

Diagnostic Value of Mid-regional Pro-adrenomedullin (MR-proADM) as a Biomarker of Invasive Bacterial Infection in Children: A Systematic Review.

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Abstract

Background

In children differentiating between the early stages of an invasive bacterial infection (IBI) and a benign self-limiting viral infection remains clinically challenging. This often leads to an over-use of antimicrobial drugs with resultant antimicrobial resistance due to the concern of not detecting a deteriorating child. Hence research into novel biomarkers for the early identification of IBI in children is of increasing interest. A more timely diagnosis through more accurate biomarkers may lead to improved clinical outcomes for children and reduced antimicrobial resistance. Mid-regional pro-adrenomedullin (MR-proADM) is a biomarker that is found at elevated levels in patients with IBI compared with those with viral infections. The aim of this systematic review was to determine the diagnostic accuracy of MR-proADM at identifying children with IBI.

Methods

We searched MEDLINE, Embase, Web of Science and Scopus from 1980 to the present day for all human clinical trials involving children that report the test accuracy of MR-proADM. Eligibility was assessed by screening titles and abstracts of articles found during the search process. This was then followed by full-text assessment and data extraction. The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool was used to assess the methodological quality of identified studies. The following test characteristics were extracted into 2 × 2 tables for all included studies: true positives, false positives, true negatives, and false negatives.

Results

A total of 501 articles were initially identified. After the removal of duplicates and abstract screening 11 texts were fully reviewed. 4 studies (totaling 1404 patients) were able to be included in the systematic analysis. Only one study was of a high quality and that study accounted for the vast majority of patients. A single study reported the diagnostic accuracy of MR-proADM for invasive bacterial infection reporting an Area under the Curve of 0.69. The paucity of available studies made meta-analysis and studies of heterogeneity impossible.

Conclusion

There is a paucity of research regarding the diagnostic accuracy of MR-proADM in the diagnosis of invasive bacterial infections in children. Initial results would suggest that MR-proADM testing alone is poor at identifying IBI in young children. It remains unclear if MR-proADM performs differently in older children or in children with signs and symptoms of IBI.

Trial registration

PROSPERO CRD42018096295

Background

Invasive bacterial infections (IBI) are defined as the identification of pathogenic bacteria from a sterile fluid or body tissue by either culture or polymerase chain reaction (PCR) techniques. IBIs are the leading cause of neonatal and paediatric morbidity and mortality [1]. As many as one in three neonatal deaths globally are attributed sepsis and meningitis [2,3]

The early diagnosis of IBI is favourable but represents a significant clinical challenge. A febrile illness is the most common reason for a child to present to hospital [4]. Most children will have a self-limiting viral infection [5], however some children presenting will have a serious IBI that is potentially life-threatening [5]. Often to aide in the diagnosis of IBI children undergo additional testing including biomarkers of infection [4]. These biomarkers are used to determine between a bacterial illness which may require antibiotics and a viral illness which doesn't require treatment. They can also help the clinician in deciding how long to continue antibiotics and to monitor response to antimicrobial therapy. Existing biomarkers used in clinical practice (Procalcitonin and C-reactive protein) have poor accuracy in the early stages of illness in differentiating between IBI and a self-limiting viral infections. This often leads to inappropriate administration of antibiotics in some children and missing potential serious illness in others. A novel biomarker that has a higher degree of accuracy in the early stages of illness could help in this clinical dilemma.

Mid-regional pro-adrenomedullin (MR-proADM) is related to the peptide adrenomedullin (ADM) which was first discovered in 1993 [6]. ADM has been found to be involved in various physiological processes. It appears to be a circulating hormone with ranging paracrine and biological activities including a potent vasodilatory effect; the normal range for ADM in healthy individuals is 2 to 4 pmol/l [7]. ADM levels appear to rise early in IBI [8]. This rise in ADM levels appears to be enhanced in the presence of hypoxia and cytokines such as interleukin-1, Interferon- γ and tumour necrosis factor [8-11]. Levels of ADM have been reported to rise less dramatically in viral infections and appear to correlate with the severity of IBI [12-15].

Adrenomedullin is difficult to measure; it is an unstable molecule which rapidly binds to receptors and has a short half-life [15]. MR-proADM is a 48 amino acid fragment of ADM produced during ADM synthesis at a ratio of 1:1. It appears to be biologically inactive but has a longer half-life than ADM and is easier to measure due to its stability in human fluids [12]. These features make MR-proADM an exciting prospect as a new biomarker for IBI in children.

The vast majority of research conducted on MR-proADM has been in adult populations. Hence a systematic review of the paediatric literature is required to understand the value of MR-proADM in diagnosing potential IBI in children. A review would be useful to assess available data reporting levels of MR-proADM in both physiological and pathological states and if these vary across the different age ranges in children (neonate to adolescent). If MR-proADM were to demonstrate a high diagnostic accuracy for identifying early IBI in the paediatric population then it could have a role in detecting those children with IBI that

require immediate therapy from those with a limited viral illness. This could help reduce the amount of children receiving inappropriate antimicrobial therapy and be part of a wider effort to reduce antimicrobial resistance. MR-proADM could also play a role in monitoring response to therapy or even identifying children with a poor prognosis that may require intensive care.

The objective of this systematic review was to determine the diagnostic accuracy of MR-proADM at detecting IBI in children under 18 years of age. The secondary objective was whether we could determine, via subgroup analyses, if the diagnostic accuracy of MR-proADM differs between newborns, neonates, infants, children and adolescents and if different optimal cutoff values exist between different age groups. These groups were chosen as they reflect the varying host immune responses and physiology in these different age groups.

Methods

Protocol and registration

Prior to conducting this systematic review a protocol was produced in adherence to the standards of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and registered prospectively on the 30/05/2018 with the International Prospective Register of Systematic Reviews (PROSPERO) - registration number CRD42018096295. The protocol underwent external peer review and was published in 2020 [16].

Eligibility criteria

Studies reporting the performance of MR-proADM in assessing children (< 18 years of age) for potential IBI were considered. Study designs considered included case-control studies, cohort studies and randomised control trials. MR-proADM was the index test considered. Testing for MR-proADM could be performed on any bodily fluid (including but not limited to blood/urine/cerebrospinal fluid) using either commercially and non-commercially available tests. The reference standard was positive blood or cerebrospinal fluid culture or PCR for pathogenic bacterial infection taken at the same time as the index test.

Information sources

An electronic search strategy was developed in collaboration with the Queen's University Belfast Medical Librarian (RF). MEDLINE, Embase, Web of Science, Scopus and the Cochrane Library inclusive of Cochrane Controlled Trials Register were searched from inception to 15th of June 2020. The Medline search strategy is attached in the supplementary material. There were no language restrictions. A targeted grey literature search was also conducted by review of clinical trials databases, conference abstracts, internet searches and review articles. Mendeley electronic reference manager was used for article retrieval.

Study selection and data extraction

Two reviewers (TW, MC) independently screened all abstracts and titles against inclusion criteria and assessed full text publications for eligibility. The same two reviewers independently judged study quality using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool [17]. Disagreements were resolved by consensus or arbitration by a third party (JMK). Using a pre-piloted data extraction tool (supplementary material), two reviewers (MC, JMK) independently extracted the following information:

- Study characteristics: author, year of publication, country, design, sample size, clinical setting, number studied, number of drop-outs with reason, and funding source.
- Population characteristics: inclusion/exclusion criteria; patient demographics
- MR-proADM Testing: timing of sampling; method of sampling
- Gold standard: Real-time PCR (e.g. TaqMan® PCR) or sterile site bacterial culture (i.e blood/cerebrospinal fluid)
- Outcomes: True positives, false positives, true negatives, and false negatives were extracted to construct a diagnostic contingency (2-by-2) table.

Where data is unavailable or incomplete the authors were contacted and asked for additional data and/or clarification of results.

Analysis

Statistical analysis and data synthesis were performed by TW and MC. MR-proADM test result data were compared to the reference test. The true positive, true negative, false positive and false negative rate were recorded and used to create a 2 × 2 tables where possible. From these tables inferred statistics were calculated including sensitivity and specificity with 95% confidence intervals. Meta-analysis to provide pooled sensitivity and specificity data were not performed due to the small number of studies available. Similarly studies of heterogeneity and sub-group analysis were not possible. All analysis was performed using Review Manager (RevMan) Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Results

Study selection

A total of 501 records were identified: 501 records from the electronic databases and 0 additional studies from the grey literature. After removal of duplicates, 334 studies were screened, and 323 studies excluded based on the title/abstract. All of the 323 studies screened and excluded were not relevant to the systematic review. There were 11 full text articles that underwent full review, and six studies were eligible for inclusion in the final systematic review [18–28]. Of the five excluded studies four were excluded because the index test was Adrenomedullin and not MR-proADM and one study was excluded because it only reported the differences in cord blood concentrations of MR-proADM in newborns with and without risk factors for infection [24–28]. Two of the six eligible studies reported on adult and paediatric data [22, 23]. The authors were contacted for any paediatric specific data, but they did not respond [22, 23]. The results of the search with exclusions are summarised in the flow diagram below (Fig. 1).

Study characteristics and risk of bias

Four studies including 1404 patients aged between day one of life and 12 years were included in the final systematic review [18–21]. One study was a prospective cohort [21] study and the other three studies were all case-control studies [18–20]. The single prospective cohort study was the largest (n = 1077) and the only one to assess the diagnostic test accuracy of MR-proADM for predicting invasive bacterial infection [21]. The three smaller case-control studies (combined n = 331) used differing definitions of sepsis as their reference standards [18–20]. These characteristics are summarised in Table 1. The methodological quality of the studies was judged using the QUADAS2 tool. Only the study by Benito et al was deemed to be applicable and at a low risk of bias [21]. The three case-control studies were all deemed to be a high risk of bias and poorly applicable to the review question (Fig. 2) [18–20].

Table 1
Study characteristics for included studies

Author	Year Published	Number of Patients	Country	Design	Clinical Setting	Funding	Dropouts	Inclusion Criteria	Exclusion Criteria	Age Range	Timing of sampling
Benito	2013	1077	Spain	Prospective cohort study	Paediatric ED	Industry	42	Fever without source	Focal infection Prior antibiotic therapy Immunodeficiency	1 to 36 months of age	Prior to antibiotic
Hagag	2010	60	Egypt	Case-control	Neonatal Intensive Care	None declared	0	20 "Mild Sepsis" 20 "Severe Sepsis" 20 "Controls"	None reported	New-borns	Prior to antibiotic
Lan	2019	139	China	Case-control	Intensive Care	State funded	0	94 "Sepsis" 25 "SIRS" 20 "Controls"	Severe chronic disease Diabetes Specific medications Burns Myocardial infarction Heart failure Rheumatic disease Death within 24 hours of admission Incomplete data sets	6 to 12 years of age	Within one hour of admission to intensive care
Oncel	2012	128	Spain	Case-control	Neonatal Intensive Care	No declared	4	31 "Proven Sepsis" 45 "Clinical Sepsis" 52 "Controls"	Maternal heart failure or preeclampsia Intracranial bleed	New-borns	Within 6 hours of diagnosis of sepsis

Results of individual studies

Only the study by Benito et al (n = 1077) provided data directly assessing the diagnostic test accuracy of MR-proADM for the identification of invasive bacterial infection in children [21]. They prospectively assessed 1077 consecutive children under three years of age with fever without source. They reported

data on 1035 children with 16 confirmed invasive bacterial infections. In the study by Benito et al MR-proADM had a reported area under the curve (AUC) of 0.69(95%CI 0.54 to 0.85). Benito et al reported that the optimal cut-off for MR-proADM in their study was 0.70 nmol/l [21].

The studies by Oncel et al (n = 128) and Hagag et al (n = 60) were both performed in newborn populations [18,19]. These case-control studies both demonstrated that MR-proADM levels were higher in the sepsis groups when compared to controls. The study by Hagag et al reported a correlation between MR-proADM levels and death ($r = 0.67$ $p < 0.05$) [19].

The study by Lan et al reported that MR-proADM levels were significantly higher in children with paediatric sepsis in the intensive care unit compared to healthy controls ($p < 0.05$). They also reported that the MR-proADM level was positively correlated with severity of sepsis ($r = 0.62$ $p < 0.05$) [20].

The paucity of available studies made meta-analysis and studies of heterogeneity impossible.

Discussion

Summary of evidence

The systematic review was designed to determine the accuracy of MR-proADM at identifying invasive bacterial infection in children less than 18 years of age. The review included four studies of 1404 patients [18-21]. Only one study was of a high quality and that study accounted for the vast majority of patients (n= 1035) [21]. The remaining studies were all of low quality due to their case-control design and lack of adherence to STARD criteria. From the available literature there is evidence that MR-proADM levels are elevated in cases of sepsis when compared to healthy controls and that levels are correlated with severity. The only study reporting the diagnostic accuracy of MR-proADM for invasive bacterial infection reported an AUC 0.69 [21]. This would suggest that MR-proADM testing alone is poor at identifying invasive bacterial infection in young children. It remains unclear if MR-proADM performs differently in older children or in children with signs and symptoms of IBI.

Limitations

The numbers of studies reporting on the test accuracy of MR-proADM for the diagnosis of invasive bacterial infections in children are small and there is only one high quality paediatric study. The available studies suggest that MR-proADM may have a role in identifying and stratifying sepsis in children, but further studies are required to understand the clinical utility of the test.

Conclusions

There is a paucity of research regarding the diagnostic accuracy of MR-proADM in the diagnosis of invasive bacterial infections in children. Initial findings indicate that MR-proADM is not a good biomarker for the diagnosis of IBI although further research is required.

Abbreviations

ADM	Adrenomedullin
AUC	Area under the curve
CRP	C-reactive protein
IBI	Invasive bacterial infection
MR-proADM	Mid-regional pro-adrenomedullin
PCR	Polymerase chain reaction
PCT	Procalcitonin

Declarations

. Ethics approval and consent to participate:

Not applicable

. Consent for publication:

Not applicable

. Availability of data and materials:

All of the individual participant data collected during this study will be available (including data dictionaries) on the Queen's University Belfast data repository.

. Competing interests:

• Funding:

This study received no funding.

• Authors contributions:

TW, MC, DR, DF, JMCK and MDS conceived and designed the review. MC co-ordinated the running of the review. All others were involved with the writing of the final manuscript and all authors have agreed the final submission.

• Acknowledgements:

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Figures

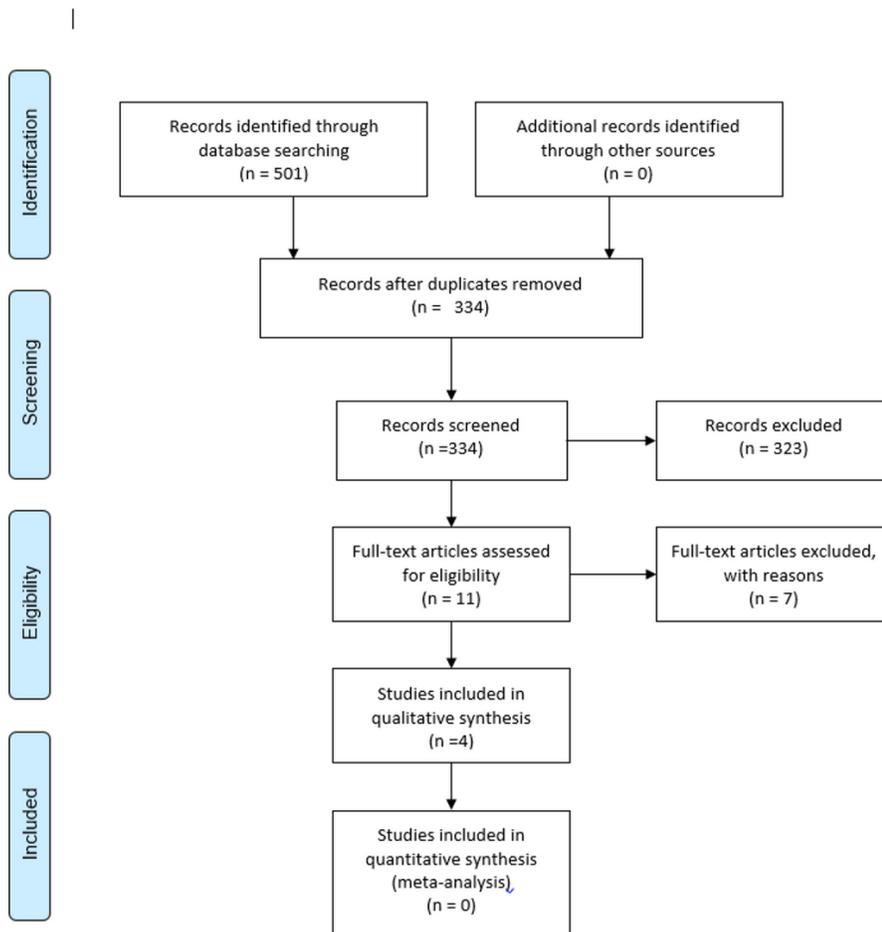


Figure 1

Flow diagram summarizing study selection

		<u>Risk of Bias</u>				<u>Applicability Concerns</u>		
		Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Benito	2013	+	+	+	+	+	+	+
Hagag	2010	-	?	?	?	-	-	-
Lan	2019	-	?	?	?	-	+	-
Oncel	2012	-	?	?	?	-	-	-

 High	 Unclear	 Low
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Figure 2

Summary study quality and risk of bias

Supplementary Files

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