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ARTICLE

Prevalence of respiratory colonisations and related antibiotic resistances among paediatric tracheostomised patients of a long-term rehabilitation centre in Italy

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Abstract Patients with brain injury are prone to bacterial colonisations because of mechanical ventilation during intensive care and the long-term retention of tracheostomical tubes during rehabilitation. Reduced levels of isolation, typical of rehabilitation, could also contribute to propagate colonisations. We evaluated the presence of bacteria through different stages of healthcare, their antibiotic resistances and their clinical impact in a rehabilitation setting. This retrospective study included all tracheostomised patients referred to the paediatric brain injury unit of the Scientific Institute IRCCS E. Medea (Italy) over a six-year period. Data were collected from antibiograms regarding the presence of bacterial species and antibiotic resistances; clinical data were collected from medical records. Antibiograms revealed bacteria and antibiotic resistances typical of intensive care, while prevalence patterns were characteristic for each species (*P. aeruginosa* and *S. aureus* prevailing in the acute setting, *K. pneumoniae*, *A. baumannii* and others in rehabilitation). Despite very frequent antibiotic resistances, consistent with Italian averages, we observed a limited clinical impact for these colonisations. We analysed risk factors correlating to the development of respiratory symptoms and found a role for the acute clinical course after brain injury (having undergone neurosurgery; duration of intensive care stay) as well as for rehabilitation (duration of coma). Our data suggest that, in a long-term perspective, an appropriate balance is yet to be found between patient isolation and social interactions, to control respiratory colonisations and antibiotic resistances without compromising rehabilitation. They also suggest that regular containment measures should be complemented by thorough training to non-medic personnel and parents alike.

Marco Pozzi and Paolo Pellegrino authors contributed equally to this work.

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Introduction

The 2012 report of the European Centre for Disease Control [1] showed an alarming prevalence of antibiotic resistance in several countries, including Italy, due to bacteria frequently associated with nosocomial pneumonia [2]. These bacteria are common in adult and paediatric intensive care units (ICUs) [3, 4] and have been associated with increased mortality rates and longer length of stay [5]. Such issues frequently involve patients with acquired brain injury (ABI) [6], who present several risk factors such as mechanical ventilation, long-lasting impairment of consciousness and having undergone surgery [7, 8]. While mechanical ventilation during short-term hospitalisation in ICUs is associated with higher risk of

developing pneumonia [9] and containment protocols are widely discussed [10, 11], information about long-term care of patients with tracheostomical tubes is scant. Patients with ABI often maintain tracheostomies out of ICUs, due to neurological deficiencies [12–14], and their presence has been associated with higher prevalence of pneumonia [15]. At the same time these patients are exposed to intense interactions with healthcare professionals and relatives who may be a prominent source of pathogens [16–19]. The adequate management [20, 21] of nosocomial pneumonia sustained by antibiotic-resistant bacteria is important for the consequences both on the clinical management choices for patients with ABI in ICUs [22] and for their long-term need of medical treatments [23]. To investigate these issues in a long-term perspective, we analysed a population of paediatric tracheostomised patients undergoing rehabilitation from ABI, focusing on the presence of bacteria during different stages of healthcare, their spectrum of antibiotic resistance and the development of respiratory symptoms.

Materials and methods

Study design and settings

The Scientific Institute IRCCS Eugenio Medea is a paediatric clinic for neurological and neuropsychiatric rehabilitation. It hosts a Severe ABI Unit that accepts patients with post-acute brain injury of various aetiologies. This retrospective cohort study evaluated medical records from the 2007–2013 time frame, focusing only on patients who suffered ABI and carried a tracheostomical tube at admission, including all available microbiological screenings performed until tracheostomy was removed. Patients were initially admitted from acute-care health facilities for their first rehabilitation stay, during which patients continuously resided in the unit. As rehabilitation usually lasts several years, patients re-entered the unit for multiple follow-up stays of variable duration; therefore, after the first discharge from the unit, patients had uncontrolled interactions with the community and other healthcare structures. Whether admitted for the first rehabilitation stay or for follow-ups, patients in the unit were hosted in non-isolated single rooms, with the full-time presence of a relative. General hygienic measures, including hand washing and clothing change, were regularly taught to parents, while further containment measures, such as prevention of contact and airborne contaminations, were only applied in cases of virulent or drug resistant bacteria. During each stay patients received neurological, cognitive and physical rehabilitation, comprising regular sessions with mechanical in/exsufflators to clear bronchial secretions. Patients were pharmacologically treated for spasticity, autonomic imbalances and pain; several antibiotic treatments were prescribed for relevant symptoms of respiratory, urinary, topical and central infections following medical judgment.

Data collection

Data regarding patient characteristics, medical interventions and complications were collected from clinical records. These comprised: gender, ABI aetiology, patient provenance, past neurosurgery, presence of paroxysmal sympathetic hyperactivity, presence of bedsores; scores relative to GOS, GCS, DRS scales; date of birth, injury, admission to rehabilitation, discharge and emersion from coma. Dates were elaborated to obtain the age of patients at ABI (date of ABI – date of birth), the time between ABI and admission to this rehabilitation unit (date of admission – date of ABI) and the duration of coma (date of emersion from coma – date of ABI; for patients who did not recover consciousness, duration of coma was levelled to the duration of follow-up); presence of central venous catheter, bladder catheter, ventricular-peritoneal shunt and feeding devices. Microbiological data were collected from antibiograms, as described in the next section. For sample stratification patients were considered as suffering from respiratory complications if any single criterion was met from the American CDC guideline for the diagnosis of ventilator-associated pneumonia [24]. Patients were assessed for the presence of respiratory symptoms daily during the rehabilitative stay and also during the follow-up visits. In this case, both the presence of acute symptoms and the presence of positive medical records contributed to the definition of symptoms. Patient consents regarding the use of anonymised data for research purposes were obtained. This study was notified to the local Ethics Committee and approved according to the Italian rules.

Microbiological screening and sampling

At admission all patients were screened to detect pathogens, while regular screenings were subsequently carried out which ranged from one per month in patients with no evident symptom and no antibiotic therapy, to one per week, in patients with symptoms and on-going antibiotic therapies. In order to perform the screenings, samples of tracheal secretions were collected by aspiration, using a sterile probe and following standard medical procedures. Samples were processed with Sputasol reagent (Oxoid) and cultured in the structure's microbiology laboratory using precast culture plates (bioMérieux). Cultures were identified and sensitivity to antibiotics was tested using the Vitek 2 automated platform (bioMérieux). Data were collected from antibiograms, regarding dates, bacterial loads and resistances to antibiotics. Colonisations were classified as acquired before rehabilitation (i.e. present at patient's admission), acquired during the first rehabilitation stay (i.e. acquired in the unit), or acquired during follow-up (i.e. acquired in healthcare or community/uncertain source). A patient was considered carrying a resistant bacterium if resistance was ever detected, thus including bacteria that became resistant or were replaced by resistant strains. Bacteria

were categorised for antibiotic-class resistances following criteria available from the literature [25].

Statistical methods

Patients were subdivided with respect to the presence of respiratory complications and differences between the two groups were tested with χ^2 (categorical variables) or analysis of variance (continuous variables). χ^2 tests were also applied to the numbers of patients who acquired colonisations during the different stages of healthcare. p values<0.05 were considered to be significant and higher p values were considered for possible trends. All statistical analyses were performed using MedCalc® (Version 12.7.8 MedCalc Software bvba).

Results

Risk factors for respiratory symptoms development

In the 2007–2013 time-frame, 65 patients carrying a tracheostomical tube were referred to our Institute for rehabilitation after ABI. Of these, 33 (50.8 %) developed respiratory symptoms. Table 1 describes the main clinical-demographical characteristics and possible risk factors of the patients under study. No significant relationship was found between any of these factors and the presence of respiratory complications in the cohort, although a non-significant difference was noted for several factors, between the symptomatic and asymptomatic groups. Symptomatic patients underwent acute neurosurgery after ABI more than asymptomatic ones (69.7 % vs. 46.2, p= 0.10). In symptomatic patients, the time between ABI and admission to rehabilitation was 50 % longer (110±108 vs. 72 ±50 days, p=0.10) and the duration of coma was 23 % lower (122±75 vs. 159±92 days, p=0.11).

Respiratory colonisation by bacterial strains

Most patients (91 %) had airways already colonised by bacteria at admission to our unit, a value reaching 94 % during the first rehabilitation stay and virtually 100 % during follow-up (1 patient only remaining persistently free of colonisations). In addition, during the first rehabilitation stay, 23 % of the patients acquired one additional respiratory colonisation and 26 % of them two or more. The numbers of patients carrying each bacterium were considered during three stages of healthcare, corresponding to the acute care preceding rehabilitation, the rehabilitation stay in the unit and finally the follow-up period in an uncontrolled setting, as long as patients still carried tracheostomical tubes (Table 2). *S. aureus* was the most frequently detected bacterium (in 73.8 % of the patients) and showed a statistically significant difference in its prevalence pattern; it was mostly found in patients before the first entry for rehabilitation (66.7 %, p<0.01) and patients who acquired it, did so predominantly in the unit (27.1 % vs. 6.3 %, p<0.01). *P. aeruginosa* was also frequent (in 72.3 % of the patients) and preferentially acquired before the first admission for rehabilitation (in 59.6 % of the cases p=0.14). By contrast, *K.pneumoniae*, detected in 32.3 % of the patients, was acquired significantly more during rehabilitation (81 %, p<0 .01) and in the unit than during follow-up (52.4 % vs. 28.6 %, p=0.02). *E. coli* and *A. baumannii*, affecting 20 % and 18.5 % of the patients, respectively, were acquired mostly during rehabilitation (*E. coli* in 76.9 % of the cases, p=0.08; *A. baumannii* 83.3 %, p=0.03), both inside and outside the unit. *S. marcescens* was rarely detected (in 12.3 % of the patients) and showed no significant prevalence pattern, while *S. capitis*, affecting only 9.2 % of the patients, was never recorded present before the first admission for rehabilitation (p=0.03) and developed essentially in the unit (in 83.3 % of the cases) (p=0.02). Less frequently diagnosed bacteria (data not shown) were *S. maltophilia*, *K. oxytoca*, *M. morganii*, other Enterobacteriaceae and other Staphylococci. *S. pneumoniae* was only detected in two patients, at one visit. No consistent seasonal pattern for colonisations was found. A graphical representation of the distribution of *S. aureus* and *P. aeruginosa* colonisations is available in Supplementary Fig. 1.

Antibiotic resistance of bacterial strains

Antibiotic resistance was frequently detected across bacteria from different patients (Table 3). *P. aeruginosa* was found to be resistant in 80.9 % of the affected patients, mostly to carbapenems and cephalosporins, followed by fluoroquinolones and aminoglicosides; 27.7 % of these patients carried multiresistant variants. *A. baumannii* proved to be resistant in 58.3 % of the patients with multiresistant strains in 33.3 % of the cases. MRSA was detected in 54.2 % of the patients carrying *S. aureus*; of these, only a minority resisted also to vancomycin (8.3 %). *S. capitis* was always found resistant to methicillin and never to vancomycin. *E. coli* was resistant in 53.8 % of the patients and ESBL-like activity had a 38.5 % prevalence; resistance to fluoroquinolones was more frequent (46.2 %) and one isolated case of carbapenems resistance was found. *K. pneumoniae* showed a similar profile and two KPC cases were detected. *S. marcescens* displayed resistance to carbapenems in one patient and ESBL-like activity in two.

Discussion

Respiratory colonisations and infections represent a relevant source of morbidity for patients who suffered ABI, both in the ICU and during the subsequent rehabilitation [22]. Care for

Table 1 Main demographic and clinical characteristics of the study population

Continuous variables		Asymptomatic patients (n=27) Mean ± SD	Symptomatic patients (n=33)	Statistical test	
				F	***p***
Duration of follow-up	Months	33±30	28±28	0.45	0.51
Age at ABI	Months	126±132	111±75	0.35	0.56
Time between ABI and admission to rehabilitation	Days	72±50	110±108	2.78	0.10
Duration of coma	Days	159±92	122±75	2.60	0.11
Colonising bacteria	Number	2.0±1.2	2.3±1.2	1.01	0.32
Acquired colonisations	Number	1.1±1.9	1.0±1.2	0.13	0.72
Categorical variables		Number of patients		χ^2	***p***
Gender	Female	10	14	0.03	0.87
	Male	17	19		
ABI aetiology	Anoxic-ischemic	12	10	2.06	0.36
	Traumatic	6	6		
	Other	9	17		
Provenance	ICU	15	19	0.44	0.80
	Neurosurgery	6	6		
	Other	4	7		
Neurosurgery (following ABI)	No	14	10	2.44	0.12
	Yes	12	23		
PSH	No	14	15	0.06	0.82
	Yes	13	18		
Bedsores	No	18	17	0.85	0.36
	Yes	9	16		
GCS	>8	0	1	0.01	0.94
	≤8	25	28		
GOS	2	25	25	3.21	0.20
	3	2	7		
	4	0	1		
DRS	7–21	1	5	0.99	0.32
	>21	25	28		
Central venous catheter	No	13	20	0.50	0.48
	Yes	14	13		
Bladder catheter	No	16	13	1.62	0.20
	Yes	11	20		
Ventriculo-peritoneal shunt	No	22	22	1.00	0.32
	Yes	5	11		
Feeding device	No	1	1	1.10	0.58
	NGT	5	10		
	PEG	21	22		

Five patients could not be included in the description and data were missing for the following categories. Provenance: 2 asymptomatic, 1 symptomatic; past neurosurgery: 1 asymptomatic; GCS: 2 asymptomatic, 4 symptomatic; DRS: 1 asymptomatic

ABI acquired brain injury, *PSH* paroxysmal sympathetic hyperactivity, *GCS* Glasgow coma scale, *GOS* Glasgow outcome score, *DRS* disability rating score, *ICU* intensive care unit, *NGT* naso-gastric tube, *PEG* percutaneous endoscopic gastrostomy

these patients is often complicated by antibiotic resistance, especially in countries where it occurs frequently [1]. All these factors have a significant clinical and economic impact in both short- and a long-term perspectives [23]. Thus, knowing the characteristics and relative burden of bacteria residing in a group of patients in one hospital unit may help identifying appropriate strategies to minimise their clinical impact. In terms of clinical variables and possible risk factors, data collected from our patients did not significantly associate with the emergence of respiratory symptoms; however, a trend of association for some of them was observed. In this respect it must be emphasised that the cohort of patients in this study is not large which affects the power of the study. The only medical procedure possibly associated with the presence of

Table 2 Prevalence of respiratory colonisations and corresponding spectrum of acquisition for the most frequently detected bacteria

Bacterium		*S. aureus*	*P. aeruginosa*	*K. pneumoniae*	*E. coli*	*A. baumannii*	*S. marcescens*	S. capitis
Affected patients (overall)	**N**	48	47	21	13	12	8	6
	% of patients	73.8	72.3	32.3	20.0	18.5	12.3	9.2
Acquired before rehabilitation	**N**	32	28	4	3	2	2	0
	% of patients	49.2	43.1	6.2	4.6	3.1	3.1	0
	% of affected	66.7	59.6	19.0	23.1	16.7	25.0	0
Acquired during the first rehabilitation stay	**N**	13	10	11	4	5	1	5
	% of patients	20.0	15.4	16.9	6.2	7.7	1.5	7.7
	% of affected	27.1	21.3	52.4	30.8	41.7	12.5	83.3
Acquired during follow-up	**N**	3	9	6	6	5	5	1
	% of patients	4.6	13.8	9.2	9.2	7.7	7.7	1.5
	% of affected	6.3	19.1	28.6	46.2	41.7	62.5	16.7
χ^2 test: acquired in the first rehabilitation stay vs. during follow-up	χ^2	6.84	0.28	5.35	*	*	*	*
	p	< 0.01	0.60	0.02	1.00	0.35	0.55	0.02
χ^2 test: acquired before vs. after beginning rehabilitation	χ^2	7.43	2.13	8.18	3.08	4.5	*	*
	p	< 0.01	0.14	< 0.01	0.08	0.03	0.27	0.03

Values are shown as numbers of patients and as percentages, of all patients (n=65) or of the affected patients

*Fisher's exact test performed instead of χ^2 due to low sample size

respiratory symptoms was neurosurgery, performed acutely after ABI, which had already been linked to an increased risk of respiratory infections in ICUs [13]. The time between ABI and rehabilitation was longer in symptomatic patients and may indicate a more severe clinical course in intensive care; this is consistent with previous work that associated longer mechanical ventilation in ICUs to a higher risk of ventilator-associated pneumonia [9]. An intriguing finding is that duration of coma was lower in symptomatic patients; as patients emerge from coma they get in closer contact with more relatives and friends, and also become eligible for advanced rehabilitation procedures, with operators that are not used to treating fragile patients. This represents a clinically relevant risk, directly related to the rehabilitation process. In this respect, the fact that rehabilitation can last for years and patients get in contact with other people in a non-controlled environment during this period, is indeed a limitation of this study. Some symptomatic cases could be caused by viral infections and, thus, not related to bacterial colonisation. These, however, were not investigated in the clinical setting we described. From the beginning of the rehabilitation to the end of follow-up the overall prevalence of respiratory colonisations increased only slightly. Involved bacteria were those typical of nosocomial respiratory infections [2], in terms of species and respective prevalence. *S. aureus* and *P. aeruginosa* showed very similar prevalence among patients (around three quarters), followed by *K. pneumoniae* with almost one third of the patients affected and *E. coli* with one fifth, while others were less represented. Importantly, more than one fourth of patients acquired more than one respiratory colonisation, a course completely different from the one commonly observed in ICUs [11]. We found interesting differences in the prevalence pattern of different species. *S. aureus* and *P. aeruginosa* colonisations mostly entered the rehabilitation unit from acute care settings, *i.e.* ICUs and neurosurgery units. Furthermore, the distribution of *S. aureus* showed a clear preference for protected nosocomial settings, as the number of newly colonised patients was maximal before rehabilitation, then decreased in the rehabilitation unit, and again decreased during the follow-up. This suggests two possible interpretations, first, that the role of physicians and nurses may be crucial for propagating *S. aureus*, and second, that as patients recover from TBI, acquisition of *S. aureus* becomes less probable. In a partially similar fashion, *P. aeruginosa* showed a trend for association with the period preceding rehabilitation, possibly indicating a tighter relation to patients' general severity. A different pattern was observed for *K. pneumoniae* and *S. capitis* that were acquired mostly during rehabilitation, with the first generally inside the unit, the second exclusively. This suggests an important influence of factors typical of rehabilitation, including intense interactions with healthcare professionals [26, 27] and relatives. While guidelines for preventing nosocomial infections are available to physicians and nurses [20, 21], no such measure is officially available for therapists, such as logopaedists and physiatrists; furthermore, parents may carry pathogens from patient to patient [17–19]. This attitude is currently dependent on personal expertise, and untrained operators or relatives could nullify the benefits of single rooms in reducing the nosocomial transmission of pathogens, as shown in ICUs [28, 29]. Finally, it should be

Table 3 Most frequently detected bacteria and related resistances

Bacteria and resistances	Patients	%
Pseudomonas aeruginosa	47	
Carbapenems	31	66.0
Cephalosporins	22	46.8
Fluoroquinolones	16	34.0
Aminoglicosides	13	27.7
Multiresistant[a]	13	27.7
Acinetobacter baumannii	12	
Carbapenems	3	25.0
Cephalosporins	6	50.0
Fluoroquinolones	5	41.7
Aminoglicosides	3	25.0
Multiresistant[a]	4	33.3
Staphylococcus aureus	48	
Methicillin	26	54.2
Vancomycin	4	8.3
Staphylococcus capitis	6	
Methicillin	6	100
Vancomycin	0	0
Escherichia coli	13	
ESBL-like	5	38.5
Carbapenems	1	7.7
Fluoroquinolones	6	46.2
Klebsiella pneumoniae	21	
ESBL-like	8	38.1
Carbapenems	2	9.5
Fluoroquinolones	9	42.9
Serratia marcescens	8	
ESBL-like	2	25.0
Carbapenems	1	12.5
Fluoroquinolones	1	12.5

[a] Multiresistance was defined as resistance to three or more classes of antibiotics [25]

emphasised that only symptomatic patients were receiving antibiotics during rehabilitation (data not shown) and this may possibly lead to more bacterial colonisations. Interestingly, *S. pneumoniae* was detected only twice in our cohort, at variance with other studies that reported higher prevalence in long-term tracheostomised patients [30]. The relative prevalence we found among species was in fact very similar to the one described in a recent review on nosocomial pneumonia [2]; possible explanations of discrepancies in the reported prevalence of *S. pneumoniae* may comprise, but are not limited to, different geographical locations (involving different provenance hospitals and environments) and treatment habits, both before and during rehabilitation.

In terms of resistance to antibiotics we found that *P. aeruginosa* was extensively resistant to carbapenems (two thirds of patients), and *S. aureus* resistant to methicillin in more than half of the patients, but uncommonly resistant to vancomycin (8.3 %). The highly prevalent resistance to fluoroquinolones may likely be related to the very high occurrence of urinary tract infections, and consequent antibiotic usage, in patients who suffered ABI (data not shown). Carbapenemase-producing strains were detected in two patients for *K. pneumoniae* and in one patient respectively for *E. coli* and *S. marcescens*, with no case of colonisation acquired in the unit. Such strains, currently emerging in southern Europe, entered the unit over the last two consecutive years and represent a warning bell for the future. As this resistance is easily acquired, special containment measures were enforced to prevent outbreaks [31], such as partial room isolation and whole unit screening, with success. Other bacteria were detected in numbers too small to allow specific comparison to large-scale studies. Of importance, data we report here are the first ones describing antibiotic resistances in a long-term ABI rehabilitation setting; available information to date was either in the form of aggregate data from ECDC [1] or from ICUs.

Overall, the picture of a paediatric rehabilitation unit we report on describes a setting where a balance must be constantly found, between the primary medical objective and related complications; rehabilitation itself is a risk factor for colonisation and infection, as social interaction and contact are encouraged, while isolation is not feasible. This is supported by the vast prevalence of bacterial colonisations that we described, which increased further during rehabilitation. However, it is possible to moderate the spreading of bacteria by applying adequate care measures on a flexible basis. Examples in the specific setting we described include the administration of antibiotics only to symptomatic patients, in order to minimise the development of resistances, and the adaptation of hygiene and containment levels to each patient's need. In order to implement these measures, training is regularly given to parents and operators (e.g. hand hygiene, clothing change and personal protection); furthermore, when multi-resistant bacteria are identified, additional care measures are implemented, such as protection from droplets and airborne contaminants, with attention to each peculiar pathogen [20, 21, 31]. Unfortunately compliance of operators from other units and parents to the suggested measures cannot be monitored. However, the clinical impact of respiratory colonisations was overall irrelevant; moreover, no patient needed to be transferred to primary care facilities for respiratory complications. Therefore, even if implemented measures are yet far from full efficiency, the chosen approaches proved to be valuable at a local level.

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