Critical Review Form
Clinical Prediction or Decision Rule

PGY-1

Webb BJ, Dascomb K, Stenehjem E, et al. Derivation and Multicenter Validation of the Drug Resistance in Pneumonia Clinical Prediction Score. Antimicrob Agents Chemother. 2016 Apr 22;60(5):2652-63.

Objectives: **to "describe the derivation of the drug resistance in pneumonia (DRIP) score, a novel model to predict the risk of pneumonia due to DRPs [drug-resistant pathogens], and the results of a prospective validation in a multicenter U.S. cohort." (p. 2653)**

Methods: **A derivation cohort of patients with pneumonia with microbiologic confirmation of the infecting organism was obtained using patients identified by a previous retrospective, observational study. Patients with pneumonia admitted to one of seven hospitals in Utah between December 2011 and December 2012 were identified in the previous database, and 267 cases were then manually reviewed for inclusion in the derivation cohort. Patients with an organism identified by sputum culture, tracheal aspirate, bronchoalveolar lavage, pleural fluid, blood culture, urinary antigen testing, or PCR that were consistent with a bacterial respiratory pathogen were included. The isolated pathogen was classified as a DRP if it was resistant to drug regimens recommended for community acquired pneumonia (ceftriaxone plus azithromycin or levofloxacin). The mean age in the derivation cohort was 63.1 years and 59.0% were male. A DRP was identified in 25% of cases.**

A novel score to predict the isolation of a DRP was derived using multiple risk factors identified from the literature and the resulting area under the curve and test performance characteristics were calculated. The HCAP criteria and six other previously described prediction models were then also applied to the derivation cohort and test characteristics for these models were calculated.

A validation cohort was then prospectively identified from four separate US hospitals. Patients with pneumonia admitted between May 2013 and May 2014 were evaluated using the same inclusion and exclusion criteria as in the derivation cohort, and only patients with a microbiologically confirmed diagnosis were included. After screening approximately 1450 admissions, 200 patients were included in the validation cohort. The mean age was 65.2 and 51.5% were male and a DRP was recovered in 33% of cases. The newly derived clinical prediction rule, HCAP criteria, and 6 other prediction models were then applied to the cohort and test performance characteristics were calculated for each.

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. Following derivation on a retrospectively enrolled cohort of patients, the novel clinical prediction rule was then prospectively validated on a new cohort of patients enrolled from four geographically disparate US tertiary care hospitals. This could therefore be considered a level 2 CRD.
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?	Yes. The authors considered a large array of potential predictive factors identified from the available literature, including prior antibiotics, recent hospitalization, residence in a long-term care facility, tube feeding, chronic lung disease, immunosuppression, chronic kidney disease, active wound care, infusion therapy, poor functional status, aspiration risk, diabetes mellitus, current smoking, pneumonia severity, cerebrovascular disease, cognitive impairment, prior colonization with a DRP, gastric acid suppression, and the presence of an indwelling catheter.
1b	Were all important predictors present in significant proportion of the study population?	Yes. Table 1 in the article catalogues the proportion of patients in the derivation and validation cohorts positive for each of the predictors. For most of these, a reasonably significant proportion of each study population were positive.
1c	Does the rule make clinical sense?	Yes. The resulting clinical decision rule (the DRIP score) is comprised of major and minor risk factors. The major risk factors were antibiotic use within 60 days, residence in a long-term care facility, tube feeding, and prior infection with a DRP within the last year. Minor risk factors included hospitalization within 60 days, chronic pulmonary disease, poor functional status, gastric acid suppression, wound care, and MRSA colonization. These criteria seem reasonable and many were included as previous HCAP criteria.
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)?	Yes. Validation occurred in a cohort of patients enrolled from four geographically disparate US tertiary care hospitals. This was, however, a rather small cohort of patients comprising a total of only 200 patients.
3	*How well did the validation study meet the following criteria?*	

3a	Did the patients represent a wide spectrum of severity of disease?	Yes. These cohorts represented a relatively more ill population, as it only included admitted patients with a microbiologically confirmed diagnosis. There were 11.2% and 12.9% of patients in the derivation and validation cohorts with a mean eCURB score for predicted 30-day mortality and 83.5% and 77.0% met criteria for sepsis. Positive-pressure ventilation was utilized in 35.0% and 28.5% of patients
3b	Was there a blinded assessment of the gold standard?	While not explicitly stated, it seems likely that the gold standard (microbiologic confirmation) was performed by staff who unaware of study objectives and predictor variables.
3c	Was there an explicit and accurate interpretation of the predictor variables & the actual rule without knowledge of the outcome?	Uncertain. In the derivation cohort, which was identified retrospectively, it is quite possible that predictor variables were interpreted with knowledge of culture results. In the validation cohort, which was enrolled prospectively, this seems much less likely. Given the fairly objective nature of the predictor variables, it is unlikely that knowledge of culture results would influence the interpretation of the predictor variables.
3d	Did the results of the assessment of the variables or of the rule influence the decision to perform the gold standard?	Likely yes. The decision to perform microbiologic testing was likely influenced by the presence of certain risk factors included in the derivation of the decision rule (and included in the final rule itself).
4	How powerful is the rule (in terms of sensitivity & specificity; likelihood ratios; proportions with alternative outcomes; or relative risks or absolute outcome rates)?	In the derivation cohort, the DRIP score had an AUC of 0.90 (95% CI 0.84 to 0.95). At a cutoff of ≥ 4 points, the score had the following test characteristics: • Sensitivity 0.76 (95% CI 0.62 to 0.86) • Specificity 0.91 (95% CI 0.85 to 0.95) • These correspond to a LR+ of 8.44 and LR- of 0.26. • These test characteristics are superior to the HCAP criteria (sensitivity 0.36, specificity 0.84) and were better than the other 6 criteria assessed with the exception of a higher sensitivity of 0.82 in the Niederman criteria. In the validation cohort, the DRIP score had an AUC of 0.88 (95% CI 0.82 to 0.93). At a cutoff of ≥ 4 points, the score had the following test characteristics: • Sensitivity 0.82 (95% CI 0.67 to 0.88) • Specificity 0.81 (95% CI 0.73 to 0.87) • These correspond to a LR+ of 4.26 and LR- of 0.23. • These test characteristics are superior to the HCAP criteria (sensitivity 0.79, specificity 0.65).

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:**	No.
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)?	N/A
2	What was the impact on clinician behavior and patient-important outcomes?	N/A

Limitations:

1. **A relatively sicker population of patients with pneumonia was enrolled, as only admitted patients with microbiologic confirmation were eligible for both the derivation and validation cohorts (spectrum bias).**

2. **The decision to perform microbiologic testing was not standardized and was likely heavily influenced by the predictor variables that were being analyzed.**

3. **While the derived DRIP score performed superior to HCAP criteria, the corresponding likelihood ratios (LR+ 4.26, LR-0.23) suggest this rule would only have a modest effect on the probability of a DRP.**

4. **While validation was conducted in a cohort enrolled in 4 separate hospitals, this only involved 200 patients, suggesting this may be better classified as level 3 CDR.**

Bottom Line:

This study derived and validated a clinical decision rule to identify patients with pneumonia at risk of a DRP. The resulting DRIP rule outperformed the anachronistic HCAP criteria, but the resulting likelihood ratios (LR+ 4.26, LR-0.23) suggest this rule would only have a modest effect on post-test probability. Additionally, the study was limited by small sample size and by the inclusion of only patients with a positive microbiologic study.