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| **Performance of next-generation molecular methods in the diagnosis of pleural space infections**  |
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| **Introduction/Aim:** Pleural space infections (PSIs) are common and associated with substantial morbidity and mortality. PSI diagnosis remains challenging due to low culture positivity rates, frequent polymicrobial involvement, and non-specific diagnostic biomarkers. Here, we compared the performance of culture-independent molecular methods with conventional culture for diagnosing PSI.**Methods:** We performed a prospective observational single-centre study of 26 patients with clinically suspected PSI and 10 control patients with non-infectious pleural effusion. In addition to routine conventional culture, microscopy and biochemistry analyses, pleural fluid was subjected to shotgun metagenomics, bacterial metataxonomics, and panbacterial quantitative PCR (qPCR). Diagnostic performance of these culture-independent techniques were then compared with conventional culture.**Results:**All culture-independent molecular techniques demonstrated superior sensitivity and negative predictive values compared with conventional culture for PSI diagnosis. Additionally, metagenomics and bacterial metataxonomics detected polymicrobial bacterial infections, with metagenomics also detecting fungi and DNA viruses within pleural fluid. Metagenomics and bacterial metataxonomics unveiled considerable microbial diversity across the pleural infection spectrum, including streptococci (*S. intermedius*, *S. pyogenes*, *S. mitis*), *Prevotella* spp. (*P. oris*, *P. pleuritidis*), staphylococci (*S. aureus*, *S. saprophyticus*), and *Klebsiella pneumoniae*. **Conclusion:** Our findings demonstrate the utility of molecular methods for more accurate PSI diagnosis, representing an important step towards improving personalised treatment and antimicrobial stewardship in suspected PSI. Routine implementation of rapid and inexpensive panbacterial qPCR followed by more advanced molecular characterization where required should be considered in the diagnostic workup of suspected PSI.**Grant Support:** Wishlist SERTF Seed Grant – $20,000.**Key Words:**Pleural space infection; metagenomics, metataxonomics, qPCR, molecular diagnostics*#,\* Authors contributed equally* |