swiss medical weekly

Original article | Published 01 October 2024 | doi:https://doi.org/10.57187/s.3573
Cite this as: Swiss Med Wkly. 2024;154:3573

Impact of respiratory tract infections on spinal muscular atrophy with focus on respiratory syncytial virus infections: a single-centre cohort study

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Summary

AIMS OF THE STUDY: Spinal muscular atrophy (SMA) is a degenerative neuromuscular disorder leading to muscle hypotonia, weakness, and respiratory and bulbar impairment. Infants with SMA have an increased risk of respiratory tract infections (RTI) including severe respiratory syncytial virus (RSV) infections. Therefore, guidelines for the treatment of SMA recommend RSV prophylaxis with palivizumab for patients aged below two years who have compromised motor functions ("non-sitters"). Since palivizumab is not approved for RSV prophylaxis in SMA patients in Switzerland, payers usually do not grant cost approvals for this indication. Therefore, this study aimed to investigate the frequency of severe RTI among SMA patients focusing on RSV infections requiring hospital treatment and to determine the long-term impact of RSV infections on the natural history of SMA.

METHODS: A single-centre cohort study at the tertiary paediatric Neuromuscular Centre Zurich, Switzerland, including data of SMA patients with a genetic-based therapy initiated below two years of age between May 2019 and December 2022. All hospitalisations were analysed with a focus on severe RTI and especially RSV infections, and their impact on nutritional and respiratory function. The costs of inpatient treatment of RSV infections were determined and compared with estimated expenses for RSV prophylaxis with palivizumab.

RESULTS: 12 SMA patients (median age at treatment initiation: 3.5 months, range: 0–17 months) were followed for a cumulative period of 25.75 years (7 SMA type 1; 5 SMA type 2 including one presymptomatic individual). With an incidence rate of 2.34 per patient-year, the risk of severe RTI was especially high in SMA type 1 (versus 0.1 in SMA type 2, p = 0.044). A total of 37 hospitalisations (279 hospital days) was necessary for the treatment of RTI in general; 9 of them were attributed to RSV infections (in 5 SMA type 1 patients; 84 hospital days). Only 3/12 SMA patients had received seasonal RSV prophylaxis with palivizumab. No RSV infections requiring hospital treatment occurred in patients while receiving seasonal RSV prophylaxis. During RTI, nutritional support had to be commonly initiated and continued after discharge. In 3/7 SMA type 1 patients, non-invasive ventilation was started during acute treatment for RTI and continued to the end of follow-up.

CONCLUSION: We observed a high risk of RTI, especially RSV infections, among young SMA patients. Failure to adhere to established care protocols, for example by omitting RSV prophylaxis, may be linked to a heightened risk of morbidity in these children.

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Introduction

Chromosome 5q-associated SMA is an autosomal recessive, neurodegenerative motor neuron disorder characterised by loss of motor neurons in the brainstem and spinal cord. SMA leads to progressive muscle hypotonia, weakness and atrophy, reduced or absent deep tendon reflexes, tongue fasciculation and respiratory and bulbar impairment [1]. SMA is caused by biallelic mutations of the *survival motor neuron 1 gene (SMN1)*, mapped on chromosome 5q11.1-13.3 and coding for the survival motor neuron protein (SMN) [2]. Owing to its broad phenotypic spectrum, SMA has been classified into subtypes 0 to 4 according to disease severity, itself based on age at manifestation and maximum motor functions achieved [3, 4]. The majority of SMA patients have a severe, infantile-onset phenotype (SMA type 1) with a mean life expectancy of 6–10 months without disease-modifying treatment. With an overall incidence of approximately 1 in 6000 to 10,000 live births [5], SMA was therefore a leading genetic cause of infant mortality prior to the introduction of disease-modifying therapies [6–9].

Recently, different disease-modifying treatment approaches were developed and introduced for the treatment of

SMA. These new treatments include nusinersen and risdiplam, two splicing modifiers of the *SMN2* gene, a low-functioning paralogue of the *SMN1* gene. Nusinersen and risdiplam were approved for the treatment of SMA in Switzerland in 2017 and 2021, respectively. In 2021, the gene-addition therapy onasemnogene abeparvovec was approved for the treatment of SMA in Switzerland. Real-world outcome data of SMA patients treated in Switzerland with nusinersen and onasemnogene abeparvovec was published recently using data that was prospectively collected within the Swiss Registry for Neuromuscular Disorders (Swiss-Reg-NMD) [10, 11]. These disease-modifying treatments have significantly changed the natural history of SMA. Therefore, recent standards of care have recommended using new phenotypic disease categories based on motor function to guide therapeutic and prophylactic interventions [12, 13].

Trajectories of respiratory function for SMA of various severities have been described [14, 15]. Progressive lung function decline increases susceptibility to RTI [16] and is considered to be the most important cause of morbidity and mortality in SMA [17, 18]. This applies in particular to the most severely affected patients with infantile-onset SMA. Even with disease-modifying treatment, lung function of patients with infantile-onset SMA might remain compromised or decline [19, 20]. This patient group, similar to patients with other severe neuromuscular diseases with impaired motor and respiratory function, has an increased risk of RTI in general and of severe RSV infections in particular [21, 22].

RSV is a common cause of lower RTI in infants and young children. The burden of RSV infections is high, since virtually all children become infected with RSV in their first two years of life [23]. In addition, 50–90% of hospitalisations due to bronchiolitis are caused by RSV [24]. RSV prophylaxis is possible using the anti-RSV monoclonal antibody palivizumab. Palivizumab is a humanised monoclonal antibody against the F-protein of RSV and should be given monthly during the RSV season. It has been shown that RSV prophylaxis with palivizumab reduces RSV-related hospitalisations and morbidity especially in vulnerable patient populations [25, 26].

In severe neuromuscular disorders, including SMA, acute RTI often lead to deterioration of the underlying condition with motor regression and need for prolonged nutritional and/or respiratory support, e.g. tube feeding and nocturnal non-invasive ventilation, respectively. Therefore, it is often accompanied by increased care requirements and need for specialised nursing care [27]. Acute RTI may also delay therapeutic measures, including implementation or continuation of disease-modifying therapies [21, 28].

Internationally recognised guidelines for the treatment of SMA recommend prophylaxis with palivizumab for children with SMA and compromised motor function ("non-sitters") aged below two years [12, 13, 29]. However, not all treatment centres adhere to these guidelines, for different reasons. For example, in Switzerland payers commonly refuse to grant cost approvals for RSV prophylaxis with palivizumab, because palivizumab is not approved in Switzerland for this condition nor generally recommended by the Swiss guidelines for the usage of palivizumab in 2016 [30].

This study aims to investigate (1) the frequency of severe RTI requiring hospital treatment, focusing on RSV infections in SMA patients aged below two years, (2) the long-term impact of RTI and RSV infections, in particular, on the need for nutritional and/or respiratory support in patients with SMA, and (3) whether non-adherence to standards of care (by omitting RSV prophylaxis) is associated with increased morbidity due to RSV infections in a population of young SMA patients followed in a Swiss tertiary neuromuscular centre.

Materials and methods

This study was conducted in the tertiary paediatric Neuromuscular Centre Zurich (Department of Paediatric Neurology, University Children's Hospital Zurich, University of Zurich, Switzerland). The Neuromuscular Centre Zurich is a national reference centre for rare neuromuscular diseases, accredited by *kosek* (*Nationale Koordination Seltene Krankheiten* / National Coordination of Rare Diseases). Treatment of SMA with genetically based, disease-modifying therapies and follow-up consultations in Switzerland are only carried out in accredited national reference centres due to corresponding regulations. Frequency of follow-up consultations immediately after initiation of SMA treatment depends on the therapy, with multiple consultations during the first four months, and are then scheduled approximately every four months in the outpatient clinic of the Neuromuscular Centre Zurich.

All patients treated in the Neuromuscular Centre Zurich with a genetically confirmed diagnosis of 5q-associated SMA and below two years of age at diagnosis and initiation of a genetic-based, targeted disease-modifying therapy during the period between 1 May 2019 and 31 December 2022 were included in the study.

The source for data extractions was the clinical information system of the University Children's Hospital Zurich. The following data of all included patients was extracted from the clinical information system: SMA type (historical types [SMA types 1 and 2] and types defined by maximal motor function [non-sitter, sitter, walker]); age at treatment onset; type of disease-modifying therapy; motor function assessment scores (depending on age and individual motor function, either the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders [CHOP Intend, total score 0–64] or the Hammersmith Functional Motor Scale Expanded [HFMSE, total score 0–66]) at treatment onset and end of follow-up; palivizumab vaccination status. In addition, any documented hospitalisation of the included patients was pulled from the clinical information system. The following data was extracted from the clinical information system for all hospitalisations: number of, the reason for, and the total duration of the hospitalisation; the duration of intensive care treatment; nutritional support before, during and after hospitalisation for RTI; respiratory support before, during and after hospitalisation for RTI; the duration of intensive care treatment with ventilation; the delay of planned interventions and the need for additional specialised support following acute hospitalisations. All this data was verified against the information obtained during follow-up visits to the outpatient clinic of the Neuromuscular Centre and documented in the consultation reports. In addition, the hospitalisation costs charged to the

payers for the treatment of RSV infections were calculated via the hospital's accounting system, and the cost of RSV prophylaxis with palivizumab was estimated on the basis of the published price. Data was transferred into a predefined Excel spreadsheet. The cut-off date for follow-up data was 30 June 2023.

The study was approved by the local ethics committee on 27 June 2023 and registered with the Swiss project database (BASEC 2023-01003). Written informed consent (general consent) was obtained from the caregivers prior to inclusion of participants in the study.

This work is mainly descriptive. If not stated otherwise, the median and range are reported. Incidence rates were calculated per patient-year. For comparison of groups, the unpaired t-test was applied for normally distributed data and the Mann-Whitney U test for non-normally distributed data. A p-value <0.05 was considered statistically significant. All analyses were performed using the statistical software GraphPad Prism version 10.2.1 for Windows (GraphPad Software; Boston, Massachusetts, USA; www.graphpad.com).

A specific study protocol has not been published.

Results

Demographics and study population

From May 2019 to December 2022, a total of 12 patients with SMA with a median age of 3.5 months (range: 0–17 months) at treatment initiation with one of the new genetic-based, disease-modifying therapies were included in this study. The cut-off date for follow-up data was 30 June 2023. Prior to this date, the study cohort was followed for a cumulative period of 25.75 years (mean follow-up duration per patient: 25.75 months [SD: 11.51]). Mean follow-up duration per patient with SMA type 1 and SMA type 2 (including the patient with presymptomatic treatment) was 26.43 (SD: 12.44) and 24.8 (SD: 11.43) months (p = 0.82). For a summary of patient demographics, treatment data and number of RTI-associated hospitalisations, please refer to table 1.

Hospitalisations

The incidence rate of all hospitalisations after diagnosis and initiation of genetic treatment was 2.14 per patient-year in the entire cohort (3.5 and 0.1 hospitalisations per patient-year in SMA type 1 and SMA type 2, respectively; p = 0.0037).

This incidence corresponds to a total of 55 hospitalisations with a total number of 347 hospital days (median 4 days, range 1–25) in 8 patients (67% of all SMA patients; 7 SMA type 1 and 1 SMA type 2). Four SMA patients did not require inpatient care during the observation period (33%; 3 SMA type 2 patients, 1 presymptomatic patient). The number of hospitalisations per patient varied between 0 and 17.

Elective hospitalisations

The incidence rate of elective hospitalisations in patients with SMA type 1 and SMA type 2 was 0.91 and 0 per patient-year, respectively; p = 0.015. In total, 14 elective hospitalisations were recorded (26% of all hospitalisations). These elective hospitalisations accounted for a total of 60 inpatient hospital days. Reasons for elective inpatient treatment (figure 1) were percutaneous endoscopic gastrostomy (PEG) feeding tube placement or change from PEG to a gastro button (n = 6), orchidopexy (n = 2), respiratory polygraphy (n = 1) and initiation/adjustment of non-inva-

Table 1:
Summary of patient demographics, motor function, treatment data and RTI.

Pt#	At treatment onset						During 1st & 2nd RSV seasons		≥3 RSV season	Severe non-RSV RTI [n]	At end of follow-up					
	SMA type		Age [m]	DMT	CHOP Intend	HFMSE	RSV prophylaxis	Severe RSV infections [n]	Severe RSV infections [n]		Age [m]	Respiratory support	Nutritional support	CHOP Intend	HFMSE	SMA type
1	1	Non-sitter	4	N	25	–	Palivizumab	0	1	1	34	–	–	44	12	Sitter
2	1	Non-sitter	2	OA	24	–	Palivizumab	0	na	2	28	NIV	gs	48	14	Sitter
3	1	Non-sitter	2	OA	13	–	Palivizumab	0	na	2	8	NIV	–	35	–	Non-sitter
4	1	Non-sitter	3	N*	7	–	–	0	1	4	49	–	–	54	27	Sitter
5	1	Non-sitter	6	OA	35	–	–	1	na	0	24	NIV	–	50	–	Sitter
6	1	Non-sitter	0	N	23	–	–	3	0	8	33	NIV	gs	50	13	Sitter
7	1	Non-sitter	3	OA	12	–	–	3	na	9	29	NIV	gs	44	–	Non-sitter
8	2	Sitter	13	N	31	–	–	0	0	0	39	–	–	48	14	Sitter
9	2	Sitter	14	N	59	25	–	0	0	0	56	–	–	-	48	Walker
10	2	Sitter	17	OA	46	14	–	0	0	1	40	–	–	64	45	Sitter
11	2	Sitter	10	OA	59	–	–	0	na	0	20	–	–	60	32	Sitter
12	ps	Non-sitter	1	OA	52	–	–	0	na	0	24	–	–	64	36	Walker

Ps: presymptomatic; DMT: disease modifying treatment; N: nusinersen; N*: switch of treatment from nusinersen to risdiplam at age 24 months; OA: onasemnogene abeparvovec; RSV: respiratory syncytial virus; na: not applicable (patient has not yet reached the 3rd RSV season); RTI: respiratory tract infection: NIV: nighttime non-invasive ventilation; gs: gastrostomy

sive ventilation (n = 4). Two elective PEG placements resulted in an extended hospital stay because of a hospital-acquired RTI (non-RSV). These hospitalisations therefore were also added to the number of acute hospitalisations due to RTI. The median duration of elective inpatient treatment was 3 days (range 1–20).

Acute hospitalisations

The incidence rate of acute hospitalisations in patients with SMA type 1 and SMA type 2 was 2.60 and 0.1 per patient-year, respectively (p = 0.022). In total, 41 hospitalisations were for acute reasons (74% of all hospitalisations). These acute hospitalisations totalled 287 hospital days. A total of 37 hospitalisations (279 hospital days including 104 days in the intensive care unit) were due to RTI (including RSV and non-RSV infections) and accounted for 90% of all acute hospitalisations. Other reasons for acute hospitalisations were gastrointestinal infections (n = 2), pyelonephritis (n = 1) and fever of unknown origin (n = 1) (figure 2).

The incidence rate of RTI-related hospitalisations in patients with SMA type 1 and SMA type 2 was 2.34 and 0.1 per patient-year, respectively (p = 0.044). Of the RTI-related hospitalisations, 28 were due to non-RSV infections (195 hospital days including 73 days in the intensive care unit) and 9 were due to RSV infections (84 hospital days including 31 days in the intensive care unit). Thus, 24% of all RTI-related hospitalisations were due to RSV infections.

The 9 RSV infections occurred in 5 patients (all SMA type 1), 2 of whom required multiple hospitalisations for RSV infections (three admissions each). In both patients, the first two hospitalisations occurred during their first RSV season which fell into the atypical summer RSV surge during the COVID-19 pandemic in 2021. These two RSV infections were one month and three months apart from each other. The third hospitalisation of these two patients occurred in their second RSV season in autumn 2022. Interestingly, two hospitalisations due to RSV infection occurred in patients during their 3rd or later RSV season. These two hospitalisations were short (2 and 3 days, respectively) and did not require intensive care treatment. No RSV infection requiring hospital treatment occurred in patients while receiving seasonal RSV prophylaxis with palivizumab.

Palivizumab vaccination status

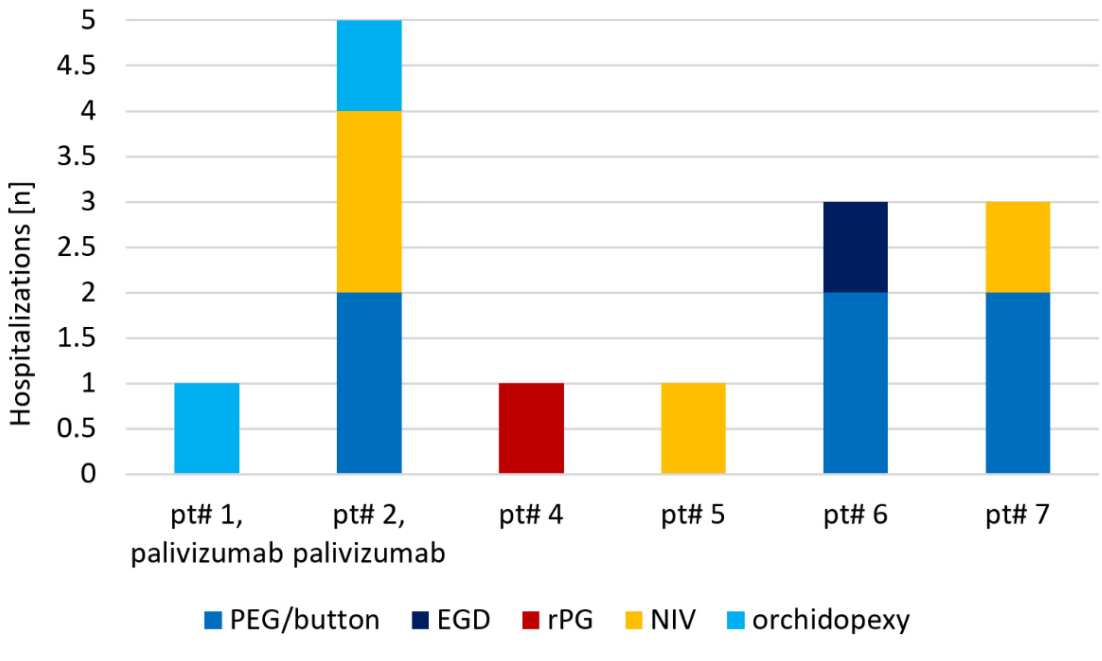
Seven patients of our cohort fulfilled the criteria of RSV prophylaxis due to their motor status (non-sitters) and age (2 years or below) according to current care recommendations [12, 29]. Of these seven patients, only three received RSV prophylaxis cost approvals from the payers for palivizumab during their first two RSV seasons. Neither of them required hospitalisation due to RSV infection while receiving seasonal RSV prophylaxis. An eighth, presymptomatically treated individual was a non-sitter by motor function when receiving a disease-modifying treatment but acquired the ability to sit before entering the first RSV season.

Long-term impact of respiratory tract infections

Nutritional support

Six of eight SMA patients who needed hospital treatment for RTI required nasogastric tube feeding during the acute phase of the hospital treatment. Only two of these patients required tube feeding during acute RTI treatment and could be discharged from inpatient treatment with oral nutrition solely. However, four of these patients remained dependent on nutritional support beyond discharge from the hospital. RSV infection was the reason for three out of four of these

Figure 1: Individual indications for elective hospitalisations. EGD: oesophagoduodenoscopy; NIV: initiation/adjustment of nighttime non-invasive ventilation; PEG/button: percutaneous endoscopic gastrostomy (PEG) feeding tube placement or change from PEG to a gastro button; rPG: respiratory polygraphy.



hospitalisations. While one patient (pt#5 in table 1) was able to switch back to oral nutrition two weeks after discharge from the hospital for RSV RTI treatment, the remaining three remained dependent on tube feeding in the long term and were still almost exclusively tube fed at the end of follow-up, after 20, 23 and 25 months. Pt#2 became permanently dependent on nutritional support during the second severe non-RSV RTI. Pt#6 and pt#7 (see table 1) were temporarily dependent on nutritional support during a first non-RSV RTI, but were initially discharged without tube feeding. During a subsequent RSV RTI, both then became permanently dependent on nutritional support. Consecutively, a PEG tube was placed in all three of these patients.

Respiratory support

Respiratory support (including high-flow therapy and BiPAP non-invasive ventilation) had to be newly introduced during seven acute hospitalisations in four patients, and pre-existing respiratory support had to be continued in four hospitalisations in one patient. In 3 of the 9 RSV-associated hospitalisations (33%), respiratory support was necessary: high-flow respiratory support during the acute phase (n = 2, for a total of 14 days); intensification of previously started non-invasive nighttime ventilation to full-time non-invasive ventilation (n = 1, for 11 days). Altogether, 25 ICU days with ventilation were attributable to RSV infections.

At the end of data collection, 5 of 12 patients (42%, all SMA type 1) were dependent on non-invasive nocturnal ventilation. In three patients (pt#3, pt#6, pt#7 – see table 1), non-invasive ventilation was started during acute treatment for RTI and was continued until the end of follow-up in all three patients. In two patients (pt#2 and pt#5 – see table 1), non-invasive nocturnal ventilation was started electively.

Delay of interventions, need for additional care

In three patients, a planned surgical intervention (PEG placement, change of PEG to button, achillotomy) had to be postponed due to an acute hospitalisation, all of them due to non-RSV RTI. The achillotomy mentioned was done later in an outpatient setting and did not require inpatient treatment.

Regular motor function assessments are mandatory following / during treatment of SMA with genetic therapies in Switzerland, in particular for extensions of cost approvals for their continuation. In two patients (one with RTI due to RSV), these assessments had to be postponed due to RTI.

Nutritional and respiratory support usually require specialised outpatient nursing services, at least in the initial phase after discharge from the hospital. For example, all four SMA patients dependent on nutritional support beyond inpatient treatment for RTI received such a home care service. In addition, these patients had a need for new or intensified existing therapies and support (e.g. orofacial therapy by a speech therapist, physiotherapy, nutritional counselling by a dietitian).

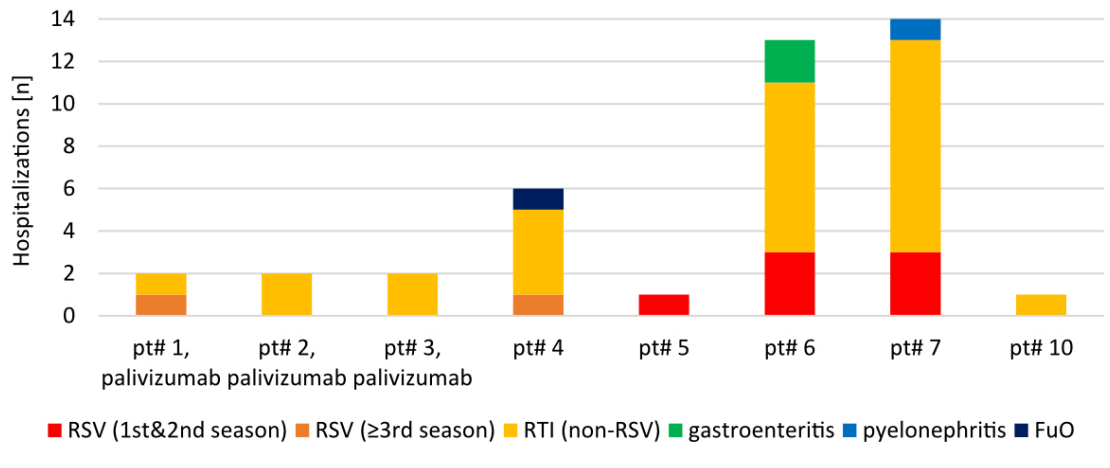
Costs due to RSV infections

RSV infections resulted in 84 days of hospitalisation, with 31 days occurring in the intensive care unit primarily because of the need for advanced respiratory support (25 ICU days with ventilation) and nutritional support.

The direct costs of RSV-associated hospitalisation amounted to more than CHF 200,000 (approximately USD 230,000), including costs for 31 days of intensive care. However, the total economic burden of these severe RSV infections on the healthcare system was much greater, since subsequent costs must be added to inpatient costs resulting, for example, from the ongoing need for respiratory and nutritional support, specialised home care services and other supportive symptomatic therapies. However, within this study, it was only possible to estimate the direct costs of inpatient treatment.

The direct costs of inpatient treatment of SMA patients with RSV infections contrast with the costs of RSV prophylaxis. In the observation period, the costs of RSV prophylaxis with palivizumab would have amounted to approximately CHF 80,000 (approximately USD 90,000) (7 patients with SMA type 1 / non-sitter below age 2 years, treatment for two seasons each).

Figure 2: Individual indications for acute hospitalisations. FuO: fever of unknown origin; RSV: respiratory syncytial virus infection; RTI (non-RSV): RTI other than RSV.



Discussion

5q-associated SMA is a neurodegenerative neuromuscular disorder leading to compromised motor functions including respiratory and bulbar function in more severely affected individuals. Respiratory muscle weakness, impaired mucus mobilisation, high prevalence of gastro-oesophageal reflux and bulbar dysfunction are well known risk factors for RTI in neuromuscular disorders in general [21, 22]. They have also been recognised as risk factors, in particular, for more severe RSV infections in neuromuscular diseases including SMA [31].

New genetic therapies have established a new era in the treatment of SMA. They significantly prolong survival and enable acquisition of motor milestones in patients with infantile-onset SMA (type 1). In more mildly affected patients (later-onset SMA, types 2 and 3), they prevent progression of neuromuscular symptoms and lead to long-term preservation of already acquired motor skills [32]. Prior to the availability of these disease-modifying treatments, most children with SMA type 1 died in the first two years of life or required permanent ventilation. Today, under treatment with these new therapies, these children with SMA type 1 survive but develop varying degrees of muscle weakness, which limits motor development and function, and potentially compromises bulbar and respiratory function. To protect this fragile SMA population, well-defined recommendations for preventive and symptomatic therapeutic measures were developed, including care recommendations for pulmonary symptoms and prophylaxis for RSV infections with palivizumab in severely affected infants with SMA ("non-sitters") below 2 years of age [12, 29].

RSV prophylaxis with palivizumab has not yet been approved for the treatment of patients with SMA in Switzerland. Payers therefore generally refuse to cover the costs of RSV prophylaxis. Therefore, the aim of this study was to investigate the role of RSV infections among severe RTI with inpatient treatment in a population for which adherence to otherwise internationally recognised standards was not possible.

In summary, our data shows that the risk of severe RSV infections requiring hospitalisation is high in SMA patients. This especially concerns patients with severely compromised motor function (SMA type 1 and/or non-sitters) during early infancy. In our cohort of 7 SMA type 1 patients / non-sitters, a total of 84 hospitalisation days, including 31 days in ICU, were necessary for the treatment of RSV infection. In our small cohort, severe RSV infection only occurred in patients without seasonal RSV prophylaxis with palivizumab. The cost of these RSV-associated hospitalisations far exceeds the estimated cost of RSV prophylaxis for the subgroup of our study cohort defined in the care standards (patients with SMA type 1 / "non-sitters" and age below two years) – even without taking into account indirect follow-up costs arising from prolonged nutritional and/or respiratory support following RSV infections. Our study shows that such support is often required in SMA patients beyond hospital treatment for severe RTI in general, especially if the reason was an RSV infection. In addition, our data shows a clear long-term impact of RSV infections for the patients. Three patients remained in need of nutritional support beyond hospitalisation. Ventilatory support was needed in 3 of 8 hospitalisations due to RSV infection and one child needed intensified ventilatory support after the hospitalisation. In addition, severe RSV infections led to a delay of planned surgical interventions and therapies. Thus, our study may indicate that non-adherence to care standards (by omitting RSV prophylaxis) might be associated with increased morbidity in the studied patient population. In addition, there is a cost to society that is potentially significantly higher than the cost of providing RSV prophylaxis according to care recommendations.

At the time of our study, RSV prophylaxis with palivizumab was broadly available in many regions worldwide. Palivizumab can prevent severe RSV infections and their long-term sequelae. In Switzerland, a consensus statement for the prevention of RSV infections with palivizumab was published by the Paediatric Infectious Disease Group of Switzerland (PIGS) in 2016 [30]. According to this statement, RSV prophylaxis is recommended for children with severe bronchopulmonary dysplasia and uncorrected haemodynamically significant congenital heart defects. Only for these indications was RSV prophylaxis reimbursed by the Swiss invalid insurance after an individual cost approval. Since July 2022, cost coverage has been provided by the mandatory healthcare insurance in Switzerland. The PIGS consensus statement specified that a general indication for RSV prophylaxis is not given for a broad range of other diseases including SMA because of the wide clinical variability of these conditions and a lack of efficacy data regarding RSV prophylaxis for these disease populations. In fact, the present report is to our knowledge the first cohort study that investigates the occurrence and consequences of RSV infections in SMA patients. The 2018 guideline of the Working Group of the Scientific Medical Societies (*Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften*, AWMF) on prophylaxis of severe RSV disease in high-risk children [33] states that patients with neuromuscular disorders and RSV infection more often require intensive care and invasive ventilation and have higher lethality. These guidelines list SMA among other high-risk diseases, such as patients with immunodeficiencies and cystic fibrosis.

Therefore, internationally recognised guidelines for the treatment of SMA and standards of care recommend prophylaxis with palivizumab for children with SMA and significantly impaired motor function ("non-sitters") aged below 2 years [12, 29].

In recent years, great progress has been made in the development of new measures for RSV prophylaxis. A new antiviral monoclonal antibody, nirsevimab, was approved for RSV prophylaxis by the European Medicines Agency (EMA) and the FDA in October 2022 and July 2023, respectively. According to the EMA prescribing information, nirsevimab is indicated in all neonates and infants during their first RSV season regardless of whether there is a predisposing underlying disease [34]. The FDA prescribing information extends the indication to children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season [35]. In addition, both the EMA and the FDA approved Abrysvo in August 2023, the first active immunisation of pregnant women for the prevention of severe RSV infections in infants from birth to 6 months of age [36, 37]. During the revision

of the present report, nirsevimab was also approved by Swissmedic in late December 2023. The approval label largely follows the FDA's decision [38]. Recently, an expert working group consisting of representatives from various Swiss medical societies, the Federal Commission for Vaccination Issues (EKIF / CFV) and the Federal Office of Public Health (BAG / FOPH) issued a new consensus statement / recommendation on the prevention of respiratory syncytial virus infections with the monoclonal antibody nirsevimab [39]. The implementation of this consensus recommendation still requires further regulatory processes, such as the inclusion of nirsevimab prophylaxis in the national vaccination recommendations and the specialty list for reimbursement by payers. This development provides improved RSV prophylaxis in many regions worldwide and may be to the benefit of patients with SMA.

Parallel to this development, SMA has been included in numerous national newborn screening programmes worldwide. In the US and Europe up to 100% and >65% of all newborns, respectively, are screened for the presence of SMA. The rationale for the inclusion of SMA in newborn screening programmes is that a significantly better prognosis is seen when therapy is initiated at a presymptomatic disease stage vs at a symptomatic stage. Presymptomatic treatment results in normal or near-normal motor development for the majority of individuals with a genetic diagnosis of SMA, at least in the first years of life [40–43]. These coincidental developments result in a rapidly decreasing SMA population at risk ("non-sitters") and at the same time improved and extended measures for RSV prophylaxis, at least in regions with appropriate approvals.

This study has several potential limitations. First, it is a single-centre cohort study relying on existing medical records. Since SMA is a rare disorder, only a comparatively small patient population could be included. Further investigations are needed to investigate the impact on severe RTI and RSV infections on patients with SMA. However, this study is one of the first to investigate the frequency of severe RSV infections in SMA and its impact on the more long-term wellbeing of affected individuals of this fragile patient group. Second, the study focused on severe RTI and RSV infections and thus might have missed milder cases not requiring hospital care and their impact on the outcome. Third, the study period coincided with the COVID-19 pandemic. The aim of this study was not to investigate the incidence of severe COVID-19 infections. However, during and following the COVID-19 pandemic, the epidemiology of RSV changed. Atypical surges in RSV cases were observed during the summer months, i.e. between typical RSV seasons [44]. Whether and to what extent the results of this study may have been influenced by a temporal association with the COVID-19 pandemic and the change of RSV epidemiology can only be speculated upon. Fourth, this study might be representative only for Switzerland and other regions where RSV prophylaxis is not routinely available.

However, this specific regional situation depicts well the consequences of non-adherence to respected care recommendations. International care recommendations for rare disorders should be respected by healthcare professionals, payers and other stakeholders involved in the care of patients with a rare disorder, especially when national or local regulations and recommendations do not include a particular rare disorder and/or do not reflect current knowledge or new developments. The study results should provide a loud voice for reinforcing current treatment recommendations for rare disorders.

Data sharing statement

The data that supports the findings of this study is available in anonymised and aggregated form from the corresponding author upon reasonable request. The data is not publicly available as it contains information that could compromise the privacy of research participants in this small cohort study.

Acknowledgments

We thank the patients and their caregivers for contributing their data. We would like to thank K. Benincasa Herr for language editing.

Authors' contributions: CTR and GMS initiated and designed the study, extracted data from the hospital's clinical information system, analysed the data and wrote the manuscript. MSt and EG extracted data from the clinical information system, analysed the data and revised the manuscript. CTR, EG and GMS were directly involved in patient care and collected clinical data during follow-up consultations. MSo analysed the data and revised the manuscript. PMMS and JT co-designed the study and revised the manuscript. All authors read and approved the final manuscript.

Financial disclosure

This research received no specific grant from any funding agency.

Potential competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. G. M. Stettner served on advisory boards of AveXis, Biogen, Novartis Gene Therapies, Pfizer and Roche. No other potential conflict of interest related to the content of this manuscript was disclosed.

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