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Research Article

Workflow Modifications and Addition of MALDI-TOF-MS Technology Improved Turn-Around-Time to Identification of Common Urine Pathogens

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Abstract

Objective: To modify both workflow and culture reading schedules to improve Turn-Around-Time (TAT) to a final urine culture report.

Methods: We incorporated Matrix Assisted Laser Desorption/Ionization-Time of Flight-Mass Spectrometry Technology (MALDI-TOF-MS) into the workflow of the culture workups for rapid identification (ID). We also modified our culture reading schedules to include a split shift reading in addition to our conventional first shift culture reading schedule.

Results: Retrospective pre-workflow (September-November 2013) and post-workflow (April, May, October 2014) modification turn-around-times were compared for sixteen different species of commonly isolated urine pathogens. A statistically significant (p-value <0.05) improvement in average TAT was noted for all species examined. Furthermore, Antimicrobial Susceptibility Testing (AST) TAT, and release of no growth culture TAT, improved significantly. The average pre-algorithm Length of Stay (LOS) was 5.345 days while the average post-algorithm LOS was 4.761 days (P=0.0005), when >10 days LOS cases were excluded.

Conclusion: Converting from conventional identification methods to MALDI-TOF-MS, in conjunction with workflow modifications such as a second culture reading time, notably improved urine culture TAT for ID and AST, as well as for release of no-growth cultures. The improved TAT in the laboratory translated to a statistically significant improvement in inpatient LOS.

Keywords: MALDI-TOF; Urine Culture; Work Flow

Introduction

Urinary Tract Infections (UTIs) are extremely common across healthcare settings, most frequently presenting with acute onset of dysuria and an increased need to urinate in a normal healthy individual [1]. It is estimated that UTIs account for roughly 8 million clinician visits annually across United States' emergency departments, urgent care, and traditional outpatient settings [2]. Data by Kalsi et al. indicated that approximately 40% of all nosocomial infections (Hospital Acquired Infections (HAIs)) are UTIs [3]. In 2014, the 2011, Hospital Acquired Infection Prevalence Survey data for acute care hospitals was published, showing an estimated 721,800 cases of HAIs within the acute care setting, of which 93,300 (12.9%) were estimated to be urinary tract infections (67.7% of Catheter-Associated Urinary Tract Infections (CAUTI), a complication of extended catheter use) [4]. The considerable morbidity associated with HAI UTIs contribute to increased healthcare costs and decreased reimbursement [2,5,6], as well as increase the potential for urosepsis (the progression from UTI to a bloodstream infection) [7,8]. Effective therapy, or rather guided empiric therapy, can be useful in preventing progression of a UTI into a septic event [7-9]. In 2002, the number of deaths from Healthcare-Associated Infections (HAIs) for urinary tract infections in U.S. Hospitals was estimated to be 13,088 [10].

The objective of this study was to modify both workflow and culture reading schedules to improve overall Turn-Around-Time (TAT), and optimally, issue a final culture report 24 hours earlier. In order to improve the timeliness of ID of common pathogens in aerobic urine cultures plus expedite setup of Antimicrobial Susceptibility Testing (AST), both an additional urine culture reading shift and Matrix Assisted Laser Desorption/Ionization-Time of Flight (MALDI-TOF-MS) Mass Spectrometry technology were incorporated. Incorporation of MALDI-TOF-MS technology into the workflow of the culture workup for rapid ID allowed for an improvement in the average ID TAT. Simultaneously, an additional culture reading per day was implemented to finalize 24 hour no growth urine cultures in a timely manner, and expedite setup of AST. Previously, the majority of species ID was achieved with conventional commercially-available ID/AST combination panels. All urine cultures, regardless of laboratory receipt time, were previously read once per day during 1st shift. The goals were rapid ID of any infectious agents, as well as rapid finalization of negative cultures.

In the context of urine cultures and incorporation of MALDI-TOF-MS specifically, most publications have focused on experimentally using MALDI-TOF-MS to identify bacteria directly from urine specimens by way of an extraction protocol [8,9,11]. Performance of MALDI-TOF-MS technology in comparison to traditional biochemical or enzymatic ID systems and expected TAT improvements for isolate ID and ID confidence have been previously described especially in the context of positive blood culture ID [12-15]. In this report we show the feasibility of incorporating both MALDI-TOF-MS technology plus incorporation of additional urine culture reading times for improving TAT to ID and also overall culture result release times. Whereas some reports show that direct from urine extraction and ID with MALDI-TOF-MS is a potentially useful concept [8,9,11], this approach is not always efficient or practical for a high-volume laboratory. This is due to the multiple steps required to perform the extraction, as well as the inherently high negativity rate of urine cultures. In our high-volume laboratory, with an average receipt of 140 urines per day and a 60-70% negativity rate, the direct from urine extraction method would be labor-intensive and present prohibitive time constraints.

Motivation for incorporation of this workflow was three-fold: 1) to provide more rapid ID to allow clinicians to administer more effective/guided empiric (absence of an AST) therapy for treatment of the UTI; 2) enable the clinicians to discharge culture negative patients in a timely manner; 3) to improve overall urine culture efficiency and output. By performing additional readings per day, it also allowed AST to be setup

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earlier, thus allowing the culture to be entirely signed out in a timelier manner. As previously indicated, it is important that the antibiotic choice is modified based on the culture results, and the earlier these results are available, the more likely that the antibiotic choices will be culture driven [7].

Materials and Methods

The study was conducted at Thomas Jefferson University Hospitals, a 951 bed acute-care teaching institution in Philadelphia, PA. The microbiology laboratory receives clinical specimens from the main hospital, an ancillary hospital, and numerous outpatient clinics. This study was approved by the Institutional Review Board (IRB Control Number: 14D.425). During a representative pre-workflow modification period of 3 months (September 2013, October 2013, November 2013), and a post-workflow modification period of 3 months (April 2014, May 2014, October 2014), all primary events were examined (Table 1). Workflow periods for the post-modification period were selected for months that contained consistent split shift staffing. An event was defined as the first positive urine culture for a patient within the examined period. Duplicate events of the same organism, if collected during a single admission event for inpatients, were excluded since the primary event would likely determine initiation of effective therapy. Historically, 1st shift was defined as 0800 h to 1600 h; 2nd through 3rd shift were defined as 1600 h to 0800 h. Pre-modification ID and AST utilized the automated BD Phoenix ID/MIC system (Becton Dickenson and Co., Baltimore, MD), MicroScan ID/AST system (Beckman Coulter, Inc., Brea, CA), or backup rapid biochemical systems such as rapid panels (Remel, Lenexa, KS). MicroScan and Phoenix performance have been elucidated previously [16-18].

Workflow modification involved addition of an additional shift urine culture reading session, while urine specimens for culture are inoculated within one hour of receipt into the laboratory on a 24 hour basis. Urine specimens received from 8:00 AM to 4:00 PM the previous day were read on 1st shift, while urine specimens received from 4:00 PM to 8:00 AM were read on a split shift (hybrid shift which overlapped 1st and 2nd shifts). The additional culture reading shift and the MALDI-TOF-MS for ID algorithm are shown in Figure 2. Culture reading can be defined as the examination of the previously incubated urine culture media plates as well as any subbing of colonies for isolates, ID of colonies, setup and reporting of AST, and reporting of no growth urine cultures per standard guidelines [19]. To further improve workflow efficiency, urine cultures were sorted into categories: No Growth (NG) at 24 hours, no growth at <24 hours, single colonies of growth, multiple colonies of growth, and potential contaminants. No growth cultures were then immediately signed out at 24 hours. No growth cultures at < 24 hours were reincubated to be read on the subsequent shift. Cultures with growth were set aside as either single colony types or multiple colony types. Cultures of probable contaminants, i.e. multiple mixed species, were signed out as such. All cultures were worked-up according to ASM Cumitech 2C guidelines [19].

Post-workflow modification utilized the Bruker Microflex LT MALDI-TOF mass spectrometer (Bruker Daltonics Inc., Billerica, MA; software version 3.1.66) for ID. MALDI-TOF-MS Biotyper technology and performance for identification have previously been described [20-22]. Briefly, MALDI-TOF identifies organisms by matching the protein fingerprint of the unknown organism to the defined organism fingerprint in the extensive organism library.

Once cultures were sorted, the isolated colonies underwent MALDI-TOF-MS analysis (Bruker Daltonics, Billerica, MA) and AST as appropriate per guidelines [19]. Individual bench technologists programmed the MALDI-TOF-MS target plate map and spotted the associated target plate in duplicate for direct colony processing. AST broth standard inoculum and panel were ordered simultaneously with target plate spotting. The MALDI-TOF-MS instrument was then operated by single centralized technologists, who also setup the AST panels. Results were reported (accepted) by the original technologist reading the plate culture (Figure 2). The MALDI-TOF-MS analysis was performed per manufacturer's recommendations and with the recommended reagents (1 μL of HCCA matrix, Bruker Daltonics, Billerica, MA). The target plate was analyzed according to manufacturer's instructions using the Bruker Biotyper software (Bruker Daltonic MALDI Biotyper, Version 3.1) paired with the Bruker Microflex LT MS.

Results

Retrospective review of pre-workflow (September-November 2013) and post-workflow (April, May, October 2014) modifications were compared for sixteen commonly isolated urine pathogens as noted in Table 1. *Staphylococcus aureus* was previously identified in our

	Pre-Workflow Modifications (Sept., Oct., Nov., 2013)	Post-Workflow Modifications (Apr., May, Oct. 2014)	P-value (<0.05 significant)
Organism	Average hrs (N) ± STDev	Average hrs (N) ± STDev	
Acinetobacter baumannii/ calcoaceticus complex	56.9 (8) ± 17.0	28.8 (10) ± 12.3	0.002
Citrobacter freundii complex	74.7 (8) ± 26.3	45.0 (23) ± 36.3	0.024
Citrobacter koserii	61.8 (17) ± 23.8	28.7 (23) ± 11.3	<0.001
Enterobacter aerogenes	52.8 (17) ± 12.8	34.1 (18) ± 14.7	<0.001
Enterobacter cloacae complex	56.3 (26) ± 19.0	34.5 (36) ± 15.9	<0.001
Enterococcus faecalis	57.2 (171) ± 18.3	33.1 (147) ± 15.1	<0.001
Enterococcus faecium	49.9 (7) ± 9.7	34.9 (56) ± 22.7	0.006
Escherichia coli	56.6 (635) ± 18.0	34.2 (828) ± 18.7	<0.001
Klebsiella oxytoca	59.8 (21) ± 18.3	31.0 (12) ± 17.9	<0.001
Klebsiella pneumoniae	56.2 (187) ± 21.2	33.0 (218) ± 16.5	<0.001
Morganella morganii	56.2 (14) ± 20.6	29.6 (13) ± 7.6	<0.001
Proteus mirabilis	62.8 (87) ± 21.5	33.9 (99) ± 17.1	<0.001
Pseudomonas aeruginosa	58.8 (85) ± 21.0	32.1 (78) ± 14.3	<0.001
Serratia marcescens	67.9 (6) ± 21.6	37.1 (14) ± 20.6	0.016
Staphylococcus saprophyticus	69.5 (21) ± 16.4	55.7 (19) ± 23.3	0.040
Stenotrophomonas maltophilia	52.1 (7) ± 19.0	30.2 (7) ± 4.0	0.022

Stdev = standard deviation; N = Number; hrs = hours

Table 1: The average turn-around-times for identification of common urine pathogens.

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laboratory by a rapid positive coagulase test and thus not included in this analysis. The average TATs, standard deviations and the p-values for each organism are indicated in Table 1. TAT was defined as the time of urine specimen receipt into the microbiology laboratory until the time that the ID was reported in the patient chart.

All isolates identified via the improved workflow algorithm showed a statistically significant improvement in TAT with p-values<0.05. Pre- and post-workflow modification average TAT and p-values are shown in Table 1. Statistical significance was determined by using an unpaired, two-tailed t test with Welch's correction. Isolates of *E. coli* were further confirmed via a lactose-fermenter phenotype plus spot indole positivity in order to fully differentiate from *Shigella*, which produces the same MALDI-TOF-MS spectra as *E. coli*. Statistically significant (p-value <0.05) improvement in average TAT and a decrease in the variation time were noted for all of the common urine isolates (pathogenic) with the exception of *E. faecium* (Table 1). *E. faecium* showed a statistically improved TAT but did show an increase in variation time to ID likely due to both the growth rate of the organism and inherit variation in culture setup times.

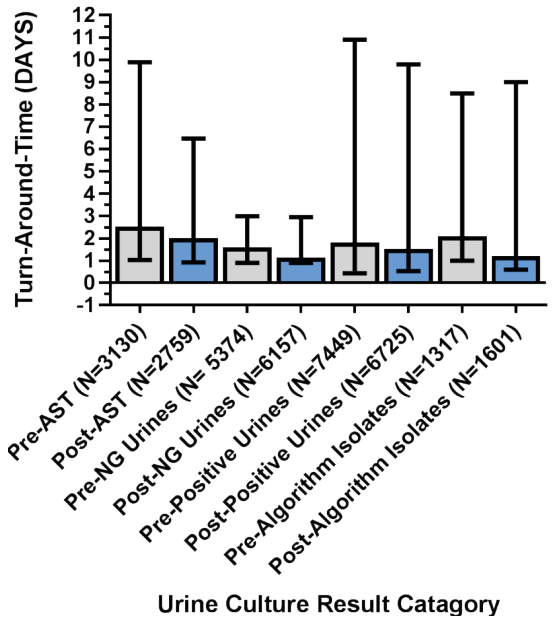
Overall TATs for both positive and no-growth urine cultures, AST reporting, and isolate ID are shown in Figure 1. The graph shows the overall TAT in days as the median value with a minimum and maximum TAT bar. The overall culture positive category includes isolates that were: identified by other methods when MALDI-TOF-MS was not validated for those particular organisms; less common isolates for a urine source such that numbers in both groups not enough for statistical analysis; mixed/potentially contaminated cultures; and cultures with insignificant colony count to justify a workup per guidelines [19]. All pre- and post-algorithm urine culture workup comparisons were statistically significant (P <0.0001).

Our patient demographic pre- and post-implementation were comparable (Table 2) and are provided so that the reader can assess that the patient population is consistent. There was a slight white and female predominance in both groups, which was not statistically significant. Table 2 provides an overview of the inpatient demographics for urine specimens examined within the inpatient population (outpatient excluded). The rate of urosepsis prior to workflow modifications was 12.03% (N = 74) while the rate post-modifications was 9.18% (N = 67), which was not statistically significant. There was no statistically significant difference in Length-of-Stay (LOS) when no inpatients were excluded from the LOS comparison for the inpatient group. Overall LOS was an average of 11.5 days in the pre-algorithm group and the post-algorithm group had an average of 11.6 days with a P=0.865, which was not statistically significant. Due to high comorbidities experienced by our patient population, we selected to remove any patients from the LOS analysis if they showed > 10 days LOS to avoid bias in the positive group. When > 10 day LOS was removed, the average pre-algorithm LOS was 5.345 days while the average post-algorithm LOS was 4.761 days with P=0.0005, which was statistically significant.

Discussion/Conclusion

Converting from conventional identification methods to MALDI-TOF-MS, in conjunction with workflow modifications such as a second culture reading, notably improved urine culture TAT for ID and AST, as well as for release of no-growth cultures (Table 1; Figure 1). The improvement in TAT was most notable for the following organisms: *Escherichia coli, Enterococcus faecalis, Klebsiella pneumoniae, Proteus mirabilis*, and *Pseudomonas aeruginosa*, all of which are frequent and significant causes of UTIs. All isolate TAT were statistically significant while the range in variability of TAT is likely accounted for based on the natural growth rate of the bacteria as well as potential growth delays based on transport times to the laboratory. Transport time (collection minus receipt into the laboratory) averaged 3.70 hours (minimum 0.4 hours; maximum 48 hours). Furthermore, incorporation of a split shift (12:30-20:30) reading section allowed MALDI-TOF-MS ID and AST set-up from urines received and plated the previous night so that AST could be reported early the following morning, thus eliminating an average of 9.72 hours (median 12.48 hours; minimum 2.64 hours; maximum 82.08 hours) delay in AST reporting (Figure 1). Targeted therapy for the patient is dependent on receipt of the AST.

A central technologist ran the spotted MALDI-TOF-MS target



NG = No growth, AST = antimicrobial susceptibility testing.

Figure 1: Overall turn-around-times urines culture and antimicrobial susceptibility testing.

	Pre-MALDI-TOF-MS Implementation (615 patient events)	Post-MALDI-TOF-MS Implementation (730 patient events)
Average Age ± STDev	64.6 ± 18.7	64.5 ± 19.1
Sex:		
Females (N)	397	504
Males (N)	218	226
Unknown (N)	0	0
Race:		
White (N)	394	462
Black (N)	153	201
Hispanic (N)	20	18
Asian (N)	0	0
Unknown (N)	23	18
Discharge Diagnosis Codes:		
SEPTICEMIA OR SEVERE SEPSIS	74	67
KIDNEY URINARY TRACT INFECTIONS	51	67
RENAL FAILURE	18	7
HYPERTENSION	5	2

N = number, STDev = standard-deviation

Table 2: Inpatient demographics.

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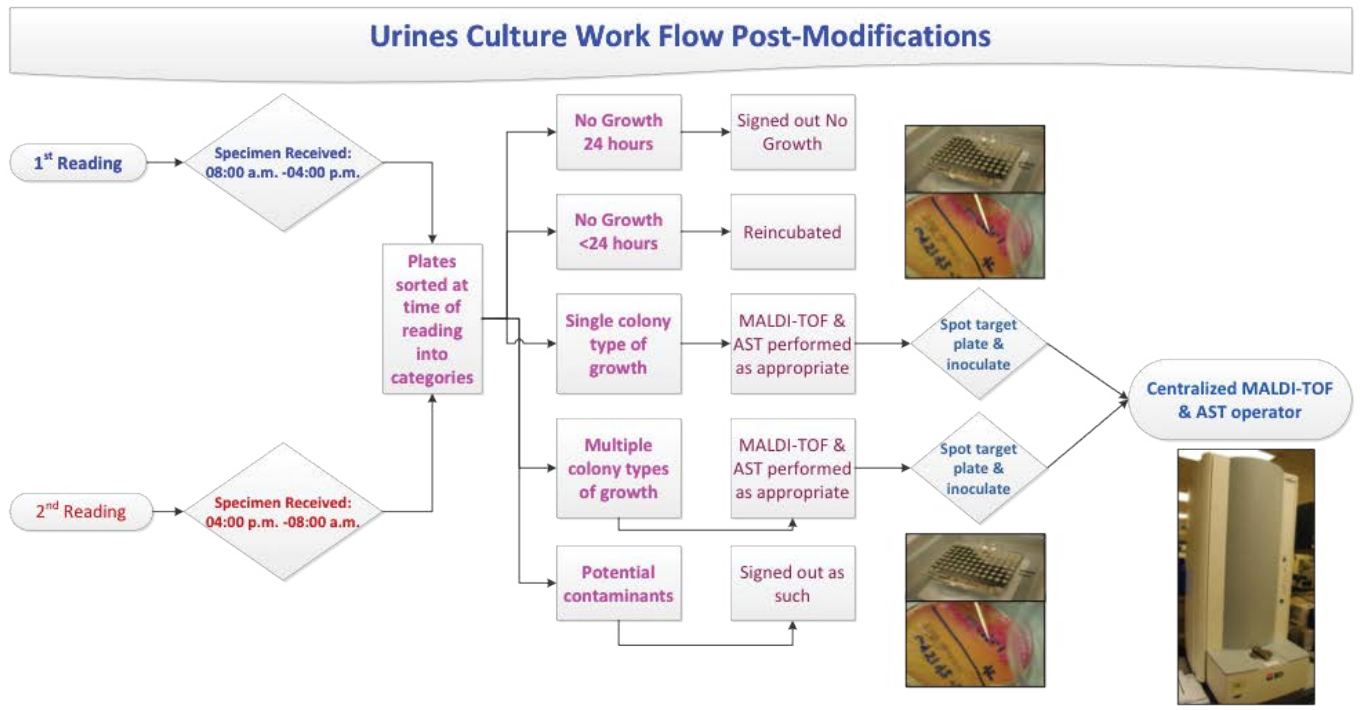

Figure 2: Post-modification urine culture workflow.

plates, setup the Phoenix AST panels, and loaded the inoculated Phoenix Panels onto the automated instrument (Figure 2). The impetus behind this workflow was to streamline processing, maximize workflow, and to ensure that multiple personnel did not cause congestion in the processing areas, impeding workflow and safety. The centralized technologist also was responsible for documenting the appropriate QC setup on each target plate. This process has been highly reliable in ensuring consistent MALDI-TOF-MS performance.

One motivation for implementation of the split shift was requests from surgical and oncology clinicians. These groups were dissatisfied with the urine culture TAT, especially in cases of 24 hour negative cultures, as this impacted discharge for high risk patients. The solution from the lab perspective was to incorporate an afternoon reading for specimens received later on the prior day, allowing 24 hour negative cultures to be signed out before accrual of an additional inpatient day as well as MALDI-TOF-MS for better efficiency and ID confidence. Release of negative urine culture can impact discharge orders for a given patient or delay certain urologic surgical procedures during pre-operation evaluation. For example, in high risk patients, such as bone marrow transplant, the clinician may want assurance of a negative urine culture (due to the risk of urosepsis) prior to discharging the patient. Lastly, discharging inpatients in a timely manner is crucial to prevent unnecessary exposure to nosocomial agents (HAIs).

The economic cost associated with incorporation of the MALDI-TOF-MS instrument and the disposable reagents as well as technologist time were comparable to those costs previously reported [15,23,24]. In order to staff split shift, we reorganized staff from 1st shift and 2nd shift to ensure daily staffing of the split shift for urine culture reading and thus did not accrue additional technologist costs through a new employee hire.

Within the inpatient population, the rates of urosepsis, renal failure and kidney urinary tract infections can significantly extend the length of stay for the affected patient. Our data showed that there was no difference in the LOS for the inpatient population tested, which is due to the wide inclusion criteria used when collecting the data. All patients, including patients with exorbitantly high number of LOS days were included in the study, since the focus of this algorithm was to universally provide improved times to release of organism ID, AST and release of no-growth 24 hour results. However, when we excluded patients with > 10 days of LOS from the LOS analysis, we did see a statistical difference between pre- and post- algorithm LOS data for patients with a urine culture positive for a common urine pathogen

The aim for incorporation of MALDI-TOF technology was twofold; to allow faster ID times to the species level, and by doing so, clinicians were provided the opportunity to apply more effective empiric antimicrobial therapy based on organism ID, coupled with the antibiogram compiled at our institution. While this study was not able to obtain antibiotics utilization data due to the current nature of medical record systems for inpatients and outpatients, this information would be something to review in the future as a consolidated electronic system becomes available. Additional options that can improve this algorithm could be incorporation of pre-culture screen methods in order to further reduce the TAT to a final urine culture negative report. Pre-culture screens also allow for decrease in the number of media plates that must be setup and read on the bench. Laboratory automation may also be an alternative since it would allow the technologists to have less initial hands-on time involved in plating the urine cultures. Overall this algorithm was shown to be effective at improving the release time of negative cultures, TAT of organism ID, and improve AST release time.

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