunity
- Immune globulin (IG)
- Hepatitis B IG
- Varicella Zoster Immune Globulin (VARIZIG)



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Immune Globulin (IG)

- Passive immunity for
 - Hepatitis A
 - Preexposure prophylaxis
 - postexposure: within 14 days and/or prior to manifestation of disease
 - Measles
 - Within 6 days of exposure in an unvaccinated person
 - Rubella
 - Postexposure prophylaxis exposed pregnant women
 - Varicella
 - Immunosuppressed patients when varicella zoster immune globulin is not available
- Dosage based on product and indication
- Drug Interactions: no live vaccines 8 to 11 mo (MMR, varicella)



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Hepatitis B IG

- Passive administration of anti-HBs
- Post-exposure prophylaxis
 - Needle stick, ocular or mucosal exposure or within 14 days of sexual exposure
- Prevention of Hep B after liver transplant
- Perinatal exposure
 - Infants born to HBsAg-positive mother
 - May be given at same time as HBV
- Dosing based on exposure type and age
- Drug Interactions: no live vaccines 8 to 11 mo (MMR, varicella)



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Varicella Zoster Immune Globulin (VARIZIG)

- Passive immunity for varicella in high-risk persons
 - Immunocompromised children and adults
 - Newborns of mothers with varicella
 - Hospitalized premature infants exposed to varicella
 - Pregnant women without immunity exposed to varicella
- Dosing based on weight in children
- Drug Interactions: no live vaccines 8 to 11 mo (MMR)



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Take Aways

- Viral infections are difficult to treat
- Prevention is best
- New vaccines and therapies emerging



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