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Hepatitis C – An Update for Nursing and Primary Care

SK HIV/HCV Nursing Education Event
September 12, 2015
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Regina Qu'Appelle Health Region

Disclosures

University of Saskatchewan

- **I have received consulting fees and honoraria from the following companies:** Merck, Gilead Sciences, Bristol Myers Squibb, Pfizer, Janssen, Boehringer-Ingelheim, Abbvie.
- **I have received funding for regional and provincial programming from the following companies:** Merck, Gilead Sciences, Bristol Myers Squibb, ViiV, Janssen, Abbvie.
- **I currently participate in clinical trials with the following companies:** Gilead Sciences, ViiV, Merck, Bristol Myers Squibb.
- If you detect **any** commercial bias, please tell me ASAP! Email: *alexander.wong@usask.ca*

Contacting Us…

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- For any questions, criticisms, patient care issues, or clarifications in southern Saskatchewan:
  - **Email:** alexander.wong@usask.ca
  - **Pager:** Call RGH switchboard at 306-766-4444 and ask for myself, ID physician on-call, or infectious diseases clinic.
  - **Clinic:** Call 306-766-3915 to speak with our clinic nurses for help with patient issues or referrals. Fax referrals to 306-766-3995.

- For referrals in central/northern Saskatchewan, contact the Positive Living Program based at RUH:
  - **Clinic:** Phone 306-655-1783, Fax 306-655-0614
  - **Web:** *https://www.saskatoonhealthregion.ca/locations_services/Services/Positive-Living/Pages/Home.aspx*

- "You test, we'll do the rest."

Patient Case

- 36M, Caucasian, healthy, presents for annual H&P. Never previously been seen by primary care.
- No identified risk factors for hepatitis C such as injection drug use, incarceration, etc.
- No recollection of previous testing.
- Active with several female partners in casual sexual relationships. No sex trade activity, no previous STDs.
- You check eHealth Portal (https://portal.ehealthsask.ca) – no testing for STDs or HIV / HAV / HBV / HCV done since 2011.
- **Do you screen for HIV? Do you screen for Hepatitis C? Do you screen for other conditions?**

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- **Do you screen for HIV? Do you screen for Hepatitis C? Do you screen for other conditions?**

Other Relevant Questions

- What tests do you order?
- What do you do when your hepatitis C “screening tests” come back positive? What do these tests mean?
- What do you tell the patient?
- What additional workup can/should you do to assist and expedite referral?
- Who can you refer to in southern / central / northern Saskatchewan for specialized care?

The SK HIV Epidemic

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- **The Epidemic is Unique.**
  - **Worldwide:** heterosexual > MTCT > MSM > IVDU
  - **NA/Europe/Australia:** MSM > heterosexual > IVDU > MTCT
  - **Saskatchewan:** IVDU > heterosexual > MSM > MTCT

- **Background**
  - Epidemic of injection drug usage, predominantly in urban cores and rural/remote reserve communities.
  - Disproportionately affected populations in these communities, namely First Nations / Aboriginal / Metis populations.
  - **Urban:** IV cocaine (similar to early years in BC)
  - **Rural:** injection of prescription drugs (benzos, stimulants, opiates).
  - **IV cocaine** → frequent usage, higher relative chaos compared to opiate usage, no available substitution therapy.

Food For Thought.

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- **Aboriginal vs. Non-Aboriginal Populations**
  - In 2011, national rate of HIV infection = 6.4 / 100K.
  - SK rate of HIV infection = 17.2 / 100K.
  - ~80% of HIV diagnoses in 2011 in Aboriginal / FN population, comprising 15.6% of SK population (Statistics Canada).
  - Therefore, rate of infection in Aboriginal population = 88 / 100K (14x national average, ~ Nigeria).
  - Non-Aboriginal infection rate = 4.1 / 100K, 36% below national average.
- **An "Epidemic of Injection Drug Use"**
  - SK has the highest reported rates of co-infection with hepatitis C and HIV in the world. In parts of SK, co-infection rates > 80%.
  - In RQHR, ~60% of HIV+ individuals are positive for anti-HCV.
  - In A-Track, ~40% of all participants were positive for anti-HCV.

Hepatitis C – Basics

- Single-stranded linear RNA virus.
- In North America, most transmissions are secondary to injection drug use.
- Sexual transmission is uncommon, but incidence higher in MSM with localized epidemics well-reported.
- **Other modes of transmission:**
  - Blood transfusion. (Risk = 1 per 1,000,000 per unit transfused.)
  - Organ transplantation.
  - Perinatal transmission. (~5% mono-infected, ~10% co-infected)
  - Percutaneous exposures.
  - Household transmissions (rare).

Hepatitis C – Basics

- **Canada:** ~300,000 infected, 1% prevalence, ~25% unaware of diagnosis, but data may be inaccurate.
- **USA:** Prevalence ~1.6%, but 3.6% in “baby boomer” cohort (born b/w 1945-1965, ages 50-70).
- Canadian screening guidelines have historically emphasized risk-factor based screening:
  - Patients who engage in risk behaviours.
  - Patients with clinical signs / symptoms suggestive of HCV.
- **Problem:** Risk factor based screening is ineffective.
  - Many providers unaware of risk factors for HCV.
  - No time or inadequate knowledge to provide counselling.

HCV – Natural History

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- Infection with hepatitis C virus causes acute hepatitis C and **MAY** cause chronic hepatitis C.
- **Acute Hepatitis C**
  - ~25% experience clinical symptoms, remainder have mild course or asymptomatic (anti-HCV+, HCV RNA+)
  - 75-80% progress to chronic infection (anti-HCV+, HCV RNA+), 20-25% will clear spontaneously (anti-HCV+, HCV RNA-)
- **Chronic Hepatitis C**
  - 60-80% of patients will develop chronically elevated liver enzymes, and if untreated, ~50% will progress to cirrhosis over 10-20 years.
  - Proportion may develop end-stage liver disease or hepatocellular carcinoma; clinical outcomes include transplantation, resection / ablation, or death.

HCV – Natural History

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- Most patients with chronic infection are asymptomatic or have mild, non-specific symptoms such as fatigue.
- Presence or absence of symptoms is not reflective of degree of underlying disease activity.
- Various risk factors predict increasing risk of fibrosis:
  - **Age:** older at time of acquisition = increased risk of progression
  - **Ethnicity:** progression slower in blacks.
  - **Gender:** males progress quicker than females.
  - **HIV Co-Infection:** accelerated fibrosis in co-infected patients.
  - **Obesity:** increased risk of hepatic steatosis and progression.
  - **Behavioural: alcohol intake**, marijuana usage (hepatic steatosis and subsequent progression of fibrosis).

Hepatitis C – Genotypes

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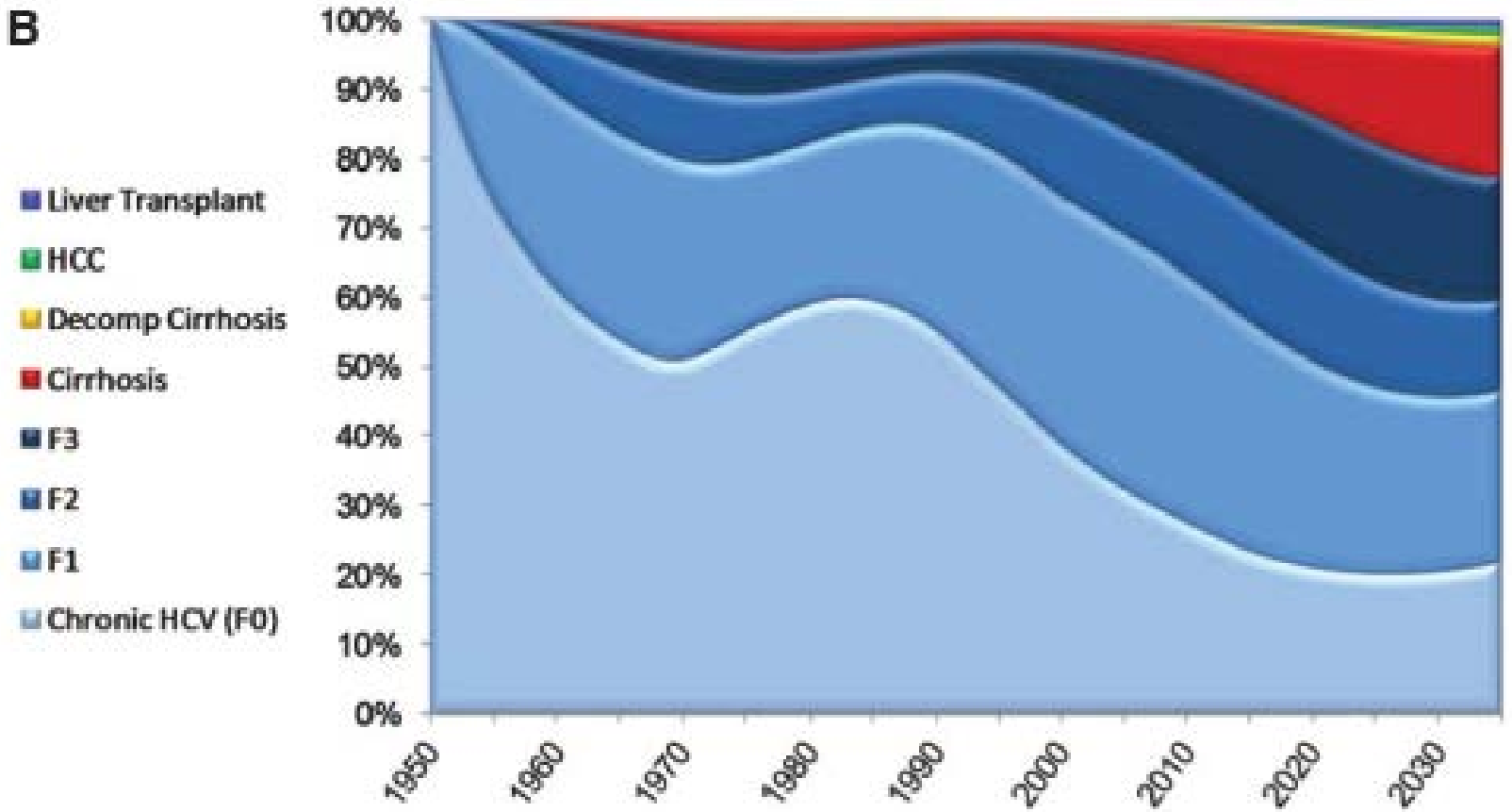
- Highly heterogeneous virus with 11 distinct genotypes, many subtypes. Most common genotypes = 1 through 6.
- Genotypes 1-3 have worldwide distribution.
  - **Genotype 1:** North America & Northern Europe.
  - **Genotype 2:** Far less common in NA & Europe.
  - **Genotype 3:** Endemic in SE Asia, less so elsewhere.
  - **Genotype 4:** Middle East, central Africa, Egypt.
  - **Genotype 5:** South Africa.
  - **Genotype 6:** Asia.
- Genotypes matter because they determine response to various forms of antiviral treatment.
- **RQHR: 61% G1**, 4% G2, **31% G3**, 5% mixed.

Hepatitis C – Impact



- Increasing burden of advanced disease as time progresses…

Myers RP et al, *Can J Gastroenterol Hepatol* 2014;28:243-50.

Hepatitis C – Impact

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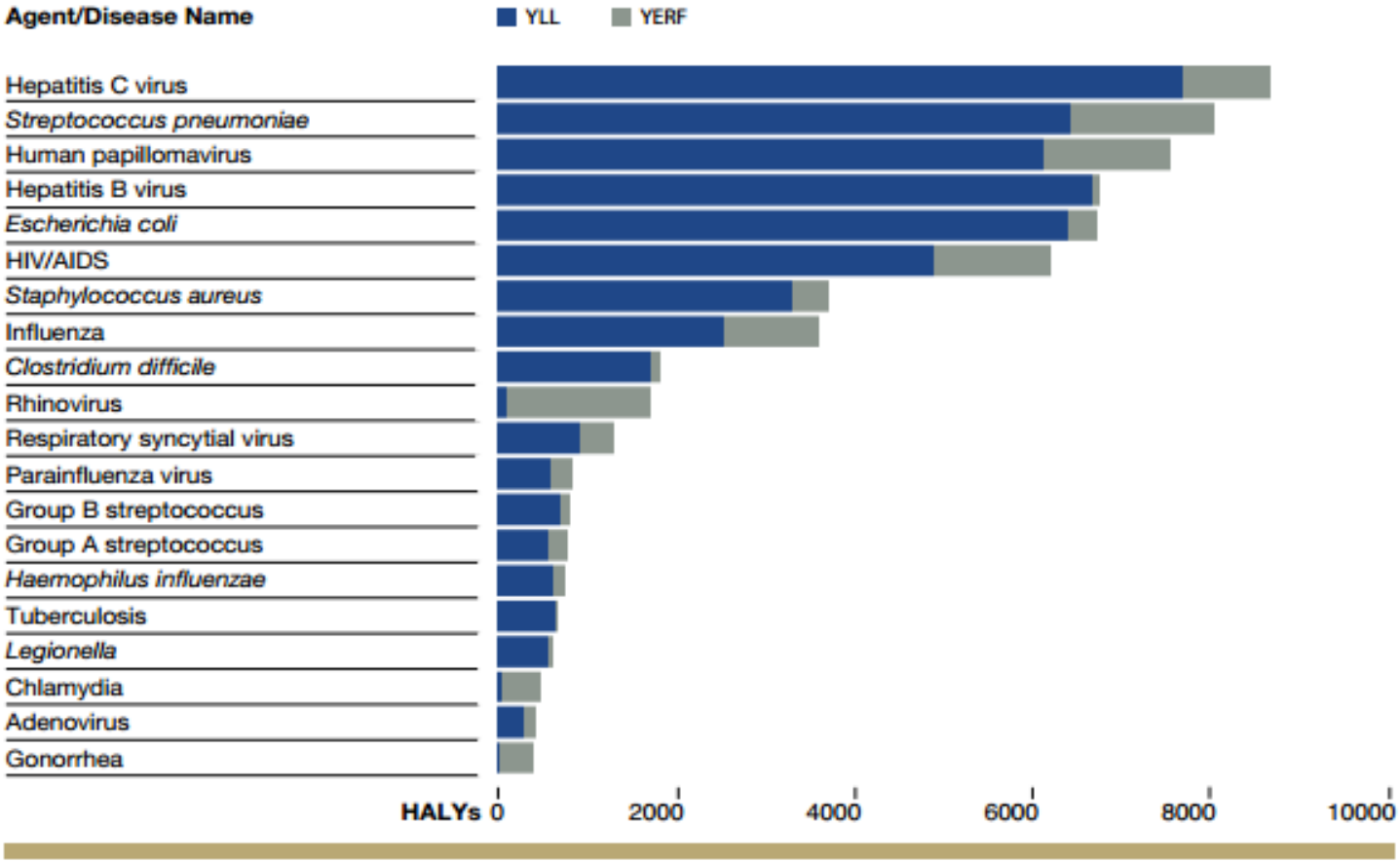
Exhibit 3.5

Years of life lost due to premature mortality (YLL), year-equivalents of reduced functioning (YERF) and health-adjusted life years (HALYs) for the top 20 pathogens, ranked by disease burden



Kwong JC, Crowcroft NS, Campitelli MA, Ratnasingham S, Daneman N, Deeks SL, Manuel DG. Ontario Burden of Infectious Disease Study Advisory Group; Ontario Burden of Infectious Disease Study, 2010.

Hepatitis C – Impact

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Estimated future lifetime cost according to disease state for men 35 to 39 years of age with hepatitis C virus infection in 2013

	Cost in 2013, $CAD
Chronic hepatitis C virus infection (F0)	51,946
F1	62,184
F2	79,926
F3	100,589
Compensated cirrhosis (F4)	133,575
Diuretic-sensitive ascites	196,770
Diuretic-refractory ascites	139,330
Variceal hemorrhage	189,398
Hepatic encephalopathy	133,505
Hepatocellular carcinoma	42,376
Liver transplant	327,608

Myers RP et al, *Can J Gastroenterol Hepatol* 2014;28:243-50.

Hepatitis C – Screening

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- **Why screen?**
  - Many individuals are unaware that they are infected.
  - Prevalence is increased in high-risk populations and baby boomers.
  - Chronic hepatitis C infection is curable, even more so now.
  - Patients whose infection is eradicated before development of cirrhosis have a life expectancy similar to those of uninfected age-matched cohorts.

- **Why NOT screen?**
  - Stigmatization with diagnosis or “feeling targeted”.
  - False positive results.
  - Lack of capacity to treat volume of newly diagnosed cases.
  - **All can be mitigated by appropriate pre-test counseling and expansion of systems to treat newly-diagnosed individuals.**

Hepatitis C – Screening

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- **Who should be screened?**
  - Anyone who has ever injected drugs, even once.
  - Anyone born in Canada b/w 1945-1975 (ages 40-70).
  - Anyone who received a blood transfusion, blood products, or organ transplant in Canada before 1992.
  - Those with evidence of liver disease (high ALT).
  - Anyone who has ever been on chronic hemodialysis.
  - Anyone infected with HIV.
  - All incarcerated individuals.
- **What do you screen with?**
  - Screen with standard 3rd generation HCV antibody test. High sensitivity (97.2-100%) and specificity (> 99%).
- **How often do you screen?**
  - If no ongoing risk, one-time screen is enough.
  - If ongoing risk, frequency of screening unclear, q 1-2 years…

Hepatitis C – Screening

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- **Before Screening…**
  - Check eHealth portal to determine whether screening has been done before. Choose the right test depending on what you find.
  - **If patient has had previous (-) anti-HCV:** if no ongoing risk, then likely no need for additional screening.
  - **If patient has had previous (+) anti-HCV:** has the patient had a confirmatory HCV RNA and genotype to differentiate b/w spontaneous clearance and chronic infection?
  - **If patient has had previous (+) HCV RNA:** have they been treated, and has an HCV genotype been performed?
  - Counsel patients carefully – (+) anti-HCV = exposure, not necessarily chronic infection.
- **What do you do with screening anti-HCV result?**
  - **(+) anti-HCV:** if no HCV RNA/genotype, then order.
  - **(-) anti-HCV:** no further testing, consider regular screening if ongoing risk.

HCV – New Diagnostics

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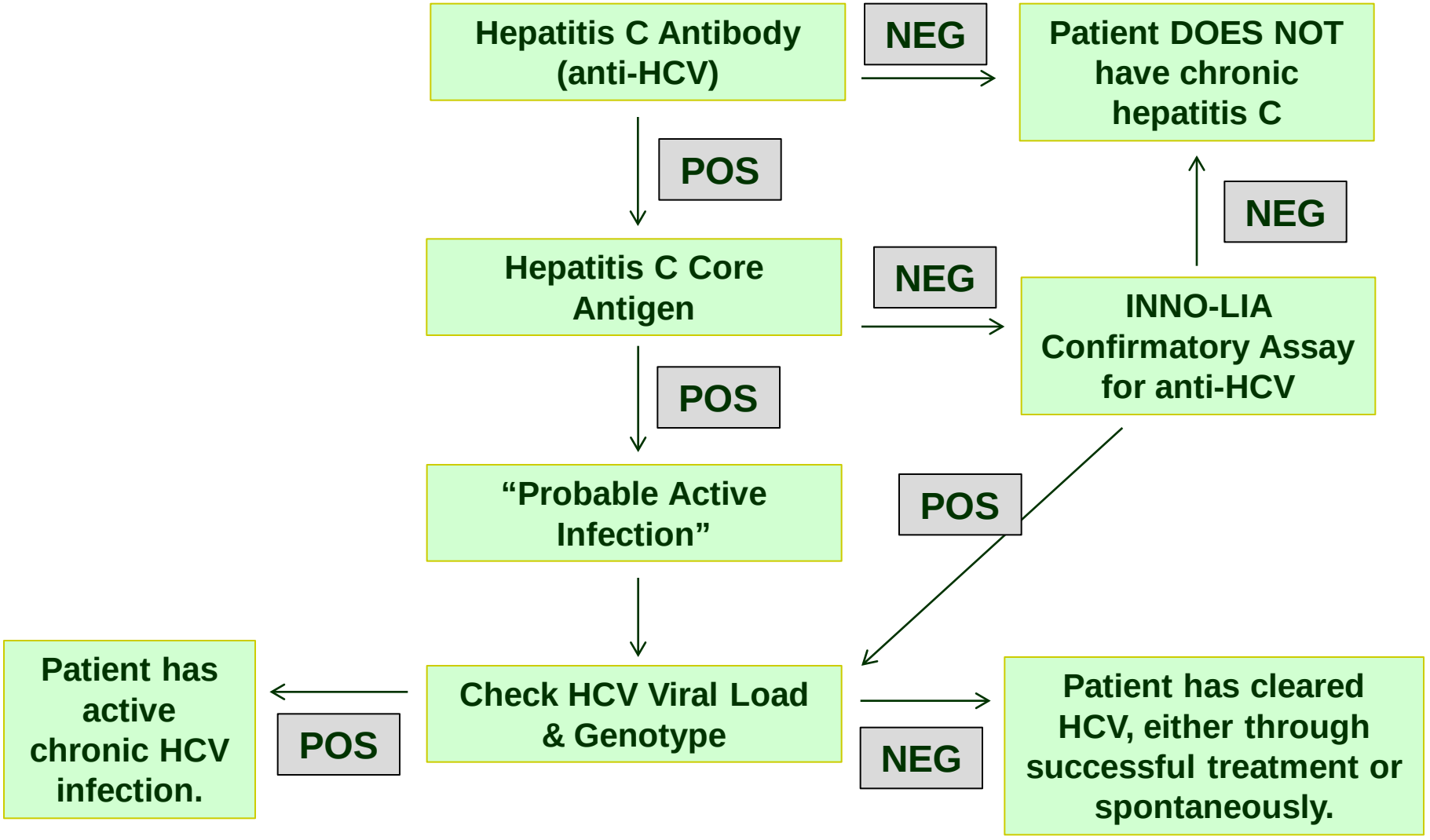
- **Hepatitis C Core Antigen Testing**
  - Hepatitis C Core Antigen Testing was introduced at SDCL in early 2015 as a quicker way to turn-around HCV screening tests.
  - Core Antigen Testing also shortens “window period” of diagnosis by ~20 days compared to traditional HCV antibody testing.
  - Acts as marker of viremia, similar to hepatitis B surface antigen.
  - Lower limit of detection ~10,000 IU/mL. SDCL performing correlation studies at present time on in-house assays to see whether antigen testing can help predict levels of HCV viremia.

SDCL Hepatitis C Protocol



Hepatitis C – Diagnosis

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- **General Rules of Thumb**
  - Positive antibody and/or antigen and positive RNA test essentially confirms the diagnosis of chronic hepatitis C, unless possibility of acute hepatitis C exists.
  - Always do genotyping at same time as RNA testing, as this information is required to determine therapeutic options.
  - Positive antibody testing does not mean chronic infection – counsel patients carefully regarding exposure vs. infection.
  - Negative antigen testing may still mean presence of viremia – careful what you say to patients.
    - "This screening test confirms that you have been exposed to hepatitis C, but we need to do more tests to know for sure whether you have hepatitis C or not."
  - Work up and refer patients with confirmed viremia only, not those with positive antibody/antigen testing only.

Hepatitis C – Treatment

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- **The "Interferon Era"**
  - **Pegylated-interferon and ribavirin for all genotypes:**
    - **Genotype 1:** 48 weeks of therapy – SVR 45%.
    - **Genotype 2:** 24 weeks of therapy – SVR 80%
    - **Genotype 3:** 24 weeks of therapy – SVR 70%
    - **Genotype 4:** 48 weeks of therapy – SVR 60%
  - **Many adverse effects.**
    - Hematologic
    - Flu-Like Symptoms
    - Neuropsychiatric
  - **Significant commitment of time and resources.**
    - 24-48 weeks of dual therapy, with many associated adverse side effects, requires expert multidisciplinary team and close monitoring.
    - Relative contraindications of social chaos & instability, mental health concerns, addictions precluded many patients from treatment candidacy.

Hepatitis C – Treatment

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- **The "Interferon-Free Era"**
  - Since 2011, direct acting anti-virals (DAAs) have been available for treatment of chronic HCV. Pace of development has been staggering.
  - Currently, 4 validated classes of DAAs in study / available:
    - NS3 PIs
    - NS5A inhibitors
    - NS5B non-nucleoside inhibitors
    - NS5B nucleoside/nucleotide inhibitors.
  - Virtually all recent studies with interferon-free therapies have suggested that HIV infection plays no role in therapeutic outcome other than with respect to drug-drug interactions.

Hepatitis C – The Present

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- **Genotype 1:** Single-tablet FDC (LDV/SOF, Harvoni™, Gilead Sciences) or 3 DAA + RBV (Holkira™, Abbvie) to achieve 96% SVR with only 8-12 weeks of therapy.
  - First true interferon-free regimens for genotype 1.
  - Excellent tolerability profile, DDIs manageable / excellent.
- **Genotype 2:** SOF (Sovaldi™, Gilead Sciences) + weight-based RBV x 12 weeks achieves 94-96% SVR.
- **Genotype 3:** DCV (Daklinza™, Bristol Myers Squibb) + SOF x 12 weeks achieves 97% SVR in non-cirrhotics.

Hepatitis C – The Future…

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- **2016-8:** Pan-genotypic interferon-free regimens, all with excellent SVR rates near 100%, 6-8 weeks of treatment, excellent DDI / tolerability profiles, some single tablet regimens.
  - Genotyping will become unnecessary.
  - Treatment “expertise” may become unnecessary once medications and side-effect profiles become so favourable.
  - Drug-drug interactions will be ongoing issue.

Hepatitis C – $$$

- **So What's The Catch?**
  - List price for 12 weeks of LDV/SOF = $65,000 CDN.
  - List price for 24 weeks of peg-IFN + RBV = $10,000 CDN.
  - **Who pays?**
- **How Do We Prioritize Therapy?**
  - Patients with advanced fibrosis and at risk of HCC or hepatic decompensation (e.g. F3/F4 based on objective measure of fibrosis).
  - Patients scheduled for liver transplantation to prevent graft re-infection.
  - Patients who continue to transmit virus through high-risk activity.
  - **Saskatchewan: F2 fibrosis (≥ 8.7 kPa for mono-infected individuals, ≥ 7.2 kPa for co-infected individuals).**

What is “Fibroscan”?

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- Ultrasound-based transient elastography is alternative to liver biopsy for assessment of hepatic fibrosis.
  - Non-invasive, simple, no risk of complications.
  - Determines degree of liver “stiffness”, usually most affected by hepatic fibrosis though other factors can play role including heart failure / central venous pressure / eating.
  - Shear waves are transmitted from transducer through liver parenchyma, and pulse-echo U/S acquisition follows propagation of shear waves and measures average speed. Results expressed in kPa.
- RQHR (Pasqua) and SHR (RUH) have stand-alone machines, accepting referrals.
- RQHR IDC likely to obtain mobile Fibroscan unit by October 2015.

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Other Relevant Questions

- **What tests do you order?**
  - **"Screen for everything"** = urine NAT for gonorrhea / chlamydia, syphilis serology, anti-HIV, anti-HCV, HBsAg, anti-HBs. (Consider anti-HBc.)
  - For high-risk patients, consider ordering HCV RNA & genotyping at same time as PCR samples require plasma
  - Check eHealth portal – if anti-HCV already done previously and no HCV RNA, then just order HCV RNA & genotyping.
- **What do you do when your hepatitis C "screening test" comes back positive?**
  - Order an HCV RNA & genotype, if not already done.
- **What do you tell the patient?**
  - If only anti-HCV positive…
  - If HCV RNA positive…

Other Relevant Questions

- **What additional workup can/should you do to assist and expedite referral?**
  - **Assess Liver Disease:** CBC, ALT, AST, GGT, ALP, Bilirubin, INR/PTT, Albumin, Creatinine, Abdominal U/S, **Fibroscan.**
  - **Viral Co-Infections:** anti-HAV, HBsAg, anti-HBs, anti-HIV.
  - **Consider Excluding Other Liver Diseases:** Alpha-1-antitrypsin, ceruloplasmin, ferritin, serum Fe, TIBC, ANA, ASMA, AMA, quantitative immunoglobulins.
  - **Contraindications:** serum/urine b-HCG, TSH.
  - **Vaccinations:** vaccinate for hepatitis A / B if required.
- **Who can you refer to in Saskatchewan?**
  - Dr. Kris Stewart (Saskatoon).
  - Royal University Hospital Positive Living Program (Saskatoon)
  - RQHR Infectious Diseases Clinic (Regina).

Summary – Hepatitis C

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- **Screening & Diagnosis**
  - Lower your threshold to screen for hepatitis C and serially screen those with identified risk. Early identification = less morbidity and mortality and quicker access to speciality care and follow-up.
  - Access **eHealth Portal** and don't mindlessly repeat what has been done before – order the right tests!
  - Population-based screening for all b/w ages 45-75 with one-time testing is appropriate.
  - Follow anti-HCV / HCV antigen testing with HCV RNA & genotyping.
- **Treatment**
  - New treatment paradigm is sea change from previous paradigm. Treatment is effective, simple, and well-tolerated. Problem remains accessibility.

HIV Testing – A Reminder

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- **Routine Testing**
  - Routine HIV screening is indicated for all between 13-65 years of age.
  - Cost-effective if seroprevalence >= 0.1%.
  - Low-risk individuals can be screened at initial visit, then every 3-5 years thereafter.
  - High-risk individuals should be screened every 6-12 months: IVDU, MSM, sex trade workers, sexual partners of HIV+ individuals, person who have sex with partners whose HIV status is unknown.
- **Targeted Testing**
  - New sexual partner whose HIV status is unknown, any diagnosed STI, any possibility of acute HIV infection (e.g. mononucleosis), signs and symptoms of chronic HIV infection.
  - **“You test, we’ll do the rest!”**