

Chao Qi¹, Richard G. Wunderink¹, Matthew Sims², Romney M. Humphries³, George Kallstrom⁴, Karen C. Carroll⁵, Fann Wu⁶, Hardy Dwight⁷, Susan Butler-Wu⁸, Matthias Klein⁹, Katja Schwarzer⁹, Robin Patel¹⁰

¹Northwestern Medicine, Chicago IL; ²Beaumont Health, Royal Oak MI; ³University of California, Los Angeles CA; ⁴Summa Health, Akron OH; ⁵Johns Hopkins Hospital, Baltimore MD; ⁶Columbia University, New York NY; ⁷University of Rochester, Rochester NY; ⁸University of Washington, Seattle WA; ⁹Curetis GmbH, Holzgerlingen, Germany; ¹⁰Mayo Clinic, Rochester MN; Corresponding author: katja.schwarzer@curetis.com

BACKGROUND

A lower respiratory tract infection (LRTi) is an acute inflammation of the lower respiratory tract caused by viruses, bacteria, parasites or fungi. Today, identification of the pathogen in an LRTi is mainly based on microbiological cultures of lower respiratory tract samples; however, results are not available for at least two days. LRTis pose a serious risk for ICU patients with high morbidity and mortality and put a significant burden on health care services around the world. The Unyvero Lower Respiratory Tract (LRT) Application, now FDA-cleared, is an automated multiplex nucleic acid amplification test, performed on the Curetis Unyvero Platform. It detects and identifies 19 respiratory bacterial microorganisms and 10 genes associated with antibiotic resistance simultaneously (see Fig.1) in approximately five hours directly from clinical specimens without requiring a bacterial isolate. Results of a U.S. multicenter clinical trial assessing this test and platform are described.

MATERIALS AND METHODS

As part of the clinical trial study, a total of 603 prospective tracheal aspirate samples were collected at nine participating hospitals across the U.S. Samples were tested with the Unyvero LRT Application and compared against standard of care microbiology. Test results were also compared against independent PCR assays followed by bi-directional sequencing. The study was complemented with data from 185 positive archived specimens and samples contrived with well-characterized strains for LRT panel markers not sufficiently covered by the previously tested study samples.

RESULTS

A total of 312 fresh samples were positive for one or more pathogens on the LRT panel. Overall weighted average sensitivity and specificity for panel microorganisms was 92.5% and 97.4%, respectively. For antibiotic resistance markers with a corresponding microorganism, overall weighted average sensitivity was 93.0% and overall weighted average specificity was 98.8%.

Unyvero LRT Panel

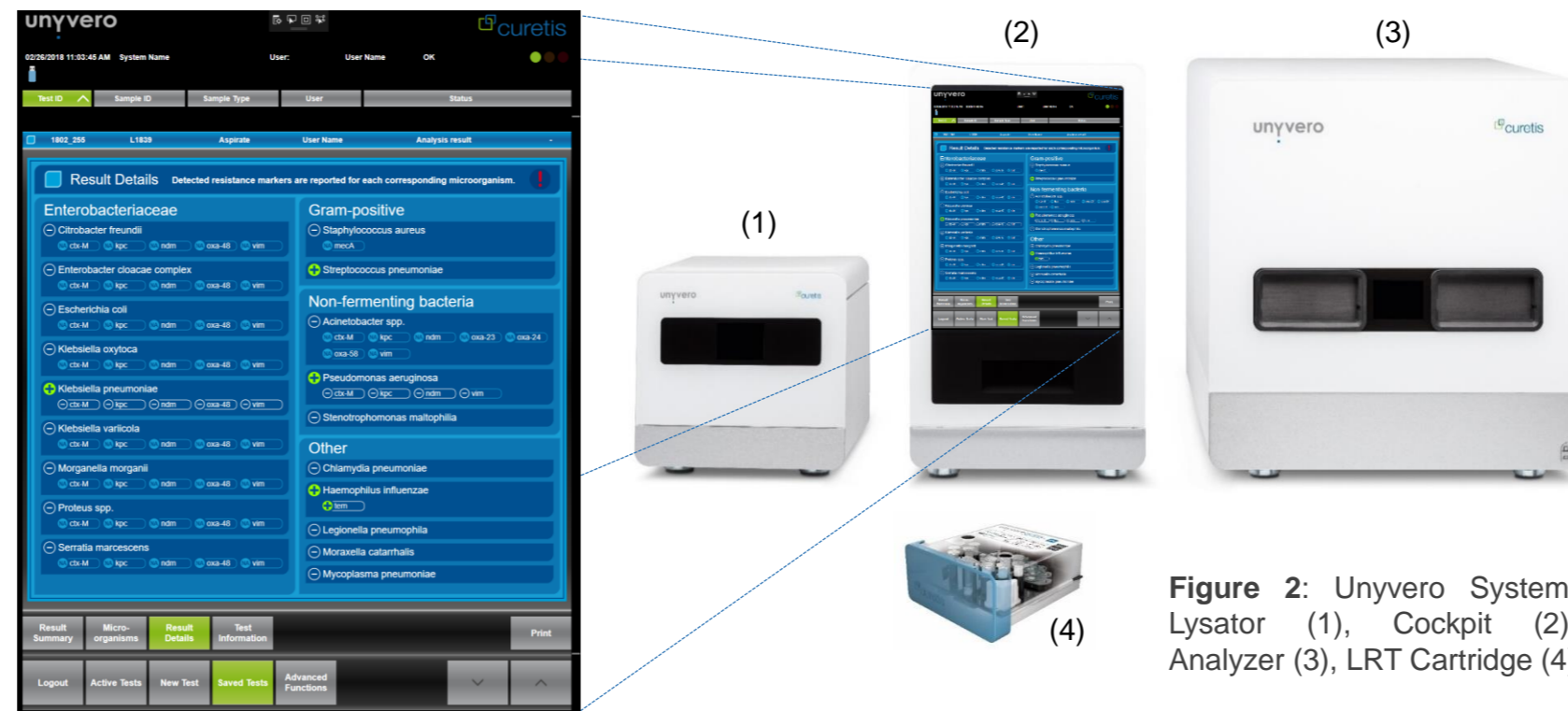


Figure 1: Result summary screen showing all microorganisms detected by the LRT application together with corresponding antibiotic resistance markers (if applicable).

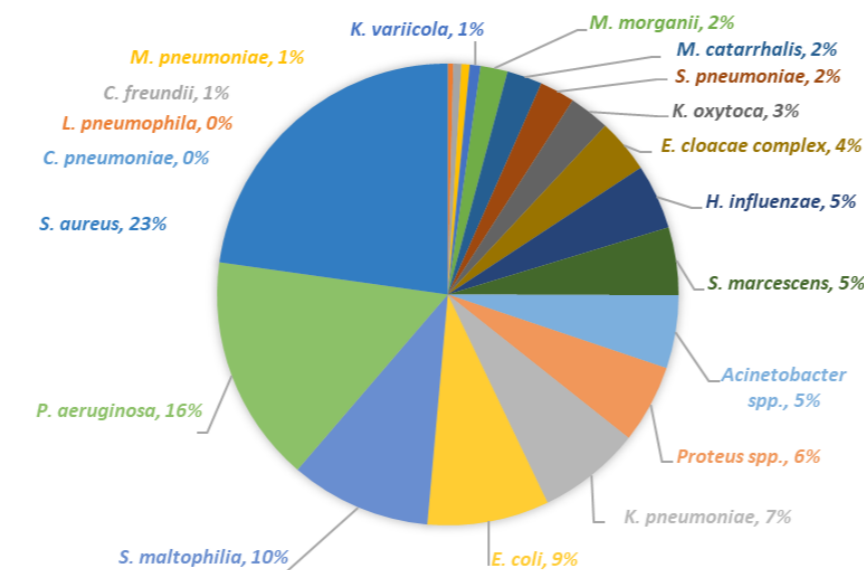


Figure 3: Expected values for microorganisms as detected by the LRT application in 603 prospective aspirate specimens.

CONCLUSION

The Unyvero LRT panel performed on the Unyvero System is a sensitive and specific test for tracheal aspirate samples and provides rapid and essential information regarding microorganisms and antimicrobial resistance genes involved in lower respiratory tract infections, which could have a significant positive impact on patient care and antibiotic stewardship.

LRT Microorganism Results

Overall weighted average
Sensitivity 92.5%

Overall weighted average
Specificity 97.4%

	Positivity TP / (TP+FN)	PPA [%] (95 % CI)	Negativity TN / (TN+FP)	NPA [%] (95 % CI)
<i>Acinetobacter spp.</i>	10/10	100.0 (72.3 - 100.0)	576/593	97.1 (95.5 - 98.2)
<i>Citrobacter freundii</i>	1/4	25.0 (4.6 - 69.9)	597/599	99.7 (98.8 - 99.9)
<i>Enterobacter cloacae complex</i>	14/15	93.3 (70.2 - 98.8)	582/588	99.0 (97.8 - 99.5)
<i>Escherichia coli</i>	23/24	95.8 (79.8 - 99.3)	557/579	96.2 (94.3 - 97.5)
<i>Haemophilus influenzae</i>	8/8	100.0 (67.6 - 100.0)	579/595	97.3 (95.7 - 98.3)
<i>Klebsiella oxytoca</i>	4/6	66.7 (30.0 - 90.3)	586/597	98.2 (96.7 - 99.0)
<i>Klebsiella pneumoniae</i>	21/24	87.5 (69.0 - 95.7)	562/579	97.1 (95.3 - 98.2)
<i>Klebsiella variicola</i>	2/2	100.0 (34.2 - 100.0)	599/601	99.7 (98.8 - 99.9)
<i>Moraxella catarrhalis</i>	1/3	33.3 (6.1 - 79.2)	588/600	98.0 (96.5 - 98.9)
<i>Morganella morganii</i>	1/1	100.0 (20.7 - 100.0)	593/602	98.5 (97.2 - 99.2)
<i>Proteus spp.</i>	10/11	90.9 (62.3 - 98.4)	573/592	96.8 (95.0 - 97.9)
<i>Pseudomonas aeruginosa</i>	64/69	92.8 (84.1 - 96.9)	514/534	96.3 (94.3 - 97.6)
<i>Serratia marcescens</i>	11/11	100.0 (74.1 - 100.0)	578/592	97.6 (96.1 - 98.6)
<i>Staphylococcus aureus</i>	81/83	97.6 (91.6 - 99.3)	481/520	92.5 (89.9 - 94.5)
<i>Stenotrophomonas maltophilia</i>	25/26	96.2 (81.1 - 99.3)	550/577	95.3 (93.3 - 96.8)
<i>Streptococcus pneumoniae</i>	7/9	77.8 (45.3 - 93.7)	588/594	99.0 (97.8 - 99.5)

Specimens with false positive LRT results were analyzed with molecular assays (PCR/bi-directional sequencing) using sample DNA extracts for presence or absence of microorganisms: presence of microorganisms was confirmed in 16/17 cases for *Acinetobacter spp.*, 0/2 for *C. freundii*, 5/6 for *E. cloacae complex*, 21/22 for *E. coli*, 14/16 for *H. influenzae*, 7/11 for *K. oxytoca*, 15/17 for *K. pneumoniae*, 2/2 cases for *K. variicola*, 12/12 for *M. catarrhalis*, 6/9 for *M. morganii*, 18/19 for *Proteus spp.*, 16/20 for *P. aeruginosa*, 13/14 for *S. marcescens*, 36/39 cases for *S. aureus*, 27/27 for *S. maltophilia*, 6/6 for *S. pneumoniae*, and 11/12 for *M. catarrhalis*.

LRT Antibiotic Resistance Marker Results

Overall weighted average
Sensitivity 93.0%

Overall weighted average
Specificity 98.8%

	Positivity TP / (TP+FN)	PPA [%] (95 % CI)	Negativity TN / (TN+FP)	NPA [%] (95 % CI)	not reported (masked)
<i>bla_{CTX-M}</i>	15/16	93.8 (71.7 - 98.9)	177/179	98.9 (96.0 - 99.7)	408
<i>bla_{KPC}</i>	6/6	100 (61.0 - 100.0)	189/189	100 (98.0 - 100.0)	408
<i>bla_{NDM}</i>	0/0	n.a.	195/195	100 (98.1 - 100.0)	408
<i>bla_{OXA-23}</i>	6/7	85.7 (48.7 - 97.4)	18/20	90 (69.9 - 97.2)	576
<i>bla_{OXA-24}</i>	2/2	100 (34.2 - 100.0)	25/25	100 (86.7 - 100.0)	576
<i>bla_{OXA-48}</i>	0/0	n.a.	138/139	99.3 (96.0 - 99.9)	464
<i>bla_{OXA-58}</i>	0/0	n.a.	27/27	100 (87.5 - 100.0)	576
<i>bla_{TEM}</i>	8/8	100 (67.6 - 100.0)	16/16	100 (80.6 - 100.0)	579
<i>bla_{VIM}</i>	2/2	100 (34.2 - 100.0)	193/193	100 (98.0 - 100.0)	408
<i>mecA</i>	54/59	91.5 (81.6 - 96.3)	53/61	86.9 (76.2 - 93.2)	483