Rapid diagnostic testing with GeneXpert improves enrollment in a randomized clinical trial for detection of methicillin-resistant *S. aureus* in acute bacterial skin and skin structure infections

ECCMID 2014
P1471

Kimberly Claeys, PharmD[1], Anthony M. Casapao, PharmD[2], Jason Pogue, PharmD[3], Nitin Bhatia, PharmD[3], Ryan Mynatt, PharmD[3], Suprat Saely, PharmD[3], Crystal Arthur, MD[3], Robert Welch, MD[3], Robert Sherwin, MD[3], Wasif Hafeez, MD[3], Donald P. Levine, MD[3], Keith Kaye, MD[3], George Delgado, PharmD[4], Christopher A. Giuliano, PharmD[1,4], Robert Takla, MD[4], Leonard B. Johnson, MD[4], Susan L. Davis, PharmD[1, 5], Michael J. Rybak, PharmD, MPH[1, 3]

Address correspondence to:
Michael J. Rybak
m.rybak@wayne.edu

1. Anti-Infective Research Laboratory, Eugene Applebaum College of Pharmacy and Health Sciences, Detroit MI 2. Husson University School of Pharmacy, Bangor ME 3. Detroit Medical Center, Detroit MI, 4. St. John Hospital and Medical Center, Detroit, MI, 5. Henry Ford Health Systems, Detroit, MI

Background

- Acute skin and skin structure infections (ABSSSIs) caused by *S. aureus* (SA) represent one of the most common infections in emergency departments (EDs), with MRSA > 50% of these infections
- Achieving appropriate treatment early for MRSA infections has been shown to improve patient outcomes
- Current clinical microbiology methods take on average 72 hours to determine if MRSA is present
- Rapid diagnostics allows for identification of pathogens within hours instead of days offering the opportunity for earlier administration of organism-specific therapy
- Clinical trials of antimicrobials require early enrollment to minimize exposure to non-study drugs and decrease cost of false starts
- One novel application of this technology may be to facilitate early enrollment in pathogen-targeted clinical trials

Study Design

- Objective: to evaluate the impact of rapid diagnostics on time to useful pathogen-related information for enrollment in a prospective clinical trial
- Patients admitted via ED with diagnosis of ABSSSI between April 2012 and December 2013
- Inclusion criteria: Adults (18 – 89 years), complicated acute skin and skin structure infections such as wound/surgical site infection, cellulitis or major abscess, parental antibiotic therapy
- Exclusion Criteria: Patients with prosthetic devices, receiving renal replacement therapy, confirmed osteomyelitis or septic arthritis, gas gangrene, complicated bacteremia, infection due to gram-negative or other gram positive, received > 24 hours of non-study intravenous anti-MRSA therapy
- Patients can be enrolled in prospective study without rapid diagnostics, such as patients with cellulitis
- Rapid diagnostic results used to enrich for patients with ABSSSIs caused by MRSA
- Cepheid (GeneXpert®), real-time polymerase chain reaction (PCR) was used as the rapid diagnostics agent
- Analysis includes descriptive statistics, one-sample T-test with $p < 0.05$ as significant

Disclosures

- Rapid PCR machines and supplies provided by Cepheid

Microbiological Methods

- If patient lesion was amenable to culture, dual-head swab was collected
  - One swab head for rapid PCR and one swab head sent to Clinical Microbiology (CM) Laboratory
- Rapid PCR testing completed by co-investigators on-site at participating EDs
- PCR provides quantitative detection of *Staphylococcal* protein A, *Staphylococcal* cassette chromosomes, and gene for methicillin resistance (*mecA*)
- Approximately handling time with travel standardized to 30 minutes for rapid PCR
- Results retuned by GeneXpert® after one hour as:
  - MRSA, SA, Non-SA
- Timing of rapid PCR results were compared to CM time for organism speciation and final susceptibilities

Results

- Of the 3950 patients screened, 111 were enrolled and 40 were amenable to cultures:
  - Abscess was most common type of ABSSSI (n = 24 or 60.0%)
    - Median diameter with erythema = 7.5 cm (3 cm – 17 cm)
  - Wound/surgical site infections were the second most common followed by cellulitis (n = 7 (18.4%) and 6 (15.7%), respectively)
    - Median lesion size = 337.5 cm^2 (77 cm^2 – 1665 cm^2)
- There was 97.5% concurrence overall between rapid diagnostics and CM
- MRSA isolates had a 93% concurrence rate (one isolate disagreement, CM reported non-SA)

Concurrence Table: Rapid PCR versus CM

Rapid PCR / Clinical Micro	MRSA	MSSA	Non-SA
MRSA	14	0	0
MSSA	0	8	0
Non-SA	1	4	14

Results

- More MRSA isolates were part of polymicrobial infections

Polymicrobial (n = 7)	
Isolate 1:	CONS & *Strep Viridans*
Isolate 2:	CONS & *Enterococcus* spp. & *P. putida*
Isolate 3:	CONS & *Strep agalactiae*
Isolate 4:	MSSA & *A. baumannii* & *K. pneumoniae*
Isolate 5:	MRSA & *K. oxytoca* & *E. cloacae*
Isolate 6:	MSSA and *S. pneumoniae*
Isolate 7:	*S. marcescens, K. pneumoniae, Viridians Strep* spp, Group G *Strep*

CONS = Coagulase Negative *Staphylococcus*

- Overall, there was a significant difference in time to results between CM and Rapid PCR for both preliminary results/speciation ($p < 0.001$) and final susceptibilities ($p < 0.001$)

Difference in Time to Results

Rapid PCR	Time to Preliminary Results (Median, Range)	Time to Final Results (Median, Range)
MRSA	23.1 hrs (19.5 to 60.8 hrs)	69.3 hrs (27.5 to 92.8 hrs)
MSSA	24.9 hrs (20.1 to 64.9 hrs)	72.9 hrs (38.55 to 95.9 hrs)
Non-SA	38.1 hrs (20.3 to 57.9 hrs)	89.4 hrs (49.3 to 154.6 hrs)

Compared to pre-defined time to rapid diagnostic results of approximately 1.5 hours

Conclusions

- ABSSSIs are a common cause of patients seeking medical care in EDs
- Within a prospective randomized trial of appropriate treatment for ABSSSIs rapid PCR testing was able to aid in pathogen identification as MRSA, MSSA, or not-SA 70 to 80 hours sooner
- This allows for clinical investigative trials to be enriched for patients with MRSA at point of care
- There was a high rate of concurrence between rapid PCR results and CM
- These results have the potential to impact future clinical trials and treatment at point of care for ABSSSIs

References

Dryden MS. Complicated skin and soft tissue infection. J Antimicrob Chemother 2010; 65 Suppl 3:iii35-44
Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2005; 41:1373-1406
Moet GJ, Jones RN, Biedenbach DJ, et al. Contemporary causes of skin and soft tissue infections in North America, Latin America, and Europe: report from the SENTRY Antimicrobial Surveillance Program (1998-2004).
Itani KM, Merchant S, Lin SJ, et al. Outcomes and management costs in patients hospitalized for skin and skin-structure infections. American journal of infection control 2011; 39:42-49
Lodise TP, McKinnon PS, Swiderski L, et al. Outcomes analysis of delayed antibiotic treatment for hospital-acquired Staphylococcus aureus bacteremia. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2003; 36:1418-1423