Can preceding symptoms predict the occurrence of hypersensitivity reaction with 3HP?

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Introduction

The treatment of TBI (Tuberculosis infection) is a critical part of achieving TB (Tuberculosis) elimination (1).

3HP (three months of weekly rifapentine and isoniazid) is an effective and shorter regimen to treat TBI which is largely well tolerated but has the significant adverse event of hypersensitivity reaction – occurring in 3.5% of those taking the regimen (2).

Objective

Being able to predict who is more likely to experience hypersensitivity allows these individuals to have their medications ceased and trial an alternative regimen.

This then allows the scale of 3HP use in the community.

Methodology

We completed a Case Control study nested within a larger study of 3HP. Cases comprised individuals developing hypersensitivity, while controls were randomly selected from those unaffected.

Baseline characteristics and symptoms in the two weeks prior to the hypersensitivity event were collected. Forward stepwise logistic regression was employed to develop a hypersensitivity prediction model.

Results

Baseline characteristics were similar between cases and controls.

The presence of preceding symptoms was significantly associated with the occurrence of hypersensitivity, with the strongest associations being fever, rash, nausea, dizziness, feeling sick and experiencing aches.

We were able to create a model to predict hypersensitivity using the following formula:

Logit (Probability of Hypersensitivity)
= - 1.7936 + 0.0166 (age) + 0.9863 (sex) + 1.4662 (fever) + 0.7520 (aches) + 0.8657 (rash) + 0.4089 (feeling sick) + 0.4642 (nausea)

Table: Association of symptoms with hypersensitivity event

	No (-) Yes (+)	Cases N = 630 n (%)	Controls N = 630 n (%)	Unadjusted Odds Ratio (95% CI)	P value
Symptoms (any)	-	191 (30.3%)	431 (68.4%)	4.97 (3.92, 6.32)	p < 0.0001
	+	439 (69.7%)	199 (31.6%)		
Fever	-	464 (73.7%)	589 (94.7%)	6.39 (4.31, 9.46)	p < 0.0001
	+	166 (26.3%)	33 (5.3%)		
Rash	-	561 (89.1%)	598 (96.1%)	3.06 (1.90, 4.95)	p < 0.0001
	+	69 (11.0%)	24 (3.9%)		
Nausea	-	542 (86.0%)	595 (95.7%)	3.58 (2.29, 5.59)	p < 0.0001
	+	88 (14.0)	27 (4.3%)		
Dizziness	-	506 (80.5%)	575 (92.7%)	3.11 (2.16, 4.46)	P < 0.0001
	+	123 (19.6%)	45 (7.3%)		
Feeling Sick	-	446 (70.8%)	556 (89.4%)	3.48 (2.56, 4.73)	p < 0.0001
	+	184 (29.2%)	66 (10.6%)		
Aches	-	363 (57.6%)	530 (85.2%)	4.24 (3.23, 5.56)	p < 0.0001
	+	267 (42.4%)	92 (14.8%)		

For 1000 individuals started on 3HP, based on the findings from our study, we would expect 70 people to experience a hypersensitivity event. Our model would correctly identify 56 out of 70 of those who would develop hypersensitivity (sensitivity 80%) and 527 out of 930 (specificity 57%) of those who would not. Accordingly, the false positive rate is 43%.

Table: Example of Prediction Function (n=1000)

		Actual		
		Hypersensitivity	No Hypersensitivity	
Model: Sensitivity 80%	Hypersensitivity	56	403	459
	No Hypersensitivity	14	527	541
		70	930	1000

Conclusion

Preceding symptoms can be used to predict who is likely to have a hypersensitivity event with 3HP and hence allow its safer use.
Next steps are to test the model's external validity.

Related Literature

1. Dye C, Glaziou P, Floyd K, Raviglione M. Prospects for tuberculosis elimination. Annu Rev Public Health 2013; 34: 271-86.

2. Sterling TR, Villarino ME, Borisov AS, et al. Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection. New England Journal of Medicine 2011; 365(23): 2155-6