Critical Review Form

Clinical Prediction or Decision Rule

Development and Validation of a Multivariable Predictive Model to Distinguish Bacterial from Aseptic Meningitis in Children, *Pediatrics* 2002; 110: 712-719.

Objective: To develop and validate a simple multivariable model to distinguish bacterial meningitis from aseptic meningitis in children using objective parameters available at the time of patient presentation (p 712).

Methods: Retrospective chart review of all children aged 29 days to 19 years admitted to Children's Hospital Boston from July 1992 through June 2000 with a final diagnosis of meningitis. Cases were identified by ICD-9 codes and data recorded on structured data sheets, although it is not clearly stated who abstracted the data, how they were trained and monitored, or whether they were blinded to the study hypothesis. The following definitions were established at the study onset:

CSF pleocytosis - > 7 wbc/mm^3

Bacterial meningitis (BM) – CSF cultures positive for a bacterial pathogen or CSF pleocytosis with positive blood culture and/or latex agglutination positive for S. pneumoniae, N. meningitides, H. influenza, or S. agalactiae. Probable contaminants were excluded.

Aseptic meningitis – CSF pleocytosis with negative bacterial cultures and negative CSF latex agglutination. Those who met this criteria, but had received antibiotics within 72-hours of LP were not included in the analysis.

Exclusion criteria included those who had undergone neurosurgical procedure, presented with clinical sepsis or purpura fulminans, concurrent non-CNS bacterial infection, or immunocompromised. Predictor variables were only considered if biologically plausible, readily available at the time of hospital presentation, and had previously been demonstrated to correlate with BM. ROC curves were inspected to determine optimal cut-off points to dichotomize continuous variables. Forward stepwise logistic regression analysis identified variables independently associated with BM and these variables were ranked by their magnitude of association with BM. Finally, binary recursive partitioning identified "the most important predictors of bacterial meningitis" which were then incorporated into the clinician friendly Bacterial Meningitis Score (BMS) which was validated on 1/3 of the cohort.

Guide		Comments
I.	***Is this a newly derived instrument* (Level IV)?**	
A.	**Was validation restricted to the retrospective use of statistical techniques on the original database? (If so, this is a Level IV rule & is not ready for clinical application).**	**No, "patients were randomly divided into 2 sets: the derivation set (n = 456, 66% of patients) and the validation set (n=240, 34% of patients)." (p. 714) This Clinical Decision Rule (CDR) is therefore a Level III level of validation tool.**

II.	**Has the instrument been validated? (Level II or III). If so, consider the following:**	
1a	Were all important predictors included in the derivation process?	The following variables were considered: date of birth, admission/discharge date, gender, medical history, duration of and peak fever, antibiotic pretreatment, occurrence and timing of seizures, peripheral absolute neutrophil count (ANC), blood cultures and several CSF tests including ANC, RBC, glucose, protein, latex agglutination, gram stain and culture. Variables such as Kernig's sign, neck stiffness, rash, and jolt accentuation of headache probably neither consistently recorded, nor sufficiently reproducible to include (see *JAMA* 1999; 282: 175-181).
1b	Were all important predictors present in significant proportion of the study population?	Table 1 (p 714) does not give a complete listing of variable prevalence. However, those listed were present in at least 5% of cohorts.
1c	Does the rule make clinical sense?	Yes, all variables are biologically plausible and readily available at any hospital.
2	Did validation include prospective studies on several different populations from that used to derive it (II) or was it restricted to a single population (III)?	Level III study, validated on an independently selected subset (1/3) of the same population (but different from the 2/3 upon which it was derived).
3	*How well did the validation study meet the following criteria?*	
3a	Did the patients represent a wide spectrum of severity of disease?	Uncertain since no markers of illness severity reported except mortality which was found in 1%, all in the derivation set.
3b	Was there a blinded assessment of the gold standard?	Presumably the microbiologists who resulted the gold standard cultures were not aware of the CDR study or patient allocation since the study had not yet been designed (data was obtained retrospectively).
3c	Was there an explicit and accurate interpretation of the predictor variables & the actual rule without knowledge of the outcome?	Not necessarily since the rule was derived retrospectively and the authors could have known culture results and outcomes on each case before actually calculating the BMS.

<table>
<tr><td>3d</td><td>Did the results of the assessment of the variables or of the rule influence the decision to perform the gold standard?</td><td>No, retrospective design so cultures were obtained before the development (or interpretation) of the BMS.</td></tr>
<tr><td>4</td><td>How powerful is the rule (in terms of sensitivity & specificity; likelihood ratios; proportions with alternative outcomes; or relative risks or absolute outcome rates)?</td><td>The data provided in the text of the results and in Figure 3 (p 716) allow one to produce the following 2x2 table from which to calculate LR’s.

Bacterial Meningitis
<table><tr><td>BMS > 2</td><td>YES</td><td>NO</td><td>Totals</td></tr><tr><td>YES</td><td>33</td><td>5</td><td>38</td></tr><tr><td>NO</td><td>5</td><td>197</td><td>202</td></tr><tr><td>Totals</td><td>38</td><td>202</td><td>240</td></tr></table>
Sensitivity = 87%
Specificity = 98%
LR+ = 43.5
LR- = 0.13

Therefore, taking a pre-test probability of bacterial meningitis of 18% (the prevalence in this cohort), a BMS > 2 would yield a post-test probability of 90.5% for bacterial meningitis. Now that is hard to beat!

The authors also analyzed the power of the rule in two subsets:
a) when pneumococcal meningitis excluded (BMS > 2 predicts BM with sensitivity 100% and specificity 97%);
b) in children < 2 months, BMS > 2 correctly identified all three cases of BM.

Finally, a BMS = 0 predicted aseptic meningitis with sensitivity 100%, specificity 73% (LR+ 3.7, LR- 0).
Bacterial Meningitis
<table><tr><td>BMS=0</td><td>YES</td><td>NO</td><td>Total</td></tr><tr><td>NO</td><td>38</td><td>52</td><td>90</td></tr><tr><td>YES</td><td>0</td><td>144</td><td>144</td></tr><tr><td>TOTAL</td><td>38</td><td>196</td><td>234</td></tr></table></td></tr>
</table>

III.	**Has an impact analysis demonstrated change in clinical behavior or patient outcomes as a result of using the instrument? (Level I). If so, consider the following:**	
1	How well did the study guard against bias in terms of differences at the start (concealed randomization, adjustment in analysis) or as the study proceeded (blinding, co-intervention, loss to follow-up)?	No impact analysis was performed.
2	What was the impact on clinician behavior and patient-important outcomes?	No impact analysis was performed.

Limitations

1) **Level III CDR derived and validated on a single site population. Before widespread dissemination and impact analysis performed, the CDR therefore requires multi-site validation.**
2) **No attempt to analyze the subset of pretreated patients who are likely a confusing, clinically important fraction of patients.**
3) **Tertiary medical center with referral of sicker, more complicated patients introducing a potential selection bias which might limit generalizability of conclusions to other settings (rural, non-academic, general hospitals).**
4) **Prospective validation would be ideal to enhance information capture, outcome assessment, and problems implementing the CDR) and should be the focus of subsequent validation trials.**

Bottom Line

Impressive methods for the single center derivation and validation of a simple, sensitive, intuitive CDR to identify the risk of bacterial meningitis in non-immunocompromised, non-neurosurgical children aged 29 days to 19 years who undergo an LP with clinical suspicion of meningitis.

If validated in children (and adults), a CDR like the BMS would be exceedingly useful to assist with the judgment of risk stratification and corresponding disposition of a high-risk, clinical condition. Although the lack of a similar CDR for adult meningitis tempts one to extrapolate these findings to older patients, such an extension of these findings is probably not warranted. Future research should evaluate the utility of the BMS (or a similar CDR) in adults.

Bacterial Meningitis Score

Predictor	Points	
	Present	Absent
Gram stain positive	2	0
CSF protein > 80 mg/dL	1	0
Peripheral ANC > 10000 cells/mm^3	1	0
Seizure	1	0
CSF ANC > 1000 cells/ mm^3	1	0

Practice recommendation of the authors:

1) **BMS = 0 in well appearing child, outpatient management pending culture results probably safe as long as ability to contact parents in case of positive culture and close follow-up both possible.**
2) **BMS > 0 inpatient antibiotics and re-evaluation indicated.**