Differing Pathways of Lower Airway Colonization and Infection According to Mode of Ventilation (Endotracheal vs Tracheotomy)

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Objectives: To determine whether the pathogenesis of lower airway colonization and infection was endogenous (via the oropharynx) or exogenous (via the endotracheal tube or tracheotomy) during the 2 modes of ventilation in the same subset of children requiring long-term ventilation.

Design: Prospective, observational cohort study.

Setting: A pediatric intensive care unit and a respiratory ward.


Measurements and Main Results: Cultures were obtained simultaneously from the oropharynx and tracheobronchial tree on admission to the pediatric intensive care unit, at placement of the tracheotomy, and afterward twice weekly. Forty-five patients were studied. Lower airways were always sterile in 6 children, 39 children (87%) developed a total of 82 episodes of colonization, and 17 (38%) progressed to 25 episodes of infection. The number of infected children was halved once they had a tracheotomy (7 children [16%]). Of the 107 episodes of colonization and infection, 41 and 66 occurred during endotracheal ventilation and via a tracheotomy, respectively. Primary endogenous episodes of colonization and infection due to bacteria present in the admission flora in the pediatric intensive care unit were significantly more common with endotracheal ventilation than during ventilation via a tracheotomy (31/41 [76%] vs 36/66 [55%]; P = .03). Secondary endogenous and exogenous episodes of colonization and infection due to bacteria associated with the respiratory ward were significantly more frequent when ventilation was continued through a tracheotomy than during endotracheal ventilation (30/66 [45%] vs 10/41 [24%]; P = .02).

Conclusions: Surveillance samples allow the distinction between primary endogenous ("imported" bacteria) from secondary endogenous and exogenous ("nosocomial" microorganisms) colonization and infection. This classification permits the development of preventive strategies to control both endogenous and exogenous pathways.


The oropharyngeal flora has been compared with the flora of the lower airways in adult patients requiring ventilation endotracheally and subsequently via a tracheotomy. Longitudinal serial samples from the oropharynx and lower airways are required for that comparison. The 3 studies in adult patients with tracheotomies showed that the microorganisms isolated from the lower airways differed from the bacteria carried in the oropharynx. Variations in patient populations and the presence of different bacterial species, however, make it difficult to compare studies. Niederman et al, in a study of 14 endotracheally ventilated patients, reported that Pseudomonas species were found more often in the tracheobronchial tree than in the oropharynx. Pediatric studies using the design of obtaining cultures simultaneously from the oropharynx and tracheobronchial tree were lacking, our group embarked on a prospective observational cohort study in 45 children requiring long-term ventilation initially via an endotracheal tube and subse-
change of tracheotomy tube, were all done under strict protocols of hygiene and sterility.6

END POINTS

There was only 1 intervention: the change of mode of ventilation, initially endotracheally and subsequently via tracheotomy. The impact of the placement of a tracheotomy was evaluated by comparing the following factors for both ventilation modes: (1) the number of children who were colonized with potentially pathogenic microorganisms (PPMs) in the lower airways; (2) the number of episodes of colonization; (3) the number of children with infected lower airways; (4) the number of infection episodes; and (5) the number of episodes of primary endogenous, secondary endogenous, and exogenous colonization and infection.

SAMPLING

Surveillance samples of the oropharynx were obtained immediately on admission to the PICU before endotracheal ventilation and before the placement of the tracheotomy, and twice weekly afterward. The reason for taking these samples is to detect the carrier state of the potential pathogens that allow us to distinguish the endogenous from the exogenous pathway.

Diagnostic samples of lower airway secretions were taken once weekly, and on clinical indication, ie, tracheal aspirates that were turbid.

ANTIBIOTIC POLICY DURING THE STUDY

Systemic antibiotics were given only in case of infection. Infection was diagnosed on the basis of clinical signs of infection, including temperature greater than 38.5°C, leukocytosis with a white blood cell count greater than $12 \times 10^3/\mu L$, and elevated C-reactive protein level to greater than 15 µg/mL, combined with purulent tracheal aspirates yielding $10^6$ colony-forming units (CFU)/mL or more.7 All requirements had to be fulfilled for the diagnosis of infection. Tracheobronchitis was distinguished from pneumonia by the absence of chest radiographic changes. Infection due to gram-positive bacteria was, in general, treated with a first-generation cephalosporin, while a third-generation cephalosporin was given in children who developed a lower airway infection caused by AGNB. Infection in general was treated with a 3-day course of antibiotics, followed by clinical reexamination of the patient.

DEFINITIONS

The following definitions were used, in accordance with van Saene et al.3

1. **Carriage** or the carrier state existed when the same bacterial strain was isolated from at least 2 consecutive throat samples, in any concentration, during a period of at least 1 week.

2. **Colonization** of the lower airways was defined as the presence of a microorganism in the lower airways; the diagnostic sample yielded less than $10^6$ CFU/mL of diagnostic sample. The concentration of leukocytes in the lower airway secretions was, in general, few (+) or moderate (++), on a semiquantitative scale of +, ++, and +++ (many).

3. **Infection** of the lower airways was defined as a microbiologically proved diagnosis of systemic inflammation. The diagnostic sample obtained from the lower airways yielded greater than or equal to $10^6$ CFU/mL of sample, and there were many leukocytes in the lower airway secretions.

Tracheobronchitis was defined as follows: (a) purulent endotracheal aspirate (white blood cells +++), (b) fever ($\geq 38.5^\circ C$), and (c) purulent tracheal aspirate with a white blood cell count greater than $12 \times 10^3/\mu L$, and elevated C-reactive protein level to greater than 15 µg/mL, combined with purulent tracheal aspirates yielding $10^6$ colony-forming units (CFU)/mL or more.7 All requirements had to be fulfilled for the diagnosis of infection. Tracheobronchitis was distinguished from pneumonia by the absence of chest radiographic changes. Infection due to gram-positive bacteria was, in general, treated with a first-generation cephalosporin, while a third-generation cephalosporin was given in children who developed a lower airway infection caused by AGNB. Infection in general was treated with a 3-day course of antibiotics, followed by clinical reexamination of the patient.

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the percentages of episodes of both colonization and infec-
with 95% confidence intervals was used for the comparison of
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ber of children colonized and infected before and after trache-
Ashwell, England) was used for analysis of the data. The num-
infection of the lower airways.
caused secondary endogenous and exogenous colonization and
microorganisms were PICU and/or respiratory ward related and
or at the time of placement of a tracheotomy. Nosocomial mi-
were not present in the patients
in healthy people and are carried by individuals with both acute
progressive pulmonary infiltrate on chest radiograph for more than
criteria as above, combined with the presence of a new or pro-
gen lower airways caused
by a PPM isolated from the lower airway secretions, and car-
by the patient in the throat, at the time of admission to the PICU and/or tracheotomy.
5. Secondary endogenous colonization and infection was
defined as colonization and infection of the lower airways caused
by a PPM isolated from the tracheal aspirate, and not carried
in the throat at the time of admission to the PICU and/or tra-
chotomy, but appearing later.
6. Exogenous colonization and infection was defined as
colonization and infection of the lower airways caused by a PPM
isolated from the tracheal aspirate that was not previously car-
rried by the child in the throat at any time.
7. Indigenous flora were microorganisms, eg, viridans strep-
tococci, carried by healthy individuals at high concentrations,
 ie, 10^6 CFU/mL of saliva or more.
8. Community PPMs were PPMs carried by varying percentages
of healthy people, including Streptococcus pneumoniae, Hae-
mophilus influenzae, and Staphylococcus aureus. They are abnormal
in healthy people and are carried by individuals with both acute
and chronic underlying diseases.
9. Hospital PPMs included AGNB such as Klebsiella, En-
terobacter, Acinetobacter, Pseudomonas, and Stenotrophomonas
species, and methicillin-resistant S aureus. They are abnormal in
healthy people and are carried by individuals with both acute and
chronic underlying diseases.
10. Nosocomial microorganisms were microorganisms that
were not present in the patients’ admission flora to the PICU,
or at the time of placement of a tracheotomy. Nosocomial micro-
organisms were PICU and/or respiratory ward related and
causative secondary endogenous and exogenous colonization and
infection of the lower airways.

STATISTICAL ANALYSIS
A statistical package (Arcus QuickStat; StatsDirect Ltd, Ashwell, England) was used for analysis of the data. The num-
ber of children colonized and infected before and after trache-
otomy was analyzed by means of McNemar 2-tailed test after
Liddell. Proportions analysis using a 2-tailed exact method
with 95% confidence intervals was used for the comparison of
the percentages of episodes of both colonization and infec-
tion, during the pretracheotomy and posttracheotomy peri-
dods. The same analysis was used to compare the different
types of colonization and infection during the 2 modes of as-
sisted ventilation: primary endogenous, secondary endoge-
nous, and exogenous. Nosocomial colonization and infection
episodes accounted for only secondary endogenous and exog-
genous categories.

RESULTS

The 45 children had assisted ventilation for a median period of 12 days (95% confidence interval, 7-24 days; range, 0-103 days) in the pretracheotomy period, via an endotracheal tube, for a total of 916 days. Assisted me-
chanical ventilation continued after tracheotomy via a tracheotomy tube for a further total of 1559 days, with a median of 12 days (95% confidence interval, 2-28 days; range, 1-281 days) (Table 2).

Of the 45 children enrolled, 6 children who required
long-term ventilation had sterile lower airways through-
out the study period whether they were ventilated via an
endotracheal route or via a tracheotomy. Of the 39 chil-
ren (87%) who developed a total of 25 episodes of infec-
tion consisting of both tracheobronchitis and pneu-
monia. A total of 122 PPMs were involved in the 107 epi-

des of colonization and infection in 39 children.

Table 1. Patient Demographics

<table>
<thead>
<tr>
<th>Factor</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at time of enrollment, mo</td>
<td>Median (range) 6.4 (0-180)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>42.8 (65)</td>
</tr>
<tr>
<td>Sex, No. M/F</td>
<td>33/12</td>
</tr>
<tr>
<td>Diagnosis, No.</td>
<td>Neurologic disorder 12 (7 Cerebral palsy, 3 Guillain-Barré syndrome, 1 status epilepticus, 1 central apnea syndrome)</td>
</tr>
<tr>
<td>Pulmonary disorder</td>
<td>4 (2 Respiratory failure, 2 bronchopulmonary dysplasia)</td>
</tr>
<tr>
<td>Airway obstruction</td>
<td>26 (10 Supralaryngeal obstruction, 6 subglottic stenosis, 3 bilateral vocal cord palsy, 2 subglottic hemangioma, 1 laryngeal papilloma, 1 tracheomalacia, 1 thoracic inlet obstruction)</td>
</tr>
<tr>
<td>Myopathic disorder</td>
<td>1 (Congenital myotonic dystrophy)</td>
</tr>
<tr>
<td>Skeletal disorder</td>
<td>2 (Kyphoscoliosis surgical correction)</td>
</tr>
<tr>
<td>Term of tracheotomy, No.</td>
<td>30/15 permanent/short-term</td>
</tr>
</tbody>
</table>

Table 2. Ventilation Periods for the 2 Forms of Ventilation

<table>
<thead>
<tr>
<th></th>
<th>Endotracheal</th>
<th>Tracheotomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilation days</td>
<td>Median 12</td>
<td>12</td>
</tr>
<tr>
<td>Range</td>
<td>0-103</td>
<td>1-281</td>
</tr>
<tr>
<td>95% Confidence interval</td>
<td>7-24</td>
<td>2-28</td>
</tr>
<tr>
<td>Total No. of ventilation days</td>
<td>916</td>
<td>1559</td>
</tr>
</tbody>
</table>

IMPACT OF PLACEMENT OF TRACHEOTOMY

Both the number of children with colonized airways and
the number of episodes of colonization increased signifi-

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A total of 81 microorganisms were isolated from the lower airway secretions of children during 67 episodes of primary endogenous colonization and infection. Community PPMs, including *S pneumonieae*, *H influenzae*, *Moraxella catarrhali*, and *S aureus*, and AGNB (mainly *Pseudomonas aeruginosa*) were equally distributed among the endotracheal ventilation episodes and the episodes incurred during ventilation via a tracheotomy. There were a total of 40 episodes of secondary endogenous and exogenous colonization and infection, yielding 42 microorganisms. There were 10 episodes of secondary endogenous and exogenous development caused by 2 community bacteria (*S aureus in both*) and 8 AGNB (*P aeruginosa in 5*) during endotracheal ventilation. After the placement of a tracheotomy, 30 episodes of secondary endogenous and exogenous pathogenesis developed and were caused by 16 “community” bacteria (*S aureus in 15*), 14 AGNB (*P aeruginosa in 7*), and 2 methicillin-resistant *S aureus*.

### Table 3. Impact of Mode of Ventilation on the Number of Colonized/Infected Children and on the Number of Episodes of Colonization and Infection*

<table>
<thead>
<tr>
<th>No./Total No. (%)</th>
<th>Endotracheal</th>
<th>Tracheotomy</th>
<th><em>P</em> Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of colonized children</td>
<td>24/45 (53.3)</td>
<td>39/45 (86.7)</td>
<td>.001</td>
</tr>
<tr>
<td>No. of colonization episodes</td>
<td>26/82 (31.7)</td>
<td>56/82 (68.3)</td>
<td>.001</td>
</tr>
<tr>
<td>No. of infected children</td>
<td>13/45 (28.9)</td>
<td>7/45 (15.6)</td>
<td>.06†</td>
</tr>
<tr>
<td>No. of infection episodes</td>
<td>15/25 (60.0)</td>
<td>10/25 (40.0)</td>
<td>.07†</td>
</tr>
</tbody>
</table>

*During both ventilation periods combined, a total of 39 children became colonized in 82 episodes, and 17 children became infected in 25 episodes.

†Not significant.

Changing the mode of ventilation from endotracheal to a tracheotomy resulted in most children (87%) being colonized with bacteria in their lower airways. However, the number of infected children was halved once they had a tracheotomy (16%). Half of all episodes of colonization and infection during ventilation via a tracheotomy were caused by microorganisms carried in the throat at placement of the tracheotomy; the other half were due to bacteria acquired on the respiratory ward. This contrasts with the microbial distribution during endotracheal ventilation: 25% PICU acquired and 75% of episodes due to bacteria present in the admission flora.

Apparently, keeping the lower airways sterile in a child with a tracheotomy is impossible. The wound created by the tracheotomy represents an anatomic aberration. The presence of a plastic device always causes a low grade of mucocutaneous inflammation. The pH of the lower airway secretions is increased and the normal position of the trachea is altered. A tracheotomy bypasses the physiologic filter system limiting bacterial invasion into the lower airways. In the presence of microbial exposure, microorganisms show an affinity for the tracheotomy rather than the oropharynx as the site of acquisition. In addition, introduction of microorganisms directly into the lower airways via the tracheotomy as a result of repeated suctioning and manipulation of the trachea represents an important exogenous pathway. However, only 16% of the children with a tracheotomy had an infection, mainly because of a substantial improvement of their underlying medical condition. The infection rate was 30% when they required intensive care including endotracheal ventilation.

Most children left the PICU for the respiratory ward once they had a tracheotomy. Half of all colonization and infection episodes were due to bacteria that the patients did not carry in their throats but acquired on the respiratory unit, mainly via the tracheotomy, ie, exogenous pathway. In contrast, 75% of all episodes that developed during endotracheal ventilation were caused by bacteria not related to the PICU but present in the oropharyngeal admission flora.

We believe that the criterion of the oropharyngeal carrier state allowed us to unravel the different routes of colonization and infection due to the change of mode of ventilation. The traditional time cutoff of 48 hours used in the 4 adult studies1-4 failed to distinguish the 3 forms of colonization and infection of the lower airways. The distinction between primary endogenous colonization and infection due to bacteria not related to the PICU and respiratory ward from secondary endogenous and exogenous colonization and infection caused by PICU and respiratory ward bacteria has proved to be helpful in unraveling the impact of the change of mode of ventilation.

Attempts to control colonization and infection of the lower airways in patients with a tracheotomy date from the epidemic of poliomyelitis in 1952.10 Lepper et al10 used aerosols of polymyxin B sulfate in 72 patients to prevent
colonization and infection by *P. aeruginosa*. While *P. aeruginosa* was effectively controlled, the polymyxin aerosols failed in controlling *S. aureus* and *Proteus* species intrinsically resistant to the polymyxins. Fifty years later, Palmer et al.\(^1\) evaluated the efficacy of aerosolized aminoglycosides, gentamicin sulfate and amikacin sulfate, delivered via a nebulizer to the lower airways of 6 patients. The investigators reported the eradication of *Pseudomonas* species, *Serratia marcescens*, and *Enterobacter aerogenes*. In the 1970s, Klastersky et al.\(^1\) instilled, intratracheally, aminoglycosides alone and in combination with polymyxin B in neurosurgical patients with tracheotomies. In the first study, 85 patients were randomized to receive either endotracheal gentamicin or isotonic sodium chloride solution.\(^2\) Both colonization and infection due to AGNB were significantly reduced. The second study in 45 patients compared gentamicin vs paromomycin sulfate plus polymyxin B.\(^3\) Again, colonization and infection caused by AGNB were effectively controlled. Although the endotracheal administration of gentamicin was better tolerated than the combination, emergence of resistant AGNB was a more serious problem in the patients receiving monotherapy compared with the combination.

The methods of aerosolization and endotracheal instillation do not take into account the pathways of colonization and infection. There is consensus that microorganisms carried in the oropharynx migrate into the lower airways, ie, the endogenous route. We found that in children with tracheotomy the exogenous route, ie, microorganisms immediately introduced into the lower airways and bypassing the oropharynx, substantially contributed to the colonization and infection of the lower airways in patients with tracheotomies. Our 5-year study using longitudinal serial sampling of both the oropharynx and lower airways enabled us to distinguish the endogenous route from the exogenous route. In addition, in comparing the oropharyngeal flora on admission to the PICU and at the time of placement of a tracheotomy, primary carriage was distinguished from secondary carriage, ie, the oropharyngeal carrier state of microorganisms acquired during the stay on the PICU and respiratory ward.

This study using carriage for classifying colonization and infection in children with tracheotomies shows that about half the population acquired nosocomial, ie, respiratory ward–associated, microorganisms. The most recent meta-analysis of selective decontamination of the digestive tract in patients receiving mechanical ventila-

### Table 4. Impact of Mode of Ventilation on the 3 Pathways Causing Lower Airway Colonization/Infection\(^*\)

<table>
<thead>
<tr>
<th>No./Total No. (%)</th>
<th>Endotracheal</th>
<th>Tracheotomy</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endogenous colonization/infection</td>
<td>31/41 (75.6)</td>
<td>36/66 (54.5)</td>
<td>.03</td>
</tr>
<tr>
<td>Secondary endogenous colonization/infection</td>
<td>5/41 (12.2)</td>
<td>13/66 (19.7)</td>
<td>.3†</td>
</tr>
<tr>
<td>Exogenous colonization/infection</td>
<td>5/41 (12.2)</td>
<td>17/66 (25.8)</td>
<td>.09‡</td>
</tr>
<tr>
<td>Colonization/infection due to “nosocomial” microorganisms</td>
<td>10/41 (24.4)</td>
<td>30/66 (45.5)</td>
<td>.02</td>
</tr>
</tbody>
</table>

*There were 107 episodes of colonization/infection. “Nosocomial” denotes microorganisms acquired on the pediatric intensive care unit during endotracheal ventilation and microorganisms related to the respiratory ward during ventilation via a tracheotomy.*

†Not significant.

### Table 5. Microorganisms Causing Colonization/Infection\(^*\)

<table>
<thead>
<tr>
<th>Ventilation Mode</th>
<th>Endotracheal</th>
<th>Tracheotomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endogenous</td>
<td>31 Episodes</td>
<td>36 Episodes</td>
</tr>
<tr>
<td>Community PPM, 17</td>
<td>Community PPM, 26</td>
<td></td>
</tr>
<tr>
<td>AGNB, 21</td>
<td>AGNB, 17</td>
<td></td>
</tr>
<tr>
<td>Secondary endogenous</td>
<td>5 Episodes</td>
<td>13 Episodes</td>
</tr>
<tr>
<td>Community PPM, 2</td>
<td>Community PPM, 6</td>
<td></td>
</tr>
<tr>
<td>AGNB, 3</td>
<td>AGNB, 7</td>
<td></td>
</tr>
<tr>
<td>Exogenous</td>
<td>5 Episodes</td>
<td>17 Episodes</td>
</tr>
<tr>
<td>Community PPM, 0</td>
<td>Community PPM, 10</td>
<td></td>
</tr>
<tr>
<td>AGNB, 5</td>
<td>AGNB, 7</td>
<td></td>
</tr>
<tr>
<td>MRSA, 2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Community microorganisms included *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Staphylococcus aureus*, while aerobic gram-negative bacilli (AGNB) consisted of *Klebsiella*, *Pseudomonas aeruginosa*, and *Stenotrophomonas maltophilia*. PPM indicates potentially pathogenic microorganisms; MRSA, methicillin-resistant *S. aureus*. Some episodes were due to more than 1 microorganism.

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REFERENCES


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