Research Note

Application of the BioFire FilmArray Blood Culture Identification Panel for Rapid Identification of the Causative Agents of Ventilator Associated Pneumonia

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Running title: BCID use to identify causative bacteria of VAP

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Abstract

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Objective. The objective of this study was to evaluate the ability of the BioFire FilmArray Blood Culture Identification (BCID) Panel to rapidly detect pathogens producing late-onset ventilator-associated pneumonia (VAP), a severe infection often produced by Gram negative bacteria. These microorganisms are frequently multidrug resistant (MDR) and typically require broad spectrum empiric treatment.

Methods. In this study, in the context of an international multicenter clinical trial (Magic Bullet), respiratory samples were collected at the time of suspicion of VAP from 165 patients in 32 participating hospitals in Spain, Greece and Italy. Microorganisms were identified using the BCID Panel and compared with results obtained by conventional microbiologic techniques.

Results. *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Klebsiella pneumoniae* were the most commonly identified species, representing 54.7% (70/128) of microorganisms. The BCID Panel showed high global specificity and negative predictive values (98.1% and 96.6%, respectively) and a global sensitivity and positive predictive value of 78.6% and 87.3%, respectively for these microorganisms. Importantly, the BCID Panel provided results in only one hour directly from respiratory samples with minimal sample processing times.

Conclusions. For these reasons, the BCID Panel could have clinically utility in rapidly ruling out causative microorganisms causing VAP, specifically MDR-Gram negative species, which could facilitate the optimization of empiric treatment in these patients.

Keywords: ventilator-associated pneumonia, FilmArray BCID panel, Gram-negative bacteria, rapid diagnosis, antibiotic resistance

Introduction

Ventilator associated pneumonia (VAP) is one of the most common causes of infection and death in intensive care units [1]. Bacterial identification in clinical respiratory samples typically requires 24-48 hours, during which patients receive empirical therapy. Inappropriate or delayed treatment of VAP leads to a poorer prognosis and higher mortality [2, 3]. Thus, the rapid availability of microbiologic testing results could positively impact patient outcomes. The FilmArray Blood Culture Identification (BCID) panel, which is able to identify 24 different microorganisms and the resistance genes, *K. pneumoniae* carbapenemase (KPC), *mecA* and *vanA/B,* has potential to facilitate point-of-care testing and provide results in one hour. The BCID panel has shown high sensitivity with blood cultures [4-7], and high concordance with conventional microbiologic methods with other types of samples [8]. However, no study has evaluated the BCID Panel in suspected cases of VAP in a large prospective study.

Methods

Samples were obtained during the Magic Bullet clinical trial, a study funded by the European Commission that evaluated meropenem and levofloxacin versus colistin and levofloxacin as empiric therapies in patients with suspected VAP from 32 hospitals in Italy, Greece and Spain. The study protocol has been described [9] and registered at ClinicalTrials.gov (identifier: NCT01292031) and EudraCT (identifier: 2010-023310-31). Respiratory samples included endotracheal/bronchial aspirates and bronchoalveolar lavage fluid. The entire clinical sample (for all sample types) was mixed with 1 ml of 0.5% N-acetylcysteine to reduce the viscosity. Half of each NAC-treated sample was used for routine processing by the clinical microbiology service at the participating hospital using automated biochemical identification, and qualitative results of cultures

were used for analysis. All clinically relevant bacterial isolates were sent to the University Hospital Virgen Macarena for independent identification by culture followed by MALDI-TOF (Biotyper 2.0 database; Bruker Daltonics) and to the Biomedical Institute of Seville for KPC gene detection after bacterial culture. An aliquot of (0.5 ml) of the NAC-treated sample was mixed with 0.5 ml of Freezing Solution (Luria-Bertani broth + 30% glycerol), frozen and sent to the Biomedical Institute of Seville. The freezing solution was optimized to permit the freezing and thawing of clinical isolates with less than 10% loss of viable bacteria during storage at -80ºC for six months (data not shown).

For analysis, frozen samples were thawed, and 200 µl were mixed with 200 µl of 0.5% N-acetylcysteine to reduce viscosity. Subsequently, 300 µl of the mix was diluted in 0.5 ml of BCID Sample Buffer of which 300 µl (corresponding to 28.1 µl of the original clinical sample) was injected into the BCID sample pouch. In order to compare the results obtained with the BCID Panel in the detection of KPC to previously described methods, the method described by Poirel *et al.* in which the KPC gene is detected by PCR was employed [10]. Genomic DNA was extracted from overnight cultures of all Gram negative isolates and used for the PCR.

The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the BCID Panel were determined by comparison to the results obtained by MALDI-TOF. Results for KPC detection from the BCID Panel were compared to results obtained by PCR, and for *mecA,* results were compared to results obtained from susceptibility testing. For all patients sampled and included in the present study, how the BCID Panel results could have changed the management of empirical therapy was evaluated. Treatment changes that could have been undertaken

upon applying the results of the BCID Panel were determined for each patient according to published guidelines [11].

Results

A total of 180 samples were collected from 165 patients upon suspicion of VAP (for 15 patients, one sample was taken from each lung during the same episode of infection). Of these, 167 were analyzed by both MALDI-TOF and the BCID Panel. The main causative microorganisms detected by both techniques were *P. aeruginosa* (21.1%; 27 of 128), *A. baumannii* (18.0%; 23 of 128) and *K. pneumoniae* (15.6%; 20 of 128) which represented 54.7% (70/128) of the total, as determined by MALDI-TOF. In the case of BCID Panel, these microorganisms represented 50% (63/126) of the total and 21.4% (27/126), 18.3% (23/126) and 10.3% (13/126), respectively (Table 1). Although results were species specific, high specificity and NPV were observed for most microorganisms. Taking into account only species that are potentially carbapenem resistant as a group (*A. baumannii*, *P. aeruginosa* and *K. pneumoniae*), values were 78.6% (95% CI = 70%-88%), 98.1% (95% CI = 96%-100%), 87.3% and 96.6% for sensitivity, specificity, PPV and NPV, respectively. In order to assess the sample type used for analysis on the performance of the BioFire assay, we performed separate analyses for bronchial/endotracheal aspirates and bronchalveolar lavage fluid. With bronchial/endotracheal aspirates values were 94.3% (95% CI = 87%-102%), 97.1% (95% CI = 96%-98%), 99.3% and 80.5% for sensitivity, specificity, PPV and NPV, respectively. For bronchoalveolar lavage fluid values were 62.9% (95% CI = 47%-79%), 100% (95% CI = 95%-105%), 92.4% and 100% for sensitivity, specificity, PPV and NPV, respectively

A total of 111 Gram-negative isolates were tested for the presence of the KPC gene by both PCR and BCID. The KPC gene was detected in 5 *K. pneumoniae* isolates by conventional PCR, all of which were all detected by the BCID panel. The BCID Panel also detected the KPC gene in 2 additional isolates of *K. pneumoniae*. Methicillin resistant *Staphylococcus aureus* was detected in 5 samples by standard methods. Only 3 of these cases were detected by the BCID Panel.

How the availability of results from the BCID Panel would have changed empiric therapy was assessed. In this context, 72 patients (48%; 72 of 150) would have received more appropriate therapy. Of these, treatment could be changed to a more appropriate antibiotic in 55 patients (36.7%; 55 of 150) and stopped in 7 patients (4.7% 7 of 150). However, in 10 (6.7%; 10 of 150) patients, the BCID Panel results would have indicated less appropriate therapy (Figure 1, Supplemental Table S1).

Discussion

Rapid identification of microorganisms causing VAP using new molecular methods could facilitate early targeted antibiotic therapy, which may improve patient outcomes [12]. This study represents the first multicenter trial that characterizes the BCID Panel for identifying microorganisms from respiratory samples without additional processing. Different studies have analyzed the BCID Panel using blood cultures, and showed high sensitivity (91-97.5 %) and specificity (77-100 %) [4, 5, 13-15]. Zheng. X. *et al.* described that the panel was able to identify 89.4 % of microorganisms in paediatric blood cultures [6] and Ray *et al*. demonstrated that the use of the BCID Panel would facilitate changes in clinical management of half the children included in the study [7]. Mico *et al*. applied the BCID Panel to other sample types, obtaining a global sensitivity and specificity of 71 % and 97 %, respectively [8]. In the current study, the

BCID Panel showed high specificity and NPV, similar to results obtained by Mico *et al.* The results presented here indicate that bacterial identification, and for some species susceptibility testing, can be achieved in as few as one hour directly from clinical samples. This contrasts with conventional culture methods which typically require 12. 24 hours for pathogen identification, and an additional 12-24 hours for susceptibility testing. Importantly, the BioFire system is designed for use at the point-of-care, which may facilitate the rapid optimization of antibiotic treatment for severe infections such as VAP.

A limitation of the study include the inclusion of heterogeneous sample types (endotracheal/bronchial aspirates and bronchoalveolar lavage fluid), although an analysis of the performance of the BioFire assay based on sample type showed that both endotracheal/bronchial aspirates and bronchoalveolar lavage fluid samples resulted in high specificity and negative predictive values. In addition, only qualitative culture data was used for comparing results of standard culture to the BioFire assay, meaning that cutoff values for diagnosing VAP were not taken into account in the present study. However, the objective of this study was de determine how the rapid availability of qualitative bacterial identification results could affect empiric treatment of VAP. In this context, using qualitative culture as a comparator for the qualitative Biofire assay has utility. It should also be noted that an inherent limitation of multicenter studies that require microbiological samples processing is the presence of differences in protocols employed for bacterial isolation and culturing.

In addition, we determined how the BCID Panel could change the selection of empirical therapy regimens. The results obtained in this study show that treatment could be improved in 41.3 % of patients, which could be of importance given the high level of antibiotic resistance in Gram negative species that produce VAP.

Transparency declaration

The authors declare that they have no conflicts of interest.

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Access to data: José Miguel Cisneros is the study coordianator for the Magic Bullet Clinical Trial.

A subset of the data presented in this manuscript were presented at the European Congress on Clinical Microbiology and Infectious Diseases Meeting in 2015.

Figure Legends

Figure 1. Schematic representing inclusion of samples and changes in antimicrobial treatment that would have been made using the results of the BICD Panel.

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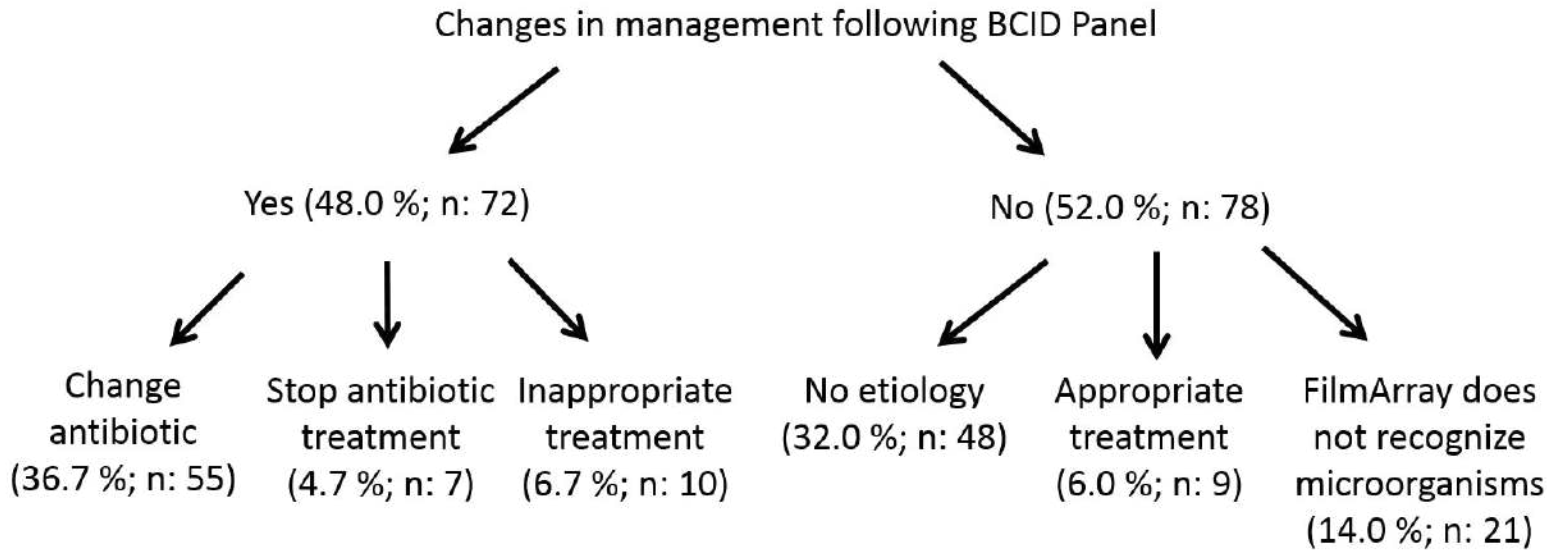
Microorganism	Positive Samples Gold Standard (n: 128)	Positive Samples FilmArray (Concordant) [n: 126 (85)]	Sensitivity (%)	95% Confidence Interval Sensitivity (%)	Specificity (%)	95% Confidence Interval Specificity (%)	PPV (%)	NPV(%)
P. aeruginosa	27	27 (24)	88.9	77-101	97.9	95-100	88.9	97.9
A. baumannii	23	23(20)	87.0	73-101	97.9	96-100	87.0	97.9
K. pneumoniae	20	13 (11)	55.0	33-77	98.6	95-103	84.6	94.2
S. aureus	17	22 (12)	70.6	46-92	93.3	91-96	54.6	96.6
E. coli	10	5 (4)	40.0	10-70	99.6	96-102	80.0	96.3
H. influenzae	8	27(5)	75.0	45-105	86.8	85-88	22.2	98.6
E. cloacae	6	2 (2)	33.3	(-4)-71	100	98-102	97.6	100
Proteus spp.	6	4 (4)	66.7	29-104	100	98-102	100	98.8
S. marcescens	6	1 (1)	16.7	(-13)-46	100	97-103	100	97.0
K. oxytoca	5	2 (2)	40.0	(-3)-83	100	98-102	100	98.2

Table 1. Table 1: Sensitivity, specificity, positive predictive value and negative predictive value of the BioFire FilmArray Blood Culture Identification (BCID) Panel compared to MALDI-TOF.


Changes in management following BCID Panel
Yes (48.0 %; n: 72)
No (52.0 %; n: 78)
Change antibiotic (36.7 %; n: 55)
Stop antibiotic treatment (4.7 %; n: 7)
Inappropriate treatment (6.7 %; n: 10)
No etiology (32.0 %; n: 48)
Appropriate treatment (6.0 %; n: 9)
FilmArray does not recognize microorganisms (14.0 %; n: 21)

PATIENT	ETIOLOGY MALDI-TOF	ETIOLOGY FILMARRAY	RANDOMIZED EMPIRIC TREATMENT	EMPIRIC VANCOMYCIN	EMPIRIC LINEZOLID	CHANGE EMPIRIC TREATMENT	TYPE OF CHANGE (1: More appropriate; 2: changeless appropriate; 3: No change)	CAUSE
1	*A. baumannii*	*A. baumannii*	Colistin	No	No	Yes	1	Remove levofloxacin
2	*A. baumannii*	*A. baumannii*	Colistin	No	No	Yes	1	Remove levofloxacin
3	*A. baumannii*	*A. baumannii*	Meropenem	No	No	Yes	1	Remove levofloxacin and change to colistin
4	*H. influenzae*	*Staphylococcus mecA - Detected H. influenzae*	Meropenem	No	No	Yes	1	Remove levofloxacin and change to ceftriaxone
5	*n.d.*	*n.d.*	Meropenem	No	No	No	3	No etiology
6	*P. aeruginosa, E. aerogenes*	*P. aeruginosa*	Meropenem	No	Yes	Yes	1	Remove linezolid and change to ceftazidime
7	*P. aeruginosa*	*P. aeruginosa*	Meropenem	No	No	Yes	1	Change to ceftazidime
8	*Serratia spp*	*n.d.*	Colistin	No	No	No	3	FilmArray does not identify microorganism
9	*A. baumannii*	*A. baumannii C. albicans*	Meropenem	No	No	Yes	1	Remove levofloxacin and change to colistin
10	*n.d.*	*n.d.*	Colistin	Yes	No	No	3	No etiology
11	*n.d.*	*n.d.*	Meropenem	Yes	No	No	3	No etiology
12	*n.d.*	*Streptococcus*	Colistin	No	No	Yes	1	Remove colistin and change to ceftriaxone
13	*S. aureus sensitive*	*C. albicans, C. tropicalis, S. aureus mec not detected, Streptococcus*	Meropenem	No	Yes	Yes	1	Remove meropenem and linezolid and change to cloxacillin
14	*K. pneumoniae*	*K. pneumoniae, Enterobacteriaceae, H. influenzae*	Meropenem	No	No	No	3	Appropriate treatment
15	*S.maltophilia, C. freundii*	*n.d.*	Meropenem	Yes	No	No	3	FilmArray does not identify microorganism

16	*E. cloacae, H. influenzae, E. coli; M. catarrhalis*	*H. influenzae*	Colistin	No	Yes	No	2	FilmArray does not identify microorganism
17	*n.d.*	*C. albicans*	Meropenem	No	No	No	3	No etiology
18	*n.d.*	*S. aureus mec detected, C. albicans*	Colistin	No	Yes	Yes	1	Remove colistin and change to vancomycin
19	*C. albicans*	*C.albicans*	Colistin		Yes	No	3	No etiology
20	*Methicillin-sensitive S. Aureus*	*S. aureus, C. albicans mec detected*	Meropenem	No	No	Yes	2	Inappropriate change because vancomycin is added
21	*Methicillin-sensitive S. aureus*	*S. aureus, H. influenzae mec not detected*	Colistin	No	No	Yes	1	Change to cloxacillin
22	*n.d.*	*n.d.*	Colistin	No	No	No	3	No etiology
23	*P. aeruginosa*	*P. aeruginosa*	Colistin	No	No	Yes	1	Change to ceftazidime
24	*E. cloacae, K. oxytoca*	*Streptococcus Enterobacteriaceae K. oxytoca H. influenzae*	Colistin	No	No	No	3	Appropriate treatment
25	*K. pneumoniae*	*Enterobacteriaceae, K. pneumonia*	Meropenem	No	Yes	Yes	1	Remove linezolid
26	*K. pneumoniae, H. influenzae*	*n.d.*	Colistin	Yes	No	No	3	FilmArray does not identify microorganism
27	*P. aeruginosa*	*P. aeruginosa*	Meropenem	No	No	Yes	1	Change to ceftazidime
28	*n.d.*	*n.d.*	Meropenem	No	No	No	3	No etiology
29	*n.d.*	*C. albicans*	Meropenem	No	No	No	3	No etiology
30	*n.d.*	*x*	Colistin	Yes	No	No	3	No etiology
31	*A. baumannii, S. marcescens*	*A. baumannii, C. albicans, Enterobacteriaceae, E. coli, Serratia, P. aeruginosa, S. pneumoniae*	Meropenem	No	No	Yes	1	Change to colistin

32	*P. aeruginosa*	*P. aeruginosa, S. pneumoniae*	Colistin	No	No	Yes	1	Change to ceftazidime
33	*n.d.*	*n.d.*	Meropenem	No	No	No	3	No etiology
34	*K. pneumoniae, P. aeruginosa*	*P. aeruginosa*	Colistin	No	Yes	Yes	1	Remove linezolid and change to ceftazidime
35	*n.d.*	*S. pneumoniae*	Meropenem	No	Yes	Yes	1	Change to ceftriaxone
36	*n.d.*	*P. aeruginosa, C. albicans*	Colistin	No	No	Yes	1	Change to ceftazidime
37	*n.d.*	*C. albicans*	Meropenem	No	Yes	No	3	No etiology
38	*P. mirabilis, K. oxytoca, S. maltophilia*	*n.d.*	Meropenem	Yes	No	No	3	FilmArray does not identify microorganism
39	*n.d.*	*n.d.*	Meropenem	No	No	No	3	No etiology
40	*n.d.*	*C. albicans*	Colistin	No	No	No	3	No etiology
41	*n.d.*	*n.d*	Colistin	No	No	No	3	No etiology
42	*P. aeruginosa*	*P. aeruginosa*	Meropenem	No	No	Yes	1	Change to ceftazidime
43	*C. koseri*	*n.d*	Colistin	Yes		No	3	FilmArray does not identify microorganism
44	*K. pneumoniae, H. Influenzae*	*H. influenzae*	Meropenem	Yes	No	No	3	FilmArray does not identify microorganism
45	*n.d.*	*n.d.*	Colistin	No	No	No	3	No etiology
46	*E. cloacae*	*Enterobacteriaceae E. cloacae complex*	Meropenem	No	No	No	3	Appropriate treatment
47	*n.d.*	*C. albicans C. glabrata*	Meropenem	No	Yes	No	3	No etiology
48	*n.d.*	*Streptococcus S. pneumoniae C. albicans*	Meropenem		Yes	Yes	1	Change to ceftriaxone

49	*E. aerogenes,* *E. coli*	*Staphylococcus* *S. aureus* *Streptococcus* *S. pneumoniae* *Enterobacteriaceae* *E. coli* *H. influenzae*	Meropenem	Yes	No	Yes	1	Remove vacomycin
50	*n.d.*	*Enterobacteriaceae* *K. pneumoniae*	Colistin	No	No	Yes	1	Change to meropenem
51	*n.d.*	*C. albicans*	Colistin	No	No	No	3	No etiology
52	*S. marcescens*	*Enterococcus* *C. glabrata*	Colistin	No	No	No	2	FilmArray does not identify microorganism
53	*n.d.*	*C. parapsilosis*	Meropenem	No	No	No	3	No etiology
54	*n.d.*	*Staphylococcus* *Streptococcus* *C. albicans* *C. glabrata*	Colistin	No	No	Yes	1	Change to cloxacill/vancomyn and linezolid
55	*n.d.*	*Streptococcus* *S. agalactiae (Group B)* *H. influenzae*	Colistin	No	No	Yes	1	Change to ceftriaxone
56	*K. pneumoniae*	*Enterobacteriaceae* *K. pneumoniae*	Colistin	Yes	No	Yes	1	Remove vancomycin
57	*A. baumannii,* *P. aeruginosa*	*A. baumannii,* *P. aeruginosa*	Colistin	No	No	Yes	1	Change to ceftazidime
58	*P. aeruginosa*	*n.d.*	Colistin	Yes	No	No	3	FilmArray does not identify microorganism
59	*n.d.*	*n.d.*	Colistin	Yes	No	No	3	No etiology
60	*E. coli*	*n.d.*	Meropenem	No	No	No	3	FilmArray does not identify microorganism
61	*E. coli*	*n.d.*	Colistin	No	No	No	3	FilmArray does not identify microorganism
62	*n.d.*	*n.d.*	Meropenem	No	No	No	3	No etiology
63	*n.d.*	*H. influenzae* *N. meningitidis*	Meropenem	Yes	No	Yes	1	Change to ceftriaxone

64	*K. pneumoniae*	*A. baumannii* *Enterobacteriaceae* *K. pneumoniae*	Colistin	No	Yes	Yes	1	Remove linezolid
65	*C. albicans*	*H. influenzae* *C. albicans*	Colistin	No	No	Yes	1	Change to ceftriaxone
66	*P. aeruginosa*	*P. aeruginosa*	Meropenem	No	Yes	Yes	1	Remove linezolid and change to ceftazidime
67	*E. aerogenes*	*Streptococcus* *H. influenzae*	Colistin	No	No	Yes	2	Inappropriate change to ceftriaxone
68	*S. maltophilia,* *K. pneumoniae*	*Enterobacteriaceae* *K. pneumoniae*	Colistin	No	No	No	3	Appropriate treatment
69	*MS S. aureus,* *E. faecium*	*C. albicans*	Meropenem	Yes	No	No	3	FilmArray does not identify microorganism
70	*P. fluorescens,* *S. aureus, P.* *aeruginosa*	*n.d.*	Colistin	No	No	No	3	FilmArray does not identify microorganism
71	*E. cloacae*	*Staphylococcus* *Enterobacteriaceae* *E. cloacae complex* *C. albicans mecA detected*	Colistin	No	No	No	3	Appropriate treatment
72	*n.d.*	*H. influenzae* *C. albicans*	Colistin	No	No	Yes	1	Change to ceftriaxone
73	*n.d.*	*n.d.*	Meropenem	No	No	No	3	No etiology
74	*n.d.*	*n.d.*	Meropenem	Yes	No	No	3	No etiology
75	*P. aeruginosa,* *P. mirabilis*	*Enterobacteriaceae* *Proteus* *P. aeruginosa*	Meropenem	Yes	No	Yes	1	Remove vancomycin and levofloxacin and change to ceftazidime
76	*P. mirabilis*	*Enterobacteriaceae* *Proteus* *C. albicans*	Colistin	No	No	Yes	1	Change to ceftriaxone
77	*P. aeruginosa,* *H. influenzae*	*H. influenzae* *P. aeruginosa*	Colistin	No	No	Yes	1	Remove colistin and levofloxacin and change to ceftazidime
78	*C. striatum, E.* *faecalis*	*Streptococcus*	Colistin	No	No	No	3	FilmArray does not identify microorganism

79	*A. baumannii, K. pneumoniae, P. aeruginosa, S. aureus*	*Staphylococcus S. aureus H. influenzae P.aeruginosa*	Meropenem	No	Yes	No	2	FilmArray does not identify microorganism
80	*n.d.*	*n.d*	Colistin	No	No	No	3	No etiology
81	*S. aureus, K. pneumoniae, P. mirabilis*	*Staphylococcus S. aureus A. baumannii Enterobacteriaceae K. pneumoniae Proteus H. influenzae KPC detected mecA not detected*	Meropenem	No	No	Yes	2	Inappropriate change to colistin
82	*n.d.*	*C. albicans*	Meropenem	No	No	No	3	No etiology
83	*n.d.*	*n.d*	Colistin	Yes		No	3	No etiology
84	*n.d.*	*H. influenzae*	Meropenem	No	No	Yes	1	Change to ceftriaxone
85	*n.d.*	*C. albicans*	Meropenem	No	No	No	3	No etiology
86	*S. epidermidis*	*n.d.*	Meropenem	Yes		No	3	FilmArray does not identify microorganism
87	*Candida spp.*	*C. albicans*	Colistin	Yes		No	3	No etiology
88	*A. baumannii*	*A. baumannii, C. albicans*	Meropenem	No	No	Yes	1	Remove levofloxacin and change to colistin
89	*P. aeruginosa*	*P. aeruginosa*	Colistin	No	No	Yes	1	Change to ceftazidime
90	*n.d.*	*C. albicans, C. glabrata*	Meropenem	No	No	No	3	No etiology
91	*n.d.*	*C. glabrata*	Colistin	No	No	No	3	No etiology
92	*A. baumannii, S. epidermidis*	*A. baumannii KPC detected*	Meropenem	No	No	Yes	1	Remove levofloxacin and change to colistin
93	*K. pneumoniae*	*Staphylococcus Enterobacteriaceae K. pneumoniae KPC and mecA detected*	Colistin	No	No	No	3	Appropriate treatment
94	*n.d.*	*n.d*	Colistin	No	Yes	No	3	No etiology

95	*S. aureus*	*Staphylococcus* *S. aureus* *Streptococcus* *H. influenzae*	Meropenem	No	No	Yes	1	Remove meropenem and cahnge to cloxacillin
96	*A. baumannii*	*n.d*	Meropenem	No	No	No	3	FilmArray does not identify microorganism
97	*E. aerogenes*	*Enterobacteriaceae*	Meropenem	No	No	No	3	FilmArray does not identify microorganism
98	*n.d.*	*n.d*	Meropenem	No	No	No	3	No etiology
99	*A. baumannii*	*A. baumannii* *C. albicans*	Meropenem	No	No	Yes	1	Remove levofloxacin and change to colistin
100	*A. baumannii*	*A. baumannii KPC detected*	Colistin	No	No	No	3	Appropriate treatment
101	*S. aureus, K. pneumoniae, R. ornithinolytica*	*Staphylococcus* *S. aureus* *Streptococcus* *C. glabrata mecA detected*	Meropenem	Yes	No	No	2	FilmArray does not identify microorganism
102	*A. baumannii*	*Staphylococcus* *S. aureus* *A. baumannii*	Colistin	No	No	Yes	1	Remove levofloxacin and change cloxacillin. Maintenance of colistin
103	*C. freundii, K. oxytoca*	*Enterobacteriaceae* *K. oxytoca, C. albicans*	Meropenem	Yes	No	No	3	FilmArray does not identify microorganism
104	*A. baumannii, E. aerogenes C. albicans*	*Staphylococcus* *S. aureus* *A. baumannii* *C. albicans*	Meropenem			Yes	1	Change to colistin and cloxacillin
105	*P. aeruginosa, Methicillin-resistant S. Aureus*	*P. aeruginosa*	Colistin	Yes	No	No	2	FilmArray does not identify microorganism
106	*n.d.*	*Acinetobacter baumannii*	Meropenem	No	No	Yes	1	Remove levofloxacin and change to colistin
107	*S. marcescens, A. baumannii*	*A. baumannii*	Meropenem	Yes	No	Yes	1	Remove levofloxacin and change to colistin

108	*P. mirabilis*	*Enterobacteriaceae* *Proteus* *H. influenzae* *P. aeruginosa*	Colistin	No	No	Yes	1	Remove colistin and change to ceftazidime
109	*n.d.*	*n.d.*	Colistin	No	No	No	3	No etiology
110	*n.d.*	*C. glabrata* *C. tropicalis*	Meropenem	No	No	No	3	No etiology
111	*C. albicans*	*C. albicans*	Colistin	No	No	No	3	No etiology
112	*n.d.*	*n.d.*	Colistin	No	No	No	3	No etiology
113	*K. pneumoniae, Enterococcus spp*	*K. pneumoniae, Enterococcus spp*	Colistin	No	No	Yes	1	Remove colistin and change to vancomycin and meropenem/cephalosporin 3G
114	*n.d.*	*C. albicans*	Meropenem	No	No	No	3	No etiology
115	*C. albicans*	*C. parapsilosis*	Colistin	Yes		no	3	No etiology
116	*E. coli*	*Staphylococcus* *S. aureus* *Enterobacteriaceae* *E. coli* *H. influenzae*	Meropenem	No	No	Yes	1	Remove meropenem and change to ceftrioxone
117	*n.d.*	*n.d.*	Colistin	No	Yes	No	3	No etiology
118	*A.fumigatus*	*C. albicans*	Meropenem	No	No	No	3	No etiology
119	*P. aeruginosa*	*P. aeruginosa* *C. albicans* *C. parapsilosis*	Colistin	No	No	Yes	1	Remove colistin and change to ceftazidime
120	Methicillin-sensitive S. Aureus	*Staphylococcus* *S. aureus* *H. influenzae mecA not detected*	Colistin	No	Yes	Yes	1	Remove colistin and linezolid and change to ceftrioxone or cloxacillin+ levofloxacin
121	*n.d.*	*n.d.*	Meropenem	No	No	No	3	No etiology
122	*Methicillin-resistant S. Aureus*	*Staphylococcus* *S. aureus mecA - Detected* *C. albicans* *C. glabrata*	Colistin	No	No	Yes	1	Remove colistin and change to linezolid or vancomycin

123	*K. pneumoniae, E. coli, C. koseri*	*Enterobacteriaceae Klebsiella pneumoniae Candida krusei Candida parapsilosis KPC - Detected*	Colistin	Yes	No	No	3	Appropriate treatment
124	*A. baumannii, S. marcescens*	*Streptococcus A. baumannii C. albicans*	Meropenem	Yes	No	Yes	1	Change to colistin
125	*E. coli*	*Enterobacteriaceae E. coli*	Meropenem	No	No	Yes	1	Remove meropenem and change to ceftriaxone
126	*P. aeruginosa, A. baumannii*	*A. baumannii, P. aeruginosa*	Meropenem	No	No	Yes	1	Remove meropenem and change to colistin+ ceftazidime
127	*K. pneumoniae, A. baumannii*	*A. baumannii Enterobacteriaceae K. pneumoniae KPC - Detected*	Colistin	No	No	No	3	Appropriate treatment
128	*P. aeruginosa, A. baumannii*	*P. aeruginosa C. albicans C. parapsilosis*	Meropenem	No	No	Yes	1	Remove meropenem and change to ceftazidime. But it should also be needed colistin
129	*P. aeruginosa, A. baumannii*	*A. baumannii Enterobacteriaceae P. aeruginosa C. glabrata*	Colistin		Yes	Yes	1	Remove linezolid
130	*n.d.*	*C. albicans*	Meropenem	No	No	No	3	No etiology
131	*n.d.*	*Staphylococcus Streptococcus Enterobacteriaceae K. pneumoniae C. albicans C. parapsilosis mecA - Detected KPC - Not Detected*	Colistin	No	No	No	3	No etiology

132	*E. faecium*	*Enterococcus* *Streptococcus* *S. pneumoniae* *C. albicans* *C. glabrata*	Meropenem	No	No	No	1	Change to ceftriaxone
133	*n.d.*	*C. albicans*	Colistin	No	Yes	No	3	No etiology
134	*n.d.*	*C. albicans* *C. glabrata*	Colistin	Yes	No	No	3	No etiology
135	*E. coli*	*n.d.*	Colistin	Yes	No	No	3	FilmArray does not identify microorganism
136	*n.d.*	*Candida albicans*	Colistin	No	Yes	No	3	No etiology
137	*K. oxytoca, C. braakii*	*Staphylococcus* *S. aureus* *Enterobacteriaceae mecA and KPC not detected*	Meropenem	No	Yes	Yes	1	Change to vancomycin
138	*K. pneumoniae, E. cloacae*	*n.d.*	Meropenem	No	No	No	3	FilmArray does not identify microorganism
139	*E. aerogenes*	*Enterococcus* *Streptococcus* *Enterobacteriaceae* *C. albicans*	Colistin	No	No	No	3	FilmArray does not identify microorganism
140	*P. aeruginosa*	*P. aeruginosa*	Meropenem	No	No	Yes	1	Remove meropenem and change to ceftazidime
141	*A. baumannii*	*Staphylococcus* *S. aureus mecA - Detected* *A. baumannii* *H.influenzae* *C. albicans*	Colistin	No	No	Yes	2	Inappropriate change. It is added vancomycin/ linezolid unnecessary
142	*n.d.*	*C. glabrata*	Colistin	No	No	No	3	No etiology
143	*n.d.*	*n.d.*	Colistin	No	No	No	3	No etiology
144	*E. ludwigii*	*Enterobacteriaceae* *C. albicans*	Colistin	No	No	No	3	FilmArray does not identify microorganism

145	*n.d.*	*Staphylococcus* *S. aureus* *C. albicans* *C. tropicalis*	Meropenem	No	Yes	Yes	1	Change to vancomycin
146	*Serratia spp, K. pneumoniae*	*H. influenzae* *C. albicans*	Colistin	No	No	Yes	2	Inappropriate change to ceftriaxone
147	*E. coli*	*Enterobacteriaceae* *E.coli* *H. influenzae* *C. albicans* *C. glabrata* *C. tropicalis*	Meropenem	No	No	Yes	1	Remove meropenem and change to cephalosporin 3G
148	*n.d.*	*n.d.*	Meropenem	No	No	No	3	No etiology
149	*A. xilosoxidans*	*Staphylococcus* *S.aureus* *C. albicans mecA not detected*	Meropenem	No	No	No	3	FilmArray does not identify microorganism
150	*C. striatum*	*Staphylococcus* *S. aureus mec detected* *H. influenzae* *C. albicans*	Meropenem	No	No	Yes	1	Change to vancomycin

Supplemental Table 1: Changes in antimicrobial treatment following BCID Panel.