

Investigating hepatitis B immunity in patients presenting to a paediatric oncology unit: Are these patients at risk of infection?

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Reminder: What is hepatitis B?

- Hepadnaviridae family
- Variety of liver diseases
- Acute and chronic hepatitis
 - Acute infection
 - self-limiting, asymptomatic illness
 - occasionally fulminating
 - Chronic hepatitis
 - asymptomatic carrier (number of years)
 - life-threatening complications - cirrhosis and hepatocellular carcinoma

Kew MC. Hepatitis B virus infection: the burden of disease in South Africa. South Afr J Epidemiol Infect. 2008;23(1):4-8

Hepatitis B in South Africa

- Endemic in sub-Saharan Africa
- Prevalence 8-20% among certain population groups
- Acute and chronic infection common in black South Africans
 - 5-16% in rural black males
 - 2.7-4% in urban black females
 - Estimated 3-4 million black South Africans with chronic HBV infection

Kew MC. Hepatitis B virus infection: the burden of disease in South Africa. South Afr J Epidemiol Infect. 2008;23(1):4-8

Hepatitis B in children in SA

- Rural areas → HBV acquired early in life (<5y)
- Development of chronic infection inversely related to age:
 - Younger age = ↑ risk of becoming chronic carrier
 - Chronic carrier → complications
 - cirrhosis
 - hepatocellular carcinoma

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Hepatitis B transmission in childhood

- Horizontal transmission predominant during early childhood (developing countries)
- Not related to sexual or perinatal exposure
- Transmission between family members in communities with poor socio-economic and hygienic conditions
- Mode unsure
 - Body fluids, mainly saliva
 - Ritual scarification and open weeping sores

Willers E, Webber L, Delpont R, Kruger M. Hepatitis B—A Major Threat to Childhood Survivors of Leukaemia/Lymphoma. *J Trop Pediatr.* 2001;47(4):220-225

HBV vaccination in SA

- HBV vaccine included in EPI-SA at 6, 10 and 14 weeks of age, from April 1995
- No 'catch-up' vaccination attempted
- Subsequent studies = expected decrease in HBV carriage rate
- Vaccinated children in SA = low HBsAg carriage 0% to 2.7%

Burnett RJ, Kramvis A, Dochez C, Meheus A. An update after 16 years of hepatitis B vaccination in South Africa. *Vaccine.* 2012;30S:C45-C51

Current vaccine strategy in SA

- Heberbiovac administered as monovalent vaccine
- Safe and compatible with other EPI antigens
- More immunogenic than other HBV vaccines
- BUT Advantages of polyvalent vaccines
 - cost reduction
 - simplified delivery logistics
 - increased levels of acceptance by families

Burnett RJ, Kramvis A, Dochez C, Meheus A. An update after 16 years of hepatitis B vaccination in South Africa. Vaccine. 2012;30S:C45-C51

Who else should be vaccinated?

- SA Guideline for the management of chronic hepatitis B: 2013
- Vaccination recommended in **individuals at risk** of HBV infection
 - haemodialysis or oncology patients
 - transplant candidates
 - receiving frequent blood or blood product transfusions
 - household contacts of HBsAg-positive individuals

Spearman CWN, Sonderup MW, Botha JF, van der Merwe SW, Song E, Kassianides C, et al. South African guideline for the management of chronic hepatitis B: 2013. SAMJ. 2013;103(5):335-349

Is hepatitis B vaccination effective?

- Highly immunogenic and effective
- Protective levels of anti-HBs (>10mIU) in 75-87% of children
- None or very few children positive for HBsAg or HBV DNA
- Duration of vaccine-induced immunity not known
- Antibody levels decline rapidly after vaccination BUT immune memory thought to extend into adulthood
- Currently no 'booster' doses recommended
- Waning of immunity → adolescents at risk of HBV infection

Jack AD, Hall AJ, Maine N, Mendy M, Whittle HC. What level of hepatitis B antibody is protective? J Infect Dis. 1999;179(2):489-492

What about immune compromised patients?

- Lower levels of anti-HBs
- Slower primary and secondary humoral responses
- Clinically significant HBV infection in immune compromised patients after loss of anti-HBs
- Boosters to keep anti-HBs above 10mIU/mL
- Additional or double doses for non-responders
- Vaccine administered when immune response likely to be maximal

Meral A, Sevinir B, Günay U. Efficacy of immunization against hepatitis B virus infection in children with cancer. Med Pediatr Oncol. 2000;35(1):47-51

HBV in paediatric oncology

- Immune compromised children with chronic HBV → enhanced viral replication
- Few able to clear HBsAg during first year of infection
- Often have high levels of infective HBsAg and HBeAg in saliva → highly infectious
- Immunosuppressive agents
 - reactivation of dormant infection, re-appearance of HBsAg
 - previous antibodies to HBsAg disappear or unable to prevent recurrence of infection
 - high risk of becoming chronic carriers of HBV

Willers E, Webber L, Delpont R, Kruger M. Hepatitis B—A Major Threat to Childhood Survivors of Leukaemia/Lymphoma. *J Trop Pediatr.* 2001;47(4):220-225

HBV in paediatric oncology

- Risk factors increasing susceptibility to HBV:
 - frequent prolonged hospital admissions
 - severe immune compromised states
 - repeated venepunctures
 - frequent blood product administration
 - destruction of mucous membranes secondary to chemotherapy
- Adverse prognostic role in terms of disease-free survival:
 - acute hepatitis leads to delays in chemotherapy
 - risks of cirrhosis and hepatocellular carcinoma

Willers E, Webber L, Delpont R, Kruger M. Hepatitis B—A Major Threat to Childhood Survivors of Leukaemia/Lymphoma. *J Trop Pediatr.* 2001;47(4):220-225

Why do this research?

- Various studies have assessed duration of immunity to hepatitis B after primary immunisation in infancy
- Immune memory to vaccination shown to be protective in a large percentage of well children, not assessed in patients on immunosuppressive therapy
- Patients have acquired hepatitis B in SBAH paediatric oncology unit despite being vaccinated (EPI-SA)
- This study reports on immunity to hepatitis B at first presentation to a paediatric oncology unit

Methods: Patients and samples

- Hospital-based audit of patient records
- All children presenting to SBAH paediatric oncology unit
- 1 January 2012 to 31 August 2013
- Demographic data and diagnosis documented
- HBV serology reviewed on all patients
- Approved by Medical Research Ethics Committee

Methods: Serology

- Routine screening hepatitis A, B, C on all new patients
- Anti-HBs antibody levels classified:
 - $>100\text{mIU/ml}$ = complete protection
 - $10\text{-}100\text{mIU/ml}$ = partial protection
 - $<10\text{mIU/ml}$ = no protection

Jack AD, Hall AJ, Maine N, Mendy M, Whittle HC. What level of hepatitis B antibody is protective? J Infect Dis. 1999;179(2):489-492

Debate: Anti-HBs antibody levels

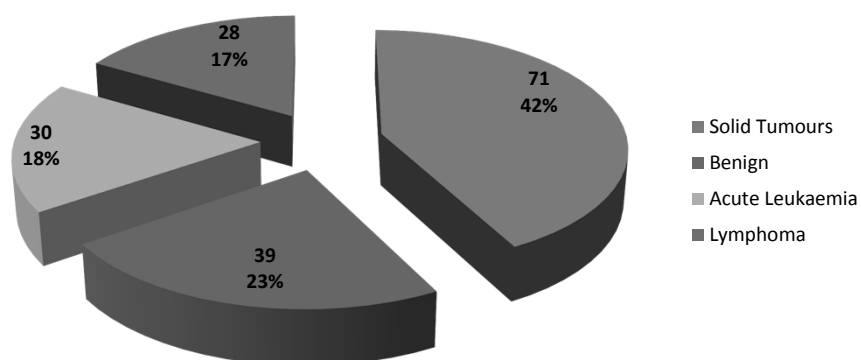
- What level is protective?
- $>10\text{mIU/ml}$ if normal immune response
- Immune memory persists in healthy children even if anti-HBs titers $<10\text{mIU/ml}$
- Immune memory not assessed in patients on immunosuppressive therapy
 - Defects in immunologic functioning
 - Immune memory may not be protective

Jack AD, Hall AJ, Maine N, Mendy M, Whittle HC. What level of hepatitis B antibody is protective? J Infect Dis. 1999;179(2):489-492

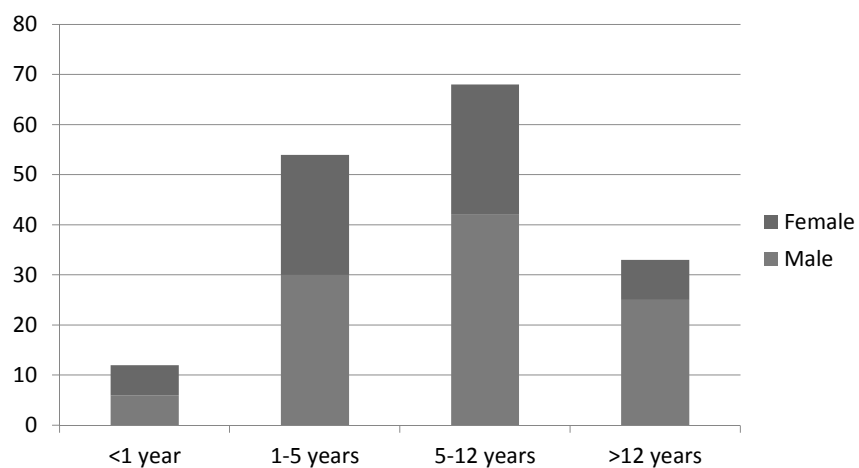
Results: Patient characteristics

- 167 patients
 - 103 boys
 - 64 girls
- 12.6% HIV positive

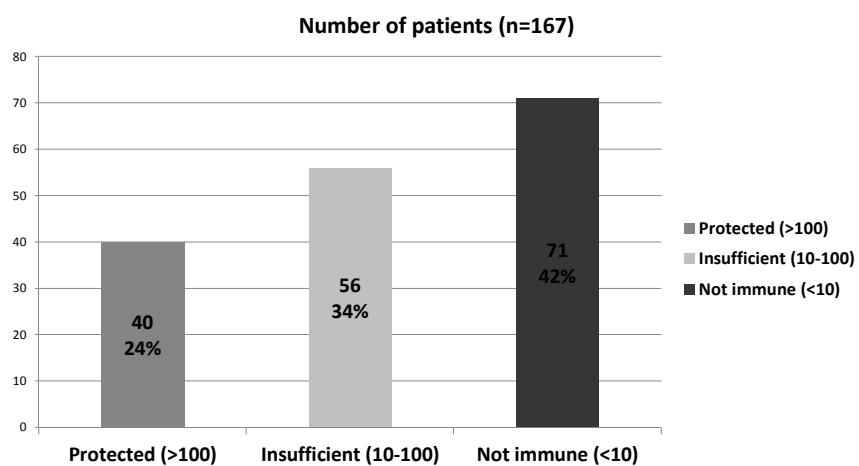
Results: Diagnoses



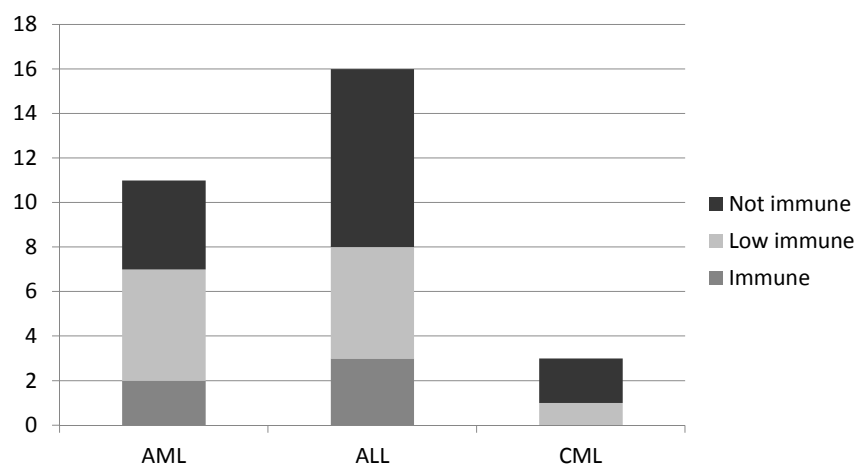
Results: Age distribution



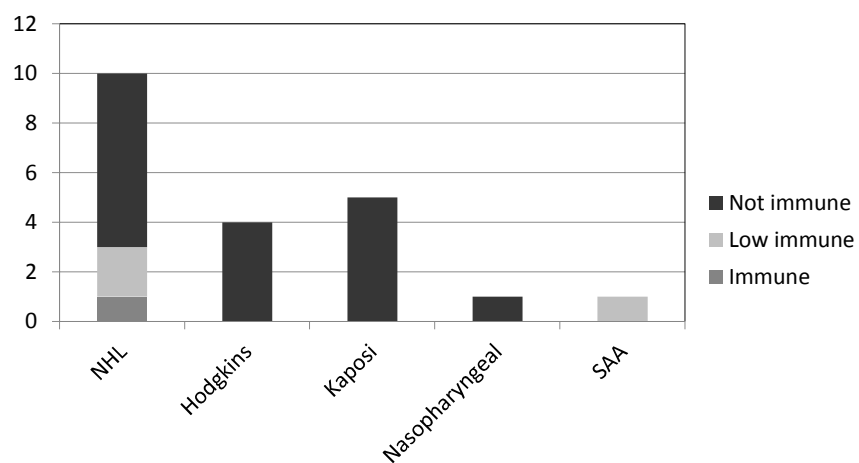
Results: Hepatitis B immunity



Results: Leukaemia group (n=30)



Results: HIV patients (n=21)



Conclusion

- Only 24% of patients immune to HBV (anti-HBs >100mIU/ml)
- Most patients (76%) at risk for infection
- Infected patients high viral loads and highly infectious
- Protection needed!

Recommendations

- All patients should be screened at first visit
- Active immunisation if anti-HBs titers <100mIU/ml
- Response to immunisation documented
- Frequent re-testing (3-monthly)
- Treatment and close follow-up of infected patients to prevent horizontal transmission

What about the general population?

- HBV is still a problem in SA
- Current immunisation schedule may not be sufficient
 - Booster needed?
 - Higher index of suspicion needed?
- Further research needed!

References

1. Kew MC. Hepatitis B virus infection: the burden of disease in South Africa. *South Afr J Epidemiol Infect.* 2008;23(1):4-8.
2. Willers E, Webber L, Delpont R, Kruger M. Hepatitis B—A Major Threat to Childhood Survivors of Leukaemia/Lymphoma. *J Trop Pediatr.* 2001;47(4):220-225.
3. Burnett RJ, Kramvis A, Dochez C, Meheus A. An update after 16 years of hepatitis B vaccination in South Africa. *Vaccine.* 2012;30S:C45-C51.
4. Spearman CWN, Sonderup MW, Botha JF, van der Merwe SW, Song E, Kassianides C, et al. South African guideline for the management of chronic hepatitis B: 2013. *SAMJ.* 2013;103(5):335-349.
5. Jack AD, Hall AJ, Maine N, Mendy M, Whittle HC. What level of hepatitis B antibody is protective? *J Infect Dis.* 1999;179(2):489-492.
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Thank you!

