D. Fernández-Vecilla, P.B. Blasco-Palacio, I.S. Pérez-Ramos et al.

Enfermedades Infecciosas y Microbiología Clínica 41 (2023) 518–523

Sarah Davila-Arias [a,*], Elena Rabadan-Rubio [b],
Alvaro Rabadan-Rubio [c], Jose Alberto Arranz-Caso [a]

[a] *Servicio de Medicina Interna, Hospital Universitario Principe de Asturias, Alcala de Henares, Madrid, Spain*
[b] *Servicio de Reumatologia, Hospital Universitario Principe de Asturias, Alcala de Henares, Madrid, Spain*
[c] *Veterinario clínico, Ciudad Real, Spain*

* Corresponding author.
E-mail address: sarah9201@hotmail.com (S. Davila-Arias).

Proposal for antimicrobial therapy stewardship of lower respiratory tract infection in mechanically-ventilated patients based upon the Biofire® Filmarray® Pneumonia Plus panel results

Propuesta para la administración de la terapia antimicrobiana en la infección del tracto respiratorio inferior en pacientes con ventilación mecánica basada en los resultados del panel Biofire® Filmarray® Pneumonia Plus

Ventilator-associated lower respiratory tract bacterial infection (VA-LRTBI) is associated with high morbidity and mortality, notably when multidrug-resistant bacteria (MDRB) are involved and empirical antimicrobial therapy (EAT) is inadequate.[1,2] Conventional semiquantitative culture-based antimicrobial susceptibility testing (AST) procedures performed on lower respiratory tract specimens return results approximately 48–72 h after specimen receipt. The BioFire® FilmArray® Pneumonia/Pneumonia plus Panel (FA-PP) (BioFire Diagnostics, LLC, Salt Lake City, UT) is a multiplex PCR panel that, in addition to respiratory viruses and "atypical" bacteria, tests for several bacteria commonly involved in VA-LRTBI (yielding semiquantitative estimates of bacterial loads) and seven genetic antibiotic resistance markers ($mecA/C$ and MREJ, bla_{CTX-M}, bla_{KPC}, bla_{VIM}, $bla_{OXA-48-like}$, bla_{IMP}, and bla_{NDM}); its use may provide clinically actionable results within about an hour of specimen reception. We and others previously demonstrated that FA-PP notably increases the diagnostic yield in LRTBI and narrows the time window for results compared with culture-based methods; this may prompt early EAT adjustment, which could be cost-beneficial by decreasing antimicrobial use and shortening the intensive care unit (ICU) stay.[3,5,8,9] Nevertheless, consensus criteria for antimicrobial stewardship according to FA-PP results need to be established. Here, we present an actionable antimicrobial stewardship algorithm (Fig. 1) for early EAT adjustment in patients with suspicion of VA-LRTBI at the ICU of the Hospital Clínico Universitario of Valencia, based upon the FA-PP results, planned to be formally evaluated beginning June 2023 upon approval by the INCLIVA (Instituto de Investigación Sanitaria, Hospital Clínico Universitario) Ethics Committee. The algorithm was built based on several assumptions mainly derived from the literature available regarding FA-PP's analytical and clinical performances[3–9]: (i) the high negative predictive value of the assay for all targets in the panel; (ii) the potential etiological relevance of all detectable bacteria at any load (limit of detection: $\geq 10^{3.5} \log_{10}/ml$; limit of quantification, $10^4 \log_{10}$ copies/ml) in patients undergoing EAT; (iii) the frequent involvement of lower respiratory tract-colonizing MDRB in VA-LRTBI; (iv) bacteria other than those targeted by the FA-PP panel could be involved in VA-LRTBI (i.e. some Enterobacterales species and *Stenotrophomonas maltophilia*). As per protocol, based on consensus guidelines[10] and local epidemiology, a combination of two antimicrobials displaying antipseudomonal activity, including a beta-lactam/beta-lactamase inhibitor (such as ceftolozane/tazobactam, ceftazidime/avibactam, meropenem or piperacillin/tazobactam) plus amikacin, quinolone or inhaled colistin, and an additional drug covering methicillin-resistant *Staphylococcus aureus* (MRSA) (mainly linezolid) is used as EAT for VA-LRTBI at our center. Proposed EAT adjustments based on FA-PP results are the following: (i) withdraw antimicrobial coverage of Gram-positive bacteria if MRSA is not detected; (ii) withdraw one of the two antipseudomonal agents if Gram-negative bacteria are not detected. In this scenario, quinolone therapy might be maintained if *S. maltophilia* is potentially relevant according to local epidemiology; (iii) maintain coverage of Gram-positive bacteria if MRSA is detected and consider discontinuing one antipseudomonal agent; (iv) discontinue one antipseudomonal agent if Enterobacterales with no genotypic resistant trait are detected; (v) withdraw EAT and administer ertapenem when extended spectrum β-lactamase-(ESBL)-producing Enterobacterales are detected; (vi) de-escalate to ceftazidime-avibactam if blaOXA-48-like-producing Enterobacterales is detected; (vii) de-escalate to ceftolozane-tazobactam if non-metallo-β-lactamase-producing *Pseudomonas aeruginosa* is detected; (viii) upon detection of metallo-β-lactamase-producing *P. aeruginosa*, administer ceftazidime-avibactam and aztreonam and inhaled colistin or cefiderocol in monotherapy; (ix) detection of *Acinetobacter baumanii* should prompt the administration of tigecycline and inhaled colistin or cefiderocol in monotherapy; (x) add oseltamivir if influenza virus is detected.

Several considerations related to the above: (i) in all the above scenarios, consider maintaining primary EAT regardless of FA-PP results when patients are severely immunosuppressed, present with septic shock, an additional infection source is suspected or MDR bacterial species not included in the panel are likely to be involved according to patient's risk factors or local epidemiology; (ii) detection of two or more Gram-negative bacterial targets harboring genotypic resistant traits (if particular fermenting and non-fermenting bacteria are detected in combination) will require individualized antimicrobial therapy tailoring; (iii) the algorithm has been designed taking into consideration the bacterial epidemiology at our ICU, which may not be extrapolatable to other settings.

The suitability of ongoing antimicrobial therapy (either adjusted or not upon FA-PP results) in terms of coverage as well as treatment duration should be re-assessed within 48 h, following receipt of microbiological results from standard semiquantitative cultures and conventional AST, taking into consideration the patient's clinical status. A concluding remark: this is a list of some of the many potential actions in terms of EAT adjustments that may be derived from FA-PP results. We naturally open our proposal for discussion, which we are confident will translate into tangible benefits for our ICU patients.
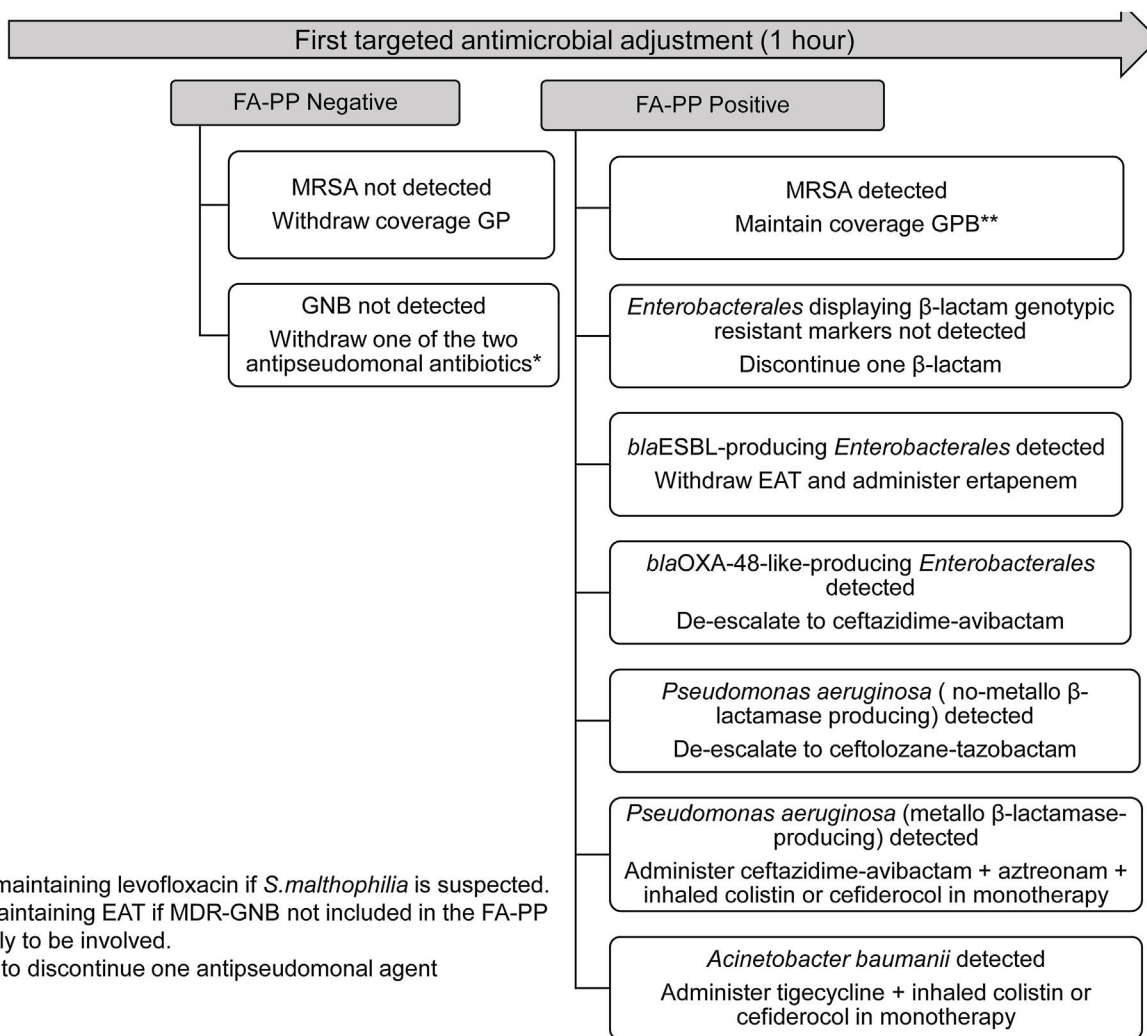
Fig. 1. Early adjustment of empirical antimicrobial therapy in patients with suspicion of ventilator-associated lower respiratory tract bacterial infection based on the BioFire® FilmArray® Pneumonia/Pneumonia plus Panel (FA-PP) results. The following microorganisms are targeted by FA-PP: *Acinetobacter calcoaceticus-baumannii complex*, *Enterobacter cloacae*, *Escherichia coli*, *Haemophilus influenzae*, *Klebsiella aerogenes*, *Klebsiella oxytoca*, *Klebsiella pneumoniae* group, *Moraxella catarrhalis*, *Proteus* spp., *Pseudomonas aeruginosa*, *Serratia marcescens*, *Staphylococcus aureus*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Chlamydia pneumoniae*, *Legionella pneumophila*, *Mycoplasma pneumoniae*, *Adenovirus*, *Coronavirus*, *Human metapneumovirus*, *Human rhinovirus/enterovirus*, *Influenza A virus*, *Influenza B virus*, *Parainfluenza virus*, and *Respiratory syncytial virus*. EAT, empirical antimicrobial therapy; ESBL, extended spectrum β-lactamase; GNB, Gram-negative bacteria; GPB, Gram-positive bacteria; MRSA, methicillin-resistant *Staphylococcus aureus*.

Authors' contributions

MAC, NC, EA and DN designed the algorithm and wrote the manuscript.

Funding

Conflict of interest

The authors have no relevant competing interest to disclose in relation to this work.

Acknowledgments

References

1. Luo W, Xing R, Wang C. The effect of ventilator-associated pneumonia on the prognosis of intensive care unit patients within 90 days and 180 days. BMC Infect Dis. 2021;21:684.
2. Torres A, Niederman MS, Chastre J, Ewig S, Fernandez-Vandellos P, Hanberger H, et al. International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia: guidelines for the management of hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) of the European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Asociación Latinoamericana del Tórax (ALAT). Eur Respir J. 2017;50:1700582.
3. Brendish NJ, Malachira AK, Armstrong L, Houghton R, Aitken S, Nyimbili E, et al. Routine molecular point-of-care testing for respiratory viruses in adults presenting to hospital with acute respiratory illness (ResPOC): a pragmatic, open-label, randomised controlled trial. Lancet Respir Med. 2017;5:401–11.
4. Ginocchio CC, Garcia-Mondragon C, Mauerhofer B, Rindlisbacher C. Multinational evaluation of the BioFire FilmArray Pneumonia plus Panel as compared to standard of care testing. Eur J Clin Microbiol Infect Dis. 2021;40:1609–22.
5. Maataoui N, Chemali L, Patrier J, Tran Dinh A, Le Fèvre L, Lortat-Jacob B, et al. Impact of rapid multiplex PCR on management of antibiotic therapy in COVID-19-positive patients hospitalized in intensive care unit. Eur J Clin Microbiol Infect Dis. 2021;40:2227–34.
6. Buchan BW, Windham S, Balada-Llasat JM, Leber A, Harrington A, Relich R, et al. Practical comparison of the BioFire FilmArray Pneumonia Panel to routine diagnostic methods and potential impact on antimicrobial stewardship in adult

hospitalized patients with lower respiratory tract infections. J Clin Microbiol. 2020;58:e00135–220.

7. Novy E, Goury A, Thivilier C, Guillard T, Alauzet C. Algorithm for rational use of Film Array Pneumonia Panel in bacterial coinfections of critically ill ventilated COVID-19 patients. Diagn Microbiol Infect Dis. 2021;101:115507.

8. Guillotin F, Poulain C, Gaborit B, Bouras M, Cinotti R, Lakhal K, et al. Potential impact of rapid multiplex PCR on antimicrobial therapy guidance for ventilated hospital-acquired pneumonia in critically ill patients, a prospective observational clinical and economic study. Front Cell Infect Microbiol. 2022;12:804611.

9. Ferrer J, Clari MÁ, Giménez E, Carbonell N, Torres I, Blasco ML, et al. The Biofire® Filmarray® Pneumonia Plus panel for management of lower respiratory tract infection in mechanically-ventilated patients in the COVID-19 era: a diagnostic and cost-benefit evaluation. Diagn Microbiol Infect Dis. 2023;105:115847.

10. Zaragoza R, Vidal-Cortés P, Aguilar G, Borges M, Diaz E, Ferrer R, et al. Update of the treatment of nosocomial pneumonia in the ICU. Crit Care. 2020;24:383.

Mª Ángeles Clari [a,1], Nieves Carbonell [b,1], Eliseo Albert [a], David Navarro [a,c,d,*]

^a *Microbiology Service, Clinic University Hospital, INCLIVA Health Research Institute, Valencia, Spain*

^b *Medical Intensive Care Unit, Clinic University Hospital, INCLIVA Health Research Institute, Valencia, Spain*
^c *CIBER de Enfermedades Infecciosas, Instituto de Salud Carlos III, Madrid, Spain*
^d *Department of Microbiology, School of Medicine, University of Valencia, Valencia, Spain*

[*] Corresponding author.
E-mail address: david.navarro@uv.es (D. Navarro).
[1] Both authors contributed equally to the present work.