

## The hypothetical impact of Accelerate Pheno™ system on time to effective therapy and time to definitive therapy in an institution with an established antimicrobial stewardship programme currently utilizing rapid genotypic organism/resistance marker identification

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**Background:** Rapid organism identification and antimicrobial susceptibility testing (AST) can optimize antimicrobial therapy in patients with bacteraemia. The Accelerate Pheno™ system (ACC) can provide identification and AST results within 7 h of a positive culture.

**Objectives:** To assess the hypothetical impact of ACC on time to effective therapy (TTET), time to definitive therapy (TTDT) and antimicrobial usage at the Detroit Medical Center (DMC).

**Methods:** Patients with positive blood cultures from 29 March to 24 June 2016 were included. ACC was performed in parallel with normal laboratory procedures, but results were not made available to the clinicians. The potential benefit of having ACC results was determined if clinicians modified therapy based on actual AST results. Potential changes in TTET, TTDT and antibiotic usage were calculated.

**Results:** One hundred and sixty-seven patients were included. The median TTET was 2.4 h (IQR 0.5, 15.1). Had ACC results been available, TTET could have been improved in four patients (2.4%), by a median decrease of 18.9 h (IQR 11.3, 20.4). The median TTDT was 41.4 h (IQR 21.7, 73.3) and ACC results could have improved TTDT among 51 patients (30.5%), by a median decrease of 25.4 h (IQR 18.7, 37.5). ACC implementation could have led to decreases in usage of cefepime (16% reduction), aminoglycosides (23%), piperacillin/tazobactam (8%) and vancomycin (4%).

**Conclusions:** ACC results could potentially improve time to de-escalation and reduce use of antimicrobials. The impact of ACC on TTET was small, likely related to the availability of other rapid diagnostic tests at DMC.

### Introduction

Sepsis is an enormous burden on society, accounting for ~850 000 emergency visits per year and up to 381 000 sepsis-related deaths annually in the USA.<sup>1,2</sup> Among patients who develop septic shock, the mortality rate is ~39%.<sup>3</sup> Early appropriate antibiotic administration among septic patients with bacteraemia is an important determinant of survival. Multiple studies have demonstrated associations between a delayed time to effective antibiotic therapy and poor outcomes.<sup>4–8</sup> The mortality rate of hypotensive patients

increases by 8% every hour that effective antibiotic therapy is delayed.<sup>9</sup>

Importantly, the negative impact of delays in time to the initiation of effective antibiotics is not limited to haemodynamically unstable patients. Even after controlling for the presence of severe sepsis or septic shock, the 14 day mortality in bacteraemic patients with inadequate empirical therapy increases 3-fold.<sup>10</sup> A recent analysis in patients with Gram-negative bacteraemia and low severity of illness demonstrated that hospital length of stay was roughly 4 days longer in patients who had inappropriate empirical

therapy compared with those who had effective empirical therapy.<sup>11</sup>

Unfortunately, initial antibiotic selection may be inappropriate in 20%–30% of patients.<sup>5–7</sup> Conversely, indiscriminate use of broad-spectrum empirical antibiotics is associated with an increased risk of adverse events and the development of resistance.<sup>12</sup> Strategies are urgently needed to guide clinician decision-making regarding early implementation of broad-spectrum therapy so that it can be provided only when necessary.

Rapid identification of the microorganism and its antimicrobial susceptibility testing (AST) profile can provide valuable information that can improve the timing and efficacy of antimicrobial therapy while limiting unnecessary broad-spectrum exposure. Recently, technologies have been developed to increase the rapidity of organism identification to 1–2 days following culture draw.<sup>13</sup> Most currently available rapid diagnostic platforms rely on identification of specific genes and/or proteins to identify the causative organism and a limited number of resistance genotypes. However, these platforms do not provide phenotypic antimicrobial susceptibility results, with susceptibility results often not being available until 3–4 days after culture.<sup>13</sup>

The Accelerate Pheno™ system (ACC; Accelerate Diagnostics, Tucson, AZ, USA) is a unique rapid diagnostic test (RDT) that both identifies an organism in <90 min and provides phenotypic antimicrobial susceptibility results within 7 h after an organism starts to grow in a blood culture.<sup>14</sup> This technology has the potential to improve the rapidity with which active antibiotics can be provided to infected patients and limit the duration of unnecessary broad-spectrum antibacterial exposure.

The goal of this study was to determine the hypothetical impact of the ACC on inpatient antimicrobial prescribing, with regard to time to effective therapy, time to definitive therapy and overall antimicrobial usage, in a hospital where antimicrobial stewardship is well established and rapid genotypic tests for organism identification are already being utilized.

## Materials and methods

### Study design and setting

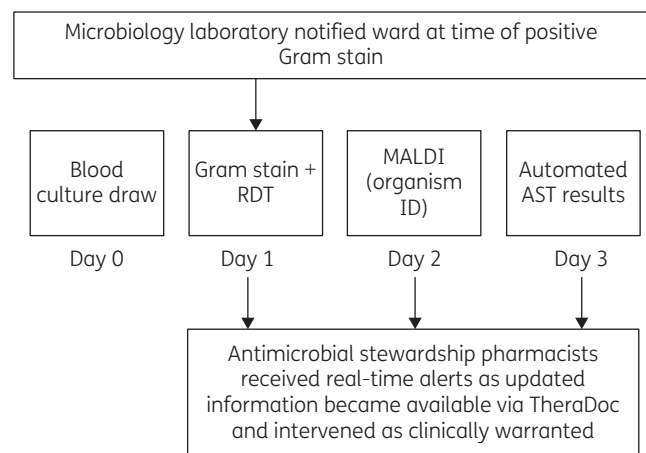
The study was a retrospective cohort analysis of patients with positive blood cultures at the Detroit Medical Center (DMC). The DMC is a tertiary-care health system located throughout metropolitan Detroit, MI, USA and consists of six acute-care hospitals with >2000 inpatient beds.

### Ethics

This study was approved by the institutional review boards of Wayne State University and the DMC.

### Study population

The study population included patients with positive blood cultures between 29 March 2016 and 24 June 2016. The patient cohort was selected as part of a previous study to determine the accuracy of the ACC ID/AST compared with conventional methods.<sup>14</sup> Unique patients were eligible if a blood culture became positive and could be tested on the ACC platform within 8 h of positivity. Patients were excluded from the study assessing the hypothetical clinical impact of ACC if the patient died or was discharged prior to the culture becoming positive or if an organism was considered to



**Figure 1.** DMC laboratory process.

be a contaminant. An organism was defined as a contaminant if the clinical team considered the organism to be a contaminant and did not treat it.

### Laboratory procedures

In this study, the hypothetical clinical performance of the ACC was compared with the standard organism identification and antimicrobial susceptibility testing procedures performed by the DMC. The DMC utilizes the BD BACTEC™ Automated Blood Culture System (BD Diagnostic Systems, Franklin Lakes, NJ, USA) for the growth and detection of microorganisms present in blood culture samples (Figure 1). During the study period, once a blood culture turned positive, a Gram stain was performed, and laboratory personnel called the nursing manager of the patient care ward where the patient was boarded to notify staff of the positive result. Subsequently, in the microbiology laboratory, two processes were performed in parallel: (i) multiplex molecular diagnostic testing was performed to identify the microorganism and to determine the presence of select resistance genes. Gram-positive organisms were tested with the Verigene® Gram-Positive Blood Culture (BC-GP) nucleic acid tests and Gram-negative organisms with the Verigene® Gram-Negative Blood Culture (BC-GN) nucleic acid tests (Luminex Corporation, Austin, TX, USA). Samples that grew yeast were tested with a fluorescence *in situ* hybridization method that uses peptide nucleic acid to identify *Candida* species; (ii) samples were subcultured onto appropriate media as indicated by Gram stain. After bacterial colonies grew, identification was performed by MALDI-TOF MS (MALDI Biotyper®; Bruker Daltonics, Billerica, MA, USA) and antimicrobial susceptibilities were evaluated using the BD Phoenix™ Automated Microbiology System (BD Diagnostic Systems, Franklin Lakes, NJ, USA). The microbiology procedures described above were performed in real time.

Following the reporting of the initial Gram-stain results to the patient ward by laboratory personnel, no subsequent notifications were provided, and testing updates only appeared in the electronic medical record. However, antimicrobial stewardship pharmacists continually monitored positive blood culture results, including results from RDTs, organism identification and antibiotic susceptibilities and intervened as clinically warranted during normal business hours.

Positive blood cultures from study patients were also tested with the ACC using pre-FDA clearance software version 1.0. The results from the ACC were not released to the clinicians and did not influence care. Samples were tested within 8 h of culture positivity. For each isolate tested, the ACC start and completion times were recorded for both identification and susceptibility results. For tests that were not run in real time, these times were extrapolated to the time that they would have been available if they had been run in real time.

## Data collection

Clinical data abstracted included demographics, comorbid conditions, microbiology data and information related to the source and clinical course of the infection. Infections were classified as hospital-acquired, health-care associated or community-acquired in accordance with referenced standards.<sup>15</sup> Comorbid conditions were used to determine the patient's Charlson comorbidity index. Acute severity of illness was assessed via the Pitt bacteremia score<sup>16</sup> and SOFA score.<sup>17</sup>

Total antibiotic usage for study patients during the admission was captured. For each antibiotic, dates and times of first dose and discontinuation were collected. Dates and times were also recorded for the following events: drawing of the initial blood culture and when it first turned positive; availability of results from the rapid genotypic testing; and availability of results pertaining to final organism identification and antimicrobial susceptibility tests.

## Definitions pertaining to antimicrobial therapy

An effective antibiotic was defined as an antibiotic with *in vitro* activity against the identified pathogen. The definitive antibiotic regimen was that which was selected by the treating team after susceptibility information was available. Escalation of therapy was defined as an antibiotic regimen that was changed from a narrower to a broader spectrum of activity. De-escalation of therapy was defined as an antibiotic regimen that was changed from a broader to a narrower spectrum of activity.

Each case was adjudicated by three investigators (C. C. C., O. H. and N. H.) to determine whether effective and definitive therapy had been provided to patients and also to determine whether effective and/or definitive therapy could have been provided more rapidly if results from the ACC had been available in real time. If adjudication decisions were not unanimous then two additional investigators (J. M. P. and K. S. K) participated in the process. It was determined that there would have been a potential benefit of having had the ACC results if, in actuality, once final antimicrobial susceptibility results became available per standard microbiology processes, the treating clinicians transitioned therapy from an ineffective to an effective antibiotic, or from an initial to a definitive antibiotic regimen.

For each patient, the time to effective therapy (TTET) and time to definitive therapy (TTDT) were calculated. TTET was defined as the difference between the time that the blood culture was drawn and the time an antibiotic with *in vitro* activity against the pathogen was first administered. TTDT was defined as the time from the blood culture being drawn to the time that the definitive regimen was provided. Potential decreases in the times to implementation of effective and definitive therapy were calculated by determining the differences in times when results became available for standard susceptibility test results and when the ACC results would have been available. If patients were transitioned to effective or definitive therapy prior to final AST results becoming available, but after the results of ACC would hypothetically have been available, the potential decreases in TTET or TTDT were calculated as the difference between the time of the actual intervention and the time ACC results would have been available plus 2 h. These 2 h were added to reflect an estimated amount of time from when the ACC results would have been made available to when therapy would be modified and administered.

The time to Verigene results was calculated as the difference (in hours) between the time that blood cultures were drawn and the time when Verigene results were available, and the time from Verigene results to effective therapy or definitive therapy was calculated and presented.

In order to evaluate the potential impact of having had ACC results on antimicrobial usage, a novel metric was assessed: individual antibiotic days/1000 inpatient bacteraemia treatment days. This metric was assessed both as a descriptor for how the cohort was actually managed and to assess the hypothetical impact the ACC could have had on antibiotic use. This metric was created by summing the total usage of each individual antibiotic as a function of total inpatient bacteraemia treatment days. For example, if a

patient received 4 days of cefepime and 6 days of ceftriaxone for the management of a Gram-negative bacteraemia, this would be described as 4 cefepime days/10 inpatient bacteraemia treatment days and 6 ceftriaxone days/10 inpatient bacteraemia treatment days. This process was then completed for each patient in the cohort and a total number of antibiotic days for each individual agent as a function of total bacteraemia treatment days for the cohort was calculated. These data were then normalized and expressed as antibiotic use per 1000 inpatient bacteraemia treatment days.

In order to assess the potential impact of the ACC on antibiotic use, consideration was given to the timing of antibiotic escalation and de-escalation that would have occurred had the ACC results been available. In the example above, cefepime was de-escalated to ceftriaxone on day 4. If it was determined that this de-escalation would have occurred 2 days earlier had the ACC results been available, the hypothetical antibiotic usage days for that patient would have been 2 cefepime days/10 inpatient bacteraemia treatment days and 8 ceftriaxone days/10 inpatient bacteraemia treatment days. This process of calculating individual hypothetical antibiotic days/inpatient bacteraemia treatment days based on ACC data having been available was completed for each patient in the cohort. Similar to the above process, a hypothetical total number of antibiotic days for each individual agent as a function of total bacteraemia treatment days for the cohort was calculated, and then normalized to 1000 inpatient bacteraemia treatment days. The relative differences between the hypothetical bacteraemia treatment days and the actual bacteraemia treatment days were utilized to assess the potential impact of ACC on antimicrobial usage.

## Results

Two hundred and twenty-five patients with positive blood cultures were screened. Twenty-two patients were excluded owing to death or discharge prior to the time of culture positivity and 36 were excluded because culture results represented contamination.

The final cohort included 167 patients with 182 pathogens isolated. The mean  $\pm$  SD age was  $54.1 \pm 23.8$  years, 79 (47.3%) were female and 40 (24%) came from long-term care facilities (Table 1). Most of the patients acquired bloodstream infections in the hospital or other healthcare facilities (134, 81.3%). Table 2 lists the causative pathogens. The most common Gram-positive organism was *Staphylococcus aureus*, of which 28/45 (62.2%) were MRSA. The most common Gram-negative organism was *Escherichia coli*. Nine (5.4%) had polymicrobial bloodstream infections. The most common sources of infection were catheter-related ( $n=41$ , 24.9%) and genito-urinary tract ( $n=35$ , 21.2%) (Table 1). Eleven patients (6.6%) died during hospitalization.

## Antibiotic therapy modifications

Antibiotic modification based on culture information occurred in most patients. De-escalation was performed in 92 patients (55.1%), escalation occurred in 40 patients (24%) and regimens remained unchanged in 35 patients (21%).

## Effective therapy

One hundred and sixty-six (99.4%) patients received effective therapy. The median TTET was 2.4 h (IQR 0.52, 15.1) for the entire cohort, and ranged from 2.2 h to 14.9 h for pathogen subgroups (Table 1). Among 156 patients who had Verigene results available, 29 (18.5%) had Verigene results prior to beginning effective therapy. The median time from when the culture was drawn to the time of effective therapy among these patients was 4.2 h (IQR 2, 9).

**Table 1.** Description of cohort, pathogen subgroups, effective antimicrobial therapy and optimal antimicrobial therapy<sup>a</sup>

Variable	Entire cohort (N=167)	GNB (N=71)	GPC (N=75)	Mixed <sup>b</sup> (N=9)	Other <sup>c</sup> (N=12)
<b>Demographics</b>					
age, mean ± SD	54.1 ± 23.8	56.7 ± 22	52.4 ± 24.9	50.1 ± 27.7	66.8 ± 2.8
female gender	79 (47.3)	36 (50.7)	31 (41.3)	4 (44.4)	8 (66.7)
residence in LTCF	40 (24.0)	14 (19.7)	22 (29.3)	2 (22.2)	2 (16.7)
Charlson comorbidity index, median (IQR)	3 (2–6)	3 (2–6)	3 (1–6)	2 (2–4)	3 (1–6)
<b>Acute severity of illness</b>					
Pitt score when culture was collected, median (IQR)	1 (0–3)	1 (0–3)	1 (0–3)	1 (1–2)	2.5 (0.5–4.5)
<b>Epidemiological categorization of infection<sup>d</sup></b>					
hospital acquired	25 (15.2)	12 (7.3)	10 (13.3)	2 (22.2)	1 (8.3)
health care facility acquired	109 (66.1)	44 (63.8)	50 (66.7)	6 (66.7)	9 (75)
community acquired	31 (18.8)	13 (18.8)	15 (20)	1 (11.1)	2 (16.7)
<b>Source of bloodstream infection<sup>d</sup></b>					
central venous catheter	41 (24.9)	12 (17.4)	21 (28.0)	2 (22.2)	6 (50.0)
pulmonary	18 (10.9)	6 (8.7)	11 (14.7)	0	1 (8.3)
genito-urinary	35 (21.2)	30 (43.5)	3 (4)	2 (22.2)	0
intra-abdominal	15 (9.1)	9 (13.0)	3 (4)	2 (22.2)	1 (8.3)
skin and soft tissue	15 (9.1)	3 (4.4)	11 (14.7)	0	1 (8.3)
other	25 (15.0)	4 (5.8)	20 (25.3)	1 (11.1)	1 (8.3)
unknown	16 (9.8)	5 (7.3)	7 (9.3)	2 (22.2)	2 (16.7)
<b>Antimicrobial management</b>					
treatment time (inpatient), days, mean ± SD	9.2 ± 7.4	7.1 ± 4.8	11.4 ± 8.1	8.5 ± 4.3	7.8 ± 4.4
<b>Potential benefits in implementation of effective treatment if AAC system results had been available</b>					
patients who received effective treatment	166 (99.4)	70 (98.6)	75 (100)	9 (100)	12 (100)
patients with potential improved time to effective treatment (% of entire cohort)	4 (2.4)	3 (4.2)	1 (1.3)	0	0
TTET <sup>e</sup> , h, median (IQR)	2.4 (0.52–15.1)	2.5 (0.6–9.4)	1.8 (0.5–12.6)	2.2 (1–21.2)	14.9 (1.6–24.7)
time from positive culture to effective treatment <sup>e</sup> , h, median (IQR)	–11.6 (–15.1 to –1.6)	–11.2 (–14.1 to –2.9)	–11.7 (–15.5 to –2.0)	–11.2 (–12.3 to 7.4)	–14.3 (–28.8 to 4.7)
potential improvement (h) from blood draw to effective treatment <sup>f</sup> , median (IQR)	18.9 (11.3–20.4)	19.1 (3.7–21.7)	18.7 (18.7–18.7)	–	–
<b>Potential improvement and time saved for implementation of definitive treatment based on AAC system results</b>					
patients who received definitive treatment	167 (100)	70 (100)	75 (100)	9 (100)	12 (100)
patients with potential improved time to definitive treatment (% of entire cohort)	51 (30.5)	31 (43.7)	18 (24)	2 (22.2)	0
TTDT <sup>g</sup> , h, median (IQR)	41.4 (21.7–73.3)	48.7 (21.7–86.9)	40.5 (23.3–68.5)	30.6 (8.8–83.9)	31.2 (15.5–70.2)
time from positive culture to definitive treatment <sup>g</sup> , h, median (IQR)	27.1 (4.8–57.3)	31.0 (6.3–63.8)	25.8 (5.3–53.4)	10.5 (–3.4 to 70.9)	5.0 (–17.9 to 53.5)
potential improvement (h) from blood draw to definitive treatment <sup>h</sup> , median (IQR)	25.4 (18.7–37.5)	30.7 (22.2–38.6)	20.5 (17.2–30.6)	18.0 (1.8–34.2)	–

Values shown are n (%) unless specified otherwise.

GNB, Gram-negative bacilli; GPC, Gram-positive cocci; LTCF, long-term care facility.

<sup>a</sup>Effective therapy is an antibiotic with *in vitro* activity against the identified infecting pathogen; optimal therapy is the definitive antibiotic regimen with the narrowest spectrum of activity needed to cover bloodstream pathogens and other concomitant infections.

<sup>b</sup>Includes any combination of GNB + GNB, GPC + GNB and GPC + GPC.

<sup>c</sup>Including *Candida* spp., anaerobes (*Prevotella* spp., *Bacteroides* spp., *Veillonella* spp.) and Gram-positive bacilli (*Bacillus cereus*, *Corynebacterium* spp., *Bifidobacterium* spp.).

<sup>d</sup>Data missing for two patients among patients with GNB and in the entire cohort.

<sup>e</sup>Evaluated among patients who received effective therapy (N=166).

<sup>f</sup>Evaluated among patients who had potential benefit to reduce time to effective therapy by using ACC system results, compared with traditional culture results (N=4).

<sup>g</sup>Evaluated among patients who received definitive therapy (N=167).

<sup>h</sup>Evaluated among patients who had potential benefit in reducing time to definitive therapy by using ACC system results, compared with traditional culture results (N=51).

**Table 2.** Pathogens included in the cohort

Pathogen	No. (%) (N=182)
Gram-positive (N = 90)	
MRSA	28 (15.4)
MSSA	17 (9.3)
<i>Streptococcus</i> spp.	19 (10.4)
<i>Enterococcus faecalis</i>	9 (4.9)
<i>Enterococcus faecium</i>	5 (2.7)
CoNS	7 (3.8)
Gram-positive bacilli	5 (2.7)
Gram-negative bacilli (N = 92)	
<i>E. coli</i>	38 (20.9)
<i>Klebsiella</i> spp.	16 (8.8)
<i>Proteus</i> spp.	8 (4.4)
<i>Enterobacter</i> spp.	7 (3.8)
<i>P. aeruginosa</i>	6 (3.3)
other	11 (6)
<i>Candida</i> spp.	6 (3.3)

Four patients (2.6%) would have benefited from a more rapid TTET if ACC results had been available. Among these patients the pathogens included ESBL-producing Enterobacteriaceae (3/4, 75%) and Gram-positive cocci (1/4, 25%). The median potential decrease in TTET for these patients was 18.9 h (IQR 11.3, 20.4).

### Definitive therapy

All the patients in the cohort received definitive therapy. The median TTDT was 41.4 h (IQR 21.7, 73.3). One hundred and seventeen patients had Verigene results available prior to the administration of definitive therapy. The median time from culture draw to Verigene results among these patients was 33.9 h (IQR 14.5, 68.4).

Fifty-one patients (30.5%) would have received definitive therapy more rapidly if ACC results had been available. In these patients the hypothetical median decrease in TTDT was 25.4 h (IQR 18.7, 37.5). In the majority of these patients, de-escalation was the treatment modification (47/51 patients, 92.2%), whereas escalation occurred in 4 (7.8%). Among cases that would have had a benefit in TTDT, Enterobacteriaceae were the most common pathogens [*E. coli* (19/51, 37.3%), *Klebsiella* spp. (9/51, 17.6%), *Proteus* spp. (4/51, 7.8%), *Enterobacter* spp. (2/51, 3.9%)], followed by MSSA (13/51, 25.5%), *Enterococcus* spp. (3/51, 5.9%), *Streptococcus* spp. (1/51, 2%) and *P. aeruginosa* (1/51, 2%).

Reasons why patients would have had no benefit in TTDT with ACC included: susceptibility tests were not performed by the ACC (but were performed by traditional methods) (22/116, 19%); de-escalation opportunities were present but not implemented (25/116, 21.6%); patients were already on definitive therapy at the time ACC results would have been available (46/116, 39.7%); and technical failure where no identification and/or no susceptibility results were available by ACC (19/116, 16.4%). Of the 46 patients who were already on definitive therapy, 25 (54%) had other RDT results available that were used to optimize therapy.

### Impact of ACC on total antibiotic usage

For the cohort, overall antibiotic use consisted of 1786 days of therapy, or 1151 days per 1000 days of inpatient bacteraemia

treatment. The most commonly used antibiotics were vancomycin (28% of treatments), ceftriaxone (16%) and cefepime (15%).

Table 3 displays the hypothetical impact that the ACC could have had on total antibiotic days of various antimicrobials. Had ACC results been available in real time, ~24 days of cefepime per 1000 bacteraemia treatment days could have been avoided, corresponding to a 16% decrease in total cefepime days. Potential decreases were also observed for aminoglycosides (23% reduction), piperacillin/tazobactam (8%) and vancomycin (4%). These reductions were primarily a result of earlier de-escalation. Conversely, usage would have increased for ceftriaxone (9% increase), ampicillin/sulbactam (33%) and fluoroquinolones (35%).

Actual and adjusted antibiotic days per 1000 inpatient bacteraemia treatment days for each antibiotic agent as well as potential days saved or added if ACC results had been available for subsets of infections are displayed in Tables 4 and 5. Table 4 describes only antibiotics that were used to treat Gram-negative pathogens whereas Table 5 describes antibiotics that were used for Gram-positive pathogens. When limiting the data to patients with Gram-negative pathogens, ~61 days (23%) of cefepime treatment per 1000 bacteraemia treatment days could have been avoided, whereas 44 days of ceftriaxone would be added per 1000 inpatient bacteraemia treatment days (14% increase). For patients who had Gram-positive cocci (GPC) (Table 5), a decrease of 21 days of vancomycin treatment per 1000 bacteraemia treatment days (5% decrease) and an increase in days of treatment with nafcillin (12.5 days, 6% increase) and cefazolin (6.5 days, 4% increase) would have occurred.

In addition, there was a relatively small amount of antibiotic use for mixed Gram-positive and Gram-negative infections ( $n=8$ ). Had ACC results been available, the total number of antibiotic days would have been decreased slightly (45 days per 1000 inpatient bacteraemia treatment days) for this population, whereas for patients with candidaemia no impact would have been seen.

## Discussion

These data describe the potential impact on TTET, TTDT and overall antimicrobial usage that implementation of the ACC could have at the DMC. There was a significant potential impact on decreasing TTDT, primarily as a function of more rapid de-escalation, with a significant shift from anti-pseudomonal  $\beta$ -lactams to third-generation cephalosporins and ampicillin/sulbactam. Nearly one-third of the patients in the cohort were determined to have had a potential benefit due to more rapid de-escalation of therapy, and this is where the ACC is likely to have its biggest impact in many institutions. Among patients who would have had a potential benefit from de-escalation, the use of broad-spectrum antibiotics would have been shortened on average by 25 h. Although data that were recently published from DMC have demonstrated a high predictive value for susceptibility to a narrow-spectrum antimicrobial when Verigene<sup>®</sup> demonstrates an absence of key resistance determinants,<sup>18</sup> clinicians often hesitate to de-escalate therapy in the absence of documented susceptibility information. This is demonstrated by a recent publication by Rivard et al.,<sup>19</sup> where the investigators showed that while Verigene<sup>®</sup> BC-GN could decrease TTET by nearly 18 h (i.e. escalation where needed), its use in practice resulted in a modest 4 h decrease in the time to de-escalation. Therefore, as the ACC provides documented susceptibility results

**Table 3.** Days of antibiotic treatment for the entire cohort with or without ACC system result availability: actual days and adjusted days of treatment per 1000 days of bacteraemia treatment<sup>a</sup>

Antibiotic	Actual days			Adjusted days per 1000 antibiotic days			Difference
	without ACC available	with ACC available	difference (with ACC – without ACC)	without ACC available	with ACC available	difference (with ACC – without ACC)	
Ampicillin	52	55	3	33.8	35.7	1.9	6%
Ampicillin/sulbactam	18	24	6	11.7	15.6	3.9	33%
Cefazolin	131.5	139	7.5	85.4	90.2	4.9	6%
Cefepime	224	187.6	-36.4	145.4	121.8	-23.6	-16%
Ceftriaxone	247	269	22	160.3	174.6	14.3	9%
Ceftaroline	37	37	0	24.0	24.0	0.0	0%
Nafcillin	175.6	182.5	6.9	114.0	118.5	4.5	4%
Piperacillin/tazobactam	25.5	23.5	-2	16.6	15.3	-1.3	-8%
Carbapenem	143.5	143	-0.5	93.2	92.8	-0.3	-0.3%
Aztreonam	21.5	20.5	-1	14.0	13.3	-0.7	-5%
Aminoglycosides	31	24	-7	20.1	15.6	-4.5	-23%
Fluoroquinolones	23	31	8	14.9	20.1	5.2	35%
Tigecycline	7	7	0	4.5	4.5	0.0	0%
Linezolid	19	19	0	12.3	12.3	0.0	0%
Vancomycin	430	411.4	-18.6	279.1	267.1	-12.0	-4%
Daptomycin	135.5	135.5	0	88.0	88.0	0.0	0%
SXT	14	14	0	9.1	9.1	0.0	0%
Fluconazole	4.5	4.5	0	2.9	2.9	0.0	0%
Micafungin	39.5	39.5	0	25.6	25.6	0.0	0%

SXT, trimethoprim/sulfamethoxazole.

<sup>a</sup>Days of inpatient treatment for the entire cohort: 1540.5.**Table 4.** Days of antibiotic treatment for Gram-negative bacteria with or without ACC system availability: actual days and adjusted days of treatment per 1000 days of bacteraemia treatment<sup>a</sup>

Antibiotic	Actual days			Adjusted days per 1000 antibiotic days			Difference
	treatment without ACC available	treatment with ACC available	difference (with ACC – without ACC)	without ACC available	with ACC available	difference (with ACC – without ACC)	
Ampicillin/sulbactam	16	22	6	30.5	41.9	11.4	38%
Cefazolin	4	6	2	7.6	11.4	3.8	50%
Cefepime	139	107.2	-31.8	265.0	204.4	-60.6	-23%
Ceftriaxone	167	190	23	318.4	362.2	43.8	14%
Piperacillin/tazobactam	19	17	-2	36.2	32.4	-3.8	-11%
Carbapenem	132	131	-1	251.7	249.8	-1.9	-1%
Aztreonam	21.5	20.5	-1	41.0	39.1	-1.9	-5%
Aminoglycosides	26	21	-5	49.6	40.0	-9.6	-19%
Quinolones	17	25	8	32.4	47.7	15.3	47%
Tigecycline	1	1	0	1.9	1.9	0.0	0%
SXT	5	5	0	9.5	9.5	0.0	0%

SXT, trimethoprim/sulfamethoxazole.

<sup>a</sup>Days of inpatient treatment for Gram-negative pathogens: 524.5.

rapidly, its use might lead to more rapid de-escalation as clinicians will clearly see the susceptibility information.

When interpreting these results, it is important to note that at DMC there is already an advanced antimicrobial stewardship

programme in place that utilizes multiple RDTs. Given that there are already processes in place to optimize antimicrobial prescribing, including use of the Verigene® platforms and active stewardship monitoring of culture results, it was not surprising that only a

**Table 5.** Days of antibiotic treatment for Gram-positive bacteria with or without ACC system availability: actual days and adjusted days of treatment per 1000 days of bacteraemia treatment<sup>a</sup>

Antibiotic	Actual days			Adjusted days per 1000 antibiotic days			Difference
	without ACC available	treatment with ACC available	difference (with ACC – without ACC)	without ACC available	with ACC available	difference (with ACC – without ACC)	
Ampicillin	39	40	1	45.8	46.9	1.1	3%
Cefazolin	127.5	133	5.5	149.6	156.1	6.5	4%
Cefepime	72.5	70	-2.5	85.1	82.2	-2.9	-3%
Ceftriaxone	61	60	-1	71.6	70.4	-1.2	-2%
Ceftaroline	37	37	0	43.4	43.4	0.0	0%
Nafcillin	179.5	190.1	10.6	210.7	223.1	12.6	6%
Quinolones	6	6	0	7.0	7.0	0.0	0%
Linezolid	19	19	0	22.3	22.3	0.0	0%
Vancomycin	368	350	-18	431.9	410.8	-21.1	-5%
Daptomycin	135.5	135.5	0	159.0	159.0	0	0%
SXT	9	9	0	10.6	10.6	0.0	0%

SXT, trimethoprim/sulfamethoxazole.

<sup>a</sup>Days of inpatient treatment for Gram-positive cocci: 852.

minimal potential impact was identified with the ACC with regard to improving TTET. It is worth noting that, at institutions where RDTs are not being used and/or stewardship interventions are not as proactive, a larger impact on TTET might be demonstrated. In addition, for institutions with a large number of antimicrobial-resistant pathogens there would likely be further opportunities to improve TTET.

Given that this analysis was performed in a convenience sample of 167 patients, significant effort was made to measure the potential impact on total antimicrobial usage in a manner that would be internally and externally valid, so that the results could be used to assess the potential impact that implementation of the ACC could have on antimicrobial use at an institution. The metric antibiotic usage/1000 inpatient bacteraemia treatment days was described and evaluated to assess potential shifts occurring in total antibiotic usage based on implementation of the ACC. Table 3 displays the impact that the ACC would have had on the study cohort. Most notably, driven by earlier de-escalation, the use of anti-pseudomonal  $\beta$ -lactams would have decreased by 10%–20%, the use of agents used for empirical ‘double coverage’ (i.e. aminoglycosides) would have decreased by nearly 25%, and the use of anti-MRSA agents would have decreased by 4%. Importantly, however, 34% of the isolates run on the ACC were excluded from this analysis due to discharge/death of the patient prior to results becoming available, the isolate being a contaminant, or technical issues. Therefore, institutions will need to determine the most cost-effective process for identifying when to utilize ACC based on local factors.

In Gram-positive organisms, having pathogen identification and/or genotypic resistance information is often sufficient to predict phenotypic resistance patterns. Thus, one strategy that institutions might implement would be to only utilize the ACC for Gram-negative pathogens. In order to assess the impact of the ACC in this setting we limited the analysis to patients with Gram-negative pathogens isolated. Table 4 demonstrates that, in this

population, significant reductions of 11%–23% for various anti-pseudomonal therapies could be achieved through improved time to de-escalation. As previously mentioned, at institutions with high rates of Gram-negative resistance or those without rapid molecular diagnostic methods (such as Verigene<sup>®</sup>) available, the ACC would likely have a greater impact on TTET as well.

There were nine patients included in the study who had polymicrobial bloodstream infection. Two of these had technical failures of the ACC. Among the remaining seven patients, the ACC identified all causative pathogens in three. In the remaining four patients, ACC results would have had a potential impact on definitive therapy of two patients. In the first patient a pan-susceptible *E. coli* was detected while an MSSA was missed by the ACC. Had the patient been de-escalated to the ultimate therapy (cefazolin) based on the *E. coli* result alone, then a positive effect on TTDT would have been realized with the ACC. In the other patient an *E. coli* was detected, but an MRSA was missed. While *E. coli* therapy could have been optimized faster with ACC (giving a benefit in TTDT for this organism), it is worth noting that if Gram-stain results were ignored this might have led to the inappropriate discontinuation of vancomycin.

There are limitations to this study that warrant mention. First, this was not an interventional study, and the potential benefit of the ACC was assessed hypothetically. The assumption was made that, had antimicrobial susceptibility information become available sooner, the same antimicrobial decisions would have been made, but at an earlier time. However, this time of response was unknown in cases where actual therapy was modified prior to actual AST results becoming available to the providers. In such cases, 2 h was added to the ACC final results time in order to account for human factors that would have impacted the benefit of the ACC (i.e. intervention by the stewardship team, entering of orders, delivery from the pharmacy, and administration by the nursing staff). In addition, this assumption might not have always been the case

if patients had been clinically unstable in earlier timeframes. Another potential limitation is that this analysis assumed real-time intervention based on ACC results regardless of the timing of when these results would become available. While this is contrary to current stewardship practices at the DMC (where real-time interventions are only made during normal business hours), we feel that it is a realistic assumption for multiple reasons: (i) given the cost of the test any justification for utilizing it in real time would require the development of a process to respond to the results regardless of when they return; (ii) given that ACC provides actual susceptibility information (and ‘susceptible’ and ‘resistant’ interpretations) instead of presence/absence of key resistance determinants, it would be much simpler to train end-user clinicians (physicians, pharmacists, etc.) on how to respond to these results in real time at all hours, given that it would be consistent with their current process of modifying therapy once susceptibility tests return.

Prospective data assessing real-time 24/7 intervention based on ACC results are needed to more clearly elucidate the impact of the ACC.

The second limitation of the study is that patients who had off-panel pathogens (i.e. Gram-positive bacilli) as well as patients for whom the ACC did not provide results owing to technical issues were not excluded, but were considered as subjects for whom the ACC would have provided no benefit. If a Gram-stain-based process was set up excluding these samples from being run on the ACC, the percentage of patients who would potentially benefit would be expected to increase.

Of note, in this study the accuracy of the ACC was not compared with traditional cultures, and categorical and essential agreements were not evaluated. As this test is FDA approved it has met the requirements for both categorical and essential agreement and our experience with the accuracy of the test has been presented elsewhere.<sup>20</sup>

In conclusion, earlier AST information provided by the ACC would have provided numerous opportunities for more rapid de-escalation and avoidance of broad-spectrum antibiotic use. Although only a small impact of the ACC on TTET was noted, this effect would likely be greater in settings where RDTs are not currently utilized.

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## Transparency declarations

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