Clinical Evolution and Disease Burden in Belgian Cystic Fibrosis Patients: effect of Newborn Screening?

Noelia Rodriguez Mier [a], François Vermeulen [b], Géraldine Daneau [c], Simeon Situma Wanyama [c], Marijke Proesmans [b]

Department of Chemical Chemistry, LHUB-ULB, Université Libre de Bruxelles, Brussels, Belgium

[a] KU Leuven, Oude markt 13 bus 5500, 3000 Leuven
[b] UZ Leuven, Herestraat 49, 3000 Leuven
[c] Sciensano, Juliette Wytsmanstraat, 1050 Brussel

noelia.rodriguezmier@student.kuleuven.be

Abstract

Objectives: We compared the clinical evolution and disease burden of 3 groups of Belgian children with cystic fibrosis (CF) depending on the mode of diagnosis: meconium ileus (MI), newborn screening (NBS) and clinical diagnosis (non-NBS) at 1-, 2- and 6 years of age.Methods: We conducted a retrospective observational cohort study based on data collected from the Belgian CF Registry report of 2016 including patients diagnosed between January 2006 and December 2016.

Results: 306 CF patients were enrolled. Age at diagnosis was the lowest in MI patients (median 0.12 months, IQR 0.00-0.36 months) but lower in NBS patients (median 1.38 months, IQR 0.82-1.74 months) compared to non-NBS patients (8.01 months, IQR 2.47-37.58 months, p-value < 0.001). Height z-scores at 1 year of age were better in NBS patients (median = -0.13, IQR -0.99 − 0.50) compared to non-NBS patients (MI median = -0.56, IQR = -01.53 − 0.02, non-NBS median = -0.54, IQR = -1.02 − 0.12, p = 0.03377). Annual prevalence of bacterial infections was not different between the 3 patient groups at the predefined time points. Burden of therapy was lower for NBS during the first 2 years of life. Lung function at 6 years of age did not show significant differences between the 3 groups.

Conclusion: This study suggests a beneficial trend for NBS as primary method of CF detection when comparing age at diagnosis, clinical evolution and burden of therapy between NBS and clinically diagnosed CF patients. A standardized care program after CF-NBS is needed to further improve the benefits of NBS.

Introduction

Cystic fibrosis (CF) is an autosomal recessive disorder primarily affecting the respiratory and the digestive system. It is caused by the presence of mutations on both copies of the cystic fibrosis transmembrane conductor regulator (CFTR) gene ( ). Absence of functional CFTR results in increased viscosity of exocrine secretions and primarily causing chronic lung infections and exocrine pancreatic insufficiency ( ). Until recently, the majority of diagnoses of CF in Belgium were made based on clinical suspicion.

Several studies have shown that starting therapy very early improves clinical outcome and prognosis, 'early' being specified as before 2 months of age (,). Therefore, it is important to diagnose CF as early as possible. Timely diagnosis can be achieved through a newborn screening program ( ). This program provides the opportunity to improve outcomes by initiating monitoring and treatment in the pre-symptomatic period ( ). It has been shown that compared with non-NBS CF patients, NBS patients are indeed diagnosed earlier and have their first clinic visit at a younger age ( ). Moreover, early diagnosis after newborn screening improves survival in cystic fibrosis patients (,).

At the time of this study, Belgium had no official program for newborn CF screening However, for many years, there have been local screening initiatives where patients were detected using cystic fibrosis newborn screening algorithms (10). The median age at diagnosis for the newly diagnosed CF patients in 2013 was 8.2 months but progressively decreased to 3.8 months in 2016 (,11). In 2016, about 18.0% were diagnosed by newborn screening (10). An official neonatal screening for CF (CF-NBS) by means of blood spot screening at the age of 3 to 5 days was introduced in January 2019 in Flanders (12,13). Wallonia and Brussels followed in January 2020 (14).

The aim of this registry study is to compare the demographics and clinical evolution of 3 groups of Belgian children with CF depending on the mode of diagnosis: meconium ileus (MI), newborn screening (NBS) and clinical diagnosis other than MI (non-NBS). We expect that CF patients with a NBS diagnosis will have a lower age at diagnosis. This could possibly lead to a better weight evolution, less burden of therapy and a better respiratory outcome.

Materials and methods

Study population

We conducted a retrospective observational cohort study based on data collected from the Belgian CF Registry (BCFR) report of 2016. Inclusion criteria for analysis were patients diagnosed with CF (typical and atypical) between January 2006 and December 2016. Typical CF was defined as having a positive sweat test and/or two CF disease - causing mutations. Atypical CF was defined as having a normal (Cl< 30 mmol/l) or intermediate (30mmol/l ≤ Cl ≤ 60 mmol/l) sweat test result or absence of 2 disease-causing mutations. Patients diagnosed after ten years of age were excluded. Within the selected patients, three cohorts are defined: patients presenting with meconium ileus at birth (MI), patients with a clinical diagnosis based on CF symptoms other than MI (non-NBS) and patients diagnosed based on newborn screening (NBS). The newborn screening cohort consists of patients with CF diagnosis after NBS during non-official temporal NBS initiative programs using a two-step algorithm of IRT/DNA (immunoreactive trypsinogen/DNA), IRT/IRT or IRT/PAP (pancreatitis-associated perotein).

Data collection

The Belgian CF Registry collects clinical and demographic data of patients followed at all seven accredited CF Referral Centers in Belgium. The data in this registry consists of an annual point summary of clinical data. Clinical data include anthropometry (height, weight and BMI), lung function (percentage predicted FEV1 and FVC), microbiology i.e., annual prevalence of recorded

pathogens, prevalence of chronic infections, days of hospitalization and of IV antibiotics and other CF treatments. Microbiological annual prevalence is defined as pathogens found at least once during the whole year (11). Chronic bacterial infections were defined according to modified Leeds criteria (15). Method of CF diagnosis, sweat test result, genotype (CFTR mutations) and pancreatic status are registered at diagnosis.

We studied the following variables for the three defined groups: age at diagnosis (in years), height z-scores, weight z-scores, BMI z-scores, FEV1% predicted (Global Lung Initiative reference equations) and point prevalence of Methicillin-resistant Staphylococcus aureus (MRSA), Pseudomonas aeruginosa and Burkholderia cepacia infections (16-18),. The following treatment parameters were studied: days of hospitalization (per year), days IV antibiotics (per year), use of hypertonic saline, oral azithromycin and acid suppression therapy (proton pump inhibitor (PPI) or histamine 2 (H2) receptor blocker. We also specifically looked at number of hospitalization and IV antibiotic treatment for more than 14 days per year. All parameters were studied at three different points in time: at 1- (T01), 2- (T02) and 6 (T06) years of age. Anthropometric measures (height z-scores, weight z-scores and BMI z-scores) were compared yearly from 1 year of age until 6 years of age (16,17). Lung functions (percentage predicted FEV1 and FVC) were compared at 6 years of age (T06).

Statistical analysis

We compared the three predefined cohorts at three time points: T01, T02 and T06. We also conducted a post-hoc analysis discarding the MI cohort to solely compare the non-NBS cohort with the NBS cohort. All data after a transplant is set to missing. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). Means (SD), medians (Interquartile range - IQR), counts (n) and proportions (%) were used to describe the demographic and clinical characteristics of each group in the study sample. Bar charts and/or line graphs were obtained to depict outcome measures. Continuous outcomes were tested for normality. Differences were tested using Wilcoxon Rank Sum or Kruskal Wallis tests. Pearson Chi-square or Fisher Exact (n ≤ 5) analyses were used to compare proportions between groups. An α value of 0.05 was set and all tests were two-tailed.

Results

Description of the cohort

In the BCFR, 1275 alive patients were registered by January 2016 with a median (IQR or range) patient age of 22.5 years (10). Since January 2006, 25 to 50 new CF diagnosis were made per year (10). A total of 306 patients were eligible for this study: MI (n = 47), NBS (n = 74) and non-NBS (n = 185). Both typical (n = 289) and atypical CF (n = 17) cases were included. Patients with an incomplete genotype (n = 28) all had a sweat chloride > 60 mmol/L and were thus categorized as typical CF. Patients with missing sweat test (n = 32) all had two disease-causing mutations identified and were thus classified as typical CF. Patients with an intermediate sweat test result i.e., 30 mmol/l ≤ Cl ≤ 60 mmol/l (n=17) all had two identified mutations but only one mutation was clearly disease-causing and were therefore categorized as atypical CF.

Within the typical CF cases (n = 289), 47 patients were MI, 175 non-NBS and 67 NBS.

Within the atypical CF cases (n = 17), 10 patients were non-NBS and 7 NBS. As expected, MI did not occur in this group.

There were 132 typical CF patients F508del homozygous with a different distribution between the 3 cohorts (72/185 (39%) non-NBS patients, 32/74 (43%) NBS patients and 28/47 (60%) MI patients, p = 0.0384) and 80 patients heterozygous for F508del mutation (49/185 (26%) non-NBS patients, 22/74 (30%) NBS patients and 9/47 (19%) MI patients, p = 0.0907). Twelve atypical CF patients were heterozygous for F508del mutation (6 non-NBS patients and 6 NBS patients).

The majority of typical CF patients were pancreas insufficient (n=255/289 (88%), 149 non-NBS patients, 59 NBS patients and 47 MI patients) and all the atypical CF cases were pancreas sufficient (n =17)).

Diagnosis

Median age at diagnosis was lower in NBS patients compared to non-NBS but was lowest in MI patients (Table 1). Excluding MI patients, NBS detected CF significantly earlier compared to non-NBS. Median sweat chloride increased from patients with a clinical diagnosis to NBS patients and finally to MI patients (Table 1). Post hoc analysis revealed that mean sweat chloride did not differ significantly between the NBS (median = 103.3 mmol/l, IQR = 83.0 – 110.0) and the non-NBS patients (median = 98.0mmol/l, IQR = 83.1 – 107.5, p = 0.3884).

Anthropometric measures

At one year of age, weight z – scores were not statistically different between the 3 groups (Fig. 1). Height z-scores however were higher in NBS patients compared to MI and clinically diagnosed patients (Fig 1). At two years of age, neither height, weight nor BMI z-scores were significantly different between the 3 groups (Fig. 2).

At six years of age, newborn screened patients had lower weight and BMI z-scores compared to non-NBS patients (Fig 3). Height z-scores were not significantly different between the 3 groups (Fig 3). The proportion of patients with height greater than or equal to the 25th percentile increased from NBS patients (51.5%) to MI patients (57.1%.) and finally to clinically diagnosed patients (77.7%, p = 0.0092). The proportion of patients with BMI greater than or equal to the 25th percentile was higher in NBS patients (69.7%) compared to MI patients (42.9%) but was highest in clinically diagnosed patients (75.5%, p = 0.0132). Weight above the 25th percentile was not statistically different between the 3 groups (p = 0.0812).

Prevalence of bacterial infections

At one year of age, the prevalence of the bacterial infections with P. aeruginosa, MRSA and B. cepacia was low and not statistically different between the 3 groups (Fig. 4), neither was the prevalence of chronic with P. aeruginosa or chronic MRSA infections.

Similarly, the prevalence of these bacterial infections and of their chronic infections at two and six years of age (at T06 also chronic Achromobacter xylosoxidans and Stenotrophomonas maltophilia infections) were not statistically different.

Burden of therapy

During their first year of life (T01), NBS patients had the lowest number of hospitalized days, followed by clinically diagnosed patients and MI patients (Table 2). The proportion of patients hospitalized for more than 2 weeks was also lower in NBS patients (13.4%) compared to clinically diagnosed (18.5%) and MI patients (34.2%, p = 0.0332). The total days of IV antibiotic treatment was lower in NBS patients compared to MI and clinically diagnosed patients (Table 2). The proportion of patients using antibiotics for more than 2 weeks was not statistically different between the 3 groups. The proportion of patients using acid suppression therapy was significantly lower in the NBS cohort (38.8 %) compared to the MI (73.7%) and non-NBS cohort (50.9%, p = 0.0027). The use hypertonic saline or oral azithromycin were not statistically different between NBS, MI and clinically diagnosed patients.

At T02, the total number of hospitalized days and days of IV antibiotics did not differ significantly between our 3 groups (Table 3). The proportion of patients using acid suppression therapy was lower in NBS patients (35.0 %) compared to clinically diagnosed (50.0 %) and MI patients (69.4 %, p = 0.0046). The use of hypertonic saline was lower in NBS patients (33.3%) compared to clinically diagnosed (54.4%) and MI patients (55.6%, p = 0.0200). Other treatments (hospitalization or IV antibiotics for more than 2 weeks or oral azithromycin) were not statistically different between the 3 cohorts.

At 6 years of age, the total number of hospitalized days and days of IV antibiotic treatment was not significantly different between the 3 groups (Table 4). The proportion of patients using acid suppression therapy was lower in NBS patients (48.5 %) compared to MI patients (61.9 %) but was lowest in clinically diagnosed patients (34.0 %, p = 0.0402). Other treatments at T06 (hospitalization or IV antibiotics for more than 2 weeks, hypertonic saline or oral azithromycin) were not statistically different between our 3 groups.

Finally, the spirometry measures (FEV1 and FVC percentages of predicted and z-scores) at T06 were not significantly different between the 3 cohorts.

Discussion

As expected, and based on registry data, age at diagnosis was lower in NBS patients compared to patients with a clinical diagnosis based on other symptoms than MI. However, advantages in outcome were less pronounced than expected. Only at 1 year of age, NBS patients had better height z-scores compared to non-NBS patients. Bacterial infections showed no differences between the 3 patient groups at the predefined time points. At 6 years of age, there was no significant difference between the 3 groups in lung function.

Burden of therapy was however lower for the NBS group mainly during the first 2 years of life. During their first year of life, NBS patients were less hospitalized and needed less antibiotics and antacids compared to MI and non-NBS patients. During their second year of life, NBS patients needed less antacids and hypertonic saline compared to MI and non-NBS patients.

The results of the current registry study regarding the age at diagnosis are similar with a national registration study in The Netherlands where the median age at diagnosis for NBS patients was 3.6 weeks compared to 31.5 weeks for clinically diagnosed patients (19). A retrospective study in Poland using a similar screening algorithm to detect CF further supports this finding with a median age at diagnosis being 1 month in NBS patients compared to 7 months in non-NBS patients (20).

Some of the earliest evidence for newborn screening regarding clinical evolution of CF patients depending on the mode of diagnosis is the Wisconsin trial (21). They concluded that early diagnosis of CF through neonatal screening improves long-term growth. The screened group had a much lower proportion of patients with weight and height data below the 10th percentile throughout childhood. A follow-up study showed that this growth benefit is sustained through puberty leading to a taller adult height in the screened versus the control group with differences in adult height being primary attributable to NBS and better prepubertal growth (22).

The evaluation of CF patients (up to 2 years old) after nationwide implementation of CF NBS in the USA showed that NBS is associated with a significant improvement in growth outcomes and reduction in P. aeruginosa infections (23). In an American CF cohort described by Collins et al. patients diagnosed after NBS have improved growth (height for age and BMI) until 15 years of age and preservation of normal pulmonary function (FEV1 and FVC) from 6 to 15 years of age (24). Acquisition or colonization of P. aeruginosa was similar between NBS and non-NBS patients in this study (24).

Comparison of the USA and Australian CF data registries to assess the impact of NBS showed that children (≤ 18 years of age) diagnosed with CF after newborn screening benefited from better BMI and lung function (FEV1) than those diagnosed clinically (25). Moreover, a retrospective study in New South Wales (Australia) concluded that height, weight, BMI and lung function (FEV1) were better in the screened group compared to non-screened patients on transfer to adult care (9). Non-screened CF patients had a higher rate of infection with P. aeruginosa before 18 years of age and lower age of P. aeruginosa acquisition when compared with NBS patients in this study (9).

Specifically, for lung function, a retrospective study in the UK found equivalent pulmonary outcomes in genetically similar patients with a screening diagnosis and clinical diagnosis although receiving fewer therapies suggesting that therapy burden is lower in newborn screened CF patients (4).

All together, these studies showed a sustained growth benefit for NBS patients, some but not all document a better lung function in NBS patients while results on P. aeruginosa infections were divided.

These differences in findings with our study could be attributed to small sample size of our study, the lack of an official NBS program in Belgium (and thus no standardized care after NBS) at the broad time period studied, reflecting not all patients included received the same treatment. Furthermore, CF patients with a clinical diagnosis already have good outcome in Belgium. This implies that hospitalized days and days of IV antibiotic treatments in this group are already low making it more difficult to detect differences with the NBS group. However, there is still room for further improvement.

Table 1. Baseline values at diagnosis by cohort.

Variable	Category	n	Mean (SD)	Median (IQR)	Pr > |Z|
Age diagnosis (years)	Meconlleus	36	0.03 (0.05)	0.01 (0.00 - 0.03)	< 0.0001
	NBS	70	0.12 (0.10)	0.11 (0.07 - 0.15)	
	Non-NBS	162	1.75 (2.15)	0.67 (0.21 - 3.13)	
Age diagnosis (months)	Meconlleus	36	0.32 (0.63)	0.12 (0.00 - 0.36)	< 0.0001
	NBS	70	1.38 (1.23)	1.27 (0.82 - 1.74)	
	Non-NBS	162	21.04 (25.85)	8.01 (2.47 - 37.58)	
Sweat test chloride	Meconlleus	26	108.14 (19.4)	107.7 (97.1 - 118.0)	0.0138
	NBS	65	96.1 (26.7)	103.3 (83.0 - 110.0)	
	Non-NBS	155	94.78 (19.6)	98.0 (83.1 - 107.5)	

Table 2. Hospitalized and IV antibiotics treatment days at T01 by cohort.

Variable	Category	n	Mean (SD)	Median IQR	Pr > |Z|
Days hospitalized	Meconlleus	38	18.6 (26.9)	10.5 (0.0 - 21.0)	< 0.0001
	NBS	67	7.1 (18.3)	0.0 (0.0 - 7.0)	
	Non-NBS	108	10.3 (19.3)	3.0 (0.0 - 12.0)	
Total Days IV antibiotics	Meconlleus	38	7.4 (10.7)	0.0 (0.0 - 16.0)	0.0225
	NBS	67	3.7 (9.6)	0.0 (0.0 - 0.0)	
	Non-NBS	108	5.7 (11.3)	0.0 (0.0 - 10.0)	

At 1 year of age (T01) it is even more difficult to prove differences in burden of treatment between NBS patients and clinical diagnosis patients because the latter have a higher median age at diagnosis making the time lapse until their first birthday much shorter. Also, some treatments may be started from diagnosis irrespective of symptoms (for example hypertonic saline). Moreover, there were slightly more atypical cases in the clinical diagnosis group. These patients usually have milder CF symptoms resulting in better mean outcomes in this group.

The main strength of the current study is that we included burden of therapy in our outcome parameters which is absent in a number of other reports on outcome after NBS. The study also included a post-hoc analysis excluding patients presenting with meconium ileus, a group of which the outcome will not change with NBS.

However, some limitations should be noted. First, we conducted a retrospective observational cohort study based on data collected from the BCFR. Data collection depended on the completeness and verification of screening and diagnostic data which cannot be guaranteed by the registry. Second, during the study period there was no official newborn screening program in Belgium, so we relied on local screening initiatives that did not all use the same screening algorithm and may not always foresee immediate referral to a CF center and start treatment. Therefore, patients may not have fully benefited from the advantages of newborn screening. This also implies that screened patients all come from some regions with screening and are thus not equally spread over Belgium. Socio-economic differences between Belgian regions and CF centers may induce significant bias. Third, this study had potentially an insufficient sample size for statistical measurement of differences between cohorts. Finally, we did not apply the Bonferroni adjustment for multiple testing correction: p < α/n to time points T01, T02 and T06.

This study was a first attempt to report on newborn screening for CF in Belgium and its potential benefits on clinical evolution and burden of therapy compared to clinically diagnosed children. The obtained results may suggest that NBS babies are currently not being followed up and treated intensively enough in Belgium.

Future research can focus on the evaluation of national NBS in Belgium and longitudinal outcome parameters after the implementation of an official newborn screening program in Flanders from 2019 and Brussels and Wallonia since January 2020 using the same screening algorithm (13,14). Further development of targeted and potentially disease modifying therapies will continue to change the course of the CF scene in Belgium.

Conclusion

Several studies have stressed the importance of implementing CF newborn screening programs. Altogether, our study showed some beneficial effects of NBS as primary method of CF detection when comparing age at diagnosis, clinical evolution and burden of therapy between NBS and clinically diagnosed CF patients. Further research is needed after implementation of NBS in Flanders in January 2019 and after national implementation of NBS in Belgium in January 2020. Standardized follow-up and therapy according to international guidelines should be offered (26).

Conflict of interest

There is no conflict of interest with other people or organizations that could inappropriately influence or bias the content of this paper.

Financial disclosure

The authors declare that there are no financial conflicts

Figure 1: *Weight and height z-scores at T01. Boxplots describing weight and height-for-age z-scores by cohort at T01.*

Figure 1: *BMI, weight and height z-scores at T02. Boxplots describing BMI, weight and height-for-age z-scores at T02 by cohort.*
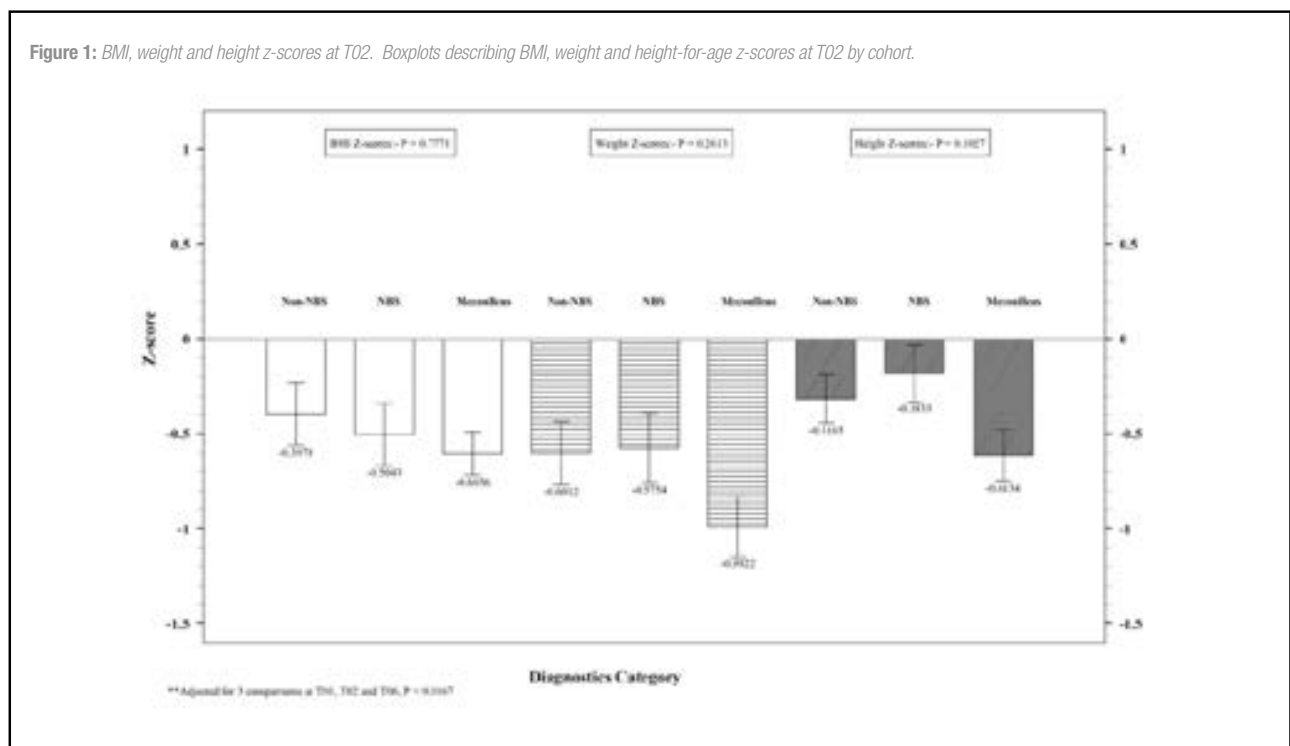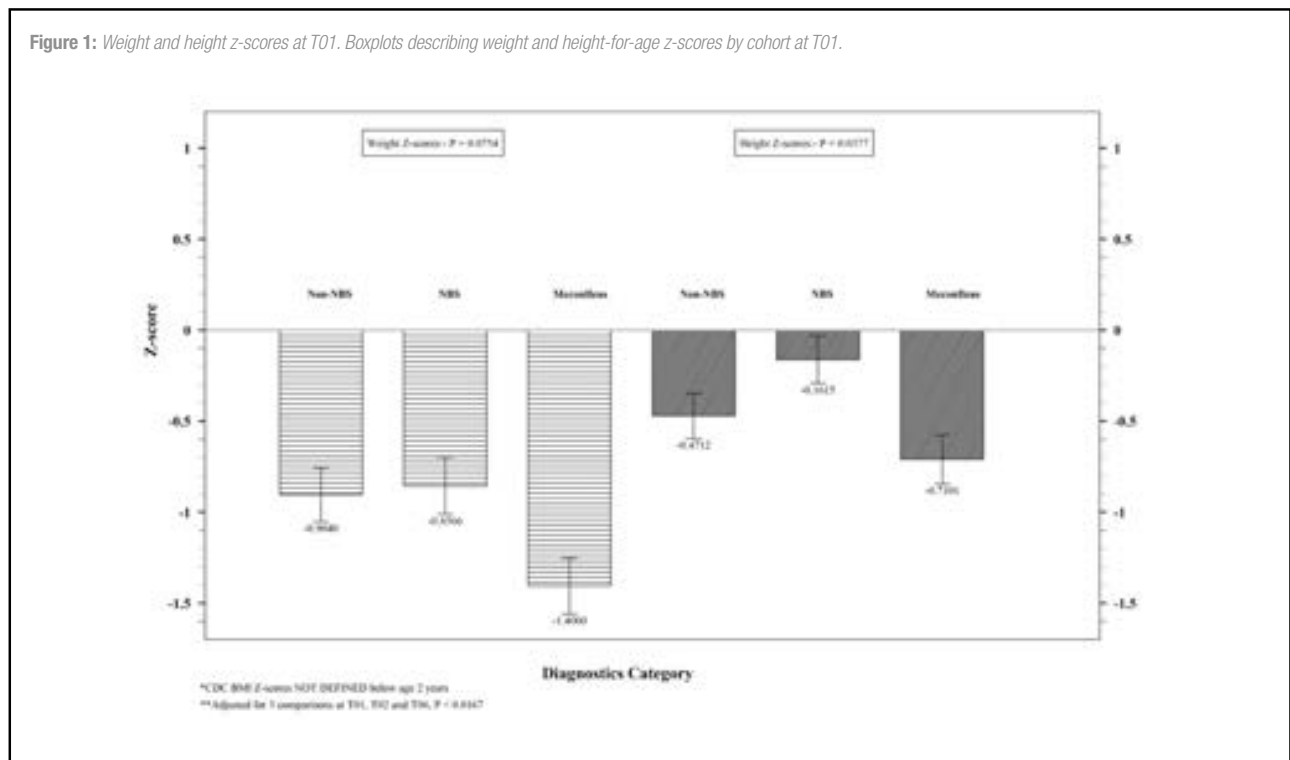
Figure 3: *BMI, weight and height z-scores at T06. Boxplots describing BMI, weight and height-for-age z-scores at T06 by cohort.*
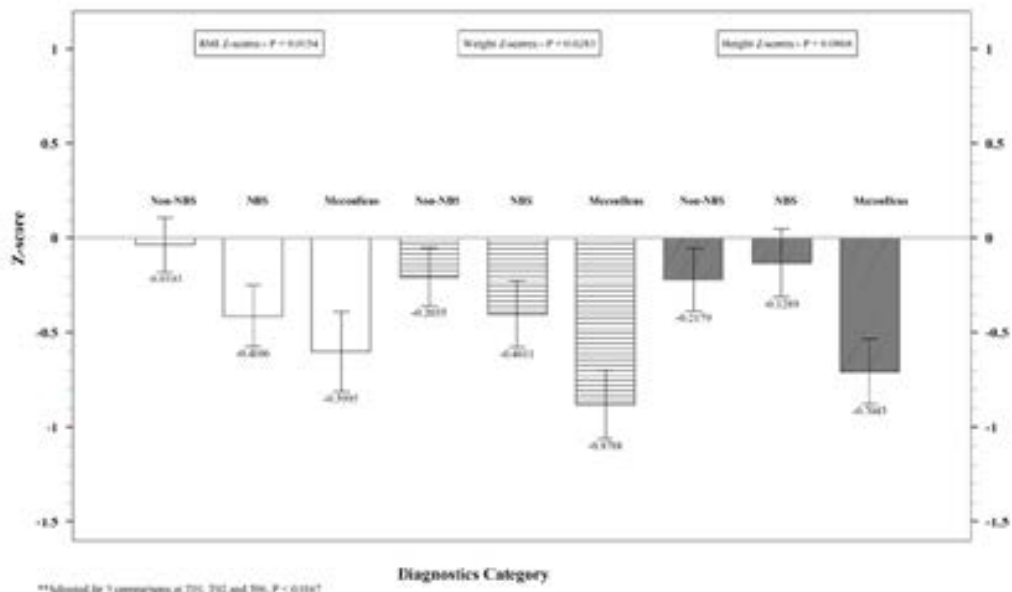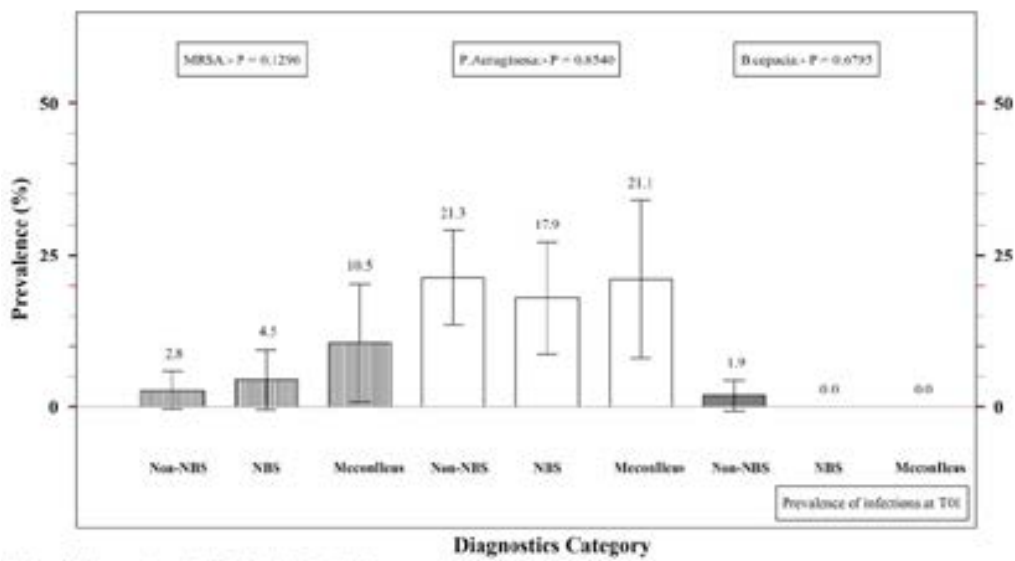

Figure 4: *Prevalence of bacterial infections at T01. Boxplots describing prevalence of MRSA, P. aeruginosa and B. cepacia infections at T01 by cohort.*

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