Methods. We analyzed ARGs among a subset of infants from the Growing Up in Singapore Towards Healthy Outcomes (GUSTO) birth cohort. The subset included 75 mostly term, healthy Singaporean infants born from November 2009 to May 2011. Stool samples were collected at Week 3 (W3), months 3 (M3), 6 (M6) and 12 (M12) were analyzed using shotgun metagenomics. Sequencing reads were assembled into contigs using MEGAHIT. ARGs were identified using ResFinder 2.1. Demographic, perinatal factors, pre- and postnatal antibiotic exposure were collected.

Results. Only 242 ARGs were identified in stool samples from 75 infants were studied. Of the 169 ARGs detected, the four most common ARGs were blaZ, fosA, tet(M) and mec(A), conferring resistance to β-lactams, fosfomycin, tetracyclines, and macrolides respectively. The number of ARGs per infant increased over time (median: W3 = 18.0, M12 = 22.0, P < 0.05). At W3, 118 ARGs were detected among 28 infants. The most prevalent ARGs were fos(A) and blaZ (both 96.4%) at W3. Among the 22 infants who had samples at W3 and M12, only six of 118 ARGs detected at W3 were also present at M12. These were mec(A), mdr(D), tet(W), erm(B), tet(M) and fosA, conferring macrolide and tetracycline resistance. Their prevalence among at M12 was 100%, 93.3%, 90.9%, 84.6%, 68.8% and 52.4%, respectively. ARGs were not associated with gender, race, delivery mode, peripartum or postnatal antibiotics in infancy. Of note, longitudinal analysis showed that only the cfr(A) gene, which confers β-lactam resistance, was not significantly associated with subsequent antibiotic exposure in pregnancy than whose mothers did not (adjusted P < 0.05).

Conclusion. In regions with high endemic antimicrobial resistance such as Singapore, the infant gut harbors a diversity of ARGs as early as 3 weeks of age. Few ARGs persisted through infancy, implying the dynamic nature of the infant resistome. The lack of association of ARGs with most clinical variables evaluated here suggests that other unrecognized factors may contribute to the plasticity of ARGs in the infant gut resistome.

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626. An Inexpensive Quantitative Method for Testing Anti-Fungal Drug Activity Using the Invertebrate Caenorhabditis elegans

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Background. Due to ethical and budgetary concerns associated with the use of vertebrate animals in research, interest in alternative models has increased over the past several decades. In the present study, we developed a Candida albicans quantitative infection model in Caenorhabditis elegans, a nonparasitic invertebrate nematode, to test the anti-fungal effects of liposomal amphotericin B (L-AmB).

Methods. To establish a lethal C. albicans infection, larval Stage 4 worms [n = 30 (group [gp])] were fed various doses of yeast (2.5 × 10^2–2.5 × 10^4 cells/gp) for 4 hours at 20°C or 30°C. The infection was evaluated by monitoring worms for mortality and determining fungal burden in worm homogenates by plating for colony forming units every 24 hours for 4 days post-challenge. To examine the worm’s ability to ingest L-AmB and to determine drug toxicity, uninfected worms were fed L-AmB (6.3–25 µg/gp) for 4 hours at 30°C, and drug toxicity evaluated by survival with drug concentrations determined by bioassay of worm homogenates. The lack of toxicity allowed us to evaluate the anti-fungal activity in worms challenged for 4 hours at 30°C with 2.5 × 10^3 yeast cells/gp and then treated with L-AmB (0.5–25 µg/gp) for 4 hours at 30°C, with survival rate and fungal burden to assess L-AmB treatment.

Results. C. albicans infection was established in worms challenged with all yeast doses, with optimum observed with 2.5 × 10^3 yeast cells/gp at 30°C (13% survival in infected worms vs. 87% in uninfected worms). We observed that uninfected worms could take up L-AmB at doses of 6.3–25 µg/gp and yet was not toxic for the worms (93–95% survival). In worms exposed to yeast and treated with L-AmB, comet-like tails consistent with apoptosis were observed at higher doses (6.3–25 µg/gp), while lower doses (1.6–3.1 µg/gp) significantly reduced the fungal burden (P < 0.05). Infected worms, not treated with L-AmB had only 10% survival, while L-AmB improved survival in a dose-dependent manner giving 40% survival for 0.5 µg L-AmB/gp and 100% survival for doses of 6.3 µg/gp and higher.

Conclusion. By using fungal burden as a readout of efficacy, along with survival, we have established a quantitative, reproducible, flexible method for examining the activity of L-AmB in C. elegans which could be expanded for use in evaluating other antifungal drugs and different pathogenic fungi.

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