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Use of Soluble Triggering Receptor Expressed on Myeloid Cells-1 (sTREM-1), Midregional Proadrenomedullin (MR-proADM) and Midregional Proatrial Natriuretic Peptide (MR-proANP) for Identification of Etiology and Assessment of Severity of Community-Acquired Pneumonia (CAP) in Children

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Background

Knowledge of etiology and severity of disease is essential in order to guide treatment decisions in patients with CAP. Signs and symptoms, radiological findings and routine laboratory tests are poorly effective in these aims. Data collected in adults suggest that sTREM-1, MR-proADM, and MR-proANP evaluation might be effective in defining etiology and severity of CAP.
This study analyzed the role of these biomarkers in children.

Materials and Methods

Healthy children 4 months-14 years old, consecutively hospitalized for clinical signs suggestive of CAP, (radiographically confirmed CAP) were enrolled. According to World Health Organization criteria, CAP were classified as alveolar or non-alveolar CAP.
From each enrolled child a blood sample and a nasopharyngeal swab were obtained. On blood, white blood cell (WBC) count, percentage of neutrophils, C-reactive Protein (CRP), procalcitonin (PCT), sTREM-1, MR-proANP and MR-proADM serum levels were evaluated.
WBC counts, neutrophil percentage and serum CRP levels were determined by the central laboratory of the hospital using routine methods. sTREM-1 concentration were measured using a commercial ELISA method (IQ Products). MR-proADM, MR-proANP and PCT levels were measured by a commercial automated immunofluorescent assay (BR.A.H.M.S).
From nasopharyngeal samples RNA/DNA was extracted (NucliSens EasyMAG automated extraction system) and used for the identification of respiratory viruses (Luminex xTAG respiratory virus panel fast assay), *Streptococcus pneumoniae* (*S.pn*; Real-Time PCR) and *Mycoplasma pneumoniae* (*M.pn;* nested-PCR). Radiological findings were coupled with results of microbiological results in order to identify the subjects with probable bacterial CAP (PB) or probable viral (PV) origin. PB CAP was defined by detection of: 1) *S.pn* and *M.pn* in the blood with chest radiograph indicative of any type of CAP, 2) a nasopharyngeal swab positive for *S.pn* associated with alveolar CAP, 3) a nasopharyngeal swab positive for *M.pn* associated with any type of CAP.
PV CAP was diagnosed in the presence of a nasopharyngeal swab positive for one or more respiratory viruses associated with non alveolar CAP.
Cases that could not be included in these groups were considered undetermined. Criteria used by the British Thoracic Society were used to establish severity of any CAP episode.
Comparison between groups (PB vs PV and severe vs non-severe CAP) were performed with conventional statistical methods.
Diagnostic performance of the biomarkers for identification of probable etiology or severity of CAP were evaluated with Receiver Operating Characteristic (ROC) curves and the area under ROC curve (AUC). The best cut-off values for different biomarkers were obtained based on the highest sensitivity and specificity through the roctab function in STATA.

Results

A total of 433 children were enrolled. CAP was ascribed to bacteria in 235 subjects (54.3%) and to one or more viruses in 111 cases (25.6%). In 87 children (20.1%) the etiology of the disease was undetermined.
S.pn and *M.pn* were considered the probable etiologic agents in 195 (83%) and in 40 (17%) PB cases, respectively. Among PV CAP, *Respiratory Syncytial Virus* (*RSV*) and *Rhinovirus* (*RV*) were detected as single pathogens in 52 (46.8%) and 12 (10.8%) children respectively. In the remaining cases (47, 42.4%) co-infection between these viruses and other viral agents were found (Fig.1). A total of 312 (72.2%) children had severe disease: among them 57%, 25% and 18% had a PB, PV or an undetermined infection respectively (Fig. 2).The levels of biomarkers evaluated according to infectious status are reported in Tab. 1. Positive and negative predictive values for each biomarkers were calculated. Regarding severity, the best results were obtained when PCT and MR-proANP were evaluated (Fig. 3). CRP and PCT had the best performances for both PB and PV CAP identification (Fig. 4).
However, all of biomarkers have low AUC values.

Fig. 1: Etiologic agent in Probable Bacterial or Viral CAP

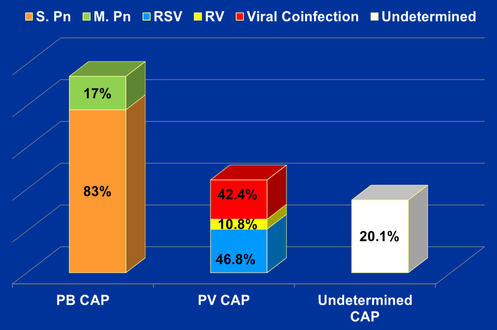
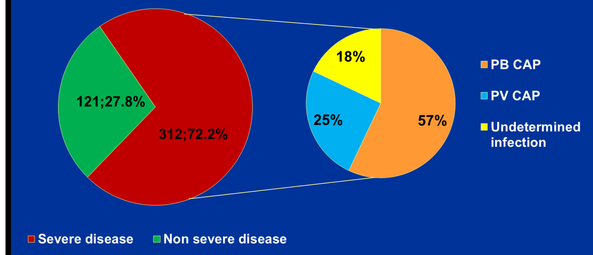


Fig. 2: Severity of CAP



Tab. 1: Level of biomarkers according to infectious status

Laboratory data	All subjects N=433 Mean ± SD (n)	Probable bacterial N=235 Mean ± SD (n)	Probable viral N=111 Mean ± SD (n)	Undetermined N=87 Mean ± SD (n)
WBC (cells/μL)	14213 ±8570 (428)	14776 ± 9104 (232)	12523 ± 6436 (111)	14886 ± 9279 (85)
CRP, mg/L	16.7 ± 42.6 (426)	21.3 ± 48.1(232)	8.0 ± 30.4 (110)	15.4 ± 38.7 (84)
Neutrophils, %	61.2 ± 20.7 (413)	63.6 ± 20.7 (222)	56.6 ± 19.7 (109)	60.7 ± 21.2 (82)
PCT, ng/mL	4.1 ± 13.9 (265)	6.1 ± 17.0 (132)	1.1 ± 3.4 (78)	3.5 ± 14.4 (55)
sTREM-1, pg/mL	95.7 ± 186.8 (405)	101.2 ± 193.1 (214)	82.5 ± 190.4 (108)	98.8 ± 165.7 (83)
MR-proANP, pmol/L	55.0 ± 48.6 (408)	53.0 ± 44.3 (222)	57.9 ± 56.2 (106)	56.8 ± 49.5 (80)
MR-proADM, nmol/L	0.44 ± 0.71 (410)	0.50 ± 0.94 (223)	0.37 ± 0.16 (106)	0.35 ± 0.17 (81)

Fig. 3: Diagnostic performance of biomarkers to predict severity of disease

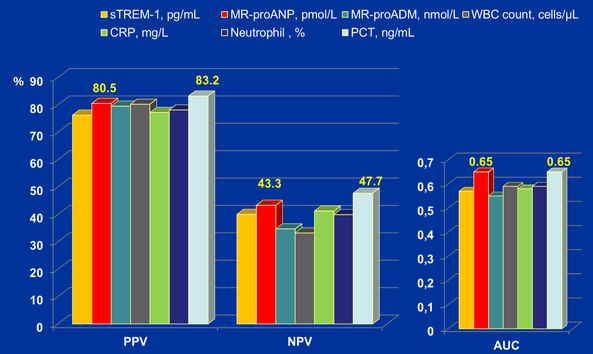
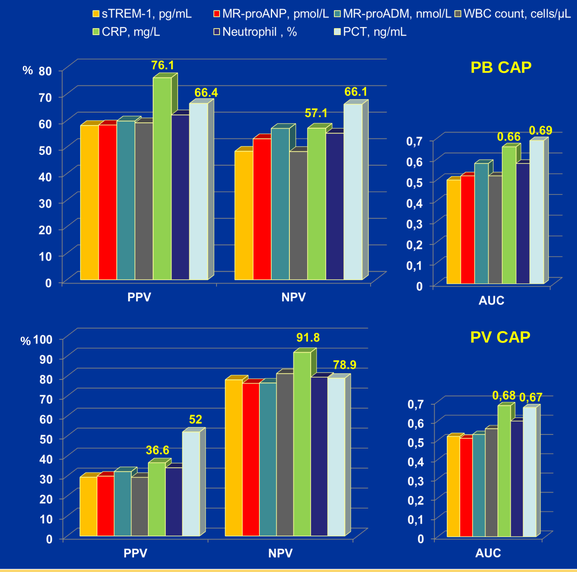


Fig. 4: Diagnostic performance of biomarkers according to infectious status



Conclusion

This study indicates that in children with CAP, sTREM-1, MR-proANP, and MR-proADM blood levels have poor abilities to differentiate bacterial from viral diseases or to identify severe cases, highlighting that PCT maintains the main role at this regard.