Treatment Experience with Voriconazole During the 2012 Fungal Meningitis Outbreak

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Background

- In 2012, nationwide distribution of contaminated methylprednisolone steroid injections resulted in an outbreak of over 750 associated infections.[1]
- The last CDC case count update in 2013 reported 64 patient deaths linked to the contaminated steroids.[1]
- *Exserohilum rostratum*, a dematiaceous, filamentous mold commonly found in grass and soil, was the most common causative organism identified.[1,2]
- Carilion Clinic treated 34 affected patients, the management of which has been described previously.[3]

TDM

- Prior studies have demonstrated the importance of voriconazole therapeutic drug monitoring (TDM) for improvements in both efficacy and safety.[4]
- The effect of dose adjustment on drug levels remains unpredictable due to the non-linear pharmacokinetics and saturable clearance pathways of voriconazole.[5]
- Greater rates of response have been demonstrated when voriconazole TDM was utilized and several studies have shown that patients who did not reach therapeutic targets (i.e. 4.5 – 5.5 mcg/mL) were less likely to respond to treatment.[6-8]
- Serum voriconazole levels > 6 mcg/mL have been associated with increased risk of adverse events.[6]

2012 OUTBREAK

- Interim treatment guidelines recommending empiric treatment with both voriconazole and liposomal amphotericin B were provided by the CDC, but optimal medication, dosages, and duration were unknown.[9]
- As a result, the Infectious Diseases team at Carilion Clinic selected empiric monotherapy with voriconazole due to concerns of theoretical antagonism with amphotericin.[3,10]

Study Objectives

PRIMARY

- Examine the relationship between voriconazole pharmacokinetics and clinical outcomes specific to the 2012 fungal infection outbreak population

SECONDARY

- Describe the effect of voriconazole pharmacokinetics and treatment duration on side effects

Methods

STUDY DESIGN

- This was a retrospective, single-center cohort study.
- The study protocol was deemed exempt by the Carilion Clinic Institutional Review Board.

SETTING AND POPULATION

- Conducted at Carilion Clinic Roanoke Memorial Hospital, a 763 - bed tertiary care facility located in Roanoke, VA.
- All patients with previous exposure to ≥ 1 contaminated steroid injection and treated at Carilion Clinic were included.
- Classification and regression tree (CART) analysis was used to identify variables associated with patient response and adverse event occurrence. Variables such as type of infection, Charlson Comorbidity Index (CCI) score, age, and associated voriconazole trough were incorporated into the analysis to examine multicollinearity and interactions.

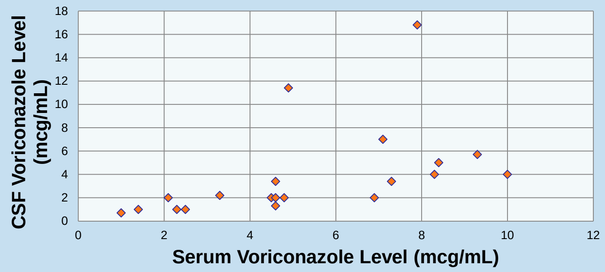
DATA COLLECTION

- Data was extracted from the Epic electronic medical record using a standardized data collection tool.

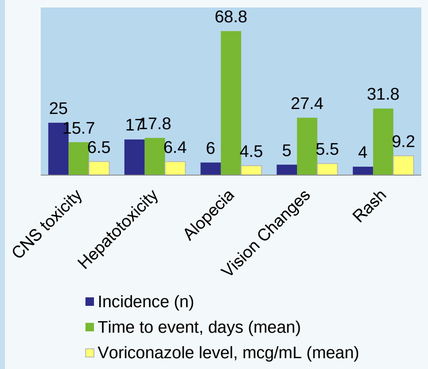
Results

Baseline Patient Characteristics	
Age, years (mean ± SD)	63.9 ± 16.7
Female gender, n (%)	19 (55.9%)
Charlson Comorbidity Index Score (mean ± SD)	0.16 ± 0.05
Infection Type, n (%)	
Meningitis	31 (91.2%)
Arachnoiditis	19 (55.9%)
Epidural or Intradural Abscess, Phlegmon	17 (50.0%)
Treatment Summary (mean ± SD)	
Length of hospital stay, days	23.9 ± 18.0
Days of intravenous voriconazole	11.0 ± 5.2
Duration of voriconazole treatment, days	102.5 ± 11.1

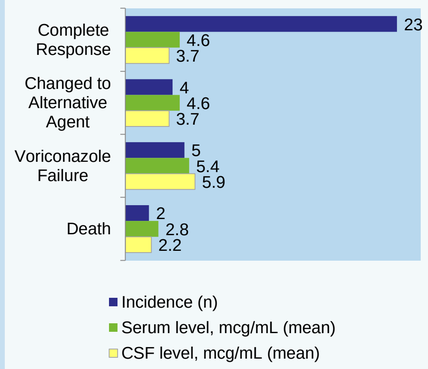
CSF Voriconazole Levels at Corresponding Serum Concentrations



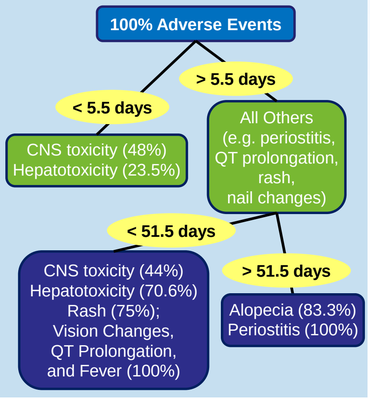
Side Effect Incidence, Time to Event, and Associated Voriconazole Level



Voriconazole Treatment Outcome and Associated Voriconazole Level



Adverse Event CART Analysis



Summary

- The study population was primarily Caucasian females (55.9%) with a mean age of 64 years.
  - Patients had an extremely low rate of comorbidities as assessed by CCI score (mean 0.16 ± 0.05).
- 67.6% (n=23) of patients met criteria for complete treatment response on voriconazole.
  - Voriconazole level was not associated with treatment response according to CART analysis.
- The most common side effects observed in this study were CNS toxicity (e.g. hallucinations or confusion), hepatotoxicity, alopecia, vision changes, and rash.
  - CNS toxicity and hepatotoxicity developed within the first week of treatment.
  - The majority of side effects occurred within the first 2 months while alopecia and periostitis only occurred with prolonged voriconazole exposure.
- Voriconazole level was not associated with adverse event development according to CART analysis.
  - The average voriconazole trough associated with an adverse event was 5.79 ± 0.72 mcg/mL.

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Disclosure: Authors of this presentation have the following to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation:

Sarah B. Green: Nothing to disclose
Marissa G. Williams: Nothing to disclose
Nathan A. Everson: Nothing to disclose

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