The Hypothetical Impact of Accelerate Pheno on Time to Effective Therapy (TTET) and Time to Definitive Therapy (TTDT) in an institution with an established antimicrobial stewardship program & rapid genotypic organism/resistance marker identification

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Abstract

The Hypothetical Impact of Accelerate Pheno on Time to Adequate Therapy (TTAT) and Time to Optimal Therapy (TTOT) in an institution with an established antimicrobial stewardship program & rapid genotypic organism/resistance marker identification

Background:
Rapid organism identification (ID) & antimicrobial susceptibility testing (AST) can improve time to adequate therapy (TTAT) and optimal (TTOT). The Accelerate Pheno™ system (ACC) can provide ID & AST results within 7 hours. The objective of this study was to assess the hypothetical impact of ACC on TTAT and TTOT in a hospital with an established antimicrobial stewardship program & rapid genotypic organism and resistance marker ID.

Methods:
Patients with positive blood cultures, at the Detroit Medical Center, from 3/29/2016 – 6/14/2016, were retrospectively reviewed. ACC was run on unique blood cultures as part of the laboratory validation of the system. ACC results were not made available to clinicians. These results were utilized to determine the hypothetical impact on TTAT and TTOT that the ACC results would have had in real time. This assessment was performed based on how clinicians modified antimicrobial therapy with regards to antibiotic choice and timing, once ID or AST were known. The assumption was that the same decisions that were made at the time of traditional AST would have been made when ACC information would have been available. In addition, the impact of ACC on total antimicrobial usage was assessed.

Results:
The analysis included 148 patients. The median actual TTAT was 2.2 hours (h) [interquartile range (IQR) 0.5 - 12.5 h]. If ACC results had been available, TTAT could have been improved in 11 patients (7%), with a median potential decrease in the TTAT of 2.3 h [IQR, 0.8 - 20.7]. The median actual TTOT was 40.7 h [IQR, 21.3 - 74.1]. If ACC results were available, improved TTOT could have been achieved in 59 patients (40%), with a median potential decrease in TTOT of 24.2 h [IQR 15.3 - 34.9]. The TTOT would have been achieved by earlier de-escalation in 53/59 (89.8%) patients. ACC implementation could have led to decreases in antibiotic usage for cefepime (17% reduction of actual use), aminoglycosides (23%), piperacillin/tezobactam (8%), and vencomycin (5%).

Conclusion:
Given the aggressive nature of empiric therapy and the availability of other rapid diagnostic tests at our center, ACC would have had e minimal impact TTAT. However, largely due to the ability to more rapidly de-escalate, ACC could have led to a more rapid TTOT in 40% of patients, and significantly reduced the use of broad spectrum antimicrobials.

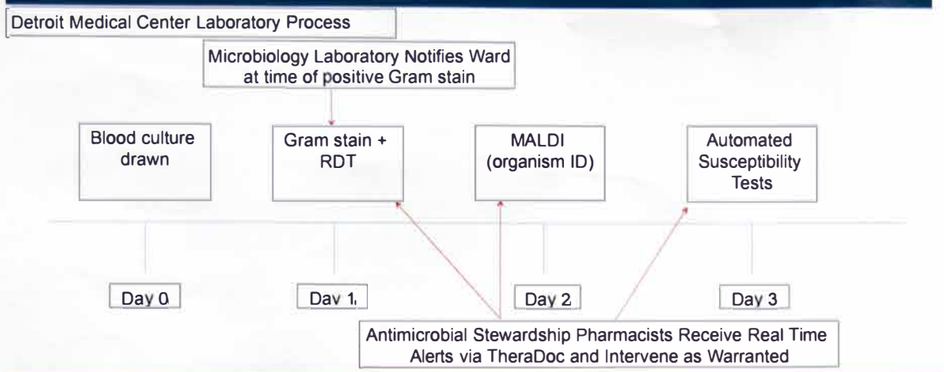
Background

- Early appropriate antibiotic administration among bacteremic patients is an important determinant of survival, with delayed time to effective antibiotic therapy associated with poor outcomes
- Conversely, indiscriminant use of broad-spectrum empiric antibiotics is associated with an increased risk of adverse events and the development of resistance
- Rapid organism identification (ID) & antimicrobial susceptibility testing (AST) can improve time to effective therapy (TTET) and definitive (TTDT).
- Most currently 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 AST results
- The Accelerate Pheno™ system (ACC) can provide ID & AST results within 7 hours.
- The objective of this study was to assess the hypothetical impact of ACC on TTET and TTDT in a hospital with an established antimicrobial stewardship program & rapid genotypic organism and resistance marker ID.

Methods

- Patients with positive blood cultures, at the Detroit Medical Center, from 3/29/2016 – 6/14/2016, were retrospectively reviewed.
- ACC was run on unique blood cultures as part of the laboratory validation of the system. ACC results were not made available to clinicians.
- These results were utilized to determine the hypothetical impact on TTET and TTDT that the ACC results would have had in real time.
- The assessment was performed based on how clinicians modified antimicrobial therapy with regards to antibiotic choice and timing, once ID or AST were known.
- ACC was compared to the standard organism identification and antimicrobial susceptibility testing procedures performed by the DMC (Figure), which included rapid multiplex automated molecular diagnostic testing to identify the microorganism and to determine the presence of select resistance genes
- The assumption was that the same decisions that were made at the time of traditional AST would have been made when ACC information would have been available. In addition, the impact of ACC on total antimicrobial usage was assessed
- An effective antibiotic was defined as an antibiotic with *in vitro* activity against the identified infecting pathogen
- The definitive antibiotic regimen was that which was selected by the treating team after susceptibility information was available
- Each case was adjudicated by 3 investigators to determine whether effective and definitive therapy had been provided to patients and also to determine if effective and/or definitive therapy could have been provided more rapidly if results from the ACC had been available in real time

Results



Description of the cohort (n = 148)			
Age (mean ±SD)	55.4±23.3	Pitt Bacteremia Score (IQR)	1 (0, 3)
Female (%)	73 (49.3)	SOFA Score (IQR)	3 (1,5)
African American (%)	94 (63.5)	Source of Bloodstream Infection	
Immunocompromised (%)	24 (16.2)	Central Venous Catheter	33 (22.6)
Congestive Heart Failure (%)	31 (21.0)	Pulmonary	16 (11.)
Diabetes Mellitus (%)	27 (18.2)	Genitourinary	33 (22.6)
Chronic Kidney Disease (%)	48 (32.7)	Intra-abdominal	14 (9.6)
Cerebrovascular Disease (%)	17 (11.5)	Skin and Soft Tissue	15 (10.3)
Dementia (%)	26 (17.6)	Other/unknown	35 (24.0)
Chronic Lung Disease (%)	46 (31.1)	Setting of Infection Onset	
Hematologic Malignancy (%)	10 (6.7)	Hospital-acquired	19 (13.0)
Solid Tumor Malignancy (%)	29 (19.6)	Health-care Associated	100 (68.5)
Charlson Comorbidity Index (IQR)	3 (2,6)	Community Onset	27 (18.5)

Microbiology (161 Isolates identified from 148 patients)			
Gram positive (N=81)		Gram negative (N = 80)	
MRSA	25 (15.5)	*E. coli*	36 (22.3)
MSSA	16 (9.9)	*Klebsiella* spp.	15 (9.3)
Streptococcus spp.	16 (9.9)	*Proteus* spp.	8 (5.0)
Enterococcus faecalis	9 (5.6)	*Enterobacter* spp.	7 (4.3)
Enterococcus faecium	4 (2.5)	*P. aeruginosa*	4 (2.5)
Coagulase negative staphylococci	6 (3.7)	Other GNR	6 (3.7)
Gram positive bacilli	5 (3.1)	*Candida* spp.	4 (2.5)

- Antibiotic modification occurred in 120 (81%) of patients: de-escalation in 85 (57.4%), escalation in 35 (23.6%)
- The median actual TTET was 2.2 hours (h) [interquartile range (IQR) 0.5 - 12.5 h]
- If ACC results had been available, TTAT could have been improved in 11 patients (7%), with a median potential decrease in the TTET of 2.3 h [IQR, 0.8 - 20.7]
- The median actual TTDT was 40.7 h [IQR, 21.3 - 74.1]
- If ACC results were available, improved TTDT could have been achieved in 59 patients (40%), with a median potential decrease in TTDT of 24.2 h [IQR 15.3 - 34.9]
- Among patients with a TTDT benefit, it would have been via earlier de-escalation in 53/59 (89.8%) patients.
- ACC implementation could have led to decreases in antibiotic usage for cefepime (17% reduction of actual use), aminoglycosides (23%), piperacillin/tazobactam (8%), and vancomycin (5%).

	Entire cohort N=148	Gram Negative N=65	Gram Positive N=70	Polymicrobial N=8	Fungi N=5
Potential benefits in implementation of effective treatment if Accelerate results had been available					
Number (%) of patients who received adequate therapy	147 (99.3)	64 (98.5)	70 (100.0)	8 (100.0)	5 (100.0)
Median (IQR) hours TTET	2.2 (0.52,12.5)	2.0 (0.4, 8.5)	1.9 (0.5, 10.6)	6.6 (1.4, 42.4)	27.4 (21.9, 36.8)
Number (%) of patients with potential improved TTET	11 (7.4)	3 (4.6)	6 (8.6)	2 (25)	0
Median (IQR) potential improvement in hours in TTET (N=11)	2.3 (0.8,20.7)	21.1 (5.7, 23.7)	1.2 (0.8, 2.3)	1.5 (0.6,2.3)	-
Potential benefits in implementation of definitive treatment based on Accelerate results					
Number of patients who received definitive treatment	147 (99.3)	64 (98.5)	70 (100)	8 (100.0)	5 (100.0)
Median hours from blood draw to definitive therapy (IQR)	40.7 (21.3, 74.1)	48.7 (21.7, 86.9)	39.3 (21.3, 66.2)	27.0 (6.4,73.9)	27.4 (21.9, 37.4)
Number (%) of patients with potential improved TTDT	59 (39.9)	32 (49.2)	25 (35.7)	2 (25)	0
Median (IQR) potential improvement in TTDT(N=54)	24.2 (15.3, 34.9)	27.6 (9.2, 38.5)	20.4 (13.7, 23.9)	19.0 (3.8,34.2)	-

Days of antibiotic treatment for the entire cohort with or without Accelerate System availability: actual days and adjusted days of therapy per 1000 days of bacteremia treatment

	Actual days of therapy			Adjusted days per 1000 bacteremia therapy days			
Antibiotic	Days of therapy without ACC	Days of therapy with ACC	Difference in antibiotic days	Days of therapy without ACC	Days of therapy with ACC	Difference in antibiotic days	Difference (%)
Ampicillin	52	55	3	33.8	35.7	1.9	6%
Amp/Sul	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	186.1	−37.9	145.4	120.8	−24.6	−17%
Ceftriaxone	247	272	25	160.3	176.6	16.2	10%
Nafcillin	175.6	182.5	6.9	114.0	118.5	4.5	4%
Pip/Taz	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	−0.6	−5%
Aminoglycosides	31	24	−7	20.1	15.6	−4.5	−23%
Quinolones	23	31	8	14.9	20.1	5.2	35%
Linezolid	19	19	0	12.3	12.3	0.0	0%
Vancomycin	430	409.3	-20.7	279.1	265.7	−13.4	−5%
Daptomycin	135.5	135.5	0	88.0	88.0	0.0	0%

Discussion

- There was a significant potential impact on decreasing the TTDT, primarily as a function of more rapid de-escalation
- Among patients who would have had a potential benefit for de-escalation, the use of broad spectrum antibiotics would have been shortened on average by 24 hours
- Although only a small impact was noted on TTET, this effect would likely be greater in settings where rapid molecular testing are not currently utilized or when focusing on more resistant organisms