

32 **Abstract:**

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34 **Introduction:** Rapid organism identification (ID) and antimicrobial susceptibility testing
35 (AST) along with antibiotic stewardship (ASP) are critical to appropriate treatment. We
36 sought to capture time for bacterial culture and initiation of appropriate therapy for
37 patients, from 2017 (without MALDI-TOF/Vitek 2 and ASP) and 2018 (with MALDI-
38 TOF/Vitek 2 and ASP).

39 **Methods:** Eligible patients admitted to our hospital with a positive sputum, blood, or
40 urine culture. Sequential patients were retrospectively obtained from March 1 to May 31,
41 2017. Seventy-seven patients from 2017 were compared to 77 patients from 2018. A
42 time-in-motion study was performed to compare time to identification (ID), AST results,
43 and ASP team intervention for the two periods. Data were entered into SPSS (ver 25)
44 for analysis. Results are reported as mean (\pm SD) or percentage.

45 **Results:** Time to organism ID was significantly faster in 2018 (2018 24.9 ± 14.4 , 2017
46 33.8 ± 17 h, $p=0.001$). Time to AST results was also significantly faster for patients in
47 2018 compared to 2017 (18.2 ± 14 compared to 28.5 ± 14.9 h, $p<0.001$). ASP team
48 recommended significantly more adjustments to empiric antimicrobial therapy in 2018
49 (28% of 2018 vs. 2% in 2017, $p< 0.001$). Length of hospital stay was significantly
50 shorter in 2018 compared to 2017 (2018 10.7 ± 11.1 days and 2017 15.5 ± 18.1 days,
51 $p=0.05$).

52 **Conclusions:** Use of MALDI-TOF/Vitek 2 leads to an average 21.5 h faster ID and AST
53 results that can be acted upon by ASP for appropriate antimicrobial recommendations.

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58 Bacterial infections in the healthcare associated setting cause significant
59 morbidity and mortality, especially when initial treatment is sub-optimal. This has been
60 clearly demonstrated especially for Gram-negative bloodstream infections (BSIs).(1)
61 Early effective antimicrobial therapy has demonstrated reductions in mortality in patients
62 with sepsis.(2) With antibiotic resistance on the rise, especially in gram-negative bacilli,
63 it is becoming increasingly difficult for clinicians to select the most optimal empiric
64 antibiotic therapy.⁽³⁾

65 Laboratory diagnosis of infections is typically dependent on routine culture and
66 phenotypic identification utilizing Gram stain and analysis of biochemical reactions,
67 along with antimicrobial susceptibility testing (AST).(4) Rapid diagnostic tests that allow
68 for earlier identification of pathogens, and in some situations, early identification of
69 resistance patterns, have been shown to reduce time to attaining optimal antibiotic
70 therapy(5-9). Additionally, with the combination of antimicrobial stewardship
71 intervention, these tests have demonstrated a reduced mortality benefit(9, 10). While
72 these tests have enhanced the management of BSIs, the use of MALDI-TOF and Vitek
73 2 for organism identification and AST along with ASP more generally was of interest to
74 explore.

75 CHI Health Nebraska is a 14-hospital health system made up of critical access
76 hospitals (5), community-based hospitals (8) and one academic medical center (400
77 beds) affiliated with Creighton University Health Science Schools (nursing, medicine,
78 pharmacy, physical and occupational therapy). Recent acquisition of a matrix assisted
79 laser desorption/ionization time-of-flight (MALDI-TOF) for organism identification and
80 Vitek 2 for AST in the centralized microbiology laboratory for all CHI Health hospitals

81 has led us to propose this quasi-experimental time-in-motion study design to determine
82 the effect on patient hospitalization outcome. The primary objective was to determine,
83 using a time-in-motion study design, the effect of integrated use of MALDI-TOF/Vitek 2
84 and ASP for patients with urine, respiratory (based on sputum culture), or BSI at the
85 academic hospital of CHI Health.

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87 **Methods:**

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89 Microbiology. For both time periods, routine cultures of urine, sputum, and blood were
90 performed using standard techniques. For blood cultures, the BACTEC system was
91 used. For the 2017 time period, organism ID and AST were performed primarily using
92 the MicroScan microdilution system performed according to manufacturer's instructions.
93 MALDI-TOF/Vitek 2 (bioMerieux, Inc. St. Louis, MO) became available for general use
94 for organism ID (MALDI-TOF) and AST (Vitek 2) in March 2018 after significant
95 verification procedures were completed. Microbiological workflow was similar to Huang
96 AM, et al.(6) except we are reporting MALDI-TOF and Vitek 2 AST from urine, blood,
97 and sputum cultures after subculture to solid media and incubated overnight.
98 Additionally, workflow was adjusted to take maximum advantage of the faster
99 turnaround time for ID and AST in that cultures were continuously examined soon after
100 a minimum of 18 hours of incubation after specimen inoculation with growth of potential
101 pathogens processed on the MALDI-TOF and Vitek 2 as soon as possible afterwards.
102 Results were then reported as they became available immediately after they were
103 verified which occurred from 6:30AM to the end of staffing (11PM weekdays and 5PM
104 weekends). Thus, there were two groups in the study; the control group (2017 time
105 period) and the experimental group (2018 time period). Consecutive patients from both

106 time periods (2017 and 2018) were eligible when one culture type was positive (i.e.
107 urine culture positive without blood culture positive) for urine and sputum cultures. BSI
108 could have more than one site with positive isolates.

109 Antimicrobial Stewardship. For the 2017 time period (control group), limited ASP was
110 available from staff pharmacists without dedicated ASP personnel. Staff pharmacists
111 were expected to make interventions as part of their normal workflow. In 2018,
112 dedicated ASP personnel were hired providing robust ASP for all CHI Health hospitals
113 (0.5 FTE ID physician and 2.5 FTE ASP pharmacist) and they replaced staff
114 pharmacist's interventions. All ASP pharmacists monitored patients through TheraDoc
115 and consulted the ID clinician for all antimicrobial recommendations. ASP pharmacists
116 were available during normal work hours (8-4:30) and made recommendations on
117 patients receiving empiric therapy with carbapenems, daptomycin, double coverage,
118 (double anaerobic coverage), all *C. difficile* positive patients, and all *S. aureus*
119 bacteremias. Since both ASP infectious diseases physician and pharmacists made
120 antimicrobial recommendations to primary care physicians (PCPs), other types of
121 recommendations were suggested including ID consult, TEE, and length of therapy as
122 examples. Both years utilized Biofire BCID (Biofire Diagnostics, Salt Lake City, UT) for
123 rapid detection system on all positive blood cultures. However, in 2018 laboratory
124 technicians increased their daily time frame when Biofire was reported for positive blood
125 cultures (7 am-10 pm). All Biofire results were paged to ASP team. The ASP
126 pharmacist kept the Biofire pager (7-5) and then handed it off to the on-call ID fellow
127 overnight and weekends. In 2017, Biofire results were reported during normal laboratory
128 hours (7 am – 5 pm) and were reviewed by the staff pharmacists as part of an inbasket

129 work queue in EPIC. ASP pharmacists were available five days/week and used
130 TheraDoc (TheraDoc ver 4.7, Hospira, Lake Forest, IL) for clinical decision support
131 software. ASP pharmacists documented their intervention in EPIC as a progress note.
132 Staff pharmacists as part of their normal duties performed weekend coverage. To
133 summarize, in 2017 (control group) rapid diagnostic testing (Biofire) was used for
134 positive blood cultures only and the Microscan instrument was used for urine and
135 sputum results without ASP team intervention. In 2018, Biofire was used for positive
136 blood cultures and called to ASP team and MALDI-TOF/Vitek 2 was used for urine and
137 sputum cultures and not called to the ASP team once positive.

138 Consent was not required because the standard of care was evaluated for quality
139 assurance purposes. The control group (March-April 2017) identified adult patients (\geq
140 19 years of age) with blood, urine, or sputum culture obtained and reported while
141 hospitalized. Charlson comorbidity index was used for parity between 2017 and 2018
142 data(11).

143 Exclusion criteria. Patients who were transferred into the hospital from an outside
144 hospital and were empirically treated for a bacterial infection or sepsis, patients
145 transitioned to comfort care or hospice within the first 72 h of antimicrobial therapy,
146 patients who expired prior to identification of the organism, and contaminant cultures
147 and patients empirically placed in isolation for “rule-out” mycobacterial pneumonia.

148 Statistical Analysis. Dichotomous data were analyzed using Chi-square or Fisher’s
149 exact test. Continuous, normally distributed data were analyzed by Student t-test.
150 Continuous, non-normally distributed data were analyzed using Mann Whitney U test.
151 Data were collected from EPIC and entered into Statistical Package for the Social

152 Sciences (SPSS, ver. 25, IBM, NY). Data will be presented as percentages or mean \pm
153 standard deviation (SD).

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155 Results:

156 In the control group (2017), a total of 77 patients (27 blood isolates, 25 sputum,
157 and 25 urine isolates) were retrospectively enrolled between March-May 2017. In the
158 MALDI-TOF/Vitek 2 group, a total of 77 patients (28 blood isolates, 24 sputum, and 25
159 urine isolates) were concurrently enrolled in the same time frame in 2018. Mean (\pm SD)
160 patient age and Charlson Comorbidity Index (CCI) were not different between the two
161 groups (Table 1). Additionally, patients were admitted to the intensive care unit 31% in
162 2017 and 32% in 2018, respectively. Microorganisms isolated included 10 (6.5%) that
163 were polymicrobial and the remaining were monomicrobial isolates. The most common
164 single isolate included *E. coli* (30%), methicillin-sensitive *S. aureus* (MSSA) (9%), *S.*
165 *pneumoniae* (8%), and *P. aeruginosa* (7%). There were no significant differences in the
166 number of isolates in the study from 2017 compared to 2018. The most common sites
167 of infection from patients in both years included urine (69, 45%), lung (55, 38%), and
168 skin (10, 6.5%).

169 In 2018, with the addition of MALDI-TOF/Vitek 2 results available, ASP team
170 intervened significantly more often for patients' empiric antimicrobial therapy compared
171 to 2017 (2018 29%, 2017 2%, $p < 0.001$). The most common intervention was to
172 change empiric therapy (59%). In 2018, the ASP team made empiric antibiotic
173 recommendations. In bacteremic patients, ASP team changed empiric antimicrobial
174 therapy in 19 of 28 (68%). For patients with positive sputum cultures, the ASP team

175 recommended to increase antimicrobial dose in 15 of 24 (62.5%). In patients with
176 positive urine cultures, the majority (84%) did not require a change in empiric therapy.
177 Additionally, time from the AST results to pharmacists making antimicrobial
178 recommendations averaged 0.13 ± 1.5 h compared to 0.24 ± 0.74 h in 2017. However,
179 hospital staff pharmacists made 2 ASP recommendations in 2017 and ASP team made
180 22 study recommendations in 2018. All but one ASP recommendations were accepted
181 in 2018.

182 The time-in-motion data collection for culture ID and AST determination
183 demonstrated significant results comparing 2017 without ASP or MALDI-TOF/Vitek 2
184 and 2018 with ASP and MALDI-TOF/Vitek 2 (Table 2). The time to receive the
185 specimen in the Microbiology Laboratory for both 2017 and 2018 averaged
186 approximately 5 h. Additionally, time from laboratory receipt of specimen until Gram-
187 stain results averaged 15 h in both 2017 and 2018. However, organism identification
188 was significantly faster averaging 10 h sooner and AST results were available 10 h
189 sooner for MALDI-TOF/Vitek 2 patients compared to 2017 without these instruments.
190 Total time for ASP team to make empiric antimicrobial changes averaged 84 h in 2017
191 and 62.5 h in 2018, a 21.5 h difference.

192 Length of hospitalization (LOS) (10.7 ± 11.1 d vs. 15.5 ± 18.1 d, $p=0.05$) and
193 length of in-patient antimicrobial therapy (6.7 ± 3.8 d vs. 8.8 ± 7.8 d, $p=0.036$) were
194 significantly shorter for the ASP and MALDI-TOF/Vitek 2 group. Of interest, the LOS
195 differences between the two groups was most dramatic in ICU, averaging 7 days
196 shorter for patients in the ASP and MALDI-TOF/Vitek 2 group, ($p<0.001$) whereas
197 patients admitted to the general medicine floor averaged 4 d shorter in the ASP and

198 MALDI-TOF/Vitek 2 group. Finally, we sought to determine which variables were
199 associated with LOS using a stepwise linear regression analysis. Variables that were
200 significant by univariate analysis were entered into the linear regression analysis to
201 determine variables that significantly correlated with LOS. After the stepwise
202 procedure, one variable was included in the model, length of in-patient antimicrobial
203 (Table 3). This significant variable captured 31% of the LOS variation ($p < 0.0001$).

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205 Discussion:

206 The use of rapid diagnostic testing including MALDI-TOF and Vitek 2 AST has
207 been proven to reduce time to organism identification. However, the incorporation of
208 the ASP team along with rapid isolate identification and AST allows rapid interpretation
209 of the results communicated to the primary care physician to make changes in
210 antimicrobial therapy. Huang AM, et al. and Perez and colleagues both conducted pre-
211 post quasi-experimental studies integrating MALDI-TOF organism identification plus
212 ASP intervention, but limited to either BSIs, or Gram-negative bacteremias,
213 respectively(6, 7). Huang, et al. enrolled 245 patients into an intervention group using
214 MALDI-TOF and ASP and 256 patients into a preintervention group for bacteremias. In
215 their study, length of ICU stay averaged 6 d shorter for the intervention group. Perez
216 and colleagues enrolled 153 patients with antibiotic resistant Gram-negative
217 bacteremias as the control group and 112 patients in the intervention group. Their LOS
218 differences averaged 6 d longer for the control group overall with the ICU LOS
219 averaging 5.3 d longer. These studies are consistent with the current study, which
220 demonstrated that, with shorter turnaround time for ID and AST using optimized

221 microbiology workflow and MALDI-TOF and Vitek 2, combined with a vigorous ASP, a
222 significant reduction in LOS was achieved. Our previous de-escalation study confirms
223 these results that shorter LOS is more exaggerated for ICU patients(12). Wenzler and
224 colleagues reported use of MALDI-TOF and ASP for pneumonia or bacteremia caused
225 by *A. baumannii*. Their results demonstrated the combination reduced time to effective
226 therapy by 41 h and was associated with an increased clinical cure for those patients.
227 Bookstaver et al. combined rapid diagnostic testing using Biofire BCID and ASP as a
228 bundle for their quasi-experimental cohort of Gram-negative bloodstream infections in
229 their multihospital health system(13). These investigators enrolled 830 patients into a
230 preintervention group and 333 patients into a postintervention group with Gram-negative
231 bacteremias. Their results demonstrated significant reductions in median time to de-
232 escalate combination antimicrobials and initiation of more appropriate empiric
233 antimicrobial therapy (before AST results were known). These investigators found
234 significant reductions in median time to de-escalate combination antimicrobials and
235 more appropriate empiric antimicrobial therapy (before AST results were known). Taken
236 together along with the results of these studies, implementation of this process
237 throughout our 14-hospital health-system with centralized Microbiology Laboratory
238 would show a significant benefit to the care of infected patients now that there are more
239 ASP pharmacists (3 covering CHI Health) and an ID physician with 0.5 FTE devoted to
240 ASP across all hospitals in the health system.

241 However, there are limits associated with this study. A lack of patient
242 randomization in the quasi-experimental study may not take into account changes in
243 standard of care from the previous year, which could impact LOS. To our knowledge,

244 both years incorporated Biofire BCID and there were no significant changes in standard
245 of care except the introduction of the ASP team to make antimicrobial
246 recommendations. The study periods were selected to minimize bias associated with
247 medical residents and fellows at our academic medical center. This study excluded
248 patients transferred into our regional hospital so all antimicrobials administration times
249 were in-hospital times and not from administrations prior to admission. The effect of
250 ASP was not directly identified in the stepwise multiple regression analysis. However,
251 length of antimicrobials was identified as the primary factor associated with LOS, and
252 ASP team did have an impact on this variable. By making appropriate antimicrobial
253 recommendations, the ASP team impacted length of therapy and indirectly (probably)
254 impacted LOS. It would be of interest to repeat this study from all CHI Health hospitals
255 in Nebraska to determine the effect of ASP team and MALDI-TOF/Vitek 2 would have
256 on these community hospitals in addition to this report since the centralized laboratory
257 receives these specimens as far away as Kearney, NE (186 miles).

258 In conclusion, use of ASP and MALDI-TOF/Vitek 2 rapid identification and AST
259 demonstrated for urine, blood, and sputum cultures a significant reduction in time to
260 isolate identification and AST results, which translated to significant reduction in
261 antibiotic length of therapy and hospital LOS.

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Table 1. Demographics of Study Patients

Variable	2017 (without ASP + MALDI-TOF/Vitek 2)	2018 (with ASP + MALDI-TOF/Vitek 2)
Age (yrs)	68.2 ± 15.3	65.8 ± 18.5
CCI	3.5 ± 2.2	3.6 ± 2.3
Percent female (%)	56	51
Admitted to ICU (%)	31	32
Isolates from:		
Blood culture (n)	27	28
Sputum culture (n)	25	24
Urine culture (n)	25	25
Blood cultures:		
Candida spp	0	2
<i>E. coli</i>	6	8
Enterococcus spp	3	0
Enterobacter spp.	1	0
Klebsiella spp.	3	1
MRSA	2	1
MSSA	3	5
<i>S. pneumoniae</i>	3	3
Proteus spp.	1	1
Serratia spp.	1	0

Streptococcus spp.	1	6
VRE	0	1
Polymicrobial isolates	3	0
Sputum cultures:		
Acinetobacter spp.	0	1
Citrobacter spp.	0	1
<i>E. coli</i>	0	1
Klebsiella spp.	2	2
<i>H. influenzae</i>	1	2
<i>M. catarrhalis</i>	0	3
MRSA	1	2
Polymicrobial isolates	3	0
Urine cultures:		
Aerococcus	0	1
Candida spp.	1	0
<i>E. cloacae</i>	1	0
<i>E. coli</i>	17	14
Klebsiella spp.	1	3
<i>S. pneumoniae</i>	1	0
Proteus spp.	1	6
Pseudomonas spp.	1	0
Stenotrophomonas spp.	1	0

326 CCI = Charlson comorbidity index; ICU = intensive care unit; MRSA = methicillin

327 resistant *S. aureus*; MSSA = methicillin sensitive *S. aureus*

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329 Table 2. Time Parameters to Identify Organism and Obtain AST

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Time Variable	2017 (without ASP + MALDI-TOF/Vitek 2)	2018 (with ASP + MALDI-TOF/Vitek 2)	Statistical significance
Culture transport time (h)	5.9 ± 6	4.7 ± 4.8	P > 0.05
Gram stain report time (h)	15.9 ± 14.2	14.9 ± 10.4	P > 0.05
Identify and report organism (h)	33.8 ± 17	24.9 ± 14.4	P = 0.001
Perform and report AST (h)	28.5 ± 14.9	18.2 ± 14	P < 0.001

331 AST = antimicrobial susceptibility testing; ASP = antimicrobial stewardship program

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335 Table 3. Length of Hospitalization Regression Analysis

Independent Variable	Hospitalization Length Coefficients (95% CI)
Constant	-0.78 (-5.24; 3.69)
Length of antimicrobial therapy	1.64 (1.05; 2.24)
Variables excluded:	Beta In:
MALDI-TOF time	0.12
Traditional ID time	0.052

Mortality	0.12
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336 CI = confidence interval