TRENDS IN BACTERIAL PATHOGENS OF LOWER RESPIRATORY TRACT INFECTIONS IN CHILDREN

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REZUMAT

Introducere: Infecțiile tractului respirator inferior (ITRI) la copii sunt o problemă de sănătate publică, uneori cu o evoluție mortală. **Obiective:** Obiectivele acestui studiu au fost identificarea agenților patogeni responsabili de apariția ITRI la copii și determinarea sensibilității bacteriilor izolate la diferite antibiotice. **Material și metode:** S-au analizat foile de observație și antibiogramele copiilor (0-18 ani) internați în Spitalul de Copii Louis Turcanu, Timisoara, în perioada decembrie 2007 - martie 2009. Identificarea bacterilor s-a făcut din spută, aspirat traheal sau bronșic și lichid pleural, iar testarea sensibilității la antibiotice s-a realizat conform metodelor standard. **Rezultate:** S-au izolat 120 de tulpini bacteriene de la 69 de copii (43 băieți și 26 fete). Au fost 22 (31,88%) nou-născuți, 18 (26,08%) copii mici (<3 ani), iar restul copii (>3 ani) și adolescenți. S-au izolat 77,5% bacterii Gram negative, 20% bacterii Gram pozitive, iar restul tulpini Gram negative non-fermentative. Majoritatea bacteriilor Gram negative izolate au fost Pseudomonas aeruginosa (31,11%), Klebsiella pneumoniae (23,65%) și Enterobacter (12,90%), pe când Staphylococcus aureus (79,1%) și Stafilococcus Coagulazo-Negativ (12,5%) au fost cele mai frecvente bacterii Gram pozitive identificate. Colistin a fost cel mai eficient antibiotic asupra bacteriilor Gram negative, urmat de Levofloxacin și Imipenem. Toate tulpinile Gram pozitive au fost sensibile la Vancomicină și Linezolid. **Concluzii:** Diagnosticul bacteriologic și supravegherea rezistenței bacteriilor la antibiotice sunt indispensabile pentru un management eficient al ITRI.

Cuvinte cheie: infecții ale tractului respirator inferior, copii, sensibilitate la antibiotice

ABSTRACT

Introduction: Lower respiratory tract infections (LRTIs) in children remain an important public health problem, with potential life-threatening complications. **Objectives:** The objectives of this study were to identify bacterial pathogens of LRTIs in children and to study their antibiotic susceptibility. **Material and methods:** We reviewed the medical charts and microbiological reports of children (0-18 years) with LRTIs admitted to Louis Turcanu Children Emergency Hospital Timișoara from December 2007 to March 2009. Bacterial pathogens were isolated from sputum, tracheal or bronchial aspirates and pleural effusion, and their susceptibility was tested using standard bacteriological techniques. **Results:** One hundred twenty bacterial strains were isolated from 69 children (43 males and 26 females). There were 22 (31.88%) newborns, 18 (26.08%) toddlers, and the rest children and adolescents. Gram-negative bacteria represented 77.5% of isolates, 20% were Gram-positive and the rest were Non-fermenting Gram-negative strains. From Gram-negative strains, Pseudomonas aeruginosa (31.11%), Klebsiella pneumoniae (23.65%) and Enterobacter (12.90%) were the majority. Staphylococcus aureus (79.1%) and Coagulase negative Staphylococci (12.5%) were the dominants from Gram-positive cocci. Colistin was the most efficient antibiotic active on Gram-negative bacteria, followed by Levofloxacin and Imipenem. All Gram-positive isolates were susceptible to Vancomycin and Linezolid. **Conclusions:** Bacteriological diagnosis and antibiotic resistance surveillance are indispensable in the effective management of LRTIs.

Key Words: lower respiratory tract infections, children, antibiotic susceptibility

INTRODUCTION

Respiratory tract infections are one of the major public health problems, affecting both children and adults; it proves to be more serious when located in the lower respiratory tract. Just 5% of respiratory infections involve the lower respiratory tract, while the rest are limited to the upper respiratory tract.

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A variety of microorganisms can cause lower respiratory tract infections (LRTIs) in children, including bacteria, viruses, parasites, or fungi. Streptococcus pneumoniae is by far the most common bacterial cause of pneumonia in young children, while Mycoplasma pneumoniae and Chlamydia pneumoniae are frequently encountered among older children and adolescents. Group A streptococcus, Staphylococcus aureus, Haemophilus influenzae type B and Moraxella catarrhalis are less frequently seen.

In young children, most of LRTIs occur during the seasonal respiratory viral epidemics, generally caused by parainfluenza virus, influenza virus, adenovirus, metapneumovirus or respiratory syncytial virus. Viral pneumonia with cytomegalovirus and herpes simplex virus should be considered even without a suspicion of maternal history. Pneumocystis pneumonia is

generally limited to immunocompromised infants while Cryptococcus neoformans may be found in patients with HIV infections. In infants, LRTIs can be also caused by milk aspiration or by a foreign body.

In North America, the annual incidence of pneumonia in children <5 years is 30-45 cases per 1,000, while in children aged 5 years and older, the annual incidence is 16-22 cases per 1,000.[1]

Despite advances in the development of strategies to prevent LRTIs, the availability of newer, safer and more potent antimicrobials and effective vaccines, LRTIs continues to be a leading cause of morbidity and mortality for children of all age groups.[2]

Children with LRTIs may present life-threatening complications, such as massive parapneumonic or pleural effusion, sepsis, empyema, pericarditis with cardiac tamponade and venous thromboembolism.[3-7] Many of these deaths and complications can be prevented by simple inexpensive measures such as early diagnosis and institution of appropriate antimicrobial therapy.

The management of pneumonia mainly consists in eradicating the responsible culprits. Antibiotics are not needed to treat pneumonia of viral etiology; sometimes they are used due to the potential for secondary bacterial infection, or when one cannot discriminate between viruses and bacteria. Therefore, antibiotics are administered if the patient is positive for pneumonia. Therefore, empirical antibiotic treatment of LRTIs is important and instituted before the etiology is known, based on the pathogens that commonly cause pneumonia in the local area as per past medical records. This fact could lead to an increase in antibiotic resistance of the common LRTIs pathogens.

Nowadays, antimicrobial resistance is a recognized problem all over the world, due to excessive use of antibiotics and frequent prescription of antibiotics in outpatient settings for each and every minor health problem.[8]

In order to select the optimal antibiotics for the initiation of the empirical treatment, studies are critical to identify the current microorganisms found in the hospital and to determine their antibiotic resistance/ susceptibility.

OBJECTIVES

The main objectives of our study were to identify bacterial pathogens of LRTIs in children and to study their antibiotic susceptibility. This report is an update for clinicians in the various antibiotic alternatives available in the treatment of LRTIs in children.

MATERIALS AND METHODS

We analyzed the medical charts and microbiology data of children with LRTIs admitted in "Louis Turcanu" Children Emergency Hospital Timisoara from December 2007 to March 2009. Children (age 0-18 years) with clinical, laboratory and radiological signs of LRTIs were eligible for inclusions in our study. Three or more of the following signs and symptoms of LRTIs were found in children: fever, cough, tachypnea (increased respiratory rate >60breaths/ min in infants 0-2 months; >50/min in infants 2-12 months; >40/min in children 1-5 years and >20/min in children aged 5 years and older), signs of respiratory distress (wheezing, expiratory grunting, cyanosis, chest retraction or nasal flaring), refusal of feeding or inability to drink.[9] Leukocytosis with neutropenia/ netrophilia, raised erythrocyte sedimentation rate and C-reactive protein were indicative for bacterial infections.[10] Radiological diagnosis of LRTIs was based on the presence of either consolidated lobar infiltrate, or large pleural effusion, or parenchymal necrosis.

Positive cultures from sputum, tracheal aspirate or pleural effusion were of great diagnostic help. Blood agar medium and MacConkey agar medium were used, and then specimens were incubated at 37°C overnight. Specimens consisting in saliva were examined by microscopy, and Gram staining was then performed only if <10 squamous epithelial cells and >25 polymorphonuclear neutrophils (PMNs) per low power field were found.[11] The colony that grew on the medium was identified to species, using several tests: for Gram-positive cocci – catalase, coagulase and optochin; for Gram-negative rods – KIA, MIU and Citrate test. For sensitivity testing, we used the diffusion method on Mueller Hinton medium, with the following antibiotic disks: Ciprofloxacin, Levofloxacin, Ticarcillin/ Clavulanate, Amoxicillin/ Clavulanate, Trimethoprim/Sulfamethoxazole, Amikacin, Gentamicin, Meronem, Imipenem, Ceftriaxone, Ceftazidime, Colistin, Vancomycin, Linezolid, Oxacillin, Erythromycin, and Clindamicyn. For quality control, strains of Escherichia coli ATCC 25922, Pseudomonas aeruginosa ATCC 27853, Klebsiella pneumoniae ATCC 700603 and Staphylococcus aureus ATCC 25923 were used. Results reading and interpreting was done following the current NCCLS standards.

Selected demographic characteristics, such as the age and sex of the patients included in the study were also taken into consideration. Our study complied with the Declaration of Helsinki and has been approved by our institutional Ethics Committee.

RESULTS

From December 2007 to March 2009, 638 lower respiratory tract specimens (sputum, tracheal or bronchial aspirate and pleural effusion) were cultured in the Microbiology Department; 112 specimens were positive for different bacteria (10.52% sputum, 83.33% bronchial aspirates and 6.14% pleural effusions). A total of 120 bacterial strains were found in these 112 samples, and antibiotic sensitivity testing was performed.

These 120 isolates were collected from 69 children aged between newborn and adolescent. Out of these, 22 (31.88%) were newborns and preterm babies, 18 (26.08%) toddlers and the rest children and adolescents, as presented in Figure 1. Male children were prevalent (62.31% versus 37.68%).

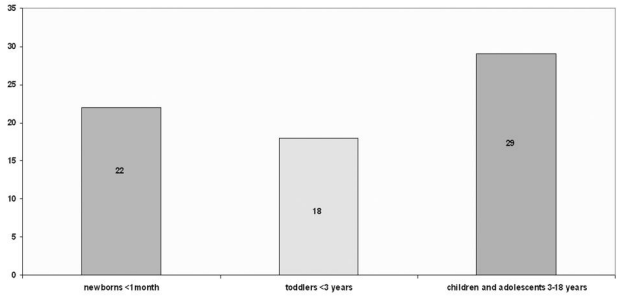

Figure 1. Distribution of children with LRTIs by age group.

Eight children (11.59%) had LRTIs with mixed bacterial etiology and one child had two bacteria and fungi (Klebsiella pneumoniae, Pseudomonas aeruginosa and Candida albicans) in his culture. From the rest, 14.16% of bacterial isolates were mixed with Candida albicans.

Gram-negative bacteria were more frequent (77.5%) than Gram-positive (20%). Non-fermenting Gram-negative bacilli (other than Pseudomonas species) represented 2.5%, as shown in Figure 2.

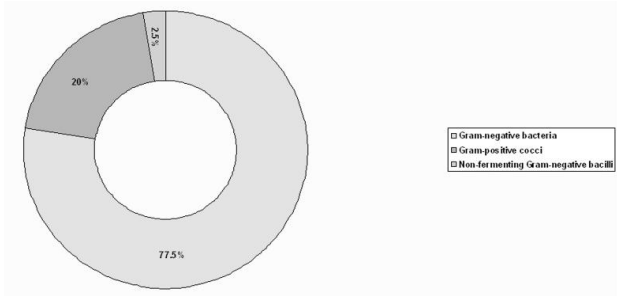

Figure 2. Distribution of culprits isolated in LRTIs.

Out of the Gram-negative, Pseudomonas aeruginosa was the most common culprit isolated (31.11%), followed by Klebsiella pneumoniae (23.65%), Enterobacter (12.90%) and E. coli (11.82%). Other rare bacteria encountered were Citrobacter, Stenotrophomonas maltophilia or Acinetobacter baumannii. Staphylococcus aureus was the dominant Gram-positive coccus (79.1%), followed by Coagulase negative Staphylococci (12.5%), while Enterococcus faecium and Streptococcus pneumoniae were identified in small percentage.

The majority of patients were admitted in Intensive Care Units. Some of them had underlying conditions, such as Duchene's muscular dystrophy, lung agenesia, congenital heart disease, hydrocephaly, meningitis, peritonitis, immunocompromised status or cerebral palsy and spastic tetraparesis. Two children had multiple episodes (four, respectively five) of LRTIs during the study period, because they had underlying conditions that can easily favor this disease: Duchene's muscular dystrophy and tracheotomy in one child, and Goldenhar disease (cleft lip, palate, and lung agenesia) in the other. A percentage of 23.18 of children had positive bacterial cultures due to life saving procedures, such as endotracheal intubation with mechanical ventilation or tracheotomy. Eight children (11.59%) developed pleural effusions, Staphylococcus aureus being the most often identified germ in these cultures (62.5%), followed by Streptococcus pneumoniae, Coagulase negative Staphylococci and Pseudomonas aeruginosa. Mortality rate in our study was 11.59%.

When analyzing the results of our study, it is easy to note that Gram-negative bacteria are sensitive to Colistin, followed by Fluoroquinolones and Carbapenems. In addition, there is a high resistance rate to the 3rd generation Cephalosporins. The antibiotic sensibility testing results are documented in Table 1.

Pseudomonas aeruginosa isolates were highly resistant to almost all antibiotics tested, Colistin being the only exception. Both Enterobacter and Klebsiella pneumoniae isolates were 100% susceptible to Levofloxacin, and E. coli was sensible to Colistin, Carbapenems, Levofloxacin and Amikacin. Citrobacter rods were resistant to Aminoglycosides and Cephalosporins, while Proteus isolates were sensible to Trimethoprim/Sulfamethoxazole, Aminoglycosides and Carbapenems. All Gram-positive bacteria were 100% sensible to Vancomycin and Linezolid, as presented in Table 2, while to Oxacillin and Erythromycin they were highly resistant.

Multidrug resistance bacteria (MDRB) were also found. Extended spectrum beta-lactamase (ESBL) producing strains were encountered in E. coli and Klebsiella pneumoniae isolates, and phenotypes resistant to Carbapenems were found in Pseudomonas aeruginosa and Acinetobacter baumannii strains,

Table 1. Antimicrobial sensibility among Gram-negative strains isolated from lower respiratory tract specimens.

Bacteria isolates (number)	Cip	Lev	Tzp	Bis	Ak	F	Ro	Mer	Imp	Co
Pseudomonas aeruginosa (29)	33.33%	27.27%	27.27%	28.57%	13.04%	18.18%	18.18%	14.28%	31.81%	76.92%
Klebsiella pneumoniae (22)	82.35%	100%	50%	50%	58.82%	38.09%	21.42%	80%	80%	30.76%
Enterobacter (12)	83.33%	100%	55.55%	62.50%	77.77%	45.45%	50%	77.77%	75%	75%
E. coli (11)	66.67%	80%	50%	36.36%	70%	44.45%	50%	83.33%	100%	100%
Stenotrophomonas maltophilia (10)	0%	80%	0%	100%	0%	0%	0%	0%	0%	0%
Acinetobacter Baumannii (4)	50%	75%	25%	50%	25%	25%	25%	25%	25%	100%
Citrobacter (2)	50%	50%	0%	0%	0%	0%	0%	100%	100%	100%
Proteus (1)	0%	0%	0%	100%	100%	0%	0%	100%	100%	100%
TOTAL (91)	**65.5%**	**72.6%**	**33.82%**	**69.44%**	**40.50%**	**27.58%**	**23.75%**	**56.96%**	**71.47%**	**87.27%**

(Cip-Ciprofloxacin, Lev-Levofloxacin, Tzp-Ticarcillin/Clavulanate, Ak-Amikacin, Bis-Trimethoprim/Sulfamethoxazole, Ro-Ceftriaxone, F-Ceftazidime, Mer-Meronem, Imp-Imipenem, Co-Colistin)

Table 2. Antimicrobial sensibility among Gram-positive strains isolated from lower respiratory tract specimens.

Bacteria isolates (number)	Lev	Aug	E	Da	Ox	Bis	Gen	Ro	Va	Lzd
Staphylococcus aureus (19)	60%	47.36%	31.25%	76.72%	58.82%	70%	70.58%	56.25%	72.72%	100%
Co N Staphylococci (4)	50%	75%	25%	75%	50%	25%	50%	25%	75%	100%
Streptococcus pneumoniae (1)	100%	0%	100%	100%	100%	0%	0%	0%	100%	100%
Enterococcus faecium (1)	100%	0%	0%	0%	100%	0%	0%	0%	100%	100%
TOTAL (25)	**64.28%**	**62.5%**	**38.09%**	**70.58%**	**57.14%**	**71.48%**	**73.68%**	**52.63%**	**100%**	**100%**

(Lev-Levofloxacin, Aug-Amoxicillin/Clavulanate, E-Erythromycin, Da-Clindamicyn, Ox- Oxacillin, Bis-Trimethoprim/Sulfamethoxazole, Gen-Gentamicin, Ro-Ceftriaxone, Va-Vancomycin, Lzd-Linezolid Co N Staphylococci-Coagulase negative Staphylococci)

while Stenotrophomonas maltophilia was resistant to Fluoroquinolones, Cephalosporins and Aminoglycosides. No Methicillin-resistant Staphylococcus aureus and Coagulase negative Staphylococci or Vancomycin-resistant Enterococcus were present in our study group.

DISCUSSIONS

In the medical literature it is stated that Gram-positive bacteria are the major culprits causing LRTIs in children.[12] Streptococcus pneumoniae continues to be a major threat and an important cause of invasive pneumonia in children less then 2 years.[13] Cases of highly lethal necrotizing pneumonia in young immunocompetent patients caused by Panton-Valentine leukocidin-producing Staphylococcus aureus (a citotoxin which increases the virulence of S. aureus) have been reported all over the world.[14,15]

Our results pointed out only a small percentage of Gram-positive bacteria, which caused pneumonia with less complications and no mortality, while Gram-negative bacteria were most often isolated, almost ¼ of them being associated with life saving maneuvers. Pseudomonas aeruginosa was the most frequent isolate, and not Streptococcus pneumoniae, Haemophilus influenzae, or atypical bacteria as documented in the medical literature. Most serious cases were younger than 3 years, and males were predominant. Similar results were found in other medical reports.[16]

The isolation of MDRB is an increasing phenomenon observed in different hospitals all over the world. In recent years, strains of Acinetobacter baumannii and Pseudomonas aeruginosa causing LRTIs in children became resistant to nearly all classes of drugs, including Carbapenems.[17,18] Colistin appears as an appropriate therapeutic alternative. Stenotrophomonas maltophilia is resistant to most of the available antibiotics such as β-lactam, Quinolones and Aminoglycosides. In our study, we found S. maltophilia to be 100% sensible to Trimethoprim/Sulfamethoxazole and highly sensible to Levofloxacin, similar to other study.[19] The presence of E. coli and Klebsiella pneumoniae resistant to 3rd and 4th generations of Cephalosporins and Aztreonam (ESBL producing strains), can be explained through the frequent use of Cephalosporins for both prophylactic and therapeutic treatment in our hospital. This fact may have exerted selective pressures leading to the emergence of MDR strains.[20]

Further, discussing about treatment, what we can observe from our study is that Colistin, Carbapenems

or Fluoroquinolones can be used as first choice empirical treatment of LRTIs in children. Colistin was found to be the most effective drug against all types of Gram-negative bacteria, followed by Levofloxacin and Imipenem. Clinical studies showed the efficacy of inhaled Colistin in treating LRTIs caused by MDR bacteria.[21,22] There is a great deal of evidence suggesting that Levofloxacin has low resistance rate, good activity levels, high respiratory penetration and is well tolerated, with good adherence.[23] It is particularly well suited for shorter courses of therapy at higher doses.[24] Previous studies already showed the efficiency of Imipenem in the treatment of LRTIs in children, alone or in association with other antibiotics (Linezolid or Ciprofloxacin).[25,26] Vancomycin and Linezolid were the drugs of choice, fully efficient, against Gram-positive bacteria. Hence, these drugs should be spared for serious cases, to avoid MDR bacteria. After identifying the etiological agent, specific antibiotics should be prescribed according to the antibiotic sensibility testing reports.

CONCLUSIONS

1. LRTIs still prevails to be a major health threat in children of all ages.

2. Our study totally contradicted the assertion that Gram-positive cocci are the dominant cause of LRTIs, as we found a majority of Gram-negative bacteria causing LRTIs in our group. Epidemiological studies should be performed more often, in order to find out the changes of culprits responsible for LRTIs in a specific area.

3. Increasing multidrug resistance of Gram-negative bacteria, in particular Pseudomonas aeruginosa, Acinetobacter baumannii and Klebsiella pneumoniae, explains the reappraisal of the clinical use of Colistin, an antibiotic discovered more than 50 years ago. Carbapenems and Fluoroquinolones are other options. Vancomycin and Linezolid are the best choice for treating Gram-positive infections.

4. Parental awareness and support can further help in preventing heath problems related to aspiration syndromes of liquids, foods and foreign bodies. Vaccinations and avoidance of community gatherings can further help decrease the incidence of LRTIs at the time of seasonal epidemics. Family physicians should be cautious against prescribing antibiotics unnecessarily. Hospital based antibiotic usage should further be limited to special cases, in order to avoid multidrug resistant strains in the future.

5. A little awareness, joint efforts and precautions can help us all tremendously to secure a healthy future.

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