2295

Streptococcus pneumoniae Related Hemolytic Uremic Syndrome (pHUS) and the Identification of Matched Cross-Country Strains by Next Generation Sequencing (NGS)

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Introduction

Hemolytic uremic syndrome (HUS) describes a presentation of acute kidney injury, microangiopathic hemolytic anemia and thrombocytopenia, which often occurs following infection, though can be genetic or autoimmune in origin. Five to 15% of HUS cases are related to *S. pneumoniae* infection, most often meningitis or pneumonia. Despite the introduction of PCV 13 and an overall decrease in incidence of invasive pneumococcal disease in children, the incidence of pneumococcal related HUS (pHUS) cases is rising. Efforts have been made to determine if certain factors increase the risk of development of pHUS in patients with suspected pneumococcal disease. These efforts are often hampered by culture collection occurring after empiric antibiotic administration, which may inhibit culture growth and limit identification. Alternative methods of microbiologic identification, such as next generation sequencing, may be useful in determining specific etiologies of syndromes such as HUS that can have infectious triggers. We present the cases of 4 children, from two distant institutions, with concern for HUS in the setting of respiratory infection ,who had blood sent for next generation sequencing to aid in diagnosis.

Background

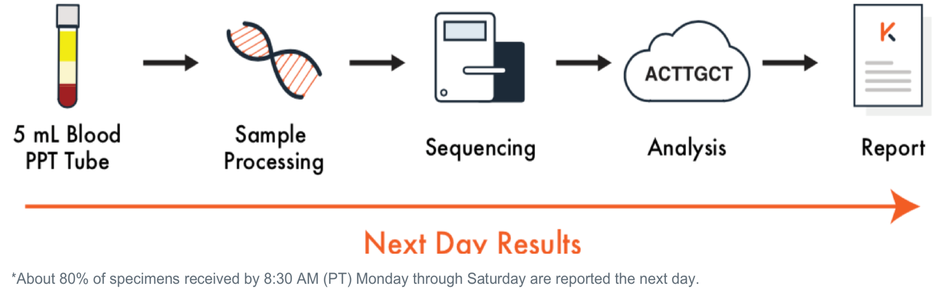
- pHUS is seen in cases of complicated pneumonia (PNA).[1,2]
- Incidence of pneumococcal related HUS (pHUS) cases is rising[2] for unclear reasons, despite use of PCV13 and an overall decrease in invasive pneumococcal disease in children[3]
- PCV13 includes serotypes 1,3,4,5, 6A, 6B, 7F, 9V, 14, 18C, 19 A, 19F, 23F
- Yield of blood cultures in patients with pneumonia is poor (<5%)[4] and often impaired by culture collection occurring after empiric antibiotic administration.

Patient Characteristics

ID	Age	PCV 13 UTD	Presenting Illness	Positive S. pneumoniae culture?	Other major interventions	Viral Co-infection
Rady 1	11 mo	Yes	Multifocal PNA with effusion	*Yes (B,R)*	CRRT, Epi/Norepi, chest tubes, ventilator, steroids	hMPV
CNMC 1	18 mo	Yes	Bilateral multifocal PNA with effusion	No	CRRT, Epi/Norepi, chest tubes, ventilator, eculizumab	RSV B
Rady 2	26 mo	Yes	Lobar PNA	No	CRRT, Epi, chest tubes, ventilator	Influenza A
Rady 3	42 mo	No	Lobar PNA with effusion; bacteremia	*Yes (B,R)*	Epi/Norepi, chest tubes, ventilator, IVIg, steroids	Influenza

R-Respiratory, B-blood, U-urine, P-pleural fluid

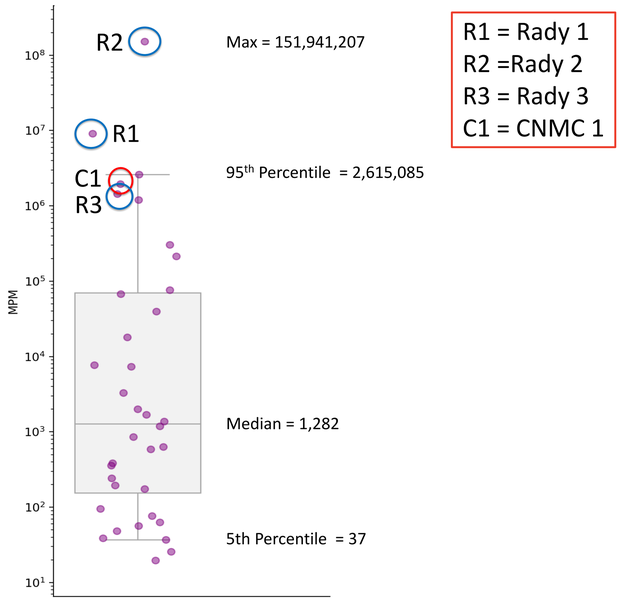
Methods



*About 80% of specimens received by 8:30 AM (PT) Monday through Saturday are reported the next day.

Results

Figure 1: MPMs (cell free DNA molecules per milliliter) of *Streptococcus pneumoniae* calls in the past 365 days



Results

All four samples were found to be positive for *S. pneumoniae* at extremely high levels (**Figure 1**). Three (3) out of 4 samples were identified as serotype 3 by NGS. The fourth sample was similar to the others but ultimately identified as serotype 12A. *S. pneumoniae* culture isolates from R1 and R3 were both independently confirmed as serotype 3.

Patient	Identification	MPM (molecules/uL)	Serotype
R1	S. pneumoniae	9,122,698	3
C1	S. pneumoniae	1,957,238	3
R2	S. pneumoniae	151,941,207	12A
R3	S. pneumoniae	1,435,748	3

Table 1: Karius NGS strain match calls

Conclusion

- NGS is useful for pathogen detection and quantitation of culture-negative infections
- Karius NGS has potential to identify clusters of disease that would likely otherwise have gone undetected.
- The extremely elevated levels of pathogen DNA, 1000-100,000 fold higher than in non-HUS cases of *S. pneumoniae* disease, may inform the pathophysiology of pHUS.
- NGS may be useful in determining specific etiologies of syndromes such as HUS that can have infectious triggers
- Serotype 3 strains of *S. pneumoniae* continue to be a common cause of pneumococcal invasive disease and pHUS, despite inclusion in PCV13.

References

1.Bender et al. Epidemiology of Streptococcus penumoniae-Induced Hemolytic Uremic Syndrome in Utah Children. Pediatr Infect Dis J. 2010; 29:712-716.
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