HIES and lows
AP - early history

Born 1993
Extensive eczema and skin infections in the neonatal period – Staph isolated on occasion
- recurrent episodes of folliculitis
- cutaneous abscesses in groin and axilla

At 3 years
- immunodeficiency diagnosed
  - initially thought to be IgG2 and IgG4 subclass deficiency with a reduced response to pneumococcal vaccine
  - commenced on IVIg
  - craniosynostosis (fused cranial bones) - optic nerve compression requiring surgical release

IgE levels ~2000kU/L
AP - on transition to adult service

2011 - 18 year old male
Established diagnosis of Hyper IgE Syndrome
  - Stat 3 mutation was confirmed on genetic testing in 2007
  - No family history of HIES

Multiple manifestations/ complications of the disease
  - Multiple pneumonias; very mild bronchiectasis
  - Skin well controlled with cetaphil wash (no furuncles) but muco-cutaneous candidiasis – oral and penile thrush, candida onychomycosis
  - Bones - first fracture aged 8; 9 fractures in total; pamidronate since ~2002

Working in hospitality (bar tender)
Completed year 12 but had missed lots of school with ↓ performance
Physically active with regular sport
Therapy

Bactrim 800/160mg daily
Fluconazole 200mg daily
IVIg 24gm monthly via peripheral cannulation
Zoledronic acid
Physiotherapy with PEP device

Specialties involved:
- Routinely: Immunology, Respiratory, Endocrinology, Dermatology, Dentist
- More peripherally: Orthopaedics
Admissions in 2011

Admission #1: 23/02 – 1/03/11
- right lower lobe pneumonia on CXR; CRP 47mg/L, N 4.4x10^9/L → Tazocin

Admission #2: 28/11 – 5/12/11
- CXR – right middle lobe collapse/consolidation; CRP 29, N 5.6 → Tazocin + topical antibiotics for ear
- Sputum M/C/S - H.influenzae - sensitive to Amp/amoxicillin, tetracycline, Bactrim

Admission #3: 19/12/11 – 9/01/12
- HRCT – dense consolidation left lower lobe
- CT Paranasal sinuses - diffuse mucosal thickening → Tazocin + ciprofloxacin
- 23/11/11 - Bronchoscopy - Pneumocystis jirovecii detected by PCR
- PCP pneumonia →IV Bactrim then oral Bactrim
Also in 2011

Ear surgery – tympanoplasty, mastoidectomy, canal plasty
  - Aspergillus fumigatus isolated on a swab (fluconazole → itraconazole)
  - Other swabs positive for Candida parapsilosis
  - operation performed privately

Fracture of 1st rib and clavicle
Chronic balanitis
Admission in 2012

Admission #4: 1/02/12 – 6/02/12

Left distal humeral fracture (fell playing tennis court) → ORIF 1/02/12 → subsequent ulnar nerve palsy with development of ulnar claw
BMD - T-scores
- lumbar spine: - 1.8
- femur: - 0.7
- radius: - 3.2

AP has 2 rows of teeth
- Definitive therapy for teeth (removal of primary dentition) decided against as risk-benefit not favourable
  - nervousness about extensive previous treatment with bisphosphonates

Sputum MCS - H.influenzae - amp/amoxycillin sens, Bactrim - resistant
Admission in 2013 + 2014

3 months in Europe!!

Admission #5: 23/08 – 26/08/13
- 2 weeks of productive cough, feeling unwell, malaise
- no focal consolidation but bilateral first rib fractures and multiple un-united upper posterior rib fractures
- CRP 30, N 8.3; IV Tazocin + gentamicin

Admission #6: 11/07 – 14/07/14
- viral pneumonia - no focal consolidation on CXR
- viral swab – positive for influenza A (H1N1) and picornavirus

2013- Sputum MCS - P.aeruginosa isolated - sensitive to gentamicin, Pip-Taz and ciprofloxacin
Admissions in 2015

Admission #7: 13/07/15 – 23/07/15
- CT Chest – left lower lobe consolidation
- left ear swab – A. fumigatus
- Tazocin and gent; gent → tinnitus; changed to ciprofloxacin

Admission #8: 26/11 – 18/12/15
- CXR – linear opacity in the left upper zone
- CRP 62 (IgE 527); Tazocin + neb Tobramycin → IV ceftazidime 2gm tds on discharge for 7-10 days

* Changed from voriconazole to posaconazole
Other tests of interest

No positive BCs in all these admissions! (probably reflects pre-treatment with antibiotics before presentation)

July 15
- Aspergillus fumigatus IgG: 20 (<50mgA/L)
- IgE Aspergillus 1.66 (<0.35 kU/L)

* Lack of appropriate CRP or neutrophil response to infection
Autosomal recessive HIES

Usually consanguineous families
Mainly due to Dock8 mutations
Are particularly prone to viral skin infections e.g. Molluscum contagiosum, Herpes simplex and zoster, human papilloma virus
Do not have the connective tissue manifestations
Mutations in STAT3 and diagnostic guidelines for hyper-IgE syndrome, JACI, 125 (2)
He came to my attention when he experienced a recurrence of infections and on further investigation and questioning revealed a history of long bone fractures. He was found to be osteoporotic. He also has abnormalities of his teeth with failure to shed his primary dentition normally. He has coarse facial features and a very high level of IgE. All of these features are consistent with the diagnosis of hyper IgE syndrome, although this remains a provisional diagnosis given the absence of a better understanding of molecular pathogenesis of this disorder.

STAT3 Mutations in the Hyper-IgE Syndrome

final confirmation did not become possible until 2007 when the genetic defect of autosomal recessive HIES was identified. We sequenced his Stat3 gene and he was found to have a heterozygous missense mutation in the DNA-binding domain, resulting in an R382Q substitution.
What does a molecular diagnosis add

Not always required – may not add to either diagnosis or management

1. Diagnostic precision/ establish unequivocal diagnosis
2. Permit accurate genetic counselling
   - allow planning of future pregnancies or their outcomes
3. Better define genotype/phenotype associations
4. Identify candidates for gene-specific therapies
5. Prognosis
Mutations in STAT3 and diagnostic guidelines for hyper-IgE syndrome
Mutations in STAT3 and diagnostic guidelines for HIES (1)

100 unrelated patients with the suspected diagnosis of HIES in a worldwide collaboration
- 61M: 39F
- Age ranged between 1 and 58 years
- 80 pts had HIES scores >40 – probable HIES
- 20 patients <40

Table 1

<table>
<thead>
<tr>
<th>CLINICAL FINDINGS</th>
<th>POINTS $^a$</th>
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<tbody>
<tr>
<td></td>
<td>0</td>
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<tr>
<td>Skin abscesses</td>
<td>None</td>
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<tr>
<td>Pneumonia (episodes over lifetime)</td>
<td>None</td>
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<tr>
<td>Parenchymal lung anomalies</td>
<td>Absent</td>
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<tr>
<td>Retained primary teeth</td>
<td>None</td>
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<tr>
<td>Scoliosis, maximum curvature</td>
<td>&lt;10°</td>
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<tr>
<td>Fractures with minor trauma</td>
<td>None</td>
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<tr>
<td>Highest eosinophil count (cells/μl)</td>
<td>&lt;700</td>
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<tr>
<td>Characteristic face</td>
<td>Absent</td>
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<tr>
<td>Midline anomaly</td>
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<tr>
<td>Newborn rash</td>
<td>Absent</td>
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<tr>
<td>Eczema (worst stage)</td>
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<td>Upper respiratory infections per year</td>
<td>1–2</td>
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<tr>
<td>Candidiasis</td>
<td>None</td>
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<tr>
<td>Other serious infections</td>
<td>Absent</td>
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<tr>
<td>Fatal infection</td>
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<tr>
<td>Hyperextensibility</td>
<td>Absent</td>
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<tr>
<td>Lymphoma</td>
<td>Absent</td>
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<tr>
<td>Increased nasal width$^b$</td>
<td>&lt;1 SD</td>
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<tr>
<td>High palate</td>
<td>Absent</td>
</tr>
<tr>
<td>Young-age correction</td>
<td>&gt;5 years</td>
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</table>
Mutations in STAT3 and diagnostic guidelines for HIES (2)

Results – of the 100 patients
- 64 carried heterozygous mutations within STAT3 (>90% were in the exons of STAT3; 5 mutations at the intron-exon boundaries, 4 in frame deletions)
- 36 did not show any mutation in the coding regions of STAT3 or their flanking intronic sequences

30pts, 17 with Stat3 mutation, 13 without
Mutations in STAT3 and diagnostic guidelines for HIES (3)

High total HIES score was strongly associated with having a mutation in STAT3 (P value 3.9e-07).

5 features are best associated with HIES:
   1. pneumonia
   2. newborn rash
   3. pathologic fractures
   4. characteristic face of Job syndrome
   5. cathedral palate

For predicting presence of a STAT3 mutation, this set of clinical features had:
   - a sensitivity of 87.5%
   - a specificity of 80.6%
   - an error rate of 15%
Transplant in HIES

Bone marrow transplantation is curative for AR-HIES with DOCK8

AD-HIES patients generally do well with intensive therapy and supportive care, and bone marrow transplantation is not usually recommended

- Mixed results but positive results in the setting of lymphoma