Session 09

Immunological Therapeutics 2

Naturopathic Medicine Department
Let’s commence with a case

... then learn how to manage this patient’s problems
Male, 35 years

• Presenting Complaints:
  – physical fatigue 6 months, progressively worsening, most significant in the mid afternoon, causing him to go home early from work 2-3 days a week
  – weight loss, commenced about 7 months ago, in first 2 months lost 9kg, has slowed but in the 7 months has lost a total of 16kg, currently weighs 64kg, height 185cm, appears gaunt
  – loose stools with increased frequency (3 times daily) and urgency, in the last 4 months
  – intermittent night sweats, every 2-3 nights, for the last 6-7 months – disturbs his sleep
  – diagnosed HIV+ 8 years prior, but refused medication until 5 months ago
Male, 35 years

• Other History:
  – worked in commercial finance, has history of long hours and high stress, with “playing hard” most nights including regular high alcohol consumption and cocaine or amphetamine use, minimal sleep
  – this lifestyle was changed 14 months ago, when he left his firm and started managing a small business with a close friend
  – alcohol is now 2-3 shots of vodka 2 times weekly, hasn’t had cocaine or amphetamines for 10 months
Male, 35 years

- Other History:
  - In the past his diet was very poor, with high sugar, high refined carbohydrate and high fat consumption (almost never prepared his own food), 7 shots of espresso a day most days
  - Since changing work he now eats muesli and fruit with full cream milk or 2 eggs and toast with tomato for breakfast, chicken salad with cheese for lunch, and dinner is varied but usually consists of red meat or fish and various vegetables; he has one fully vegetarian day per week
  - Snacks on fruit, or dried fruit and nuts
  - One espresso with 1 sugar in morning and another mid afternoon
Male, 35 years

- Whole Lemon Drink (recommended by friend):
  - whole lemon quartered
  - 1.5 cups water
  - 2 dessert spoons flaxseed oil
  - 2 capsules of liquid lecithin (pricked and squeezed)
  - 1 capsule of vitamin E (1000 IU – pricked and squeezed)
  - piece of fresh ginger (about 4cm round)
  - blended together and then strained
  - drinks half mid morning and half late afternoon
Male, 35 years

• Physical Examination & Investigations:
  – CD4: 350 (5 months ago)
  – viral load: > 100,000 (5 months ago)
  – slight elevation in GGT (5 months ago)
  – mild submandibular, suboccipital and axillary lymphadenopathy

• Medications
  – HAART – commenced 5 months ago
keep this case in your mind as we move into the lecture

... and we will revisit this patient again later
Approach to the patient with allergic & hypersensitivity disorders
Key points

• Allergic & hypersensitivity disorders can manifest rapidly (and often dramatically) after exposure to the agent, or may be delayed or even chronic in nature

• Identification and avoidance of triggers is important
  – in some environmental allergies & sensitivities this may be difficult, or for other reasons undesirable
  – the more severe the reaction, the more total avoidance is required
Key points

• Ensuring that cutaneous and mucosal barriers are adequate is important
  – this can include skin, nasopharyngeal and lower respiratory mucosal surfaces, and gastrointestinal
  – thus herbal approaches can include with tissue restoratives, and also often includes improving GIT and hepatobiliary function and integrity

• Comorbidities can include frequent or chronic infections of the affected area
  – recurrent or chronic inflammation predisposes the affected tissue to infection
Primary classes of medicines for allergies & hypersensitivities

- **Anti-allergics**
  - *Albizia lebbeck*
  - *Scutellaria baicalensis*
  - *Nigella sativa* seed oil

- **Anti-inflammatories**
  - *Glycyrrhiza glabra*
  - *Scutellaria baicalensis*
  - *Rehmannia glutinosa*
  - *Solidago virgaurea*
  - *Vitis vinifera* seed (high doses for acute)

- **Immunomodulators**
  - *Echinacea spp.*
  - *Picrorrhiza kurroa*
  - *Tylophora indica* (care)

- **Bitters**
- **Cholagogues & choleretics**
- **Hepatoprotectives**
- **Relevant tissue restoratives** (e.g. mucosal trophorestoratives)
## Short activity (15 min)

compare & contrast these medicines

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Primary Action</th>
<th>Secondary Action</th>
<th>Primary phytochemistry</th>
<th>Other Notes</th>
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<tr>
<td>Albizia lebbeck</td>
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<td>Scutellaria baicalensis</td>
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<td>Glycyrrhiza glabra</td>
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<td>Solidago virgaurea</td>
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Approach to the patient with autoimmune disorders
Autoimmunity

- Characterised by chronic inflammation with a loss of tolerance to ‘self’ or ‘auto’ antigens.

- The causes for this loss of tolerance, the shift from normal immune function to autoimmune pathology, are poorly understood but are generally agreed to be multifactorial, involving a combination of genetic, environmental, hormonal and immune factors.

(Bradbury & Hatley, 2014, p.593)
Autoimmunity

- A small proportion of our immune system at any given time presents with self antigens and the immune system does not react to them. This is termed ‘tolerance to self’.

  (Janeway et.al. 2001)

- In autoimmunity there is a loss of tolerance. This shift is not well understood but is “…generally agreed to be multifactorial, involving a combination of genetic, environmental, hormonal and immune factors.”

  (Bradbury & Hatley, 2014, p.593)
Autoimmunity

- How genotypes manifest takes account of environmental factors and how these interact with genes.

- Factors include:
  - Viral and bacterial infections (e.g. superantigens triggering CD4 cells)
  - Certain chemicals and drugs
  - Mechanical injury – molecular mimicry and bystander activation
  - Dietary antigens (e.g. coeliac disease)

(Bradbury & Hatley, 2014, p.595)
Autoimmunity

Inflammatory Mechanisms
- Cytokines (first and third signal)
- T-cells
- CD4+ and CD8+ cells
- T helper 1 and T helper 2 hypothesis

(Radbury & Hatley, 2014, p.597)

Risk Factors
- Altered immune function
- Exposure to chemicals
- Diet and Lifestyle
- Hormones
- Stress

(Radbury & Hatley, 2014, pp.598-599)
Autoimmunity: Genetic Factors

<table>
<thead>
<tr>
<th>Auto-immune Disease Examples</th>
<th>Gene Implicated</th>
<th>% Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankylosing spondylitis</td>
<td>HLA-B27</td>
<td>87.4%</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>HLA-DR3</td>
<td>2.5%</td>
</tr>
<tr>
<td>Graves disease</td>
<td>HLA-DR3</td>
<td>3.7%</td>
</tr>
<tr>
<td>Systemic Lupus Erythematosus (SLE)</td>
<td>HLA-DR3</td>
<td>5.8%</td>
</tr>
<tr>
<td>Insulin Dependent Diabetes Mellitus (IDDM)</td>
<td>HLA-DR3 &amp; HLA-DR4</td>
<td>25%</td>
</tr>
<tr>
<td>Rheumatoid Arthritis (RA)</td>
<td>HLA-DR4</td>
<td>4.2%</td>
</tr>
</tbody>
</table>

- Genotypes may present, but given the percentage of presentation manifestation of the disease has to incorporate other factors i.e. environmental implications.

(Janeway et.al. 2001)
Autoimmunity: Environmental Factors

These include:

- Viral and bacterial infections (e.g. super-antigens triggering CD4 cells)
- Certain chemicals and drugs
- Mechanical injury:
  - molecular mimicry - immune system is unable to differentiate between self antigens and foreign antigens
  - bystander activation - infected cells activate inflammation signalling triggering the destruction of ‘bystander’ healthy cells. (Fujinami et.al, 2006)
- Dietary antigens (e.g. coeliac disease) (Bradbury & Hatley, 2014, p.596)
Autoimmune Reactions

Type I immune responses are reduced in most cases.

- Autoimmunity reactions have similar mechanism/processes as the hypersensitivity reactions without the foreign antigen & reduced type I response (no IgE)

Type II immune responses are common.

- Induction of IgG or IgM to autoantigens located on cell surfaces.
- This causes cellular or receptor damage via complement dependent lysis, anti-receptor antibodies, antibody dependent cellular cytotoxicity.
- Examples include auto-immune haemolytic anaemia, Hashimoto’s thyroiditis, Graves disease, Myasthenia gravis.

(Janeway et.al. 2001, Kumar & Clark, 2009)
Autoimmune Reactions

Type III immune responses are common.

- Immune complex formation occurs forming autoantibodies to soluble auto-antigens. This can be local or systemic.
- Examples include Rheumatoid arthritis (RA), Systemic Lupus Erythematosus (SLE).

Type IV immune responses present.

- This type of immune reaction occurs in organ specific autoimmunity. T cell responses are directly involved in causing the tissue damage.

(Janeway et.al. 2001, Kumar & Clark, 2009)
Autoimmune Reactions

Sustaining factors implicated in autoimmunity include:

- A self antigen presents which is identified as still a component of the body.
- The body lacks the ability to eradicate this antigen so the disease persists.
- Dependent on the antigen involved and the mechanism of action determines the clinical expression of the disease.
- The immune reaction may be local or systemic.

(Janeway et.al. 2001, Kumar & Clark, 2009)
Autoimmune Reactions

**Mechanism of Damage**

- Direct cell death
- Inflammatory damage (IL-1, TNF-α)
- Bind to tissue & recruit complement
- Bind to antigens & create immune complexes
- Bind to surface receptors altering function

(Kumar & Clark, 2009, p.74)
Information Gathering

- Is it organ-specific or systemic autoimmune disease?
  - Identify specific organ/systems/tissues involved and restore

- Address risk factors
  - Genetic, environment, oestrogen status, stress, diet

- Modulate inflammation

- Address behavioural/lifestyle issues
  - Exercise, unresolved grief, negative thought patterns, unsupportive relationships

(Bradbury & Hatley, 2014, p.620)
Treatment Considerations

- **Boswellia serrata**
  - Boswellic acids – non steroidal anti-inflammatory agents, inhibit 5-lipooxygenase activity, suppress leukotriene
  - Note: may inhibit drug detoxification enzymes therefore may potentiate 95% of pharmaceutical drugs

- **Harpagophytum procumbens**
  - Iridoid glycosides (e.g. harpagoside) – inhibit COX-2, pro-inflammatory cytokines (e.g. TNF-alpha)
  - Note: Increases gastric acid secretion – CI in Crohn’s disease and ulcerative colitis, some evidence to suggest interaction with anti-arrhythmic medications

(Sarris & Wardle, 2010, pp.552-555)
Treatment Considerations

- *Curcuma longa* and curcumin
  - *C. longa* demonstrated therapeutic effects in a wide range of auto-immune disease;
  - Curcumin – non-steroidal anti-inflammatory

- *Urtica dioica* (leaf and root)
  - Inhibits NF-κB (TNF-alpha inducer)

- *Tylophora indica* (care)
  - Suppression of cellular (T-cell) immunity

- *Hemidesmus indicus*
  - Inhibit TNF-alpha and IL-8

- *Foeniculum vulgare*
  - Blocks TNF-alpha

(Sarris & Wardle, 2010, pp.552-555)
Other useful medicines & approaches

- Other anti-inflammatories
  - *Glycyrrhiza glabra*
    - possibly reduces immune reactivity through glucocorticomimetic activity
  - *Rehmannia glutinosa*
  - *Bupleurum falcatum*

- Tissue restoratives
  - depending upon the affected tissue(s)

- Adaptogens
  - to improve resilience to stress, including the stress of chronic disease

- Analgesics
  - as needed

- Depuratives
  - traditional approach

- Antimicrobials (various)
  - if an infection is an initiating or sustaining factor
Approach to the patient with HIV/AIDS
“Human immunodeficiency virus (HIV) infection results from 1 of 2 similar retroviruses (HIV-1 and HIV-2) that destroy CD4+ lymphocytes and impair cell-mediated immunity, increasing risk of certain infections and cancers. Initial infection may cause nonspecific febrile illness. Risk of subsequent manifestations—related to immunodeficiency—is proportional to the level of CD4+ lymphocyte depletion. HIV can directly damage the brain, gonads, kidneys, and heart, causing cognitive impairment, hypogonadism, renal insufficiency, and cardiomyopathy. Manifestations range from asymptomatic carriage to acquired immune deficiency syndrome (AIDS), which is defined by serious opportunistic infections or cancers or a CD4 count of < 200/μL. HIV infection can be diagnosed by antibody, nucleic acid (HIV RNA), or antigen (p24) testing. Screening should be routinely offered to all adults and adolescents. Treatment aims to suppress HIV replication by using combinations of ≥ 3 drugs that inhibit HIV enzymes; treatment can restore immune function in most patients if suppression of replication is sustained.”
Definition & Clinical Considerations


- AIDS can involve an enormous range of individual conditions affecting almost all body systems.
- As a result clinical manifestations can be highly variable between different individuals, and in the same individual at different stages of their disease.
“Paradigms of natural medicine state to avoid or minimize the use of higher force (drug, surgery, radiation) interventions. Yet no therapies current are as effective as HAART* in suppressing viral load or increasing CD4 numbers. The current standard of care delays HAART in asymptomatic patients while CD4 count is consistently between or above 200-300 cells/μL and/or plasma viral load is <50,000-100,000 copies/mL. HAART must be considered and not discouraged. Regardless of HAART, HIV-positive patients benefit from nondrug therapies. Naturopaths must apply the entire therapeutic order to maximise quality of life and longevity. Stay current with arising possibilities. Ensure patient safety from adverse drug-nutrient interactions. Understand mechanisms of HAART and common nutrients used by HIV-positive patients.”

*HAART = highly active antiretroviral therapy
(a range of different types of individual and combined drug regimes)
3 Stages of Holistic Treatment

1. CAM Only Treatment
   • Blood parameters within normal limits; generally well
   • Proactive approach on maintenance of good health

2. CAM & HAART
   • Parameters declining; some health issues developing
   • Similar approach to above whilst monitoring parameters and manifestations for 2-4 months. If decline continues HAART should be introduced.

3. HAART Only or HAART & Minimal CAM
   • Blood parameters continuing to decline; patient very unwell
   • Consider herb/nutrient/drug interactions; minimise adverse reactions to medications; optimise GIT health, complement antiviral medications with herbal antivirals
Therapeutic Objectives

1. Reduce viral load
   • Antivirals
     • *Momordica charantia* (Bitter Melon)
     • *Spirulina platensis*
     • *Camellia sinensis*
     • *Ganoderma lucidum, Lentinus edodes*
     • *Glycyrrhiza glabra* (debatable if oral administration works)
     • *Hypericum perforatum* (care with concurrent drug regimes)
Therapeutic Objectives

2. Strengthen immune function

• Immunomodulators
  • *Ganoderma lucidum, Lentinus edodes*
  • *Uncaria tomentosa*
  • *Astragalus membranaceus*

• Adaptogens
  • *Withania somnifera*
  • *Eleutherococcus senticosus*
  • *Panax ginseng, P. quinquefolius*
3. Reduce oxidative stress

- Antioxidants
  - *Curcuma longa*
  - *Camellia sinensis*
  - *Vitis vinifera*
  - *Scutellaria baicalensis*
  - *Silybum marianum* (particularly useful in minimising some drug adverse reactions)
  - α-lipoic acid, CoQ10
Therapeutic Objectives

4. Reduce inflammation
   • inhibitors of TNF-α & NF-κB expression
     • *Curcuma longa*
   • eicosanoid synthesis modifiers
     • *Curcuma longa*
     • *Scutellaria baicalensis*
     • fish oil
Therapeutic Objectives

5. Promote naturopathic diet and lifestyle

• Diet
  • protein rich wholefood diet
  • extreme care if patient is vegetarian
  • specific supplementation as required

• Exercise therapy
  • tai chi, qi gong, yoga

• Meditation
  • tai chi, qi gong, yoga
Therapeutic Objectives

6. Support vitality

• Adaptogens
  • *Panax ginseng, P. quinquefolius*
  • *Eleutherococcus senticosus*
  • *Withania somnifera*

• Digestive & nutritional support
  • GIT anti-inflammatories, demulcents, gut restoratives, carminatives, and aromatic bitters as required
  • L-glutamine, probiotics
7. Manage opportunistic infections

- Antimicrobials specific to the infection/body system
  - *Baptisia tinctoria*
  - *Cymbopogon citratus, Citrus limon*
  - *Thymus vulgaris*
  - *Tabebuia avellanedae*
  - *Melaleuca alternifolia* essential oil
  - *Olea europea*
  - *Melissa officinalis*
8. Reduce wasting/promote anabolism
   • adaptogens
     • *Withania somnifera*
     • *Panax ginseng* (low dose), *P. quinquefolius*
   • protein supplementation
   • testosteromimetics
     • *Tribulus terrestris*
   • adrenal restoratives
     • *Glycyrrhiza glabra*
9. Manage mood & promote stress adaptation

• antidepressants
  • *Hypericum perforatum* (care with interactions)
  • *Avena sativa* seed or straw

• thymoleptics
  • *Melissa officinalis, Turnera diffusa*

• nervine sedatives
  • *Passiflora incarnata, Scutellaria lateriflora*

• counseling
Clinical Tips

• Echinacea controversy
  – extrapolations of research data inconclusive and human clinical trials in HIV/AIDS are largely lacking
  – thus safety and efficacy are largely unknown

• At some stage or other, almost every tool in the herbalist/naturopath’s box can be of use in helping people with HIV/AIDS. The key is highly individualised treatment, and an integrated care-giving team helping the patient.
Case Tutorial (1-1.5 hrs)

... let’s return to our patient
Male, 35 years

- Presenting Complaints:
  - physical fatigue 6 months, progressively worsening, most significant in the mid afternoon, causing him to go home early from work 2-3 days a week
  - weight loss, commenced about 7 months ago, in first 2 months lost 9kg, has slowed but in the 7 months has lost a total of 16kg, currently weighs 64kg, height 185cm, appears gaunt
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• Medications
  – HAART – commenced 5 months ago
Case tutorial requirements

- Divide into 2-3 groups, and each group works individually, and then presents their findings at the end.

- What is your diagnosis?
  - why?

- What are your treatment objectives?
  - why?
  - are they SMART, holistic, patient-centred, individualised and rational?

- What methods/actions would you choose to achieve your objectives?
  - why?

- What herbs are most appropriate for each method/action?
  - why?

- Build your final formula with amounts and dosage instructions (see table on next slide).
<table>
<thead>
<tr>
<th>Latin binomial</th>
<th>DER</th>
<th>Chosen dose per week</th>
<th>Amount per bottle</th>
<th>Relevant action(s)</th>
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**Dosage & instructions**

Other herbal prescriptions (e.g. infusions, topicals, tablets/capsules)? Provide dosage and instructions, and rationale.
Pre-reading for Session 10
Read before your next Session

• Merck Manual Professional Version
  – Approach to the dermatologic patient
  – Acne vulgaris
  – Rosacea
  – Psoriasis

• Weiss & Fintelmann
  – Dermatologic Disease (p293-313)
References


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• Bryant, B Knights, K, 2011. *Pharmacology for Health Professionals*, 3rd edn, Mosby Elsevier


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