In view of the study limitations, we should avoid making a definitive conclusion that resistance training is an effective treatment to delay functional decline in patients with Charcot-Marie-Tooth disease. However, adverse events were few and mild, lending support that this type of exercise is not harmful. Understanding of the therapeutic response to exercise in neuromuscular disease is an important area of study. Simultaneously, disease-modifying therapies are now available[10] or being used in clinical trials, making it difficult to assess the role of exercise alone in some neuromuscular populations. When possible, exercise therapy should be assessed in randomised controlled trials, and adaptive study designs or combination therapy might be used when available treatment-naive patient populations are scarce or when benefits to the concomitant therapy are known, or both. The role of adjuvant exercise therapy in enhancing benefits of drug therapies should be explored.

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Asthma diagnosis in children: more evidence needed

With about 1–18% of the population worldwide being affected, wheeze and asthma are the most prevalent chronic respiratory diseases during childhood and adulthood.[1] As such, many children each day will enter an outpatient clinic or a paediatrician's office needing diagnostic tests for suspected asthma. If it were only that simple. Individuals with suspected asthma symptoms vary substantially in their complaints and clinical manifestations despite common pathophysiological factors that lead to the final common pathway of (sometimes only partly) variable airway obstruction due to a range of triggers, which results in symptoms such as wheeze, difficulty breathing, chest tightness, and cough.[2,3]

What is the best way then to diagnose asthma during childhood? Importantly, no single test exists for the diagnosis of asthma in adults, and especially not in children. In diagnostic investigation of patients of all ages, clinical observations (ie, suggestive symptoms) need to be complemented by objective measurements. These tests aim to rule in asthma and to rule out important differential diagnoses by identifying variable airway obstruction or airway inflammation. In mathematical terms, asthma diagnosis depends on the patient's pretest probability of having a diagnosis (suggestive symptoms and history) in combination with both sensitivity and specificity of further corroborating objective tests such as lung function. Beyond the individual symptom level, this includes the precision of used tests (ie, both their positive and negative predictive values). Therefore, asthma diagnosis is a common clinical task that needs to be taken seriously, and the importance of such diagnosis is reflected by a range of recommendations.[1,4,5]

The present asthma management guidelines by the British Thoracic Society/Scottish Intercollegiate Guidelines Network allude to the fact that the diagnosis of asthma is primarily a clinical one.[4] To prevent misdiagnosis, the UK National Institute for Health and Care Excellence (NICE) developed additional guidance


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for asthma diagnosis incorporating objective tests in addition to suggestive clinical observations.[6] Although the NICE guidance is mainly based on data extrapolated from adults and yet to be effected in the UK, it proposes an algorithm with a predefined sequence of four lung function measurements for use in the paediatric context.[6] The algorithm starts with spirometry as a first-line measure, followed by a bronchodilator reversibility test, measurement of exhaled nitric oxide as a marker of allergic airway inflammation, and, if needed, recording of peak expiratory flow variability over 2–4 weeks.[6] However, the dilemma is that although the clinical symptoms themselves are already poor predictors for asthma, test results can vary over time, as a result of both the variable nature of the underlying pathophysiology and the resulting asthma symptoms.[4] Moreover, lung function criteria are limited in their usability, especially during childhood if more or less fixed cutoffs irrespective of age are used.[7] In addition, many difficulties exist with regards to peak expiratory flow recordings or the so far absent universal definition of bronchodilator reversibility in children. These issues have immense implications on the combination of the aforementioned pretest probabilities for asthma diagnosis and on further objective tests and their precision.

The issue of applying guidelines in children that originate from studies in adults becomes evident in the study by Clare Murray and colleagues[8] in *The Lancet Child & Adolescent Health*. The authors assessed the usefulness of the newly proposed NICE diagnostic algorithm for asthma diagnosis in children aged 13–16 years during regular follow-up visits as part of a well established population-based birth cohort, the Manchester Asthma and Allergy Study (MAAS).[9] To simulate asthma assessment in the primary care setting, Murray and colleagues did their analyses in a subgroup of study participants with recent asthma symptoms who were not already on regular treatment with inhaled corticosteroids.[8] Unsurprisingly, the authors found only poor agreement between the proposed NICE algorithm and their definition of asthma in children aged 13–16 years, which is questionnaire-based and follows widely used epidemiological classifications.[8] Only two of 89 symptomatic children met the algorithm's definition of asthma, but neither met the epidemiological definition. Although adherence to the NICE algorithm under real-life settings resulted in a substantial number of false-positives, many children diagnosed with asthma by the MAAS criteria would not have been identified if the proposed NICE algorithm was followed.[8]

In view of the scarcity of available population-based data on lung function in acutely symptomatic children who are not on controller medication, Murray and colleagues used the data they had already at hand. As they acknowledge in their discussion,[8] this subgroup of the MAAS birth cohort (ie, adolescents not on regular controller treatment) is unlikely to be a valuable proxy for children with asthma symptoms in real-life settings. In mathematical terms, this issue translates to the problem of whether the patients with asthma used for the analyses by Murray and colleagues have a similar distribution of pretest probability for asthma diagnoses, in combination with the precision of further objective tests as proposed by the NICE algorithm, to that of children with newly presenting asthma symptoms.

Nevertheless, the study by Murray and colleagues[8] is essential and, despite its limitations, the clinical message of the Article is an important one: algorithms to diagnose disease based on data extrapolated from adults should not be used in children and especially not without a proper reflection of their limitations. As such, until data have been collected in a setting that resembles the real-life situation in everyday practice, these data are the best we can get for now. Ideally, data would be gathered in children with new-onset symptoms and therefore at an early stage of disease, who did all the diagnostic tests while being acutely symptomatic, and were not yet on regular treatment with inhaled corticosteroids. However, although we may wish for these ideal data and perfect guidelines for asthma diagnosis in children, better evidence is unlikely to become available, at least not in the near future.

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Defining sepsis (with or without positive blood cultures)

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Over the years, a key issue with studies on sepsis has been how best to define this condition. Clear consensus definitions are now in place to acknowledge that what we call sepsis actually represents a bad infection—ie, an infection with some organ dysfunction attributed to it (panel).[1] By contrast with colonisation, infection typically includes a host response, usually with fever and associated tachycardia, and an altered white-blood-cell count (usually an increase, but sometimes a decrease in the most severe cases). Infections can be associated with positive blood cultures (ie, documented bacteraemia) or not (sometimes simply because blood samples for culture were not taken).

The ongoing difficulty with terminology was highlighted around 25 years ago when a North American consensus conference committee[2] proposed that sepsis be called an infection with some signs of host response (the systemic inflammatory response syndrome [SIRS] criteria), leading to confusion between the words infection and sepsis. This confusion resulted in an apparent increase in the incidence of so-called sepsis worldwide.[3] In the paediatric population, some clinicians still apply criteria proposed by Goldstein and colleagues[4] more than 10 years ago to define sepsis, which include the presence of SIRS.

In *The Lancet Child & Adolescent Health*, Philipp Agyeman and colleagues[5] report outcomes of 1181 episodes of blood culture-proven bacterial infection in children (aged <17 years), using data obtained prospectively from ten paediatric hospitals in Switzerland over 4 years. The authors included patients with positive blood cultures and suspected infection and SIRS, as per the Goldstein definition.[4] They used the term "blood culture-proven bacterial sepsis" to describe these cases, although whether this should be called sepsis remains open to debate. The authors noted a low proportion of meticillin-resistant staphylococci (eight [1%] of 1181 episodes) and carbapenemase-resistant organisms (five [<1%] of 1181); indeed, Switzerland has a low incidence of resistant microorganisms compared with other countries in Europe.[6,7]

Agyeman and colleagues reported organ dysfunction in 455 (39%) of 1181 episodes of documented bacteraemia, a finding that is hard to interpret but not too surprising. Children with organ dysfunction and

***Panel:* Current vocabulary for infection and sepsis**

Colonisation
Presence of bacteria without host response—eg, gut colonisation, tracheal colonisation in intubated patients

Infection
Microbial invasion of sterile or non-sterile organs, usually associated with a host response—eg, fever and associated tachycardia, altered leucocytosis, increased C-reactive protein or procalcitonin

Bacteraemia
Documented presence of microorganisms in the blood (ie, positive blood culture)

Sepsis
Organ dysfunction associated with an infection

Septicaemia*
Sepsis with bacteraemia

Septic shock
Sepsis with signs of altered tissue perfusion and lactic acidosis

*Old term and not meaningful so largely abandoned.