1224. Investigation of Infectious Etiologies in the Lower Respiratory Tract from Pediatric Patients with Unexpected Cardiopulmonary Deterioration using Next-Generation Sequencing

Suguru Takeuchi, MD[1]; Jun-ichi Kawada, MD, PhD[1]; Kazuhiro Horiba, MD, PhD[2]; Makoto yamaguchi, MD[3]; Toshihiko Okumura, MD[1]; Takako Suzuki, MD[1]; Yuka Torii, MD, PhD[1]; Shinji Kawabe, MD, PhD[4]; Sho Wada, MD[4]; Takanari Ikeyama, MD[4]; Yoshinori Ito, MD, PhD[1]; [1]Nagoya University Graduate School of Medicine, Nagoya, Aichi, Japan; [2]Research Institute of Environmental Medicine (RIeM), Nagoya University, Nagoya, Aichi, Japan; [3]Department of Pediatrics, Nagoya University Graduate School of Medicine, Nagoya, Aichi, Japan; [4]Aichi Children's Health and Medical Center, Obu, Aichi, Japan

Session: P-55. New Approaches to Diagnostics

Background. In pediatric patients, unexpected cardiopulmonary deterioration with or without following cardiopulmonary arrest (CPA) are rare events, but can be caused by any of several etiologies, including infectious diseases. The most common cause of out-of-hospital CPA in children ≤12 years old was sudden infant death syndrome (SIDS), whereas infectious diseases were responsible for approximately 10% of the CPA cases. However, the role of infection may have been underestimated as triggers of SIDS or CPA. This study aimed to investigate the infectious etiologies in pediatric patients with unexpected cardiopulmonary deterioration using next-generation sequencing (NGS).

Methods. A total of 16 pediatric patients who were admitted to the pediatric intensive care unit with unexpected cardiopulmonary deterioration with or without following CPA were enrolled. Ten bronchoalveolar fluid (BALF) and six transtracheal aspirates (TTA) samples obtained in the acute phase were used to prepare NGS libraries. The libraries were sequenced on HiSeq and analyzed using metagenome analysis tools.

Results. In ten of 16 patients, one or more bacterial/viral pathogens were detected in the BALF or TTA specimens using NGS. Compared to the conventional culture and viral antigen test results, an additional 6 bacterial (e.g., *Chlamydia trachomatis*) and 4 viral pathogens (e.g., coxsackievirus A6 and human coronavirus NL63) were identified by NGS in four of ten patients in whom no causative pathogen had been identified by conventional culture and viral antigen tests. A summary of the detected pathogens is listed in Table 1. Notably, sequencing results allowed us to define genotypes for all of the detected viruses in a single NGS assay per patient. Furthermore, based on phylogenetic analysis of the VP1 region, the coxsackievirus A6 strain detected in this study belongs to lineage E2 and harbors an amino acid change (T283A), a substitution that has potential to cause severe illness.

Table 1

Table 1. Patient characteristics and detected pathogens

Pt No.	Age	Sex	Underlying disease	Diagnostic category	Sample type	NGS results (RPM)		Conventional test results[d]
						Bacteria	Virus	
1	6y0m	M	-	CPA	BALF	-	-	-
2	9y8m	F	-	Acute cardiac failure Arrhythmia	BALF	*S. pneumoniae* (101)	HRV-A49 (742)	-
3	0y5m	M	-	Acute respiratory failure	BALF	-	-	-
4	0y2m	F	-	Acute respiratory failure	BALF	*A. guillouiae* (99)	-	-
5	1y3m	F	Emanuel syndrome TOF[a]	Acute cardiac failure	BALF	***M. catarrhalis*** (111) ***H. influenzae*** (78)	HCoV-NL63 (79)	***H. influenzae*** (2+) *S. pneumoniae* (1+) ***M. catarrhalis*** (±)
6	0y2m	M	-	Acute cardiac failure	BALF	-	-	-
7	0y5m	M	-	CPA	BALF	***S. pneumoniae*** (16,417)	-	*H. influenzae* (2+) ***S. pneumoniae*** (2+) *α-Streptococcus sp.* (2+)
8	0y6m	M	-	CPA	BALF	***M. catarrhalis*** (230)	-	*S. pneumoniae* (3+) *H. influenzae* (3+) ***M. catarrhalis*** (3+)
9	1y4m	F	West syndrome[b]	CPA	BALF	-	Coxsackievirus A6 (86)	-
10	9y11m	F	-	Fulminant myocarditis	BALF	-	-	-
11	4y7m	M	-	CPA Fulminant myocarditis	TTA	-	-	-
12	1y7m	F	-	Fulminant myocarditis	TTA	***S. pneumoniae*** (6,126) *S. oralis* (1,451)	**HRSV- A** (1,651)	***S. pneumoniae*** (2+) *H. influenzae* (2+) **HRSV**[e]
13	d17	F	-	Acute cardiac failure Pneumonia	TTA	*C. trachomatis* (76)	-	-
14	6y0m	F	Epilepsy[c]	Acute cardiac failure	TTA	***P. aeruginosa*** (1,508)	PIV-3 (243)	*P. fluorescens/putida* (±) ***P. aeruginosa*** (±) *α-Streptococcus sp.* (±)
15	0y3m	M	-	CPA	TTA	***S. oralis*** (1,783) ***S. pneumoniae*** (1,602) ***S. mitis*** (1,058) *R. mucilaginosa* (869) *S. salivarius* (768)	-	***S. pneumoniae*** **(2+)** ***α-Streptococcus sp.*** (2+) *M. catarrhalis* (±)
16	5y4m	F	-	Acute myocarditis	TTA	-	-	-

Abbreviation: BALF, bronchoalveolar lavage fluid; CPA, cardiopulmonary arrest; HCoV-NL63, Human coronavirus NL63; HRSV, Human respiratory syncytial virus; HRV-A49, Human rhinovirus A49; PIV-3, Parainfluenzavirus 3 (Human respirovirus 3); RPM, reads per million; TOF, Tetralogy of Fallot; TTA, transtracheal aspirates. Bold letters indicate identical pathogens between NGS and conventional tests.

[a]A patient with Emanuel syndrome and TOF after Rastelli repair.

[b]A patient with West syndrome after group B streptococcal meningitis.

[c]A patient with epilepsy after acute encephalopathy.

[d]All detected pathogens by conventional methods except for human respiratory syncytial virus in patient 12 reflected bacterial culture test results with transtracheal aspirates.

[e]Positive for antigen test.

Conclusion: Our results suggest that viral and bacterial infection are common triggers in unexpected cardiopulmonary deterioration in pediatric patients. NGS has the potential to contribute to the clarification of the etiology of pediatric critical illness.

Disclosures. **All Authors**: No reported disclosures

1225. Next-Generation Sequencing in Clinical Practice: A Survey of Infectious Disease Providers

Shilpa Vasishta, MD[1]; Christopher J. Graber, MD, MPH[2]; Tara Vijayan, MD, MPH[3]; [1]UCLA, Los Angeles, California; [2]VA Greater Los Angeles Healthcare System/UCLA, Los Angeles, California; [3]UCLA David Geffen School of Medicine, Los Angeles, California

Session: P-55. New Approaches to Diagnostics

Background. Next-generation sequencing (NGS) has emerged as a promising diagnostic tool in Infectious Diseases (ID). The platform offers high sensitivity, detecting difficult-to-isolate organisms. However, limitations remain in employing NGS broadly, including high cost, unstandardized methods, and unclear significance of many results. To date, there is no consensus on appropriate use of NGS. Here, we describe perceived utility of NGS among ID physicians at one academic medical center.

Methods. A survey exploring four clinical scenarios was disseminated electronically to ID attendings and fellows. Scenarios #1 (immunocompetent patient without localizing signs) and #2 (immunosuppressed patient with localizing signs) were followed by questions exploring likelihood of sending NGS. Scenarios #3 (immunocompetent patient with prosthetic joint infection) and #4 (immunosuppressed patient with cavitary lung lesion) were followed by questions exploring interpretation of NGS data.

Results. Twenty-six physicians responded. Respondents were more likely to send NGS for an immunosuppressed than an immunocompetent patient (8/26 vs. 2/26 respondents, p=0.024), with more respondents noting in the latter casethat NGS might "yield unhelpful/misleading results" (26 /26 vs. 17/23, p=0.0054) or might "not be cost-effective" (21/26 vs. 13/23, p=0.066). Those with over five years of experience tended to be more likely to send NGS (8/27 vs. 2/23 responses across two scenarios, p=0.065), noting more frequently that NGS might "yield a diagnosis not otherwise considered" (16/25 vs. 6/23 responses, p=0.0084) and"avoid painful/high-risk testing" (16/26 vs. 8/23 responses, p=0.062). In scenarios with available NGS data, nearlyhalf (21/49 responses across two scenarios) favored obtaining further diagnostics.

Conclusion. Our results suggest that patient immunosuppression is a salient factor in determining clinical utility of NGS and that physician experience may affect utilization. While NGS is perceived as a useful adjunct to existing data to guide initial management, results are still interpreted with caution and rarely supersede more established methods for definitive diagnosis. Further study is needed to guide evidence-based NGS use.

Disclosures. **All Authors**: No reported disclosures

1226. Performance of a Host Response Test for Bacterial/Viral Discrimination in Immunocompromised Patients

Rachael E. Mahle, BS[1]; Sunil Suchindran, PhD[2]; Ricardo Henao, PhD[2]; Julie M. Steinbrink, MD[2]; Thomas W. Burke, PhD[2]; Micah T. McClain, MD, PhD[2]; Geoffrey S. Ginsburg, MD PhD[3]; Christopher W. Woods, MD, MPH, FIDSA[4]; Ephraim L. Tsalik, MD, MHS, PhD, FIDSA[4]; [1]Duke University School of Medicine, Durham, NC, USA, Durham, North Carolina; [2]Duke University, Durham, NC; [3]Duke University School of Medicine, Durham, NC; [4]Duke University School of Medicine, Durham, NC, USA; Durham VA Health Care System, Durham, NC, USA, Durham, North Carolina

Session: P-55. New Approaches to Diagnostics

Background. Difficulty distinguishing bacterial and viral infections contributes to excess antibiotic use. A host response strategy overcomes many limitations of pathogen-based tests, but depends on a functional immune system. This approach may therefore be limited in immunocompromised (IC) hosts. Here, we evaluated a host response test in IC subjects, which has not been extensively studied in this manner.

Methods. An 81-gene signature was measured using qRT-PCR in previously enrolled IC subjects (chemotherapy, solid organ transplant, immunomodulatory agents, AIDS) with confirmed bacterial infection, viral infection, or non-infectious illness (NI). A regularized logistic regression model estimated the likelihood of bacterial, viral, and noninfectious classes. Clinical adjudication was the reference standard.

Results. A host gene expression model trained in a cohort of 136 immunocompetent subjects (43 bacterial, 41 viral, and 52 NI) had an overall accuracy of 84.6% for the diagnosis of bacterial vs. non-bacterial infection and 80.8% for viral vs. non-viral infection. The model was validated in an independent cohort of 134 IC subjects (64 bacterial, 28 viral, 42 NI). The overall accuracy was 73.9% for bacterial infection (p=0.03 vs. training cohort) and 75.4% for viral infection (p=0.27). Test utility could be improved by reporting probability ranges. For example, results divided into probability quartiles would allow the highest quartile to be used to rule in infection and the lowest to rule out infection. For IC subjects in the lowest quartile, the test had 90.1% and 96.4% sensitivity for bacterial and viral infection, respectively. For the highest quartile, the test had 91.4% and 84.0% specificity for bacterial and viral infection, respectively. The type or number of immunocompromising conditions did not impact performance.

Illness Etiology Probabilities