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Interventions and Management

1. Toxins (Basel). 2015 May 11;7(5):1629-1648.

Best Clinical Practice in Botulinum Toxin Treatment for Children with Cerebral Palsy.

Strobl W, Theologis T, Brunner R, Kocer S, Viehweger E, Pascual-Pascual I, Placzek R.

Botulinum toxin A (BoNT-A) is considered a safe and effective therapy for children with cerebral palsy (CP), especially in the hands of experienced injectors and for the majority of children. Recently, some risks have been noted for children with Gross Motor Classification Scale (GMFCS) of IV and the risks are substantial for level V. Recommendations for treatment with BoNT-A have been published since 1993, with continuous optimisation and development of new treatment concepts. This leads to modifications in the clinical decision making process, indications, injection techniques, assessments, and evaluations. This article summarises the state of the art of BoNT-A treatment in children with CP, based mainly on the literature and expert opinions by an international paediatric orthopaedic user group. BoNT-A is an important part of multimodal management, to support motor development and improve function when the targeted management of spasticity in specific muscle groups is clinically indicated. Individualised assessment and treatment are essential, and should be part of an integrated approach chosen to support the achievement of motor milestones. To this end, goals should be set for both the long term and for each injection cycle. The correct choice of target muscles is also important; not all spastic muscles need to be injected. A more focused approach needs to be established to improve function and motor development, and to prevent adverse compensations and contractures. Furthermore, the timeline of BoNT-A treatment extends from infancy to adulthood, and treatment should take into account the change in indications with age.

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2. Dev Med Child Neurol. 2015 May 11. doi: 10.1111/dmcn.12797. [Epub ahead of print]

Reliability and practicability of the straight leg raise test in children with cerebral palsy.

Marsico P, Tal-Akabi A, Van Hedel HJ.

AIM: Preventing restrictions to lower limb movement is part of the treatment given to children with cerebral palsy (CP). Such restrictions can be assessed using the 'straight leg raise' (SLR) test. This study investigated the interrater reliability and practicability of the SLR test in children with CP. METHOD: Experienced physiotherapists examined 23 children with CP (6-18y; eight females, 15 males) twice. The SLR hip range of motion (ROM) was measured using an electrogoniometer, and the test was rated based on sensitizing manoeuvres and biceps femoris muscle activity. Practicability was investigated by evaluating children's subjective feedback on the tolerable ROM.

RESULTS: Intraclass correlation coefficients for the SLR hip ROM varied, ranging from 0.84 (95% CI 0.61-0.93) to 0.93 (95% CI 0.87-0.96). Physiotherapists substantially agreed on SLR ratings (Cohen's kappa=0.73). Biceps femoris muscle activity decreased significantly with the release of tension on the sciatic nerve. All children were able to communicate the location and sensation of the maximally tolerated position. **INTERPRETATION:** The SLR test proved to be reliable and practicable in children with CP and might improve clinical reasoning processes. Lower limb movement restrictions in these children may partly be related to limitations in sciatic nerve mobility. Further studies should investigate if the SLR test could estimate activities in children with CP.

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3 *Pediatr Phys Ther.* 2015 May 13. [Epub ahead of print]

Daily Intervention for Toddlers With Cerebral Palsy in GMFCS Level V: A Case Series.

Heathcock JC1, Baranet K, Ferrante R, Hendershot S.

PURPOSE: To describe a daily physical therapy (PT) intervention program and outcomes for 2 toddlers with spastic quadriplegia, Gross Motor Function Classification System (GMFCS) level V, and to evaluate the feasibility of using a daily program in an urban children's hospital outpatient setting. **SUMMARY OF KEY POINTS:** Two toddlers, GMFCS level V, received 2 hours of PT intervention based on motor learning principles 5 days a week for 4 consecutive weeks. Gross Motor Functional Measure (GMFM-66, GMFM-88) and the Bayley Scales of Infant Development, Third Edition, were used as pre- and postoutcome measures. The daily, high intensity intervention was well tolerated. Improvements in motor function, language, and cognitive skills were found. **STATEMENT OF CONCLUSION:** A daily PT program appears feasible and may improve overall development in toddlers with cerebral palsy in GMFCS level V.

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4. *Disabil Rehabil.* 2015 May 13:1-6. [Epub ahead of print]

Bridging the gap: the role of Psychiatrists in caring for adults with cerebral palsy.

Cassidy C, Campbell N, Madady M, Payne M.

PURPOSE: Individuals with cerebral palsy (CP) experience a significant gap in care as they move from interdisciplinary pediatric programs to limited or non-existent care in the adult sector. A lack of knowledgeable adult care providers has repeatedly been identified as a challenge in transitioning those with CP from pediatric to adult care. The objective of this study was to determine the extent to which Psychiatrists provide care to adults with CP and to identify barriers to their engagement with this population. **METHOD:** A survey was distributed to Psychiatrists across Canada. Results were analyzed descriptively using SPSS software. **RESULTS:** Most Psychiatrists provide care to very few adults with CP (10 or less), but over 80% feel that Psychiatry is the most appropriate specialty to provide disability-related care to adults with CP following their pediatric discharge. Among the most frequently identified barriers to caring for this population were lack of accessible resources (i.e. social work, funded therapy, equipment) and lack of referrals. **CONCLUSIONS:** Psychiatrists are willing and appropriate partners in transitioning patients with CP to adult care. Barriers to Psychiatrists' engagement with this population appear to be amenable to change. **Implications for Rehabilitation** A lack of knowledgeable and interested adult practitioners has repeatedly been identified as a challenge in transition planning for young adults with cerebral palsy (the vast majority of whom survive into adulthood). Psychiatrists are ideally suited to manage adults with cerebral palsy, yet in this survey-based study, a majority of Canadian Psychiatrists report caring for less than five adults with cerebral palsy on a regular basis. Barriers to further psychiatric involvement in this population were reported to include lack of accessible resources and lack of referrals.

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5. Indian J Pediatr. 2015 May 15. [Epub ahead of print]**Social, Psychological and Financial Burden on Caregivers of Children with Chronic Illness: A Cross-sectional Study.**

Khanna AK1, Prabhakaran A, Patel P, Ganjiwale JD, Nimbalkar SM.

OBJECTIVES: To explore social, psychological and financial burden on caregivers of chronically diseased children. **METHODS:** Participants were recruited from ambulatory and hospital areas in pediatrics department following informed consent. Parents who were caregivers of children 18y or below in age with chronic illness were included. Socio-demographic details were collected using a semi structured questionnaire, adapted from Family Burden Interview Schedule (FBIS). The psychological well-being of caregivers was assessed using Patient Health Questionnaire (PHQ-9) and Generalized Anxiety Disorder (GAD-7). Descriptive analysis and ANOVA was done for comparing mean scores of responses to analyze financial, psychological and social burden across different diagnosis. **RESULTS:** A total of 204 (89 females:115 males) participated. Only 27% were receiving some benefits from government or hospital side. No depressive symptoms were reported by 25% caregivers, while 37% reported mild and 38% moderate to severe depressive symptoms. No anxiety symptoms were reported by 33%, while 50% reported mild and 17% moderate to severe anxiety symptoms. No association was seen between gender of the caregiver and depressive or anxiety symptoms. Significantly higher financial and social burden was seen in cerebral palsy and cancer groups vis-a-vis other diseases, being least in thalassemia. Disruption of routine life was highest in cancer group caregivers followed by those in cerebral palsy group. **CONCLUSIONS:** Most caregivers reported moderate depressive symptoms and mild to moderate anxiety symptoms. Cerebral palsy caused more social and financial burden on family vis-a-vis thalassemia. Social and financial burden on families of remaining diseases was comparable.

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6. PLoS One. 2015 May 13;10(5):e0125854. doi: 10.1371/journal.pone.0125854. eCollection 2015.**Accuracy of Two Motor Assessments during the First Year of Life in Preterm Infants for Predicting Motor Outcome at Preschool Age.**

Spittle AJ, Lee KJ, Spencer-Smith M, Lorefice LE, Anderson PJ, Doyle LW.

AIM: The primary aim of this study was to investigate the accuracy of the Alberta Infant Motor Scale (AIMS) and Neuro-Sensory Motor Developmental Assessment (NSMDA) over the first year of life for predicting motor impairment at 4 years in preterm children. The secondary aims were to assess the predictive value of serial assessments over the first year and when using a combination of these two assessment tools in follow-up. **METHOD:** Children born <30 weeks' gestation were prospectively recruited and assessed at 4, 8 and 12 months' corrected age using the AIMS and NSMDA. At 4 years' corrected age children were assessed for cerebral palsy (CP) and motor impairment using the Movement Assessment Battery for Children 2nd-edition (MABC-2). We calculated accuracy of the AIMS and NSMDA for predicting CP and MABC-2 scores ≤ 15 th (at-risk of motor difficulty) and ≤ 5 th centile (significant motor difficulty) for each test (AIMS and NSMDA) at 4, 8 and 12 months, for delay on one, two or all three of the time points over the first year, and finally for delay on both tests at each time point. **RESULTS:** Accuracy for predicting motor impairment was good for each test at each age, although false positives were common. Motor impairment on the MABC-2 (scores ≤ 5 th and ≤ 15 th) was most accurately predicted by the AIMS at 4 months, whereas CP was most accurately predicted by the NSMDA at 12 months. In regards to serial assessments, the likelihood ratio for motor impairment increased with the number of delayed assessments. When combining both the NSMDA and AIMS the best accuracy was achieved at 4 months, although results were similar at 8 and 12 months. **INTERPRETATION:** Motor development during the first year of life in preterm infants assessed with the AIMS and NSMDA is predictive of later motor impairment at preschool age. However, false positives are common and therefore it is beneficial to follow-up children at high risk of motor impairment at more than one time point, or to use a combination of assessment tools.

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7. J Paediatr Child Health. 2015 May 15. doi: 10.1111/jpc.12919. [Epub ahead of print]**Tertiary paediatric emergency department use in children and young people with cerebral palsy.**

Meehan E, Reid SM, Williams K, Freed GL, Babl FE, Sewell JR, Rawicki B, Reddihough DS.

AIMS: The aim of this study was to describe the pattern of tertiary paediatric emergency department (ED) use in children and young people with cerebral palsy (CP). **METHODS:** A retrospective analysis of ED data routinely collected at the two tertiary paediatric hospitals in Victoria, Australia, cross-matched with the Victorian Cerebral Palsy Register. Data pertaining to the ED presentations of 2183 registered individuals born 1993-2008 were obtained. **RESULTS:** Between 2008 and 2012, 37% (n = 814) of the CP cohort had 3631 tertiary paediatric ED presentations. Overall, 40% (n = 332) of presenters were residing in inner metropolitan Melbourne; 44% (n = 356) in outer Melbourne; and 13% (n = 108) in regional Victoria. Presenters were more likely than non-presenters to be younger, non-ambulant and have epilepsy. In total, 71% of presentations were triaged as Australasian Triage Scale 1-3 (urgent), and 44% resulted in a hospital admission. Disorders of the respiratory, neurological and gastrointestinal systems, and medical device problems were responsible for 72% of presentations. **CONCLUSION:** Many of the tertiary paediatric ED presentations in this group were appropriate based on the high admission rate and the large proportion triaged as urgent. However, there is evidence that some families are bypassing local services and travelling long distances to attend the tertiary paediatric ED, even for less urgent complaints that do not require hospital admission. Alternative pathways of care delivery, and strategies to promote the management of common problems experienced by children and young people with CP in non-paediatric EDs or primary care settings, may go some way towards reducing unnecessary tertiary paediatric ED use in this group.

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Prevention and Cure

8. PLoS One. 2015 May 14;10(5):e0126743. doi: 10.1371/journal.pone.0126743. eCollection 2015.**Disproportionate fetal growth and the risk for congenital cerebral palsy in singleton births.**

Streja E, Miller JE, Wu C, Bech BH, Pedersen LH, Schendel DE, Uldall P, Olsen J.

OBJECTIVE: To investigate the association between proportionality of fetal and placental growth measured at birth and the risk for congenital cerebral palsy (CP). **STUDY DESIGN:** We identified all live-born singletons born in Denmark between 1995 and 2003 and followed them from 1 year of age until December 31st, 2008. Information on four indices of fetal growth: ponderal index, head circumference/ abdominal circumference ratio, cephalization index and birth weight/ placenta weight ratio was collected. Cox proportional hazards regression models were used to estimate adjusted hazard ratios (aHR) and 95% confidence intervals (CI). All measurements were evaluated as gestational age and sex specific z-scores and in z-score percentile groups, adjusted for potential confounders, and stratified on gestational age groups (<32, 32-36, 37-38, 39, 40, ≥41 weeks). **RESULTS:** We identified 503,784 singleton births, of which 983 were confirmed cases of CP. Head/ abdominal circumference ratio (aHR:1.12; 95% CI:1.07-1.16) and cephalization index (aHR:1.14; 95%CI:1.11-1.16) were associated with the risk of CP irrespective of gestational age. Birth weight-placental weight ratio was also associated with CP in the entire cohort (aHR:0.90; 95%CI:0.83-0.97). Ponderal index had a u-shaped association with CP, where both children with low and high ponderal index were at higher risk of CP. **CONCLUSIONS:** CP is associated with disproportions between birth weight, birth length, placental weight and head circumference suggesting pre and perinatal conditions contribute to fetal growth restriction in children with CP.

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9. PLoS One. 2015 May 12;10(5):e0125769. doi: 10.1371/journal.pone.0125769. eCollection 2015.

Being Small for Gestational Age: Does it Matter for the Neurodevelopment of Premature Infants? A Cohort Study.

Bickle Graz M, Tolsa JF, Fischer Fumeaux CJ.

BACKGROUND: Whether being small for gestational age (SGA) increases the risk of adverse neurodevelopmental outcome in premature infants remains controversial. **OBJECTIVE:** to study the impact of SGA (birthweight < percentile 10) on cognition, behavior, neurodevelopmental impairment and use of therapy at 5 years old. **METHODS:** This population-based prospective cohort included infants born before 32 weeks of gestation. Cognition was evaluated with the K-ABC, and behavior with the Strengths and Difficulties Questionnaire (SDQ). Primary outcomes were cognitive and behavioral scores, as well as neurodevelopmental impairment (cognitive score < 2SD, hearing loss, blindness, or cerebral palsy). The need of therapy, an indirect indicator of neurodevelopmental impairment, was a secondary outcome. Linear and logistic regression models were used to analyze the association of SGA with neurodevelopment. **RESULTS:** 342/515 (76%) premature infants were assessed. SGA was significantly associated with hyperactivity scores of the SDQ (coefficient 0.81, $p < 0.04$), but not with cognitive scores, neurodevelopmental impairment or the need of therapy. Gestational age, socio-economic status, and major brain lesions were associated with cognitive outcome in the univariate and multivariate model, whereas asphyxia, sepsis and bronchopulmonary dysplasia were associated in the univariate model only. Severe impairment was associated with fetal tobacco exposure, asphyxia, gestational age and major brain lesions. Different neonatal factors were associated with the use of single or multiple therapies: children with one therapy were more likely to have suffered birth asphyxia or necrotizing enterocolitis, whereas the need for several therapies was predicted by major brain lesions. **DISCUSSION:** In this large cohort of premature infants, assessed at 5 years old with a complete panel of tests, SGA was associated with hyperactive behavior, but not with cognition, neurodevelopmental impairment or use of therapy. Birthweight <10th percentile alone does not appear to be an independent risk factor of neurodevelopmental adverse outcome in preterm children.

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10. Dev Med Child Neurol. 2015 May 12. doi: 10.1111/dmcn.12800. [Epub ahead of print]

Grey matter injury patterns in cerebral palsy: associations between structural involvement on MRI and clinical outcomes.

Reid SM, Dagia CD, Ditchfield MR, Reddihough DS.

AIMS: In a population cohort of children with grey matter injury (GMI) and cerebral palsy (CP), we aimed to describe and classify magnetic resonance imaging characteristics specific to GMI, and to identify key structure-function associations that serve as a basis for rating GMI in clinically relevant ways. **METHOD:** Symmetry, extent of cerebral injury, and pathological pattern for 54 children (37 males, 17 females) with CP and a predominant GMI pattern on chronic-phase magnetic resonance imaging were related to gross motor function, motor type and topography, epilepsy, intellectual disability, blindness, and deafness. **RESULTS:** Relative to mild GMI where there was no pallidal abnormality, severe GMI, comprising pallidal abnormality alone or in conjunction with other deep nuclear and generalized cortical-subcortical involvement, was strongly associated with Gross Motor Function Classification System levels IV to V (OR 35.7 [95% CI 3.5, 368.8]). Involvement of the basal ganglia was associated with non-spastic/mixed motor types, but predominantly where cortical-subcortical grey and white matter involvement was not extensive. The prevalence of epilepsy was highest where there was diffuse cortical-subcortical involvement and white matter loss. **INTERPRETATION:** Better understanding of structure-function relationships in CP and GMI, and how to rate the severity of GMI, will be helpful in the clinical context and also as a basis for investigation of causal pathways in CP.

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11. *Pediatr Res.* 2015 May 15. doi: 10.1038/pr.2015.94. [Epub ahead of print]**Neonatal DTI early after birth predicts motor outcome in preterm infants with periventricular hemorrhagic infarction.**

Roze E, Benders MJ, Kersbergen KJ, van der Aa NE, Groenendaal F, van Haastert IC, Leemans A, de Vries LS.

BACKGROUND: To determine the association between early neonatal diffusion tensor imaging (DTI) and the development of unilateral spastic cerebral palsy (USCP) in preterm infants with periventricular hemorrhagic infarction (PVHI). **METHODS:** Preterm infants with PVHI were assessed with early (≤ 4 weeks after birth) and term-equivalent age MRI-DTI. Involvement of corticospinal tracts was assessed by visual assessment of the posterior limb of the internal capsule (PLIC) on DTI (classified asymmetrical, equivocal, or symmetrical) and by an atlas based approach calculating fractional anisotropy asymmetry index in the PLIC. Motor outcome was assessed at ≥ 15 months corrected age. **RESULTS:** Seven out of 23 infants with PVHI developed USCP. Their PLIC was visually scored as asymmetrical in 6 and equivocal in 1 on the early DTI. Thirteen out of 16 infants with a symmetrical motor development had a symmetrical PLIC on early DTI, the remaining 3 were equivocal. All infants with USCP had a fractional anisotropy asymmetry index of >0.05 (optimal cut-off value) on early DTI. In infants with a symmetrical motor development ($n=16$), 14 had an asymmetry index ≤ 0.05 whilst 2 had an index >0.05 . **CONCLUSION:** DTI in preterm infants with PVHI within a few weeks after birth is associated with later motor development.

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12. *Stem Cells Dev.* 2015 May 15. [Epub ahead of print]**Involvement of Immune Responses in the Efficacy of Cord Blood Cell Therapy for Cerebral Palsy.**

Kang M1, Min K, Jang J, Kim SC, Kang MS, Jang SJ, Lee JY, Kim SH, Kim MK, An SS, Kim M.

This study evaluated the efficacy of umbilical cord blood (UCB) cell for patients with cerebral palsy (CP) in a randomized, placebo-controlled, double-blind trial and also assessed factors and mechanisms related to the efficacy. Thirty-six children (ages 6 months to 20 years old) with CP were enrolled and treated with UCB or a placebo. Muscle strength and gross motor function were evaluated at baseline and 1, 3, and 6 months after treatment. Along with function measurements, each subject underwent ^{18}F -FDG-PET at baseline and 2 weeks after treatment. Cytokine and receptor levels were quantitated in serial blood samples. The UCB group showed greater improvements in muscle strength than the controls at 1 (0.94 vs. -0.35, respectively) and 3 months (2.71 vs. 0.65) after treatment ($P_s < 0.05$). The UCB group also showed greater improvements in gross motor performance than the control group at 6 months (8.54 vs. 2.60) after treatment ($P < 0.01$). Additionally, PET scans revealed decreased periventricular inflammation in patients administered UCB, compared to those treated with a placebo. Correlating with enhanced gross motor function, elevations in plasma pentraxin 3 and interleukin-8 levels were observed for up to 12 days after treatment in the UCB group. Meanwhile, increases in blood cells expressing Toll-like receptor 4 were noted at 1 day after treatment in the UCB group, and were correlated with increased muscle strength at 3 months post-treatment. In the present trial, treatment with UCB alone improved motor outcomes and induced systemic immune reactions and anti-inflammatory changes in the brain. Generally, motor outcomes were positively correlated with the number of UCB cells administered: a higher number of cells resulted in better outcomes. Nevertheless, future trials are needed to confirm the long-term efficacy of UCB therapy, as the follow-up duration of the present trial was short.

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