The impact of nutrition on visuocognitive development in perinatal brain injury

Dr Morag Andrew
University of Oxford Department of Paediatrics
Introduction

• Early brain development
• Brain plasticity
• Vision: a window on the developing brain
• Nutritional intervention studies
• The Dolphin studies
  • Methods
  • Cohort data
  • Trial experience
• Conclusions
Early brain development

- 60-fold increase in brain weight between 2\textsuperscript{nd} trimester and age 2 years
- Increase of brain surface area with cortical folding and gyrification
- Cortical gray matter volume \( \times 4 \)
- Subcortical gray matter or basal ganglia increases by 70%
The cortical subplate

- Largest transient zone between 15-30 weeks
- Rich in pre-and post-synaptic elements
- Intense synaptic activity
- “Waiting” compartment for thalamocortical fibres
- Remains up to 6 postnatal months
- Rich substrate may underlie potential for plasticity

Judas M et al. Front Hum Neurosci 2013 Aug 2;7:423
Clinical evidence of brain plasticity

- **Motor cortex**
  - Maintenance of ipsilateral motor tracts

- **Somatosensory cortex**
  - Thalamocortical fibres bypass lesion to reach target cortex

- **Visual cortex**
  - Re-routing of thalamocortical fibres to reach target visual cortex
  - Visual functions can be re-located to adjacent “non-visual” cortical areas

Staudt M et al. *Neurology* 2006;67:522
Vision: a window on the developing brain

- Major function of the human brain
- Develops rapidly in early life
- Accessible
- Base for development of cognition, communication, social interactions
Cortical visual systems

‘DORSAL’ stream
V1 ➔ V2 ➔ V5 ➔ PPC

“where” or “how”

‘VENTRAL’ stream
V1 ➔ V2 ➔ V4 ➔ IT

“what” or “who”

posterior parietal cortex (PPC)
inferior temporal (IT) cortex
Connections of cortical modules

Ventral and dorsal cortical streams

Connections of cortical modules

Ventral   dorsal
Nutrition and the developing brain

- Brain growth is energy costly
  - Adult brain consumes 20-25% resting metabolic rate (RMR)
  - Newborn brain consumes 87% RMR
- Adequate nutrition essential for neurogenesis and glial cell formation
- Likely “critical periods” after which repair impossible despite replenishment
  - Varies across different brain regions
  - Particularly relevant following preterm birth
Early nutrition intervention studies

• Nutrient rich preterm formula vs standard term formula for preterm infants
  • Improvement in motor and mental (BSID) development in preterm formula group
  • Incidence of CP lower in preterm formula group
  • Higher IQ in preterm formula group aged 7.5-8 years
  • Improved verbal IQ age 16 years (sub-group)
    – Larger caudate nucleus in males in preterm formula group

Early nutrition intervention studies

• Macronutrient intake in perinatal brain injury
  • Prospective double blind randomised trial
  • Infants n=16
    – ≤32 weeks with white matter disease
    – Severe neonatal encephalopathy
• High or average energy and protein diet from term
• Primary outcome OFC at 12 months
  • Secondary outcomes corticospinal tract (CST) diameter, length and weight
• >1 SD difference in OFC at 12 months CGA
• Increased CST diameter, weight and length in high energy and protein group

Dabydeen L et al. Pediatrics 2008; 121;148-156
LCPUFA supplementation trials

• Cognitive deficits in children fed formula lacking DHA
  • Routine 0.35% DHA supplementation of infant formulae

• LCPUFA supplementation in neonates:
  • Higher Bayley PDI at 30 months
  • Improved attention up to 2 years
  • Improved mental processing at 4 years
  • Improved eye-hand coordination
  • Improved visual acuity
IPD Meta-Analysis of 4 large LCPUFA supplementation trials in term and preterm infants

<table>
<thead>
<tr>
<th></th>
<th>Groningen</th>
<th>Leicester 1</th>
<th>Leicester 2</th>
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<tbody>
<tr>
<td>DHA</td>
<td>0.3%</td>
<td>0.32%</td>
<td>0.17%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Duration of supplementation</td>
<td>2 months</td>
<td>6 months</td>
<td>Until discharge</td>
<td>Until discharge</td>
</tr>
</tbody>
</table>

“does not have a clinically meaningful effect on neurodevelopment as assessed by Bayley scores at 18 months”

Beyerlein A et al. JPGN 2010;50:1-7
The DINO trial

- RCT High dose (1% total fatty acids) enteral feed vs standard enteral feed (0.3% total fatty acids)
- D2 to D4 of life until term corrected age.
- 657 infants < 33 weeks
- Bayley Mental Development Index (MDI) higher in supplemented girls but not boys
- Improved visual acuity in cases versus controls at 4 months CGA

Makrides M et al. JAMA 2009;301:175
DHA, choline and UMP are essential for biosynthesis of new neuronal cell membrane

The Kennedy reaction for membrane biosynthesis
UMP, DHA and choline increase brain phosphatide levels in rats

DHA, uridine and choline increase synaptic elements in the developing brain

UMP, choline and DHA increase synaptic spine density

Food finding errors in gerbils

The Dolphin studies

• Primary Hypothesis
  – Early nutritional intervention with adequate amounts of “neurotrophic” precursors improves neurodevelopmental outcome in infants at risk of neurodevelopmental impairment

• Secondary Hypothesis
  – Early nutritional intervention with adequate amounts of “neurotrophic” precursors improves visual function in infants at risk of neurodevelopmental impairment
Trial participants Dolphin 1 (D1)

- JRH/RBH/WPH
  - Neonates $\leq 30+6$ weeks
    - IUGR $< 9$th centile
  - Neonates $\leq 37$ weeks
    - Grade II/III/IV GMH-IVH
    - Pathological temporo-parietal flare on CUSS
  - Term babies
    - Sarnat Grade II/III HIE
      - Moderately abnormal EEG
    - MRI abnormalities PLIC/BG/Thalami/Cortex
- Stratification
  - Gender, gestation, neuroimaging changes
Trial participants Dolphin 2 (D2)

- Recruited from child development centres across Thames Valley
- 1-18 months with a suspected or confirmed diagnosis of cerebral palsy
- Stratified by age, gender, CP type and visual impairment
Study design

- Pilot study
- 102 subjects (62 D1, 40 D2)
- Double blind randomised placebo controlled trial
- All infants receive dietetic and nutritional support plus
  - neurotrophic supplement or
  - placebo substance
- Two year intervention period
Micronutrient intake

• Supplement added to milk feed
• 2g per kilo
• Intervention group
  – neurotrophic feed supplement
    • DHA (1% total fatty acids)
    • EPA
    • AA
    • Choline
    • UMP
    • supportive vitamins and minerals and trace elements.
• Placebo
  • supportive vitamins and minerals and trace elements
Study measures

• **Primary outcome measure:**
  – Composite cognitive score of Bayley Scales Infant Development III (BSID III)

• **Secondary outcome measures:**
  • Visual Event Related Potentials (VERP) latency
  • Fixation Shift test performance and latency
  • Atkinson Battery of Child Development for Examining Functional Vision (ABCDEFV) score
  • Vineland Adaptive Behaviour Scales (VABS) score
  • Anthropometry
  • Brain choline uptake MRI/MRS
Pattern (phase)-Reversal Visual Event Related Potentials (PR-VERP)

- Assesses integrity and maturity of visual system
- Brain responses to repeating image, recorded from occipital scalp
  - contrast change
- VERP latency measures delay in transmission of stimulus information to visual brain
- Two latency measures used
  - Transient and calculated
Comparison of P1 and calculated VERP latencies in typically developing infants (TDI)

Calculated VERP latency is longer and remains higher in infants with PBI compared to TDI.

![Graph showing latency over CGA (weeks) at time of assessment](image-url)

- Normal/Mild
- Moderate
- Severe
- No brain injury

$p=0.00$
Calculated VERP latency in PBI compared to TDI

Calculated latency vs. CGA (weeks) at time of assessment
Retention

- Thirty withdrawals across both studies (29%)
  - Baseline assessments not completed (n=9)
  - Family circumstances (n=5)
  - Comorbidity (n=5)
  - Moved area (n=3)
  - Possible cow’s milk protein intolerance (n=3)
  - Poor feed tolerance (n=2)
  - Unable to tolerate supplement (n=2)
  - Death (n=1)
Feedback from participants

- Clinicians
  - Poor reliability of early abnormal neurology
  - Reluctance to discuss CP diagnosis under 2 years
  - Uncomfortable introducing research during a “breaking bad news” consultation

- Family
  - Sense of altruism
  - Regaining some control
  - Additional “layer” of support during a difficult time
  - High percentage uptake in preschool follow on trial
Conclusions

• Appropriate macro and micronutrient nutrition is imperative for healthy brain growth and development
• Daily nutritional supplementation of infants with perinatal brain injury is possible
• Larger multi-centre trial is indicated
• Family experience of trial participation positive
With thanks to....

Participating families

And...

Professor Peter Sullivan
Dr Jeremy Parr
Professor Oliver Braddick
Professor Janette Atkinson
Dr Gerardine Quaghebeur
Christine Montague-Johnson
Karen Laler
Bonnie Baker
Transient (P1) VERP latency

- measures delay in transmission of visual information to visual brain
- low repetition rates (2-4 reversals/sec)
- Easy to tell beginning and end of one waveform from next
PR2 transient latency in perinatal brain injury (PBI) compared to TDI

![Graph showing PR2 transient latency (ms) vs. CGA (weeks) at time of assessment. The graph indicates different categories of brain injury: Normal/Mild, Moderate, Severe, and No brain injury. The p-value is given as p=0.015.](image-url)
Calculated latency

• High repetition rate (> 4 reversals/sec)
  – Brain responses merge into regular rhythm
  – “Steady state” VERP

• Phase of signal component shows timing of brain response relative to the stimulus event

• Signal phase at two or more temporal frequencies used to produce “calculated latency”

• Reflects timing of the whole waveform, not just to onset of cortical activation as with P1 latency
The Fixation Shift test identifies early attentional deficits in infants with PBI

- Frontal and parietal networks (dorsal streams) control attention disengagement and shifting
- The Fixation Shift (FS) Test measures ability to shift gaze from a central target to a new lateral target
- Infants with PBI make more errors than typically developing infants (TDI)
- Performance to 7 months corrected gestational age (CGA) predicts cognitive outcome at 2 years of age in PBI
Fixation Shift Test

- 20 randomly presented sequences left and right under non-competition and competition conditions
- Direction of eye and/or head movements recorded by hidden operator unaware of FS sequence
- Number of correct refixations and response latency secondary outcome measures
FSC performance

[Box plots showing median % correct FSC and median latency FSC across Normal/Mild, Moderate, and Severe MRI grading.]

Median % correct FSC:
- Normal/Mild: ~80%
- Moderate: ~60%
- Severe: ~50%

Median latency FSC (s):
- Normal/Mild: ~6 s
- Moderate: ~8 s
- Severe: ~10 s

Outlier data points are indicated by individual symbols.
Mechanisms of brain injury

# Neuroimaging grading system

<table>
<thead>
<tr>
<th></th>
<th>Normal/mild</th>
<th>Moderate</th>
<th>Severe</th>
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<tbody>
<tr>
<td>Preterm brain injury</td>
<td>• Normal • Grade I/II intraventricular haemorrhage (IVH) • Ventricular index (VI) &lt;13mm at term equivalent age (TEA) OR • VI &lt; 97th percentile for CGA</td>
<td>• Grade III IVH • Non-cystic periventricular leukomalacia (PVL) • VI 13-15mm TEA OR • VI &gt;97th percentile but &lt; 4mm above 97th percentile for CGA</td>
<td>• Grade IV IVH • Periventricular haemorrhage infarction (PVHI) • Cystic PVL • Subcortical leukomalacia • VI at TEA &gt;15mm OR • VI &gt;4mm above 97th percentile for GA • Basal ganglia (BG) lesions • Focal infarction</td>
</tr>
<tr>
<td>Cranial ultrasound scan</td>
<td>cUSS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(cUSS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Term hypoxic ischaemic</td>
<td>• Focal subtle abnormalities of BG with normal appearance of the posterior limb of internal capsule (PLIC) • Periventricular white matter changes difficult to differentiate from normal appearances, not classified as abnormal • Changes confined to cerebral cortex and subcortical white matter (WM)</td>
<td>• Multi-focal lesions in BG with equivocal or abnormal signal intensity within PLIC • Small focal lesions of without loss of grey matter (GM)/WM differentiation</td>
<td>• Widespread abnormalities involving all BG/thalamic structures and PLIC • Larger areas of abnormality with loss of GM/WM differentiation, consistent with infarction • Central GM hyperechogenicity +/- more extensive cortical and subcortical hyperechogenicity</td>
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<tr>
<td>encephalopathy</td>
<td>MRI</td>
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<tr>
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<td>• Focal, non-territorial infarct</td>
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D2 clinical diagnoses

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<td>Quadriplegia</td>
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<tr>
<td>Diplegia</td>
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<tr>
<td>Hemiplegia</td>
<td>15</td>
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<tr>
<td>Evolving motor disorder</td>
<td>8</td>
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</table>
Management of Anxiety in ASD

Giovanni Giaroli, M.D., M.Sc., PGDipCAT
London Medical Centre, 144 Harley Street London
Laboratory of Molecular Psychiatry, Division of Psychiatry, University College London
Conflict of interests

<table>
<thead>
<tr>
<th>Speaker</th>
<th>Advisory and consultancy</th>
<th>travel</th>
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<tr>
<td>Ely Lilly</td>
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<tr>
<td>Shire</td>
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<td>Ely Lilly</td>
</tr>
<tr>
<td>Janssen</td>
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</table>
In the clinic……

- Daniel
- 14
- Referred for anxiety and depression and school refusal
- Diagnosed with MDD
- Prescribed with SSRI
- But……
In the clinic...

- Hx: tantrums, poor socialization, poor imagination, not fitting in
- Inattention, daydreaming, EF deficits
- ADOS IV: above cut off for ASD
- ..........
- dispute
Key Points

• How do we define ASD and anxiety: symptom or syndrome
• Defining concepts of comorbidity
• Epidemiology
• How to assess it
• Psychological Treatment
• Medical treatment
ASD and DSM5

- Neuro-developmental Disorders (ADHD, ID, etc)
- Dyad of symptoms
- A) deficit in social communication and social interaction
- B) Restricted, repetitive stereotyped interests, activities, behaviors
- Categorical approach
- Dimensional approach
ASD and DSM 5

- Concerns
- Specificity vs sensitivity
- Asperger vs Kanner

- Positives
  - Non discriminant validy of different diagnosis
  - Not any more bin diagnosis (PDD NOS)
Types of anxiety which may present with ASD

ANXIETY DISORDERS ACCORDING TO DSM 5

- PANIC DISORDER WITH/WITHOUT AGORAPHOBIA
- AGORAPHOBIA WITHOUT PANIC DISORDER
- SPECIFIC PHOBIA
- SOCIAL PHOBIA
- GENERALIZED ANXIETY DISORDER
- ANXIETY DUE TO ANOTHER MEDICAL CONDITION
- SEPARATION ANXIETY
- SELECTIVE MUTISM
Types of anxiety which may present with ASD

OBSESSIVE COMPULSIVE AND RELATED DISORDERS ACCORDING TO DSM 5

- OBSESSIVE COMPULSIVE DISORDER
- BODY DYSMORPHIC DISORDER
- HOARDING DISORDER
- TRICHOTILLOMANIA
- EXCORIATION DISORDER
Types of anxiety which may present with ASD

TRAUMA AND STRESSOR RELATED DISORDERS
- REACTIVE ATTACHMENT DISORDER
- PTSD
- ACUTE STRESS DISORDER
- ADJUSTMENT DISORDER

SLEEP DISORDERS, SOMATIZATION DISORDERS ETC
(this list is not complete!)
Comorbidity

- Co-morbidity refers to the co-existence of two or more discrete disorders in the same individual at the same time (Caron & Rutter, 1991)

- Concurrent co-morbidity means the disorders are present at the same time of the assessment (Elia et al, 2008)

- Lifetime co-morbidity implies that the two conditions occur at any time over one’s life (Elia et al, 2008)
Epidemiology

- Various studies 22-84% children with ASD have anxiety
- Recent meta-analysis shows 39% of ASD children have anxiety: specific phobia 30%, OCD 18%, social anxiety 18%.
- Recent RCT showed that if ASD children have anxiety 91% have 2 or more anxiety disorders

(summarized in Vasa & Mazurek, 2015)
Typical vs atypical anxiety

- Ongoing debate on what is anxiety what is core symptom of ASD

- Typical anxiety: children with ASD have symptom of anxiety according DSM (true comorbidity use of scales)

- Atypical anxiety: social avoidance, compulsiveness, specific phobia (beards, toilets), distress when exposed to sensory stimuli (noises, touch, texture etc), resistance to change routine or rituals

- Study on 59 ASD children shows it is the case for both scenarios

(Kerns et al, 2014)
How do we measure it?

- 36 different measures, including parent-, self-, clinician-, teacher-rated instruments have been used to measure anxiety in children with ASD (Grondhuis & Aman, 2012)

- Most instruments are not validated
  
a) risk of overlapping of symptoms ASDxAnxiety ie: items on avoidance of social situations

b) High prevalence of low IQ
How do we measure it?

- Systematic review of literature found three instruments robust in their measuring properties:
  - 1) the Spence Children’s Anxiety Scale (revised) (SCAS)
  - 2) the revised Children’s Anxiety and Depression Scale (RCADS)
  - 3) The Screen for Child Anxiety Related Emotional Disorders (SCARE)

(Wigham&McConachie, 2014)
Where can I find the scales
For free please?

1) www.scaswebsite.com
2) www.childfirst.ucla.edu/Resources.html
3) psychiatry.pitt.edu/sites/default/files/Documents/.../SCA RED%20Child.pdf
Whatever you use…

Try to combine few methods of discrimination:

- Clinical assessment
- Parent rating
- Teacher rating
- Child rating (depending on IQ)

(Kaat et al, 2013)
Causality of association: few points

- Anxiety severity independent from ASD severity
  (Renno & Wood, 2013)

- Social anxiety negatively correlated with social and communication impairment

- Panic and OCD positively correlated with repetitive restricted behaviors
  (Hallett et al, 2013)

- Anxiety is not insistence on sameness

- Anxiety associated with behavioral problem, irritability and aggression
  (Gotham et al, 2012)
Risk factors

- Gender

- Age (younger children had higher rate of OCD and SAD; older children had higher rate of GAD)

- IQ: (higher IQ had higher rates of anxiety in children, in older children higher verbal IQ but not nonverbal IQ associated with anxiety)

- Executive Function deficits (less able to process and regulate emotions, inflexibility etc)

  (Vasa & Mazurek 2015)
Fancy risk factors

- Genetic risk (maternal phobic anxiety and hostility conferred risk of anxiety in adolescent probands with ASD)  
  (Mazefsky et al 2010)

- “Brain lactate as a potential biomarker for comorbid anxiety disorder in ASD” (at MRI spectroscopy underpinning mitochondrial dysfunction)  
  (Goh et al 2015)
Treatment: what works?

- CBT

Meta-analysis for high function ASD (Sukhodolsky et al, 2013)
8 studies, 469 participants (252 treatment, 217 comparison)
ES for clinician-rated outcome $d=1.19$ (CI=0.23-2.14),
ES for parent-rated outcome $d=1.21$ (CI=0.5-1.97)
5 studies with self-report $d=0.68$ (CI=0.17-1.54)

Heterogeneity!
Treatment: what works?

- Recent RCT: 33 adolescents with ASD + Anxiety, randomized to TAU and BIACA (behavioral intervention for anxiety in children with ASD-UCLA group)

- Treatment based on exposure, challenging irrational beliefs, behavioral support to caregivers, communication and interaction skills

- 79% on BIACA much-very much improved at CGI

- 29% on TAU much-very much improved at CGI

- No difference on RCADS

(Wood et al, 2015)
Meds: what is happening?

- Retrospective observational study (Spencer, 2013)
- 33,565 children with ASD: 64% had at least one prescription for psychotropic drugs
- 33% had 2 or > classes of drugs
- 15% had 3 or > classes of drugs
- Median length was 346 days
Meds: what is the evidence?

- Normally developing children great evidence on CBT and/or SSRI for treatment of anxiety

Walkup, 2008

- Most recent systematic review of treatment for ASD + Anxiety (Vasa et al, 2014):
  1) 2 studies on citalopram (chart reviews)
  2) 1 study on fluvoxamine (open label, no control)
  3) 1 study on buspirone (open label, no control)
Meds: what is the evidence?

- Small studies (15-22 participants)
- 6 weeks to 15 months
- Citalopram showed reduction of anxiety, aggression stereotypies and preoccupations (59%), 24 % did not respond, 19% had to discontinue given activation as adverse effect.
- Fluvoxamine did not reduce anxiety or OCD, adverse effect in 72% of children (activation in 50%)
- Buspirone brought results (73%), mild side effect
Key Points

• How do we define anxiety: symptom or syndrome
• Defining concepts of comorbidity
• Epidemiology
• How to assess it
• Psychological Treatment
• Medical treatment
Thank you!
Why PCO UK?

• CYP Health Outcomes Forum
  – Highlighted poor outcomes, poor comparisons with other European countries

• Areas to address:
  – Medicines Safety
  – Paediatric training, skills and competence
UNEXPLAINED / UNACCEPTABLE VARIATIONS IN HEALTHCARE:

REPORT OF THE CHILDREN AND YOUNG PEOPLE’S HEALTH OUTCOMES FORUM 2013/14

These include:

- a 3 fold variation in admission of term babies into neonatal units;
- a 4 fold variation in admissions to hospital for bronchiolitis or asthma;
- a 3 fold variation in tonsillectomy rates;
- the rate of deaths from non-accidental injury showing a 3-fold variation after outliers;
- deaths from accidental injury showing a 3-fold variation across the regions after exclusions; and
- measles, mumps and rubella vaccine rates of uptake range from 69.7% to 95.3% and human papilloma virus vaccination rates in girls vary from 62.3% to 97.2% by local authority.
RCPCH RESPONSE:

• Jan 2014 : a proposal to address
  – Medicines Safety
    • Quality Improvements for safe prescribing
  – Improvements in skills and competence
    • Access to on-line paediatric knowledge in primary care
    • Based on NICE guidance & paediatric speciality groups
Collaborative Approach

American Academy of Pediatrics

Dedicated to the Health of All Children™

Royal College of Paediatrics and Child Health

Leading the way in Children’s Health

PCO Programme

RCPCH

RPSGB

RCGP

RCN

& Others

AAP

Royal College of General Practitioners

Royal College of Nursing

Royal Pharmaceutical Society
PCO infrastructure

DH Policy Team
NHS England

DH/NHS England Steering Group
Chair: Dr Jackie Cornish

Programme Board (operational)
Chair: Dr Hilary Cass

Partnership Group (strategic)
Co-Chair:
Dr Hilary Cass, Dr Maureen Baker

RCPCH Executive Ctte

QI Network project
Chair: Dr Melanie Clements

Expert Advisory Group

Clinical Content project
Chair: Dr Hilary Cass

Editorial Board
Chair: Dr Jan Dudley

Technical Platform project
Technical Architect: Stephen Moffitt
Q1: At the point-of-care, what online resources do you use when looking for paediatric clinical information? (tick all that apply)

- The Green Book: Immunisation against infectious disease: 141
- Patient.co.uk: 108
- NHS Evidence: 99
- NHS Choices: 71
- GP Notebook: 64
- Spotting the Sick Child: 32
- British Medical Association Website: 23
- Map of Medicine: 20
- WellChild: 14
- Healthy Child programme: 14
- Headsmart: 15
- GP Online: 8
- Best Beginnings: 4
- Pulse: 4
- MindEd: 4
- Other: 82
Q2: How important are recommendation and accreditation when you choose your online clinical advice and guidance?

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<tr>
<th>Requirement</th>
<th>Very Important</th>
<th>Quite Important</th>
<th>Not Very Important</th>
<th>Not at All Important</th>
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<tbody>
<tr>
<td>Has National Accreditation</td>
<td>102</td>
<td>119</td>
<td></td>
<td>213</td>
</tr>
<tr>
<td>Provided by NHS</td>
<td>82</td>
<td>124</td>
<td></td>
<td>30 9</td>
</tr>
<tr>
<td>Recommended by another professional body</td>
<td>80</td>
<td>125</td>
<td></td>
<td>35 5</td>
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<tr>
<td>Recommended by a Royal College</td>
<td>115</td>
<td>113</td>
<td></td>
<td>15 2</td>
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<tr>
<td>Recommended by colleagues</td>
<td>103</td>
<td>127</td>
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<td>15</td>
</tr>
</tbody>
</table>

N = 245
Q3: At the point-of-care, what online resources do you use to direct your patients and families to for further information? (tick all that apply)

- Patient.co.uk: 149
- NHS Choices: 131
- Medicines for Children: 95
- Great Ormond Street Hospital for Children: 49
- Contact-a-Family: 41
- College Websites: 17
- WellChild: 13
- infoKID: 11
- Headsmart: 10
- GP notebook: 7
- Best Beginnings: 5
- MindEd: 5
- Other: 26

Total: 230
Rigorous Editorial Process

- Senior Editorial team
- Start with existing material – e.g. AAP Quick Reference
- Review for
  - Applicability to UK environments
  - Match against approved guidance (e.g. NICE, SIGN)
  - Suitability for primary care advice
  - Language & style (copy editing)
- Resulting content reviewed by Editor
- Overall review & governance by Lead Editor
- Supported by a dedicated Staff Editor
PCO production process

STAGE 1
First edit

STAGE 2
Finalise Review

STAGE 3
Clinical Expert / GP / trainee / AAP Review

STAGE 4
Copy Edit

STAGE 5
Pharmacy Check

STAGE 6
Consultation
What is Paediatric Care Online?

Paediatric Care Online is an online decision support system for all child healthcare professionals. It supports daily practice by providing immediate, accessible information to inform decisions at point of care, together with a repository of supporting reference material and patient information.

It is relevant for all healthcare professionals who see children at 'point-of-first contact' in the UK including GPs, Emergency Department teams, practice nurses, children's nurses, health visitors and paramedics.

Available on desktop, tablet and smartphone devices it has a responsive design that enables easy and quick access to information with a powerful search function utilising the latest semantic search technology.

Paediatric Care Online is packed with top resources:

- Over 90 Key Practice Point decision support tools covering the common signs and symptoms and critical care situations.
- Public Health England's "Green Book" Immunisation against infectious diseases in a fully indexed and searchable format.
- The British National Formulary for Children covering the prescribing, dispensing, monitoring and administration of medicines to children.
- Links to patient and carer information and resources accredited by the Information Standard.
- Links to resources and e-learning content for child health professionals to support and enhance their paediatric knowledge and practice.
- Access to the US-based AAP Text Book of Pediatric Care with more than 3,000 pages of content and images.
KEY PRACTICE POINTS

Providing a ‘roadmap’ for common signs and symptoms and critical care situations
Key Practice Points
Decision Support Tools

Comprehensive guides covering commons signs and symptoms in children and critical care situations.

- Anaphylaxis
- Increased Intracranial Pressure
- Oedema
- Hepatomegaly
- Haematuria
- Anaemia and Pallor

- Concise and easy-to-navigate decision support tools for point-of-care situations.
- 90 topics covering common signs and symptoms and critical care situations.
- Offers clinically assured advice based on National Clinical guidance where available.
PCO: DECISION SUPPORT TOOLS ‘KEY PRACTICE POINTS’
• Standard template makes important information for all child health professionals easy to access such as “Red Flags” and When to Refer”

• Numerous links to patient information and support resources.
'Red Flag' Symptoms and Signs

Ask about:
- Possibility of pregnancy
  - Consider sexual abuse
    - See When to suspect child maltreatment [NICE clinical guideline CG89, section 1.2]
- Symptoms of raised intracranial pressure
  - See Delayed or arrested puberty [Headsmart; be brain tumour aware]
- Pubertal arrest
- Sudden weight loss
- Possibility of an eating disorder
  - See Eating disorders: Core interventions in the treatment and management of anorexia nervosa, bulimia nervosa and related eating disorders [NICE clinical guideline CG9]

Look for:
- Faltering growth, short stature, and extremes of body mass index
- Lack of development of secondary sexual characteristics
- Signs of androgen insensitivity syndrome
  - Scant pubic hair and axillary hair, with normal breast development
- Signs of androgen excess
  - Hirsutism
  - Acne
- Clitoromegaly
- Imperforate hymen or a transverse vaginal septum
PCO: powerful search and index platform.

Search Results for **swelling**

Showing 1 – 20 of 83

**Content Type**
- BNFC Lookup (51)
- The Green Book (30)
- Key Practice Points (2)

**Key Practice Points**

**Oedema**
... Ask about: Oedema (**swelling** or puffiness') is the accumulation of fluid in the interstitial tissues. Look for: *Please note: whilst these resources have been developed to...

**Key Practice Points**

**Haematuria**
... (petechiae / purpura) Redness / **swelling** of joints School-aged children with microscopic haematuria may be observed for up to 2 years before more extensive testing is undertaken. Haematuria...

**The Green Book > Japanese encephalitis > Adverse reactions**

**IXIARO ®**
... hardening, **swelling** and itching at the injection site, influenza-like illness, pyrexia and fatigue. ...
Decision Support: Building on existing materials

- Links to other resources
  - Medicines for Children
  - InfoKid
  - MindEd
  - NHS Choices
  - RCPsych – Mental Health Advice
- HeadSmart
- Together for Short Lives
- RCGP/NSPCC Safeguarding Children Toolkit
Resources for Families

Medicines for Children

Medicines for Children leaflets provide parents and carers with practical, reliable information about medicines prescribed to children. The leaflets cover the most common medicines prescribed to children. They are written in plain English, and answer frequently asked questions or common concerns parents and carers have, including:

- How do I give this medicine?
- What if I forget to give it or give too much?
- Are there any possible side-effects?

The project has been accredited by the Information Standard since 2011.

Medicines for Children is a partnership project between RCPCH, NPPG and the family charity WellChild.

infoKID

infoKID provides high quality information for parents and carers about kidney conditions in babies, children and young people, including symptoms, causes, diagnosis, treatment and management. Currently, there are 23 kidney conditions covered from AKI, CKD and glomerulonephritis to UTIs and vesicoureteral reflux and reflux nephropathy.

InfoKID is a partnership between the Royal College of Paediatrics and Child Health, the
Resources for Health Professionals

HeadSmart

The HeadSmart education module has been designed to help health professionals improve their knowledge of brain tumour presentation in children and young people and the links between brain structure and function. By the end of it you should know some of the common symptom and sign combinations that are caused by brain tumours in different locations, as well as understand the common ways in which brain tumours present and some of the diagnostic difficulties that occur in children with brain tumours.

MindEd

MindEd provides simple, clear guidance on children and young people's mental health, wellbeing and development to any adult working with children, young people and families, to help them support the development of young healthy minds.

It does this through bite-sized chunks of e-learning, that are free, completely open access, and available on tablets, phones or computers.

Healthy Child Programme

The Healthy Child Programme 0-18 is a series of e-learning programmes developed for NHS healthcare professionals on child and adolescent health promotion. These e-learning
Paediatric Care Online supports daily clinical practice by providing immediate, accessible information to inform decisions at point of care.

Key Practice Points
Decision Support Tools

- Anaphylaxis
- Increased Intracranial Pressure
- Oedema
- Hepatomegaly
- Haematuria
- Anaemia and Pallor

Green Book
Immunisation against infectious disease

- Immunisation Schedule
- Measles
- Varicella
- Consent
- Meningococcal
- Contraindications and special

Find out more about the PCO Partnership

Child Health News

New guidance for looked after children: posted: 17/04/15
Paediatricians, nurses and GPs unite to protect UK's most vulnerable children and young people...

Political parties make manifesto pledges on child health: posted: 17/04/15
Ahead of May's General Election, the political parties have published their manifestos. Read the highlights on child health...

All babies to be vaccinated against Meningitis B: posted: 15/04/15
RCPC almost reaches agreement on Government's announcement that a deal has been reached on the vaccine...
PCO RESOURCES

BNF for Children
Essential practical information to help healthcare professionals prescribe, monitor, supply, and administer medicines for childhood disorders.

- Paracetamol
- Ibuprofen
- Ranitidine
- Salbutamol
- Beclomethasone
- Dipropionate
- Montelukast

Browse All Drugs >

- BNFc - new electronic platform
- Information is searchable and relevant drugs linked in both Green Book and Key Practice Points
- Data is updated from new information from BNFc
<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Display Name</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>A</strong></td>
</tr>
</tbody>
</table>

- Abacavir
- Abacavir with Dolutegravir and Lamivudine
- Abacavir with Lamivudine
- Abacavir with Lamivudine and Zidovudine
- Abatacept
- Acetazolamide
- Acetylcholine Chloride
- Acetylcysteine
- Aciclovir
- Acitretin
- Acrivastine
- Adalimumab
- Adapalene
- Adapalene with Benzoyl Peroxide
- Adenosine
PCO Resources

Green Book
Links to KPPs
Working with Public Health England

Current Green Book only available on pdf – but on PCO is now in fully indexed and searchable form

Free to all visitors of PCO – no subscription required

Continually updated as revised chapters are released
Immunisation against infectious disease

11: The UK immunisation schedule

The routine immunisation schedule

The overall aim of the routine immunisation schedule is to provide protection against the following vaccine-preventable infections:

- diphtheria
- tetanus
- pertussis (whooping cough)
- *Haemophilus influenzae* type b (Hib)
- polio
- meningococcal serogroup C disease (MenC)
- measles
- mumps
PCO-UK – What Next?

• Beta site launch in late September.
  • To register as an early adopter to test and access the beta site email pco@rcpch.ac.uk

• Phase 2 Content:
  • Developing an app
  • Child Protection Companion
  • Content to further support work in Child Protection and Mental Health
  • Link to CPD diary?
  • Link to NIHR research studies?
  • NICE accreditation
  • Webinar:
    • Spotting the Sick Child
PCO-UK: CONCLUSIONS

• Unique resource
  – provides information in a ‘rapid access’ ‘decision-aid’ format, accessed through presenting signs and symptoms (and critical care situations), rather than conditions

• The engagement with speciality groups and GPs is strengthened by the opportunity to signpost to excellent resources that may not be in widespread use.

• Crucially the programme offers the opportunity to operate across primary/secondary care boundaries through professional liaison and future integration across primary and secondary care IT systems
Self-injurious behaviour in children with developmental delay: From response to strategy

Chris Oliver

The Cerebra Centre for Neurodevelopmental Disorders

School of Psychology

University of Birmingham

UK
The size of the problem

Three causes or drivers:
A role for pain and discomfort
A learned behaviour
Behaviour dysregulation

The case for early intervention
Self-injury in people with Severe Intellectual Disability

- Shown by 20-40% of individuals with SLD
- Associated with greater degree of intellectual disability, some genetic disorders and autism spectrum disorder
- Can be chronic and resistant to intervention (84% persistence over c. 20 years)
- Human and economic costs: pain and discomfort, family and carer stress, relationship breakdown, medication effects, compromised quality of life and accomplishment, placement breakdown.
- Economic costs are likely to be significantly underestimated
- Lack of appropriate ‘clinical’ intervention. (SIB, 1987, psychological 2%, medication 40%)............ recent data
Survey of 296 parents of children with severe intellectual disability in Birmingham

Percentage of parents needing help for children showing frequent CB

Percentage of parents with children who show frequent CB who have seen psychology, psychiatry or community nurse in last three months

With: Loraine Ruddick, Jane Petty, Monique Bacarese-Hamilton
Self-injurious behaviour in all people with intellectual disability

- Prevalence 4 -10%
- Scratching, biting, headbanging and hitting
- “…. the impact forces of SIB …. are near the low end of forces generated in boxing blows and karate hits….,” (Newell and Bodfish, 2002)

At each stage, how easy is it to intervene and what are the human and economic costs?
The size of the problem

Three causes or drivers:
A role for pain and discomfort
A learned behaviour
Behaviour dysregulation

The case for early intervention
Pain and discomfort

- The assessment of pain
  - FLACC (Merkel et al., 1997)
  - NCCPC (Breau et al., 2004)
  - QABF (Paclawskyi et al., 2000)

- Behavioural correlates of pain and challenging behaviour:
  - More pain behaviours in those showing challenging behaviour?
  - Higher prevalence of challenging behaviour in those with health problems?
  - More challenging behaviour in those with suspected health problems

- Social/operant causes and pain behaviour?

- New directions in assessment
  - Temporal relationships

www.findresources.co.uk
Pain and discomfort

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Other outrageously expensive smartphones are also available

Kate Eden, Cerebra PhD studentship holder
Pain and discomfort

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Comparison of pain behaviours in children at high risk for challenging behaviour (teacher ratings)

(U=31.5; p<.001)

Kate Eden, Cerebra PhD studentship holder
Pain and discomfort

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Comparison of pain behaviours in children with Tuberous Sclerosis Complex

(U=27; p<.001)

Kate Eden, Cerebra PhD studentship holder
Pain and discomfort

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  – Temporal relationships

Relative risk of frequent self-injury in children and adults with ASD given the presence of health problems

(99% CI)
• Pain in nonverbal children
  – Pain sensitivity
  – Pain perception
  – Pain communication
• Parental report
• Advocacy
The size of the problem

Three causes or drivers:
   A role for pain and discomfort
   A learned behaviour
   Behaviour dysregulation

The case for early intervention
Social Communicative Function of Self-Injurious Behaviour: Positive Reinforcement

- **Need for others to do or give something**
- **Increase in chance of CB**
- **REWARD**
  - Positive Reinforcement
- **ENGAGE**
  - Comfort
  - Reprimand
  - Offer
  - Restrain
  - Occupy
  - Distract
- **ACTION**
- **SIB**
- **AVERSIVE!**
  - Concern
  - Frustration
  - Anxiety
  - Confusion
  - Distress

- Increase in chance of CB
- REWARD
- ENGAGE
- ACTION
- SIB
- AVERSIVE!
A learned behaviour

- Differences across environments
  - Comparison of rates/types of behaviour across environments by record keeping and/or observation.

- Pattern of self-injury and co-occurring behaviours
  - SIB stops with environmental or social change, preceded by precursor behaviours (protest, attempts to solicit attention, requests), SIB is 'directed' toward another person (eye contact, facing toward).

- Associated with social events
  - Behaviour systematically varies with social events (usually, low attention, demands and denials) or appears correlated with these events.
A learned behaviour

• Behavioural interventions
  – Functional analysis
  – Functional communication
  – Actively managing consequences
  – Safety

• Medium term intervention
The size of the problem

Three causes or drivers:
A role for pain and discomfort
A learned behaviour
Behaviour dysregulation

The case for early intervention
Behaviour dysregulation

• A red flag
• Speculative at present
• Self\preferred restraint as an empirical risk marker
Behaviour dysregulation

Self-restraint behaviours
- Attempts to trap or restrict arms (usually) using clothing, furniture or objects. Can be 'symbolic'.

Seeking restraint from others
- 'Asks' to be held (usually arms), distress and SIB if denied.

Preferred imposed restraint
- Actively assists in putting on splints, gloves, helmets etc. Distress and SIB if removed.
Can we identify higher risk within a young high risk group?

Can we predict onset from behavioural risk markers?
<table>
<thead>
<tr>
<th>Putative Risk Marker</th>
<th>Description of putative risk marker</th>
<th>Odds Ratio (CI)</th>
</tr>
</thead>
</table>
| Degree of Intellectual Disability | Greater severity  
More severe deficit in adaptive behaviour on a measure of self-help skills  
The presence of lower levels of ability on a standardised measure of self-help skills (child sample)  
Level of ID (mild, moderate, severe/profound)  
Severe/profound ID vs mild/moderate | 4.06 (2.56-6.43)  
3.15 (CI not reported)  
3.84* (1.60 – 9.19)  
2.11 (1.64 – 2.72)  
7.19 (3.27–15.82) |
| Autism              | Presence on various measures  
Meeting criteria for autism on a standardised measure  
Diagnosis of autism | 5.6 (1.39-22.56)  
2.67+ (1.45-4.91)  
1.70 (1.03–2.80) |
| Genetic Syndromes   | Cri du Chat syndrome  
Cornelia de Lange syndrome  
Fragile X syndrome  
Prader Willi syndrome  
Lowe syndrome  
Smith Magenis syndrome  
Down syndrome | 9.04 (2.93-27.88)  
6.47 (2.48-16.86)  
2.88 (1.22-6.82)  
2.91 (1.23-6.91)  
4.92 (1.71-14.17)  
35.53 (6.32-199.92)  
0.24 (0.055–0.997)  
0.36 (0.20 – 0.64) |
| Health Problems     | The presence of one or more health problems (child sample)  
Visual impairment | 3.54 (1.49 – 8.40)  
1.94 (1.01–3.72) |
| Sensory sensitivity | Tactile hypersensitivity | 2.23 (1.23–4.04) |

The prevalence of self-injury and aggression across syndromes

Prevalence in ASD

1 in 2
• Two surveys

80%
• Persistence over 3 years

Richards, Moss, Nelson & Oliver, 2012; Richards, Moss, Nelson & Oliver, In Review
15 month follow up
(SLD n = 417)

<table>
<thead>
<tr>
<th>Behaviour</th>
<th>No behaviour at either stage</th>
<th>Remission</th>
<th>Incidence</th>
<th>Persistence</th>
<th>One year Incidence (%)</th>
<th>Persistence in participants with behaviour at T1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggression</td>
<td>57.04 (235)</td>
<td>9.47 (39)</td>
<td>12.38 (51)</td>
<td>21.12 (87)</td>
<td>8.25</td>
<td>69.05 (87)</td>
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<tr>
<td>Destruction</td>
<td>70.32 (289)</td>
<td>7.3 (30)</td>
<td>12.65 (52)</td>
<td>9.73 (40)</td>
<td>8.43</td>
<td>57.14 (40)</td>
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<tr>
<td>Self-injury</td>
<td>76.16 (313)</td>
<td>7.06 (29)</td>
<td>7.06 (29)</td>
<td>9.73 (40)</td>
<td>4.71</td>
<td>57.97 (40)</td>
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<tr>
<td>One or more forms</td>
<td>46.62 (193)</td>
<td>10.6 (44)</td>
<td>14.49 (60)</td>
<td>28.5 (117)</td>
<td>9.66</td>
<td>72.67 (117)</td>
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## Predicting onset

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</tr>
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<td>Restricted Behaviours and Interests</td>
<td>Aggression</td>
<td>1.34</td>
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<td>Overactivity/</td>
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<tr>
<td>Impulsivity</td>
<td></td>
<td>(.76, 2.34)</td>
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<tr>
<td></td>
<td>Aggression</td>
<td>2.42 *</td>
</tr>
<tr>
<td></td>
<td>Destruction</td>
<td>2.07*</td>
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<td></td>
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Risk and development of severity

- Environmental influences
- Child characteristics
<table>
<thead>
<tr>
<th>Behaviour</th>
<th>Risk</th>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td></td>
<td>1. Annual screen for 2 years</td>
<td>1. Generic advice: on early signs, vigilance, action, referral, preventative behavioural intervention</td>
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<tr>
<td></td>
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<td>2. Remove from screening register</td>
<td>2. 6 monthly screen</td>
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<tr>
<td>Present</td>
<td></td>
<td>1. Generic behaviour management advice</td>
<td>1. High level intervention</td>
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<tr>
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**Generic advice:** written, AV and multimedia materials, sessional telephone advice line, help with referrals (advocacy support), self-help facilitated groups, school based drop-in clinics

**Low level intervention:** informant based or interview functional analysis, referrals for health conditions, pain and discomfort assessment, FCT.

**High level intervention:** descriptive and experimental functional analyses, assessment of pain via controlled analgesic trials, sessional trials of behaviour intervention and management with evaluation, family support.
Context

• Proactive identification (engagement, point of contact)
• Family resources
• Other behavioural problems (specific and nonspecific)
• Health economics
<table>
<thead>
<tr>
<th>Complexity</th>
<th>Self-injury</th>
<th>Temper outbursts</th>
<th>Motivation for social contact</th>
<th>Sleep disorder</th>
<th>Impulsivity</th>
<th>Aggression</th>
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<td>Smith-Magenis</td>
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<td>Cornelia de Lange</td>
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<td>Cri du Chat</td>
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</tbody>
</table>
Severity of behaviour over time:

- Not identified as a problem
- Identified as a problem requiring management
- Identified as a problem requiring intervention
- Identified as a problem requiring additional resources
- Identified as a problem requiring specialist placement

Time
Early intervention

- Do we know enough yet?
- If not now, when?
- What are the human and economic costs of not doing this?
- The question is not “What should we do?” but “Are we prepared to do it?”.
- We do not have any money so we will have to think.
Paediatrics and Child Health

The continuously updated review of paediatrics and child health (formerly Current Paediatrics)

SYMPOSIUM: RESPIRATORY
Paediatric applied respiratory physiology – the essentials 279
A. K. Gokhman
Robinder G Khemani
Christopher J Newth
Aetiology of asthma 287
A. J. Henderson
Management of severe asthma in children 291
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The management of acute bronchiolitis in children 298

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Child and adolescent obesity 315
Marta Pena
Marj Kashiemi

PERSONAL PRACTICE
Self-injurious, aggressive and destructive behaviour in young children with a moderate to profound intellectual disability 322
Louise Hardley
Gwen Adams
Doug Sieglin
Chris Oliver

Some resources

c.oliver@bham.ac.uk
www.researchgate.net
www.findresources.co.uk
Debbie Allen, Jane Appleby, Ian Apperly, Sarah Beaumont, Sarah Beck, Lisa Collis, Fay Cook, Louise Davies, Kate Eden, Ruth Fishwick, Christina Goredema, Sarah Gorniak, Glyn Humphreys, Abby Marr, Jonathan Martin, Anna Mitchell, Chris Oliver, Jan Oyebode, Jane Petty, Laurie Powis, Barzan Rahman, Donna Reid, Caroline Richards, Kristina Stockdale-Juhlberg, Penny Tunnicliffe, Lucy Wilde, Kate Woodcock.

Core Funding

Cerebra

Grant Support

Medical Research Council
The Big Lottery
Baily Thomas Foundation
Cornelia de Lange Syndrome Foundation
Research Autism
Birmingham Children’s Hospital
Angelman Syndrome Foundation (USA)
Newlife
National Autistic Society
Economic and Social Research Council
Jerome Lejeune Fondation
Tuberous Sclerosis Association
NIHR
Leverhulme

www.cnnd.bham.ac.uk
C.Oliver@Bham.ac.uk
What is the significance of repetitive behaviour and overactive\impulsive behaviours beyond empirical prediction?
Oliver et al. (2011) *Journal of Autism and Developmental Disorders*
Predicting self-injury and self-restraint in ASD

Health
- OR = 2.33

RRBI
- OR = 3.94
- OR = 2.62

OI

Self-injury

ID
- OR = 3.84

Health
- OR = 3.54

OI
- OR = 5.71

Frequent Self-injury

SIB
- OR = 2.08

RRBI
- OR = 3.13
- OR = 2.74

Self-restraint
Some closing thoughts

• Early intervention: Are we nearly there yet?
• Confounding variables in the prediction of parental stress?
• Extending causal models:
  – A neuropsychological account (compromised EF and behaviour dysregulation)
  – Different risk markers for different behaviours
  – Implications for parent\carer\teacher led interventions
Debbie Allen, Jane Appleby, Ian Apperly, Sarah Beaumont, Sarah Beck, Lisa Collis, Fay Cook, Louise Davies, Kate Eden, Ruth Fishwick, Christina Goredema, Sarah Gorniak, Glyn Humphreys, Abby Marr, Jonathan Martin, Anna Mitchell, Chris Oliver, Jan Oyebode, Jane Petty, Laurie Powis, Barzan Rahman, Donna Reid, Caroline Richards, Kristina Stockdale-Juhlberg, Penny Tunnicliffe, Lucy Wilde, Kate Woodcock.
The size of the problem

Three causes or drivers:
  A role for pain and discomfort
  A learned behaviour
  Behaviour dysregulation

The case for early intervention
Percentage of mothers meeting criteria for mild, moderate or severe depression on HADS

[Bar chart showing the percentage of mothers meeting criteria for mild, moderate or severe depression on HADS for different conditions. The conditions include Autism, 1p36, SMS, CdLS, AS, PWS, PMS, FXS, TSC, RTS, DS, Soto, 8p23, and Total.]
Percentage of mothers meeting criteria for mild, moderate or severe depression on HADS
Percentage of mothers meeting criteria for mild, moderate or severe depression on HADS

- Autism
- 1p36
- SMS
- CdLS
- AS
- PWS
- PMS
- FXS
- TSC
- RTS
- DS
- Soto
- 8p23
- Total

End stage renal failure

General Population