



Management of neuromuscular disease

EPNS Neuromuscular Course



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Declarations

- » PI in clinical trials for PTC Therapeutics, Summit
- » Consultancy for Santhera and Biogen
- » Conference fees and travel by PTC therapeutics



Topics

- » Principles of management
- » General management
- » Disease specific treatment



Aggregation of Marginal Gains

■ 1% Improvement
■ 1% Decline



Put simply...how small improvements in a number of different aspects of what we do can have a huge impact to the overall performance

David Brailsford
Performance director
British cycling team



Diagnosis and management of Duchenne dystrophy, part 1: diagnosis, and psychosocial management

Part 1: diagnosis, and social management

Disorder: muscular dystrophy (DMD) is a severe, progressive genetic muscle disease. Symptoms include muscle weakness, difficulty walking, and difficulty breathing. The U.S. Centers for Disease Control and Prevention (CDC) estimates that approximately 1 in 3,500 boys are born with DMD. The RANQ Corporation Group, a leading provider of genetic testing and counseling services, has developed a comprehensive genetic testing program for DMD. The program includes a detailed family history, a physical examination, and a series of genetic tests. The tests are performed on a blood sample and can identify the specific gene mutation responsible for the disorder. The results of the tests are then used to provide a diagnosis and to guide treatment options. The RANQ Corporation Group also offers genetic counseling services to help families understand the implications of the test results and to make informed decisions about future family planning.

Introduction

X-linked disease in Man (OMIM) web
 site. ¹⁰ Affected individuals do
 properly understand and treat as
 results due to proximal (or
 arising from the use of the flame
 approximately 5 years of a
 muscle strength decrease
 and cardiac output
 intervention, the so-
 Non-progressive, the
 project.

DMD occurs in the dystrophin gene which leads to an absence of the protein leading to 13 years of life expectancy.

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Diagnosis and management of Duchenne muscular dystrophy, part 2: implications for multidisciplinary care

Analysis and management of the acute coronary syndrome, part 2: infarction

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Consensus Statement for Spinal Muscular Atrophy

Consensus Statement Care in Spinal Muscular

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Consensus Statement on St
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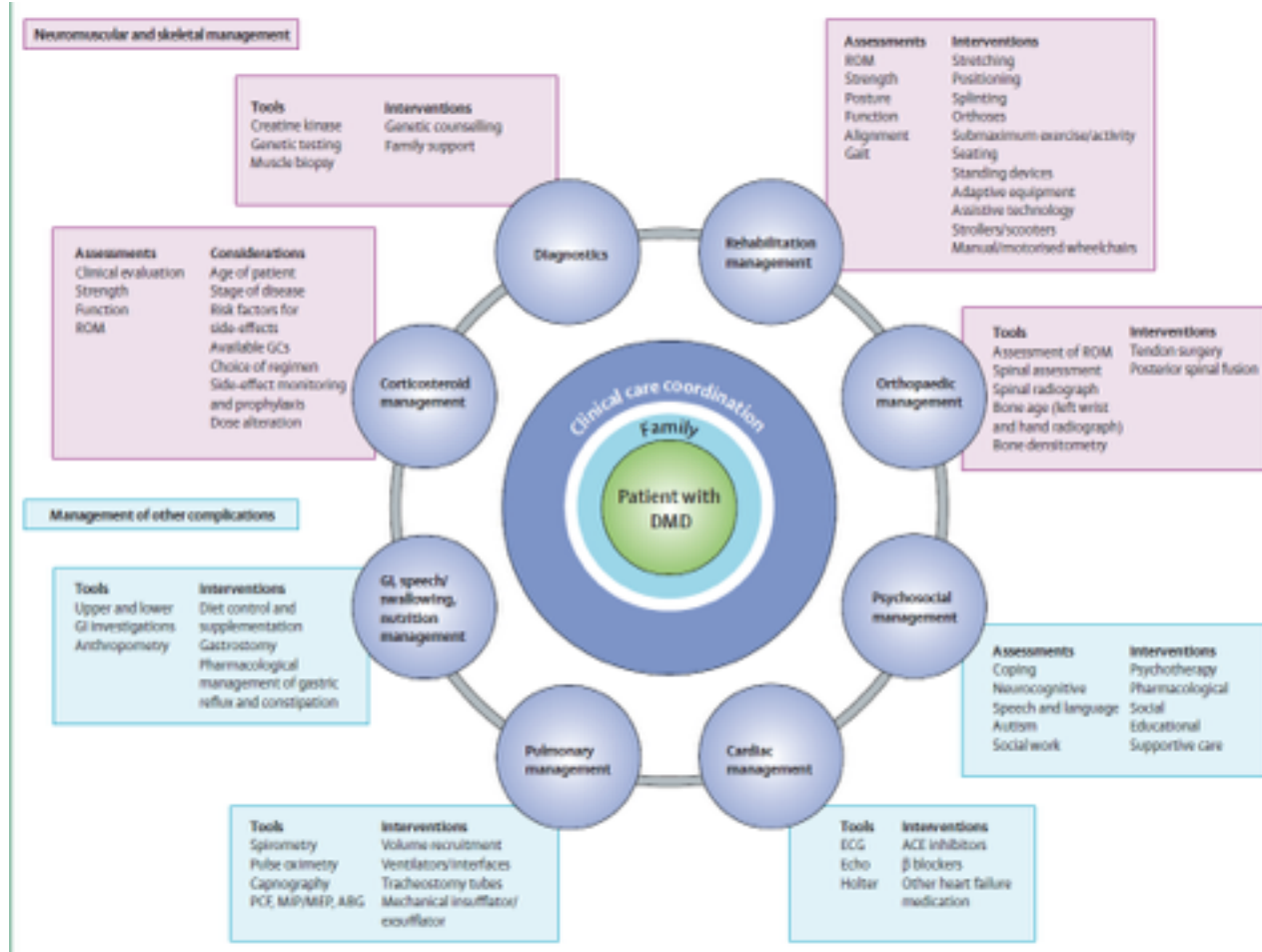
BMJ Journals

General

- Diagnosis & anticipation of complications
- Family support
- Swallowing/Nutrition
- Respiratory
- Cardiac
- Orthopaedic
- Rehabilitative
- End-of-life care



Management NMD



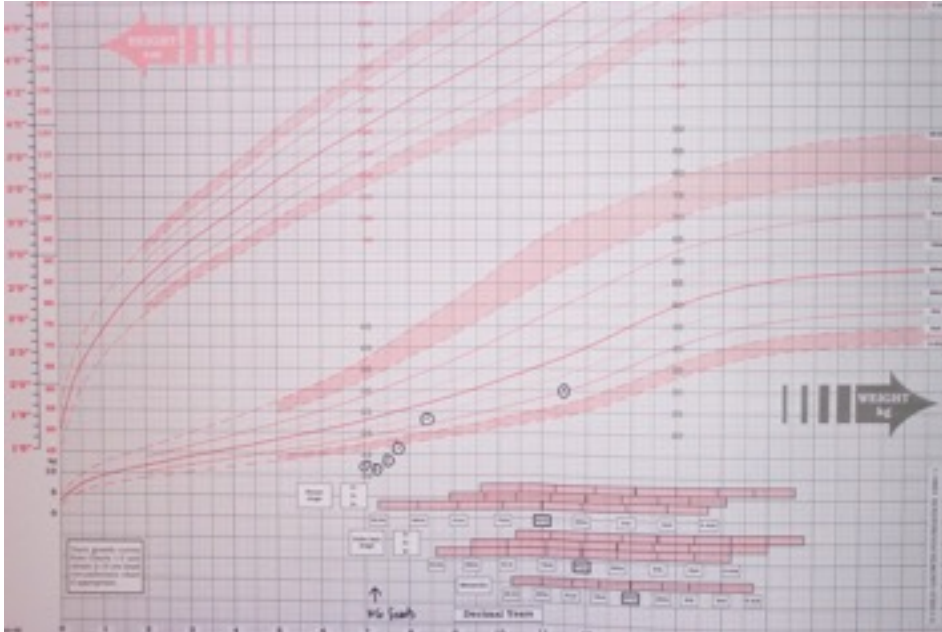
Dr Saif The Surgery Manchester Road BURNLEY	Dr Stephen Aplin Burnley, Pendle & Rossendale PCT 35/33 Kenyon Road Lancashire BL6 5JN
Sally Wood - Hospital at Home Editor Burnley General Hospital Cottonwood Avenue BURNLEY BB10 2PQ	Dr Gray Social Worker Child Development Centre Rushey Hall Cotton Road BURNLEY
Heaven Ryan - Team Leader Chadbrook House Manchester Road BURNLEY BB11 2JH	Mr John Robinson Manager Complex Packages of Care Huddersfield and Ribblesdale PCT Rat Hall Court Clayton Business Park (Clayton & Hunsley) ACCRINGTON BB5 5LN
Corvida Howarth - Physio Manager East Lancashire Hospitals NHS Trust Rushey Hall Cotton Road BURNLEY	Dr Ian Hughes Community Physiotherapist East Lancashire Hospitals NHS Trust Rushey Hall Cotton Road BURNLEY
Dr Imelda Hughes Consultant Paediatric Neurologist BNCH	Dr J Pava Consultant Respiratory Paediatrician BNCH
Dr Robert Vales Director Intensive Care - PICS BNCH	Elaine Lloyd - Physiotherapist BNCH
Lynne Burney - Dietician BNCH	Aimee Dyer Occupational Therapist BNCH
Jo Parke/Robina Howarth SALT - BNCH	Deanna Gifford Children's Services Manager Burnley, Pendle & Rossendale PCT 35/33 Kenyon Road Lancashire BL6 5JN
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Lynne Cress - Case Study Manager Burnley, Pendle & Rossendale PCT 35/33 Kenyon Road Lancashire BL6 5JN	Cathy Evans - Head of Paediatric OT East Lancashire Hospitals NHS Trust Rushey Hall Cotton Road BURNLEY
Interpreting via Tel 276 8817	Val Corran - Director of Nursing Burnley, Pendle & Rossendale PCT 35/33 Kenyon Road Lancashire BL6 5JN
Aden Hall Special Educational Psychologist Area Education Office (East) The Galah Centre St James Square ACCRINGTON BB5 5JH	Ms & Mrs Mahomed
Udo Roberts Head of Service Agreements Trust Headquarters - Contracts Department 2nd Floor Calvert House Manchester Royal Infirmary Oxford Road MANCHESTER M13 9WL	

Diagnosis

- Accurate and timely
- Good practice diagnostic disclosure
 - Explanation of diagnosis
 - Prognosis
 - Genetics
 - Management plan
 - Support
 - Resources



Nutrition



Swallowing

Slow at meals
Coughing on eating/drinking
SALT assessment
Videofluoroscopy

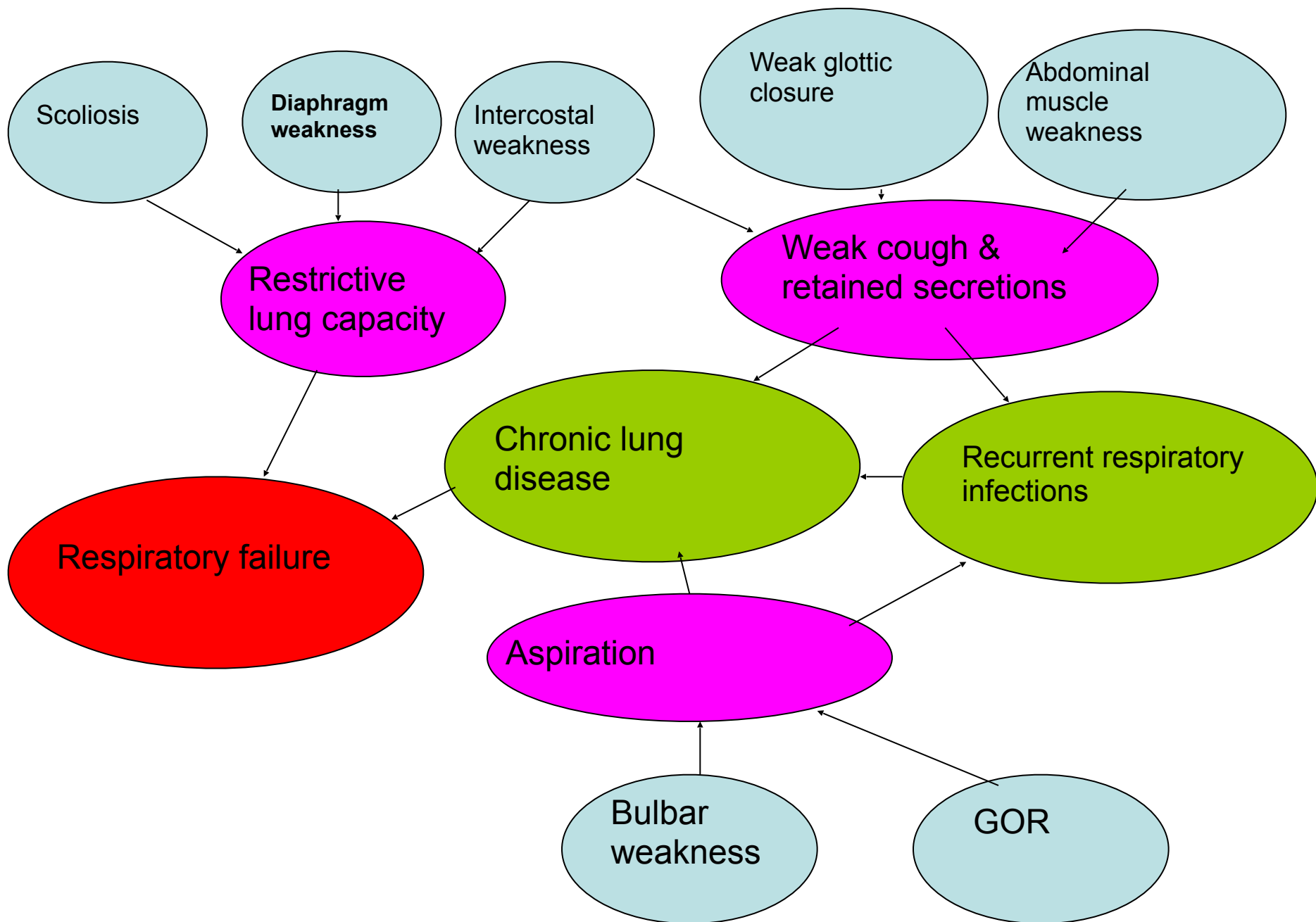
Respiratory problems in NMD

- Inevitable in progressive conditions
- Different in different conditions
- Nocturnal hypoventilation first manifestation of respiratory failure



Pathophysiology of respiratory complications in NMD

- Diaphragmatic weakness
- Intercostal weakness
- Abdominal muscle weakness
- Bulbar weakness
- Weakness of glottic closure
- Gastroesophageal reflux
- Scoliosis



What can be done?

Management – respiratory infection

- Prevention
 - Vaccination – flu and pneumococcal
 - Feeding assessment & advice
 - GOR treatment – medical/surgical
 - Assisted coughing – manual/mechanical
- Treatment of infection
 - Early antibiotic
 - Iv antibiotic
 - Assisted coughing

Nocturnal Hypoventilation

- Initially REM sleep
- Transient hypercapnia
- Frequent arousals
- Sleep fragmentation



Nocturnal hypoventilation

- FVC <60%
- Symptoms
 - Restless sleep
 - Morning headache
 - Lethargy
 - Loss of appetite, weight loss
- Assessment
 - Polysomnography
 - Overnight SaO₂ & pCO₂



Polysomnography

- SaO_2 , pCO_2
- Sleep staging EEG, EOG, EMG
- Apnoea – cessation of airflow >10 sec
- Hypopnoea – reduction in airflow or chest wall movement with $\downarrow \text{SaO}_2$ at least 4%
- Apnoea-hypopnoea index



Benefits of NIV

- Prolongation of life

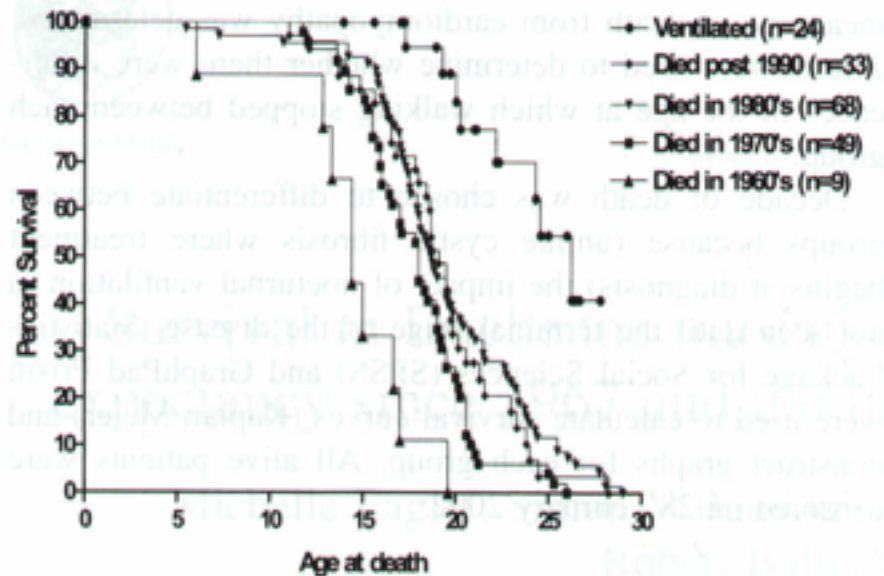


Fig. 2. Survival curves (Kaplan Meier) showing percentage survival of ventilated versus non-ventilated patients 1967–2002. (Includes live patients censored on 28th February 2002.) Legend; Log rank test for non-ventilated vs. ventilated patients post-1990 ($P = 0.0001$).

Benefit of NIV - palliation of symptoms

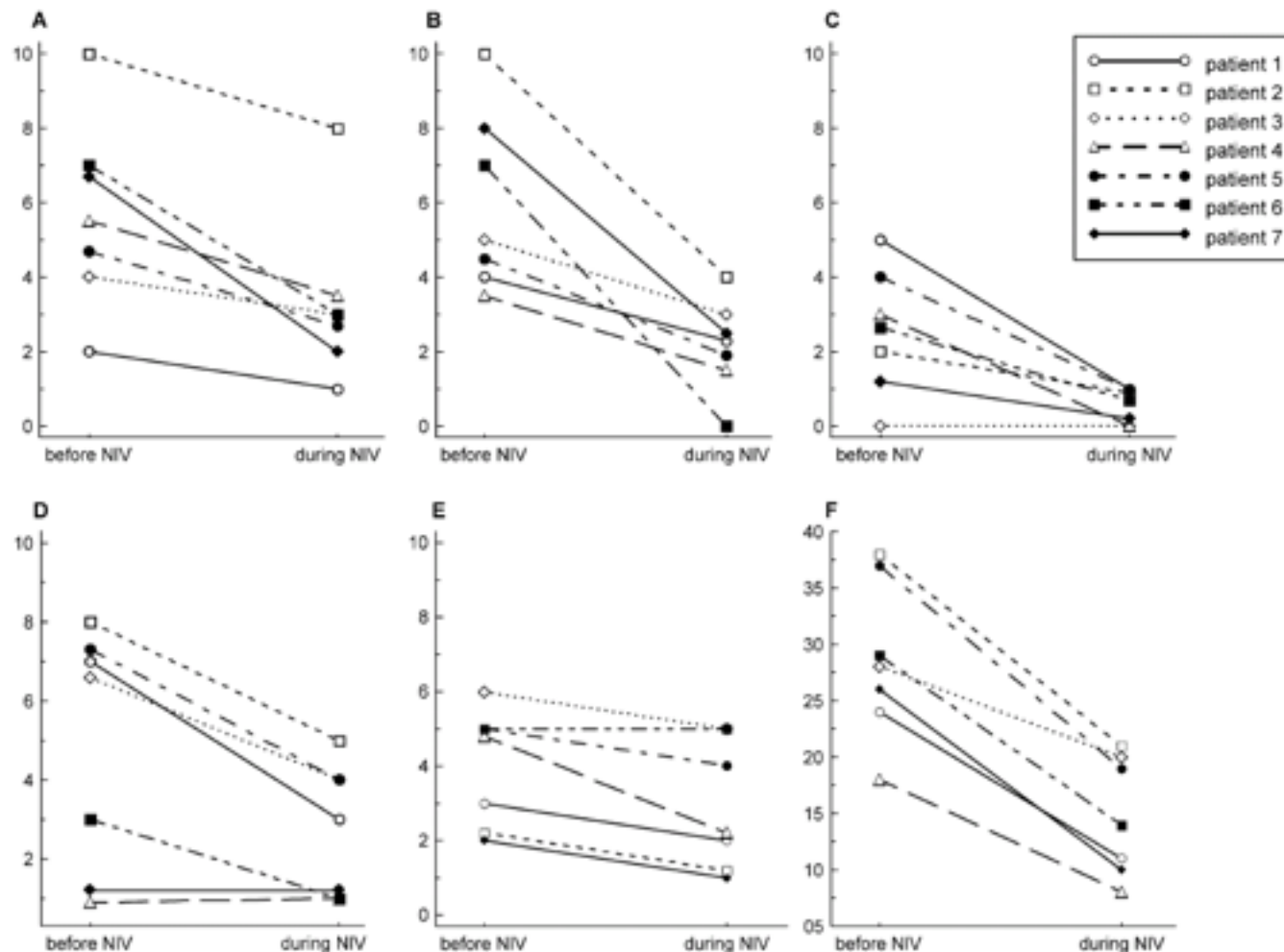


Fig. 2. Impact of NIV on symptoms (before vs. after institution of NIV). Improvements in (A) sleep disturbance (5.7 ± 2.6 vs. 3.3 ± 2.2 points); (B) nocturnal sweating (6.0 ± 2.4 vs. 2.1 ± 1.2 points); (C) morning headaches (2.6 ± 1.7 vs. 0.6 ± 0.5 points); (D) nausea/ lack of appetite/feeding difficulties (4.9 ± 3.1 vs. 2.7 ± 1.7 points); (E) impaired concentration (4.0 ± 1.6 vs. 2.9 ± 1.6 points) and (F) total score (28.7 ± 7.1 vs. 14.9 ± 5.5 points ($P < 0.005$ for all)).

★ Roachell's Star Chart



~~Fri~~ wed
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Thur
3 1/2 hrs



Fri
2hrs



Sat
4hrs



Sun
2 1/2 hrs



Mon
12 hrs



Tue
6hrs



Wed
6hrs



Thur
11hrs

Benefits of NIPPV

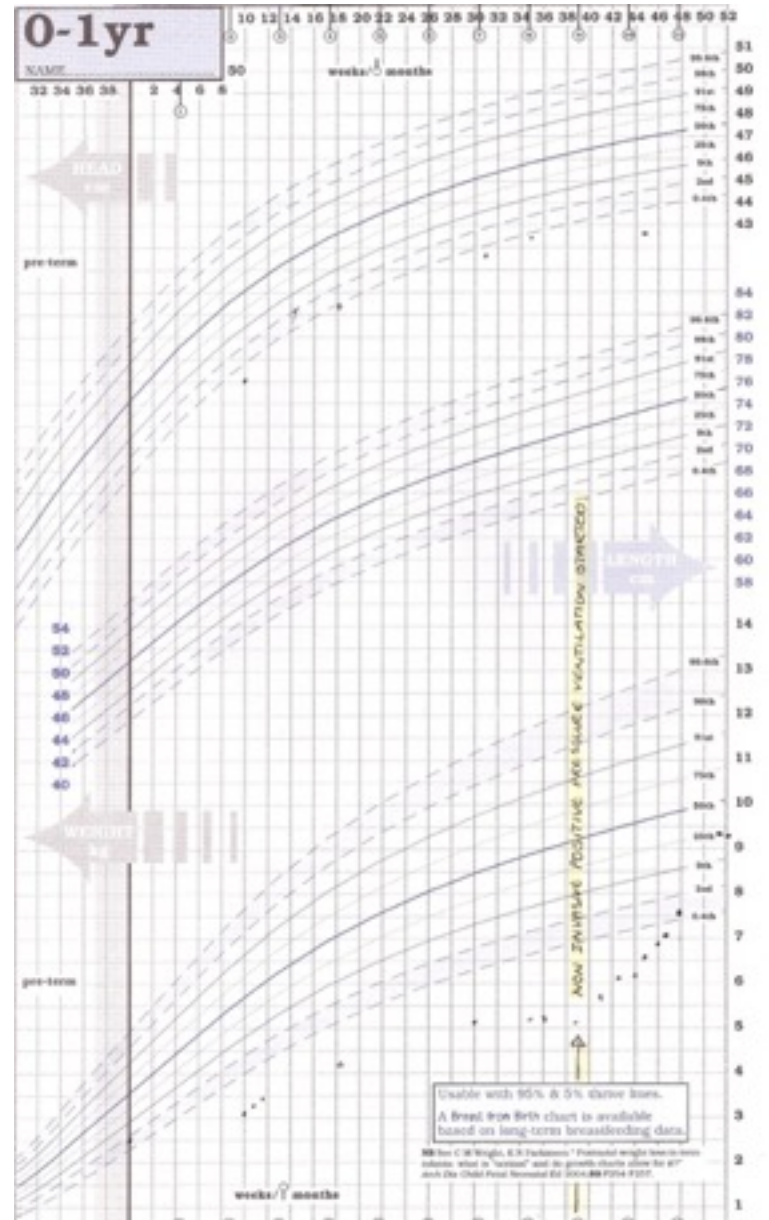
- Prolongation of life
- Palliation of symptoms
- Improves quality of life
- Is well tolerated
- Reduces hospital & PICU admission



NIV Complications

- Skin breakdown
- Dry mouth (65%)
- Nasal congestion & dryness (25%)
- Eye irritation (24%)
- Runny nose (35%)
- Sinusitis (8%)
- Nose bleeds (4-19%)
- Gastric distension (sporadic)
- Pneumothorax (rare)





Patterns of respiratory involvement



DMD

- Fairly predictable
- Loss of ambulation
- Scoliosis
- Sleep disordered breathing
- Respiratory infections
- Cardiomyopathy
- Natural history modified by steroids



SMA

- Intercostal weakness
- Diaphragmatic sparing
- Bulbar weakness
- Retained secretions,
recurrent infections



Rigid spine syndromes

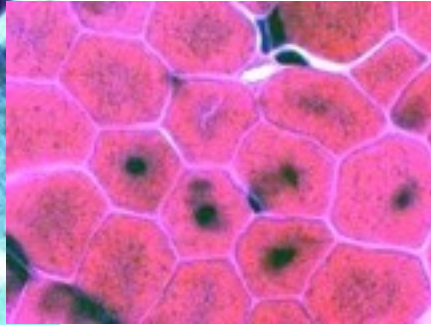
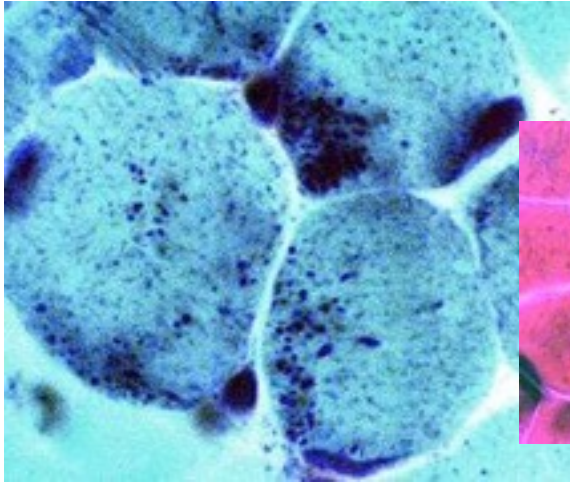
- RSMD, Minicore disease, EDMD
- Early respiratory failure

Selective diaphragmatic involvement

SMARD
EMARD
BVVL



Congenital myopathy



- Neonatal respiratory failure – nemaline & myotubular myopathy
- Core myopathy may develop respiratory failure while ambulant



Cardiac

- DMD <10 every 2 years, >10 annual
- Myotonic dystrophy annual ECG
- EDMD, LGMD1B, MYH7, predisposition to arrhythmia



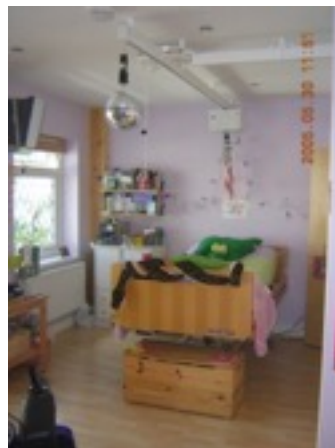
Orthopaedic

- Contractures
 - Splinting
 - Serial casting
 - Surgery
- Scoliosis
- Postural management

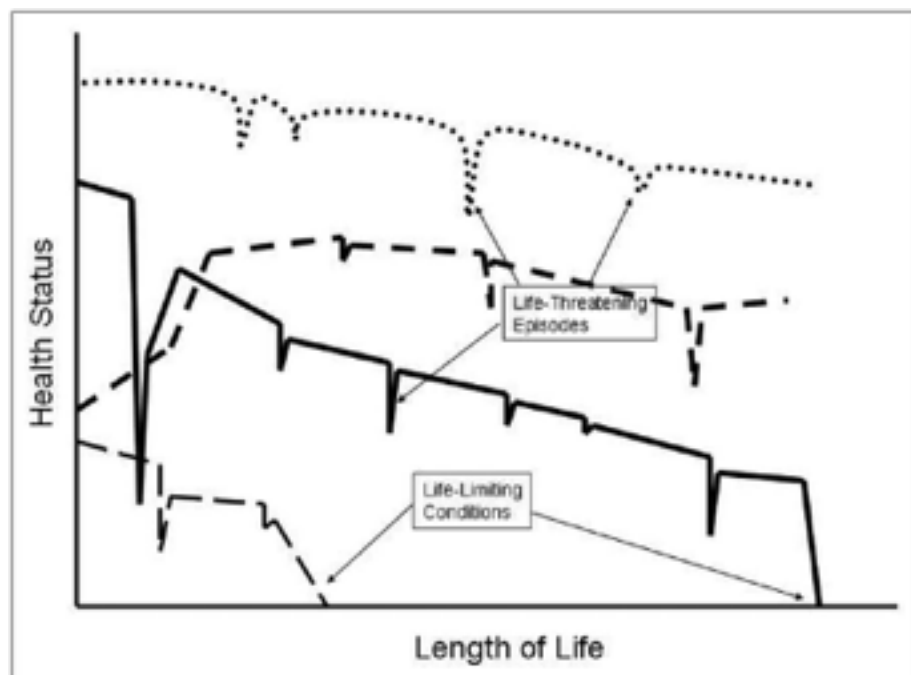


Rehabilitative

- Mobility
- Education
- Housing



Palliative & End-of-life care



ROYAL MANCHESTER CHILDREN'S HOSPITAL

Central Manchester University Hospitals NHS Foundation Trust

ALLERGIES

Name: _____ DOB: _____

Address: _____

Post code: _____

Hospital No. _____ NHS No. _____ Date: _____

Child and Young Person's Advance Care Plan Collaborative

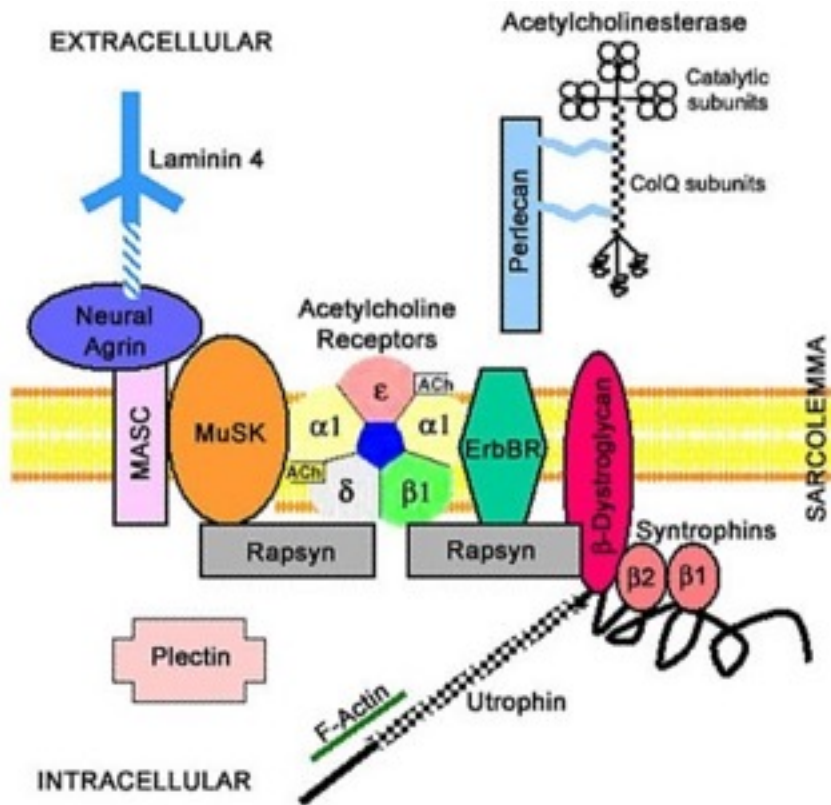




Collaborators: Asher Hey Children's Hospital, Dorset County Hospital, Gloucestershire Hospitals NHS Foundation Trust, Hales & Douglas House Hospices, Kent & Medway C&YP Palliative Care Network, Queen's House & Jacksonville, North Hampshire NHS Trust, North West Children's Palliative Care Network, Oxford University Hospitals NHS Trust, Peterborough Hospital, Portsmouth Hospitals NHS Trust, Royal Berkshire NHS Foundation Trust, Royal Manchester Children's Hospital, Robert Minto Trust, Southampton Children's Hospital, St Mary's Hospital and of Wigan, Together for Short Lives, West Midlands Paediatric Palliative Care Network

Congenital Myasthenic syndromes

- Weakness fluctuates, worse in intercurrent illnesses
- May be episodic apnoea
- May be treatable



Disease specific treatment

» DMD

- » steroid
- » ataluren
- » idebenone
- » eteplirsen

» Congenital myasthenic syndromes

- » pyridostigmine, salbutamol, 3,4-DAP, ephedrine

» Pompe disease ERT

» SMA Nusinersen

» Inflammatory myopathy, CIDP immune modulation

» Myasthenia gravis pyridostigmine, immune modulation



Glucocorticoid corticosteroids for Duchenne muscular dystrophy (Review)

Manzur AY, Kuntzer T, Pike M, Swan A



Authors' conclusions

There is evidence from randomised controlled studies that glucocorticoid corticosteroid therapy in Duchenne muscular dystrophy improves muscle strength and function in the short-term (six months to two years). The most effective prednisolone regime appears to be 0.75 mg/kg/day, given daily. In the short term, adverse effects were significantly more common but not clinically severe. Long-term benefits and hazards of glucocorticoid treatment cannot be evaluated from the currently published randomised studies. Non-randomised studies support the conclusions of functional benefits but also identify clinically significant adverse effects of long-term treatment. These benefits and adverse effects have implications for future research studies and clinical practice.

DMD natural history

- Mean age of diagnosis 4.6 years
- Median age wheelchair dependence 10 years
- Median age death 15 years



Steroid benefits

- Prolonged ambulation
- Preserved pulmonary function
- Reduced scoliosis
- ? Preserved cardiac function



Steroid side effects

- Weight gain
- Short stature
- Behaviour
- Reduced bone mass and vertebral fractures
- Delayed puberty
- Adrenal suppression
- Cataract
- Hypertension
- Gastrointestinal symptoms
- Cushingoid appearance
- Hirsutism
- Death



Variations in practice

Griggs et al Muscle & Nerve 2013;48:27-31

- 105 Treat-NMD clinicians
- Steroids not used in 10 clinics
- 29 different regimens
 - 0.75mg/kg/day prednisolone
 - Intermittent (10 days)
 - 0.9mg/kg/day deflazacort
 - 5mg/kg/day weekends



Benefits & adverse events intermittent v daily steroids Ricotti et al

- Median loss of ambulation
 - 12 yrs intermittent
 - 14.5 yrs daily
- Divergence after 7 years
- Cushingoid features, behaviour & hypertension more common in daily
- BMI mean z score higher in daily
- Height restriction more severe in daily



Steroids – unanswered questions

- Long term benefits v side effects
- Which steroid?
- What dosage regimen?
- When to start?

FOR-DMD

- Randomised controlled multicenter
- 3 arms
 - Prednisolone 0.75mg/kg/day
 - Deflazacort 0.9mg/kg/day
 - Prednisolone 0.75mg/kg intermittent (10 days)



Summary

- Management is:
 - Interdisciplinary
 - Multifaceted
 - Requires attention to detail

