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Abstract category: 3. Bacterial susceptibility and resistance / f. Clinical outcome of resistant infections (retrospective and prospective studies, excl clinical trials of new drugs)

Antibiotic coverage and association with mortality in neonates with sepsis in LMIC

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Background

Neonatal sepsis has a high mortality in low-/middle-income countries (LMICs). Increasing antimicrobial resistance threatens to undermine the effectiveness of WHO-recommended antibiotics. We aimed to determine the effect of concordant/discordant antibiotics on mortality in LMICs.

Methods

Between 2018-2020, the global NeoOBS observational cohort study enrolled hospitalised infants aged <60 days with clinically diagnosed sepsis (≥2 clinical/laboratory criteria) after a baseline blood culture. Local laboratories identified organisms, and antibiotic susceptibility was determined using locally reported susceptibility results (EUCAST/CLSI) and EUCAST interpretive algorithms where not tested/unknown. Antibiotic regimens were defined as concordant if all pathogen(s) found were susceptible to ≥1 antibiotic given, and discordant if any pathogen was resistant to all antibiotics. We estimated the effect of baseline antibiotic coverage on death on IV antibiotics within 15 days using adjusted (cause-specific) Cox models, and of continuous discordant antibiotics (time-updated) vs initiating concordant antibiotics using marginal structural models with inverse probability weighting, with/without 1-day lag for antibiotics and varying assumptions of colistin susceptibility.

Results

Of 3083 infants enrolled in LMIC sites, 506(16%) had bacterial pathogen(s), of whom 475 received baseline IV antibiotics with known coverage (284(60%) concordant, 191(40%) discordant), 18 including colistin. 341/142 infants had a Gram-negative/Gram-positive pathogen (n=8 had both), respectively, most frequently *Klebsiella pneumoniae* (n=128;27%) and *Acinetobacter* spp. (n=72;15%). Overall, cumulative incidence of death on IV antibiotics by day 15 was 17.1% (95%CI 13.8-20.6%). In cause-specific models, lower mortality risks associated with baseline concordance strengthened assuming reduced activity of colistin at lower or any dose (**Table 1**). 158/191 (83%) initiating discordant antibiotics switched to concordant antibiotics/became culture-negative. Adjusted and upweighted associations showed similar patterns, e.g. with 20%, 48% and 55% mortality reduction associated with concordant versus continued discordant antibiotics as defined by susceptibility results, when considering colistin inactive at <100,000 IU/kg/day or when considered inactive completely (**Table 1**). Results were similar with/without 1-day lag.

Conclusion

Whilst we did not find conclusive evidence for an association between antibiotic coverage and mortality, mortality reductions were greater assuming that colistin had reduced susceptibility. Limitations include modest sample size and the heterogenous mix of pathogens and antibiotics.

Models for death on IV antibiotics [$]	**HR/OR** (concordant vs discordant)	**95% CI**	**p-value**
No lag, until 15 days: n=81 deaths			
Baseline coverage, Cox model	0.69	(0.43 – 1.11)	0.12
Baseline coverage, Cox model, assume colistin inactive if <100,000 IU/kg/day	0.65	(0.40 – 1.04)	0.071
Baseline coverage, Cox model, assume all colistin inactive	0.57	(0.35 – 0.92)	0.021
Standard MSM with IPW	0.81	(0.38 – 1.74)	0.59
Standard MSM with IPW, assume colistin inactive if <100,000 IU/kg/day	0.62	(0.32 – 1.17)	0.14
Standard MSM with IPW, assume all colistin inactive	0.53	(0.28 – 0.99)	0.047
1 day lag, until 15 days: n=75 deaths			
Baseline coverage, Cox model	0.68	(0.42 – 1.10)	0.12
Baseline coverage, Cox model, assume colistin inactive if <100,000 IU/kg/day	0.61	(0.37 – 0.99)	0.047
Baseline coverage, Cox model, assume all colistin inactive	0.53	(0.32 – 0.87)	0.013
Standard MSM with IPW	0.80	(0.39 – 1.66)	0.56
Standard MSM with IPW, assume colistin inactive if <100,000 IU/kg/day	0.52	(0.26 – 1.01)	0.053
Standard MSM with IPW, assume all colistin inactive	0.45	(0.23 – 0.86)	0.016

Notes: MSM: marginal structural models; IPW: inverse probability weighting. [$] All models were adjusted for WHO region, baseline NeoSep Severity Score (predictor of mortality at baseline), gram class of pathogen.
For all MSMs, participants who were not covered at baseline were censored the day they became covered post-baseline (newly culture-negative, switch to concordant antibiotics, new isolation of a pathogen to which existing antibiotics were susceptible), and participants who continued on discordant antibiotics were upweighted using inverse probability weights; weights were derived from separate models with outcome "newly covered" and predictors as above plus time-updated NeoSep Recovery Score (predictor of day-to-day mortality after presentation) and repeat blood culture taken yes/no. Of 18 receiving colistin at baseline (median 105,662 (IQR 59,589-120,463) IU/kg/day), n=11 were covered by colistin only (of whom 4 received <100,000 IU/kg/day), n=3 by colistin AND one other antibiotic, n=3 by another antibiotic but not colistin, and n=1 infant was not covered by any antibiotic taken.