The art of immunosuppression for AIH (and IBD)

Gideon Hirschfield
University of Birmingham, UK
g.hirschfield@bham.ac.uk

NHS National Institute for Health Research

The patient!

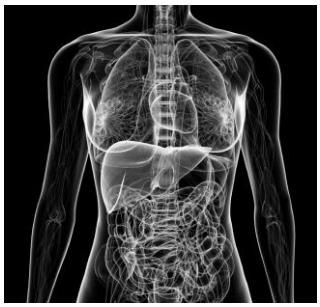


Image taken from http://www.sanger.ac.uk/about/press/2011/110313.html

Brave carer: the patient is more than just themselves

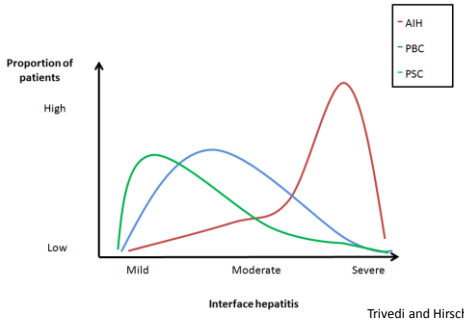
http://www.mirror.co.uk/3am/tv-film-news/brave-youngsters-who-losing-out-4610996

The consultation

- Me: You're looking jaundiced today- that's a big change compared to last time I saw you C.
- C: Yeah, I'm really itchy and my eyes have gone yellow.
- Me: Oh, you may need more steroids while we work out what is going on.
- C: No- them things make me fat and ugly.

The art: individualized care

Autoimmunovir ™



Trivedi and Hirschfield

Guidelines are guidelines

http://criticalworld.net/files/2011/12/guidelines1.jpg

Table 1 Causes of medication nonadherence

- Limited communication between clinician and patient
- Developmental issues in adolescence
- Limited trust by the patient and society for health care providers and health care systems
- Complexity of the health care system
- Unhappiness with or lack of knowledge regarding medication adverse effects
- Circumscribed understanding of psychiatric problems by the patient/caregivers
- Cost of treatment
- Complications of comorbid conditions

http://www.psychiatrictimes.com/child-adolescent-psychiatry/strategies-improve-medication-adherence-youths

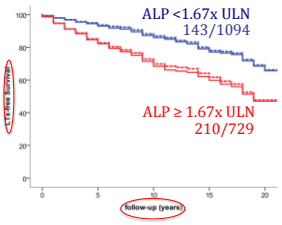
Strategy	Potential Advantages
Adherence education	• Encourages patients to learn about medications
Directly observed therapy	• Might encourage adherence • Helps reporting of treatment-related adverse effects
Discuss adherence barriers	• Encourages identification of barriers to adherence and consider potential solutions to overcome them
Encourage pill sorting	• Helps establish routine
Medication diary	• Helps establish routine • Allows identification of patterns of missed doses
Reminder alarms	• Helps establish routine
Support group	• Provides social support to take medications as prescribed, report treatment-related adverse effects

http://www.hepatitisc.uw.edu/doc/151-1/potential-strategies-to-maximize-adherence-during-chronic-hepatitis-c-treatment.jpg

Why do we use immunosuppression?

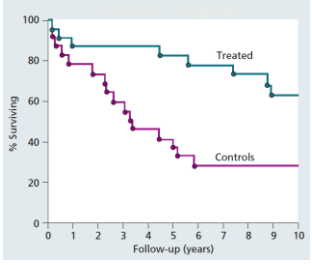
- Quality of life
  - Stool frequency
  - Fatigue
  - Pain
  - Fear
- Quantity of life
  - What do patients understand?
  - What do they choose?

The false dawn



Lammers et al. EASL 2013 International PBC Supergroup

Be clear where benefits exist



Kirk AP, Jain S, Pocock S *et al. Late results of the Royal Free* Hospital prospective controlled trial of prednisolone therapy in hepatitis B surface antigen negative chronic active hepatitis. *Gut 1980;* ***21: 78–83.***

BRITISH MEDICAL JOURNAL
LONDON SATURDAY OCTOBER 29 1955

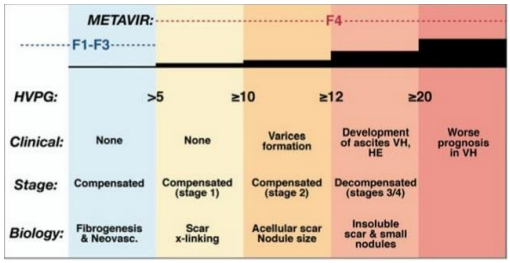
CORTISONE IN ULCERATIVE COLITIS
FINAL REPORT ON A THERAPEUTIC TRIAL

TABLE IX.—*Position at the End of Nine Months' Follow-up*

	First Attacks		Relapses	
	Cortisone Group	Control Group	Cortisone Group	Control Group
Symptom-free throughout	21	8	23	26
Alive with symptoms:				
(a) Mild — Intermittent	5 } 11	3 } 6	10 } 17	4 } 12
(a) Mild — Continuous	6 }	3 }	7 }	8 }
(b) Severe — Intermittent	2 } 5	4 } 8	2 } 9	5 } 11
(b) Severe — Continuous	3 }	4 }	4 }	6 }
Alive with ileostomy	3	7	11	5
Dead	3*	9†	4‡	6§
Totals	43	38	64	60

* Includes 2 deaths after ileostomy.
† Includes 7 deaths after ileostomy.
‡ 1 suicide, 1 death from haemolytic anaemia after blood transfusion and 2 after ileostomy.
§ Includes 2 deaths after ileostomy.

"Cirrhosis is a series of progressive stages, not a single stage"



Gastroenterology 134:6; 1655-1669, May 2008.

Establish the diagnosis and prognosis

- Unless you are clear how can your patients be clear they need to take your therapy
  - Make a diagnosis
  - Give an opinion on stage and severity
  - Communicate a plan

Simplified criteria for diagnosis of AIH

Variable	Cutoff	Points	Cutoff	Points
ANA or SMA*	≥ 1:40	1	≥ 1:80	2
or LKM			≥ 1:40	2
or SLA			positive	2
IgG	> ULN	1	> 1.1 X ULN	2
Histology	Compatible with AIH	1	Typical of AIH	2
Absence of viral hepatitis			yes	2
	Probable AIH*	≥ 6 points	Definite AIH*	≥ 7 points

Maximum number of points for all autoantibodies is 2, total is 8 points
*It is not clear what distinguishes "probable" and "definite".

Hennes et al. Hepatology 2008; 48:169

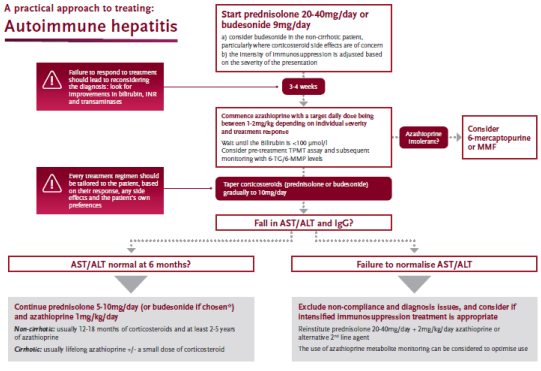
Agree what the treatment goals are

Goal

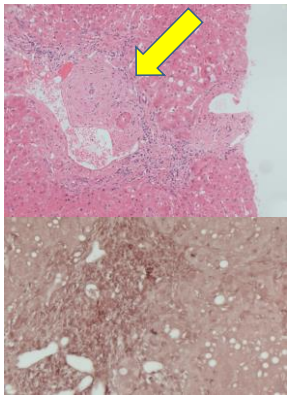
- Be honest
  - Is it to make them feel better- IBD >AIH
  - Is it to make them live longer – AIH>IBD

Team work

- Physician
  - Your son is so sick I can't see him surviving the next few days or being well enough for a transplant
- Surgeon
  - Your son is so sick, but I won't give up on him and I'm prepared to operate on him even if he dies in theatre



- 68 year old man
- Type 1 AIH
  - Fluctuating liver transaminases
  - Normal ALP
  - Normal MRCP
  - Normal colonoscopy

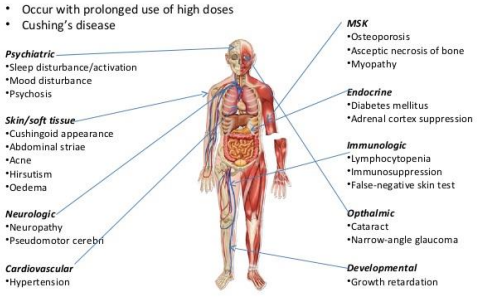


The workforce

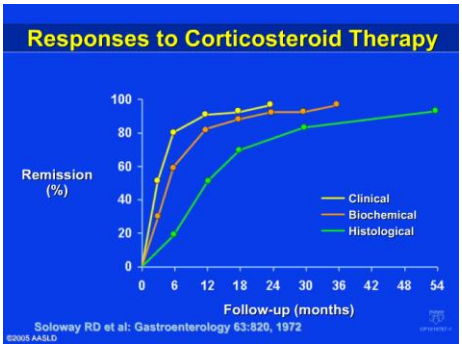
- Prednis(ol)one/Budesonide
- Azathioprine/Mercaptopurine
- Mycophenolate mofetil
- Tacrolimus/Ciclosporin
- Methotrexate
- Biologics
  - Anti-TNF
  - Anti-B cell
  - Lymphocyte recruitment

Adverse effects

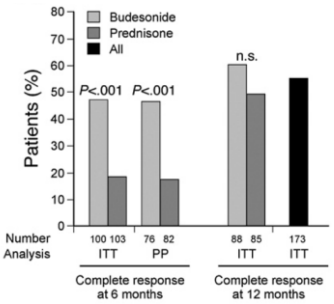
- Occur with prolonged use of high doses
- Cushing's disease



Google search

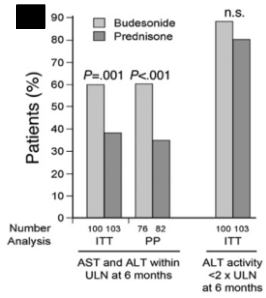


Complete response (defined as serum AST and ALT within normal range and absence of steroid-specific side effects) for the intention-to treat (ITT) and per protocol (PP) populations.



Manns et al. Gastro 2010

Complete biochemical remission rate at month 6 compared with the biochemical remission defined as ALT activity <2x ULN at month 6



Manns et al. Gastro 2010

Side Effects

Table 3. Predefined Steroid-Specific Side Effects Observed and Reported Throughout Segment A

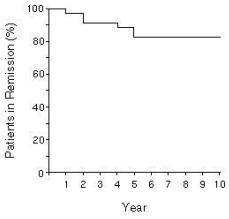
	ITT		PP	
	Budesonide (n = 100)	Prednisone (n = 103)	Budesonide (n = 76)	Prednisone (n = 82)
No SSSEs throughout segment A, n (%)[a]	72 (72.0)	48 (46.6)	55 (72.4%)	37 (45.1)
At least 1 SSSE throughout segment A, n (%)[b]	26 (26.0)	53 (51.5)	21 (27.6)	45 (54.9)
Moon face	10 (10.0)	43 (41.7)	8 (10.5)	36 (43.9)
Acne	8 (8.0)	15 (14.6)	7 (9.2)	13 (15.9)
Hirsutism	9 (9.0)	3 (2.9)	8 (10.5)	3 (3.7)
Skin striae	2 (2.0)	4 (3.9)	1 (1.3)	4 (4.9)
Buffalo hump	1 (1.0)	4 (3.9)	1 (1.3)	4 (4.9)
Diabetes[c]	4 (4.0)	0	4 (5.3)	0
Increased intraocular pressure	0	0	0	0
Glaucoma	0	0	0	0

Manns et al. Gastro 2010

Azathioprine and prevention of relapse

Monotherapy with azathioprine at 2mg/kg

Remission for >1 year with prednisone (5-15mg/od) and azathioprine (1mg/kg)/kg)



No. of Patients										
Total eligible for analysis	70	66	59	49	42	38	35	34	31	30
Cumulative total with relapses	2	5	5	6	7	7	7	7	7	7
Cumulative total excluded	2	6	13	23	30	34	36	38	41	42

Johnson PJ et al. N Engl J Med 1995;333:958-963.

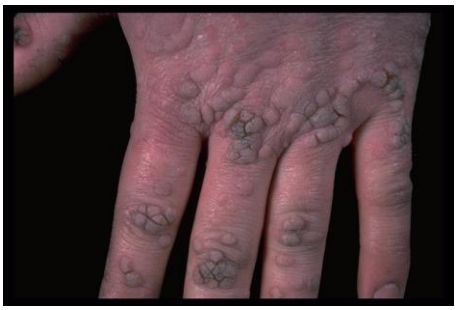
Real world outcomes

		All deaths		All deaths or transplants	
	No. of subjects	No. of observed events	SMR (95% CI)	No. of observed events	SMR (95% CI)
All	245	72	1.63 (1.25–2.02)	81	1.86 (1.49–2.26)
Age at diagnosis (y)					
Younger than 45	73	8	5.16 (1.51–8.80)	14	10.2 (4.76–2.57)
45–65	109	35	1.83 (1.21–2.45)	38	1.99 (1.35–2.64)
Older than 65	66	29	1.25 (0.79–1.72)	29	1.26 (0.79–1.72)
Presented since 1987	192		1.59 (1.11–2.06)		1.76 (1.26–2.26)
First decade	245	32	1.42 (0.89–1.98)	36	1.55 (1.03–2.06)
Second decade	115	35	2.22 (1.55–3.09)[a]	37	2.36 (1.66–3.25)[a]
Third decade	28	5	1.31 (0.42-3.05)	8	2.26 (0.98-4.45)

	Liver-related death or transplantation		All-cause death or transplantation	
	Hazard ratio (95% confidence interval)	*P* value	Hazard ratio (95% confidence interval)	*P* value
Decompensation at presentation	5.63 (2.54–9.37)	<.001	3.92 (2.40–6.38)	<.001
Failure to normalize serum ALT levels within 12 months of starting treatment	5.52 (2.55–14.67)	<.001	4.27 (2.05–8.89)	<.001
No. of relapses per decade	1.19 (1.08–1.31)	<.001	1.12 (1.01–1.25)	<.001
Nontreatment with azathioprine	3.96 (1.85–8.49)	<.001	2.71 (1.59–4.60)	.001
Cirrhosis (at presentation or developing subsequently)	9.96 (1.3–44.0)	.004	1.34 (0.77–2.31)	.295
Age at presentation (y)	1.022 (0.997–1.05)	.061	1.05 (1.03–1.07)	<.001

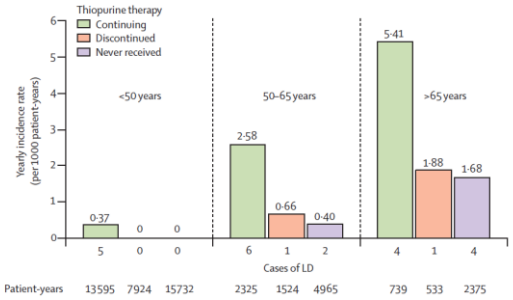
Gastroenterology 2011; 140:1980-1989

Viral warts...



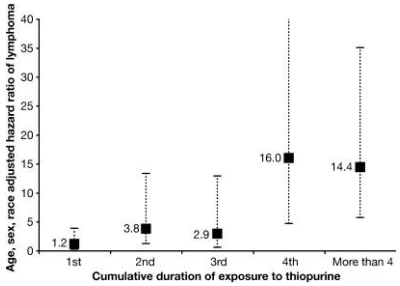
http://www.tti.library.tcu.edu.tw/DERMATOLOGY/vi/img0043.jpg

Incidence rates of lymphoproliferative disorders according to thiopurine exposure grouped by age at entry in the cohort



Lancet 2009; 374: 1617–25

Duration of exposure and lymphoma risk



Gastroenterology 2013 145, 1007-1015.

Disease control before conception and during pregnancy is associated with the best outcomes for mothers and babys

http://easy4weightloss.com/wp-content/uploads/2014/06/Pregnancy-Massage.jpg

AIH and pregnancy

Effect of therapy on maternal and foetal pregnancy outcomes.

	Live birth rate	Terminations	Miscarriage	Gestation <37 weeks	Gestational flare	Post-partum flare	Any flare
Prednisolone monotherapy	20/27 (74%)	3/27, (11%)	4/27, (15%)	37 (28–40)	2/20, (10%)	7/20, (35%)	8/20, (40%)
Azathioprine ± prednisolone	21/32 (65%)	6/32, (19%)	4/32, (13%)	38 (32–39)	0/32, (0%)	7/32, (21%)	7/32, (21%)
Any therapy (prednisolone, tacrolimus, azathioprine)	42/61 (68%)	10/61, (16%)	8/61, (13%)	38 (28–40)	2/61, (3%)	15/61, (24%)	16/61*, (26%)
No therapy	17/20 (85%)	2/20, (10%)	0/20, (0%)	38 (27–39)	3/20, (15%)	8/20, (40%)	10/20*, (50%)

* $p < 0.05$.

Foetal outcomes in women with AIH.

	Live birth rate	Prematurity <37 weeks	SCBU
Cirrhosis vs. no Cirrhosis ($n = 33$) ($n = 48$)	19/33 vs. 40/48, $p = 0.02$	5/19 vs. 7/40, $p = 0.43$	4/19 vs. 2/40, $p = 0.07$
Maternal disease remission > 1 year ($n = 52$) vs. no remission ($n = 29$)	38/52 vs. 21/29, $p = 0.95$	8/38 vs. 4/21, $p = 0.99$	3/38 vs. 3/21, $p = 0.65$
Therapy ($n = 61$) vs. no therapy ($n = 20$)	42/61 vs. 17/20, $p = 0.25$	6/42 vs. 6/17, $p = 0.07$	5/42 vs. 1/17, $p = 0.66$
AIH gestational flare ($n = 5$) vs. no gestational flare ($n = 76$)	4/5 vs. 55/76, $p = 0.99$	2/4 vs. 10/55, $p = 0.18$	2/4 vs. 4/55, $p = 0.047$

R.H. Westbrook et al. / Journal of Autoimmunity 38 (2012) J239eJ244

	Side-effects	FDA category
Azathioprine	Lymphopenia, hypogammaglobulinaemia, thymic hypoplasia	D
Ciclosporin A	Premature labour, low birthweight, neonatal hyperkalaemia, renal dysfunction	C
Mycophenalate mofetil	First trimester loss, microtia. Increased risk of congenital malformations	D
Prednisolone	Cleft palate, intrauterine growth retardation, premature rupture of membranes, fetal adrenal hypoplasia	C
Tacrolimus	Similar side-effects to ciclosporin. Neonatal malformation rates of 4%	C

FDA=US Food and Drug Administration. Pregnancy category C: animal reproduction studies have shown an adverse effect on the fetus, but no adequate and well controlled studies in human beings exist. Potential benefits might warrant use of the drug in pregnant women despite potential risks. Pregnancy category D: positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in human beings. However, potential benefits might warrant use of the drug in pregnant women despite potential risks.

Lancet 2010; 375: 594–605

Drug	US FDA pregnancy category	Recommendations for pregnancy	Recommendations for breastfeeding
Aminosalicylates			
Balsalazide	B	Low risk	No human data; potential diarrhea
Mesalamine	B	Low risk	Limited human data; potential diarrhea
Olsalazine	C	Low risk	Limited human data; potential diarrhea
Sulfasalazine	B	Low risk; give 2 mg folate daily	Limited human data; potential diarrhea
Antibiotics			
Amoxicillin/clavulanic acid	B	Low risk	Probably compatible
Quinolones: ciprofloxacin	C	Avoid	Limited human data; avoid prolonged courses
Metronidazole	B	Low risk; avoid T1	Limited human data; potential toxicity
Rifaximin	C	No human data; animal teratogen	No human data
Biologics			
Adalimumab	B	Low risk	Limited human data; probably compatible
Certolizumab	B	Low risk	Limited human data; probably compatible
Infliximab	B	Low risk	Limited human data; probably compatible
Natalizumab	C	Limited human data	Limited human data; probably compatible
Corticosteroids			
All corticosteroids, including budesonide	C	Low risk; avoid T1	Compatible
Immunomodulators			
Azathioprine/6MP	D	Animal teratogen; low risk	Low risk; probably compatible
Cyclosporine	C	Low risk	Limited human data; potential toxicity
Methotrexate	X	Contraindicated	Contraindicated
Tacrolimus	C	Low risk	Limited human data; potential toxicity
Thalidomide	X	Contraindicated	No human data

Expert Rev. Clin. Immunol. 6(4), 643–657 (2010)

The art is in being honest and being flexible