Update on \textit{C. difficile} infection: New bugs and new drugs

Kevin W. Garey, Pharm.D., M.S., FASHP
Chair, Department of Pharmacy Practice and Translational Research
Professor of Pharmacy Practice,
Houston, TX

Acknowledgements

- Past and/or ongoing research grant support from Merck, Cubist, Summit, and Astellas
- Consultancy for Merck, Summit, and Seres Therapeutics
Objectives

• Take a best guess on what treatment of *Clostridium difficile* infection will look like in the near future
• What does next generation fecal microbiota transplantation (FMT) look like (and is it possible).
• Are there any (less gross) ways to prevent/cure dysbiosis

A History of *C. difficile*

1893 - pseudomembranous colitis first described
1935 - isolated in stool
1978 - *C. difficile* responsible for antibiotic associated diarrhea
1996-2003 CDC reports rate of CDI increased from 31 cases per 100,000 persons to 61 cases per 100,000 persons

2005 – US continues to report increased CDI
2008-11 – England directs significant resources to control CDI (and MRSA)

Current – continued persistence of RT 027 in North America and decrease incidence in Europe

2. The *Clostridium difficile* PCR ribotype 027 lineage: a pathogen on the move Valiente, E. et al. Clinical Microbiology and Infection, Volume 20, Issue 5, 396 –404
Hypervirulent *C. difficile*

An Epidemic, Toxin Gene–Variant Strain of *Clostridium difficile*

L. Clifford McDonald, M.D., George E. Killgore, Dr.P.H., Angela Thompson, M.M.Sc.,
Robert C. Owens, Jr., Pharm.D., Sophia V. Kazakova, M.D., M.P.H., Ph.D., Susan P. Sambol, M.T.,
Stuart Johnson, M.D., and Dale N. Gerding, M.D.

Incidence of hypervirulent strains of *C. difficile*, 2005

<table>
<thead>
<tr>
<th>Health Care Facility</th>
<th>Date of Onset of Outbreak</th>
<th>No. of Isolates Tested</th>
<th>BI/NAP1 Strain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Georgia</td>
<td>Oct. 2001</td>
<td>46</td>
<td>29 (63)</td>
</tr>
<tr>
<td>Illinois</td>
<td>July 2003</td>
<td>14</td>
<td>6 (43)</td>
</tr>
<tr>
<td>Maine, Facility A</td>
<td>March 2002</td>
<td>13</td>
<td>9 (69)</td>
</tr>
<tr>
<td>Maine, Facility B</td>
<td>July 2003</td>
<td>48</td>
<td>30 (62)</td>
</tr>
<tr>
<td>New Jersey</td>
<td>June 2003</td>
<td>12</td>
<td>9 (75)</td>
</tr>
<tr>
<td>Oregon*</td>
<td>April 2002</td>
<td>30</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Pennsylvania, Facility A</td>
<td>2000–2001</td>
<td>18</td>
<td>7 (39)</td>
</tr>
<tr>
<td>Pennsylvania, Facility B</td>
<td>Oct. 2003</td>
<td>6</td>
<td>3 (50)</td>
</tr>
<tr>
<td>Total</td>
<td>187</td>
<td>96</td>
<td>31</td>
</tr>
</tbody>
</table>

* Isolates were not collected until after the peak of the outbreak.

Increasing mortality and complications due to CDAD

Table 1: Patients with Clostridium difficile-associated diarrhea (CDAD) in the Estrie region of Quebec who died within 30 days after diagnosis or who had complicated CDAD, 1991–2003

<table>
<thead>
<tr>
<th>Period</th>
<th>No. of patients with CDAD*</th>
<th>No. (%) who died within 30 days after diagnosis</th>
<th>Adjusted OR (95% CI)†</th>
<th>No. (%) who had complicated CDAD‡</th>
<th>Adjusted OR (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991–1992</td>
<td>169</td>
<td>8 (4.7)</td>
<td>1.0</td>
<td>12 (7.1)</td>
<td>1.0</td>
</tr>
<tr>
<td>1993–1994</td>
<td>217</td>
<td>11 (5.1)</td>
<td>1.7 (0.5–5.3)</td>
<td>14 (6.5)</td>
<td>1.0 (0.4–2.7)</td>
</tr>
<tr>
<td>1995–1996</td>
<td>215</td>
<td>13 (6.0)</td>
<td>1.6 (0.5–5.0)</td>
<td>17 (7.9)</td>
<td>0.9 (0.3–2.2)</td>
</tr>
<tr>
<td>1997–1998</td>
<td>192</td>
<td>11 (5.7)</td>
<td>1.1 (0.4–3.7)</td>
<td>13 (6.8)</td>
<td>0.6 (0.3–1.7)</td>
</tr>
<tr>
<td>1999–2000</td>
<td>248</td>
<td>19 (7.7)</td>
<td>1.5 (0.5–4.6)</td>
<td>28 (11.3)</td>
<td>1.2 (0.5–2.9)</td>
</tr>
<tr>
<td>2001–2002</td>
<td>244</td>
<td>21 (8.6)</td>
<td>1.6 (0.5–4.7)</td>
<td>28 (11.5)</td>
<td>1.1 (0.5–2.3)</td>
</tr>
<tr>
<td>2003</td>
<td>390</td>
<td>54 (13.8)</td>
<td>3.0 (1.1–8.4)</td>
<td>71 (18.2)</td>
<td>2.2 (1.0–4.9)</td>
</tr>
<tr>
<td>p value</td>
<td></td>
<td></td>
<td>&lt; 0.001§</td>
<td>&lt; 0.001§</td>
<td>&lt; 0.001§</td>
</tr>
</tbody>
</table>

Note: OR = odds ratio, CI = confidence interval.
*Includes only patients for whom enough information was available to assess these outcomes.
†Adjusted for age, sex, initial treatment, immune status, and tube feeding and surgery in the 2 months preceding diagnosis; 1991–1992 was used as the baseline period.
‡Presence of one or more of the following: megacolon, peritonitis, colostomy, shock requiring vasopressor therapy, death within 30 days after diagnosis.
§χ² test for trend.
¶χ² test, comparing 2003 with all other years.

Pepin, J. et al. CMAJ 2004;171:466-472

Time course of toxin production by hypervirulent strain compared to control

Warney Lancet 2005;366:1079
C difficile nomenclature

- All these are synonymous terms:
  - Toxinotype III: PCR analysis of PaLoc
  - PCR ribotype 027: European typing method
  - REA Group BI (bee eye): Typing method by Dale Gerding (Hines, IL)
  - PFGE: Nap-1: CDC typing method
- Work currently being conducted to make ribotyping the preferred typing method in the USA and Europe

Who you calling “hypervirulent”

Michigan: Derivation (n=310/34 severe) and validation (n=433/45 severe) of predictors of severe CDI (ICU admission, colectomy, or death). After accounting for disease presentation severity, ribotype did not predict outcome

<table>
<thead>
<tr>
<th>Predictor*</th>
<th>Derivation OR (95% CI)</th>
<th>P Value</th>
<th>Validation OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypervirulent ribotype:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>027/078 vs non-027/078 (reference)</td>
<td>0.82 (.07-.10.0)</td>
<td>.874</td>
<td>1.34 (.53-3.16)</td>
<td>.516</td>
</tr>
<tr>
<td>White blood cell count: Leukocytosis (&gt;12 000 cells/mL) or leukopenia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(&gt;4000 cells/mL) vs normal (reference)</td>
<td>4.27 (1.14–19.46)</td>
<td>.041</td>
<td>2.32 (1.07–5.18)</td>
<td>.035</td>
</tr>
<tr>
<td>Low albumin level (g/dL)</td>
<td>0.25 (.07-.77)</td>
<td>.025</td>
<td>0.47 (.25–.87)</td>
<td>.018</td>
</tr>
</tbody>
</table>

Walk et al. CID 2012;doi:10.1093/CID/CIS78
..and there are more ribotypes than just 027

A lot of ribotypes are associated with CDI

Many ribotypes are virulent, including 027

<table>
<thead>
<tr>
<th>Ribotype</th>
<th>Severe CDI presentation</th>
<th>Severe CDI outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>027 (n=170)</td>
<td>54.7%</td>
<td>18.9%</td>
</tr>
<tr>
<td>014-020 (n=118)</td>
<td>22.9%</td>
<td>4.2%</td>
</tr>
<tr>
<td>FP11 (n=74)</td>
<td>31.4%</td>
<td>8.6%</td>
</tr>
<tr>
<td>078-126 (n=42)</td>
<td>21.4%</td>
<td>9.5%</td>
</tr>
<tr>
<td>001 (n=35)</td>
<td>42.9%</td>
<td>8.6%</td>
</tr>
<tr>
<td>FP24 (n=35)</td>
<td>37.1%</td>
<td>22.9%</td>
</tr>
<tr>
<td>17 (n=23)</td>
<td>39.1%</td>
<td>17.4%</td>
</tr>
<tr>
<td>FP8 (n=19)</td>
<td>36.9%</td>
<td>10.5%</td>
</tr>
<tr>
<td>053-163 (n=16)</td>
<td>37.5%</td>
<td>6.25%</td>
</tr>
<tr>
<td>FP16 (n=16)</td>
<td>35.3%</td>
<td>11.2%</td>
</tr>
<tr>
<td>FP9 (n=16)</td>
<td>25.0%</td>
<td>18.8%</td>
</tr>
</tbody>
</table>

Aitken et al. ICHE 2015

You are all now expert C diff ribotypers

- 027 is definitely a virulent ribotype
- .....but, there are lots of ribotypes that are equally virulent
  – Treat the patient, not the bug!
- Without a doubt, the ribotype 027 strain has put a large focus on the value of strain typing in *C. difficile*.
- Now, let’s use some antibiotics!
The Impact of *Clostridium difficile* Infections (CDI)

Of patients with CDI given metronidazole or oral vancomycin, 25% will experience recurrent CDI.

Lessa CF et al. NEJM 2015;372:825-34.

[Diagram showing the cycle of *Clostridium difficile* infection and treatment options.]

Britton et al. 2014
Expanding treatment goals for CDI

Essential: Correct dysbiosis  Kill the organism  Adaptive immunity

Optional but nice: Safe and convenient  Also affects toxins and spores  Short vs. long-term

Adamu and Lawley. Curr Opin Microbiol 2013

There has been an explosion in treatment possibilities for CDI

Current: Probiotics  FMT  Metronidazole  Vancomycin  Fidaxomicin  IVIG

Future: 2nd generation FMT  non-tox C diff M3  Suromycine  Cadazolid  SMT-19969  Monoclonal antibodies vs. C diff toxins  Toxoid vaccines
Current European CDI guidelines

CDI

- Non-severe CDI
  - Metronidazole
  - Vancomycin
  - Fidaxomicin

- (Risk of) first recurrence
  - Vancomycin
  - Fidaxomicin
  - Metronidazole

- Severe disease or complicated course
  - Vancomycin
  - Fidaxomicin
  - Metronidazole

Green: strongly supports use; Blue: moderately supports use; Grey: minimally supports use; Red: recommend to not use

Clin Microbiol Infect 2014

More recently, metronidazole has been shown to be globally inferior to vancomycin (tolevamer phase III RCT)

Explosion in treatment possibilities for CDI minus

Current: Probiotics
- FMT
- Vancomycin
- Fidaxomicin
- IVIG

Future: 2nd generation FMT
- non-tox C diff M3
- Surotomycin
- Cadazolid
- Ecobiotics
- SMT-19969
- Monoclonal antibodies
- vs. C diff toxins
- Toxoid vaccines

New antibiotics coming soon for C diff

- Surotomycin
  - Kissing cousin to daptomycin
  - Great phase II
  - Just finished phase III

- Cadazolid
  - Novel fluoroquinolone-oxazolidinone
  - Great phase II
  - Entering phase III

- SMT-19969
  - Now called ridinilazole. MOA: Unknown
  - Great phase II
  - Entering phase III
Surotomycin

- Novel cyclic lipopeptide antibiotic disrupts bacterial cellular membrane (think dapto)
- Lacks activity against Gram-negative aerobes and facultative anaerobes (Bacteroides)
- Still kills Gram-positives (think dapto)
- Non-absorbable
- Good in a hamster model

Alam et al. AAC 2015;59:5165-70

Surotomycin: great in vitro activity, no affect on spores

Endres, Basseres et al. AAC 2016
Surotomycin: No affect on toxins

A

B

C

Surotomycin: No effect on host response

A

B

C

D
All of this data justified a phase II study

But the phase III study was a total bust!
Summary of new drug properties

<table>
<thead>
<tr>
<th>Drug</th>
<th>Kill C diff</th>
<th>Spare microbiota</th>
<th>Decrease toxins</th>
<th>Affects spores</th>
<th>Good phase II</th>
<th>Good phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surotomycin</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Cadazolid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ridinilazole</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Cadazolid**

- Protein synthesis inhibitor with weak inhibition of DNA synthesis (think linezolid meets levo)
- Kills other gut bacteria (especially bifidobacteria, a gut anaerobe)
  - But less than previous studies with linezolid or fluoroquinolones for unknown reasons
- Non-absorbable
- Good in a hamster model

Locher et al. AAC 2014;58:901-8
Locher et al. AAC 2014;58:892-900
Chilton et al. JAC 2013;697-705
Cadazolid: Great in vitro activity


Cadazolid: Also affects C. difficile toxins

Cadazolid may inhibit spore formation


Cadazolid phase II study

Louie et al. AAC 2015;59:6266-73
Cadazolid phase III

- In progress
- Cadazolid 250 mg BID vs. vancomycin 125 mg QID
- Think it will be successful?

Summary of new drug properties

<table>
<thead>
<tr>
<th>Drug</th>
<th>Kill C diff</th>
<th>Spare microbiota</th>
<th>Decrease toxins</th>
<th>Affects spores</th>
<th>Good phase II</th>
<th>Good phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suromycin</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Cadazolid</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>??</td>
</tr>
<tr>
<td>Ridinilazole</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Ridinilazole

• MOA: Unknown (but I will show you some cool data)
• Super narrow spectrum (clostridia only)
• Non-absorbable
• Good in a hamster model

Goldstein et al. AAC 2013;57:4872-6
Sattar et al. JAC 2015;70:1757-62

Ridinilazole: Great in vitro activity
(no affect on spores / not shown)

Basseres, Endres, et al. JAC 2016;71:1245-51
Ridinilazole: significantly decreases toxin production and affect host response

Ridinilazole: phase II study

Ridinilazole was superior to vancomycin for sustained clinical response
(Difference: 21.1%; 95% CI: 3.1-39.1%)

Vickers ASM Annual 2016
Ridinilazole phase III

- About to start
- Ridinilazole 200 mg BID vs. vancomycin 125 mg QID
- Can you imagine going into a phase III study without knowing how your drug works?

Ridinilazole is effective at killing *C. difficile* vegetative cells after 24h treatment

Basseres, Endres, et al. JAC 2016;71:1245-51
Concentration dependent cell lengthening phenotype

Ridinilazole treatment affects septum formation

---

*\(p<0.05\)
***\(p<0.001\)
Ridinilazole MOA (Best guess)

- Inhibits cell division by prevention of septum formation
- I’m going to take a guess that this is a protein synthesis inhibitor
- Confirmatory experiments: pending!

Summary of new drug properties

<table>
<thead>
<tr>
<th>Drug</th>
<th>Kill C diff</th>
<th>Spare microbiota</th>
<th>Decrease toxins</th>
<th>Affects spores</th>
<th>Good phase II</th>
<th>Good phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surotomycin</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Cadazolid</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>??</td>
</tr>
<tr>
<td>Ridinilazole</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>??</td>
</tr>
</tbody>
</table>
Final thoughts on new antibiotics

• As more and more C diff antibiotics hit the market (hopefully), decisions on what to use will become a little more complicated than ‘can we afford it’!
• Anyone notice that clinical cure rates are only so so (approx 80%).
• I wonder if rationale combination therapy in the future may improve this!

Explosion in treatment possibilities for CDI: Augment immune response!

Current: Probiotics
FMT
Vancomycin
Fidaxomicin
IVIG

Future: 2nd generation FMT
non-tox C diff M3
Ecobiotics
Surotomycin
Cadazolid
SMT-19969

Monoclonal antibodies vs. C diff toxins
Toxoid vaccines
Serum concentrations of IgG antibodies against toxin A, toxin B, and non-toxin antigens

Kyne et al. Lancet 2001;357:189-93

Monoclonal antibody: phase II study

Phase III studies of actoxumab (acto) and bezlotoxumab (bezlo): Overall

Coming soon to an infusion clinic near you!

• FDA Antimicrobial Drug Advisory Committee (June 9th, 2016)
  – “vote of 10 to 5 with one abstention, that Merck has provided substantial evidence of the safety and effectiveness of bezlotoxumab for the prevention of \textit{C. difficile} infection recurrence in patients aged 18 years and older.”
  – \url{http://www.fda.gov/AdvisoryCommittees/Calendar/ucm496386.htm}

• Stay tuned!
Explosion in treatment possibilities for CDI:

Correct dysbiosis!

Current:
- Probiotics
- FMT
- Vancomycin
- Fidaxomicin
- IVIG

Future:
- 2nd generation FMT
- Non-tox C diff M3
- Surotomycin
- Cadazolid
- Monoclonal antibodies vs. C diff toxins
- Ecobiotics
- SMT-19969
- Toxoid vaccines

FMT for patients with recalcitrant CDI
Recurrent *C. difficile* colitis: case series involving 18 patients treated with donor stool administered via a nasogastric tube

<table>
<thead>
<tr>
<th></th>
<th>Before stool transplant</th>
<th>After stool transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>N/a</td>
<td>2 (unrelated)</td>
</tr>
<tr>
<td># of Recurrence</td>
<td>64 (2-7)</td>
<td>1</td>
</tr>
</tbody>
</table>

Aas. CID 2003;36:580-5

Duodenal infusion of donor feces for recurrent *C. difficile* infection

RCT of PO vanco + FMT (n=16), PO vanco alone (n=13), or PO vanco + bowel lavage (n=13). Study stopped prematurely due to superiority of FMT

Resolution: no diarrhea without relapse after 10 weeks

Changes in the Composition of the Human Fecal Microbiome After Bacteriotherapy for Recurrent CDI

A. Dendrogram of the 16S-based T-RFLPs obtained from fecal material from the patient and the donor before and after fecal transplantation. B, Distribution of bacterial species in feces of the donor and the patient before and after fecal transplantation.

Next Generation FMT

- Probiotic cocktails (Kefir)
- Designer biotherapeutics
  - Non-toxigenic *C. difficile*
  - SER-109, Seres Therapeutics
Protocol utilizing a staggered and tapered antibiotic treatment regimen for the treatment of recurrent Clostridium difficile infection that has failed to respond to standard antibiotic therapy.

25 patients with recurrent CDI that were not able to perform FMT. Twenty-one of the 25 patients (84%) remained free of diarrhea during the following 9 months. The 4 patients who relapsed permanently resolved their diarrhea after a conventional 2-week course of oral vancomycin 125 mg 4 times daily followed by a 2-week course of rifaximin 200 mg twice daily. All 4 patients remained symptom-free at 12 months of follow-up.

<table>
<thead>
<tr>
<th>Antibiotic Time Course</th>
<th>Metronidazole Dose/Frequency</th>
<th>Vancomycin Dose/Frequency</th>
<th>Kefir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeks 1-2</td>
<td>250 mg Q 6h</td>
<td>125 mg Q 6h</td>
<td>150 mL TID</td>
</tr>
<tr>
<td>Weeks 3-4</td>
<td>750 mg Q 72h</td>
<td>375 mg Q 72h</td>
<td>150 mL TID</td>
</tr>
<tr>
<td>Weeks 5-6</td>
<td>500 mg Q 72h</td>
<td>250 mg Q 72h</td>
<td>150 mL TID</td>
</tr>
<tr>
<td>Weeks 7-8</td>
<td>250 mg Q 72h</td>
<td>125 mg Q 72h</td>
<td>150 mL TID</td>
</tr>
<tr>
<td>Weeks 9-15</td>
<td></td>
<td></td>
<td>150 mL TID</td>
</tr>
</tbody>
</table>

Non-toxigenic C. diff (NTCD): phase II study

CDI patients given NTCD or placebo immediately after finishing antibiotic therapy

Gerding et al. JAMA 2015;313:1719-27
SER-109. Fractionated and encapsulated spores from healthy donor stools

CDI patients given SER-109 immediately after finishing antibiotic therapy

Patients given SER-109 had a microbiome that looked like the average population

Red represents microbiome prior to SER-109, yellow represents after SER-109, and blue represents samples from the human microbiome project
Expanding the Role of FMT

• Case reports and case series has documented positive effects of FMT in the following conditions:
  – GI diseases
    • Ulcerative colitis, Crohn’s disease, irritable bowel syndrome, idiopathic constipation
  – Not traditional GI diseases
    • Insulin resistance, metabolic syndrome, morbid obesity, Parkinson’s disease, autism

FMT and obesity

• Energy metabolism is a well recognized function of gut microbiota
  – Low dose antibiotics increases farming animal weight for unknown reasons (via killing of gut microbiota?).
• Similar effects have been shown in humans
  – Antibiotic prophylaxis for streptococcal infections in the 1950’s increased weight of these otherwise, young healthy males compared to placebo-treated males
    • J Nutr 1955;56:151-61

An obesity-associated gut microbiome with increased capacity for energy harvest

Germ-free mouse

Obese mouse

Germ-free mouse given FMT from obese and non-obese mice.

Weight gain assessed

Non-obese mouse

Transplanting stool from an obese mouse lead to increased weight gain in the mouse vs. transplant from the non-obese mouse.

Stool from obese mouse

Stool from non-obese mouse

Turnbaugh et al. Nature 2006;444:1027-3
Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome

18 patients with metabolic syndrome underwent bowel lavage by random assignment with an allogenic (from lean donor) or autologous gut microbiota transplant (autologous: reinfusion of own collected feces)

Vrieze et al. Gastroenterol 2012 Jun 20

Insulin sensitivity improved after FMT from allogenic donors

But, let’s not get carried away.
Let’s start wrapping this up

• Remember, only about 1 in 5 antibiotics that enter phase I trials make it to an indication
• But, I think the higher urgency to discover new anti-infectives for C diff is producing viable candidates
• I think the future of ID may be as much host augmentation as it is bug killing.
I do see a world where this is commonplace for most infectious diseases!

Update on *C. difficile* infection: New bugs and new drugs

Kevin W. Garey, Pharm.D., M.S., FASHP
Chair, Department of Pharmacy Practice and Translational Research
Professor of Pharmacy Practice,
Houston, TX