The Challenge of MDR and XDR infections

Friday, 14th September 2018
Casa de la Convalescència,
Barcelona - Spain

CLOSTRIDIIOIDES DIFFICILE,
MORE DIFFICULT THAN EVER

BENOIT GUERY
Disclosures

✓ Boards
  – Astellas, Pfizer, MSD

✓ Grants
  – Combioxin, HZI, GlycoMimetics, Vaincre la Mucoviscidose, Fondation Santo Suarez, Astellas
The Challenge of MDR and XDR infections

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CDI: more difficult than ever....

- Old actors
- New actors...
- Old habits..... Dying hard...

Resistance to Guidelines ranging from classic to extreme resistance...
Molecules we all know…

Vancomycin

Metronidazole

Fidaxomicin

Fecal microbiota transplantation
<table>
<thead>
<tr>
<th>Available drugs</th>
<th>Vancomycin per os 125 mgx4/j</th>
<th>Metronidazole per os (IV) 500 mgx3/j</th>
<th>Fidaxomicin 200 mgx2/j</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spectrum</td>
<td>Medium</td>
<td>Large</td>
<td>Narrow</td>
</tr>
<tr>
<td>GI Absorption</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Side effects</td>
<td>Low occurrence</td>
<td>Neurologic</td>
<td>Low occurrence</td>
</tr>
<tr>
<td>Fecal concentrations (/g)</td>
<td>3100 µg/g</td>
<td>0.4-14.9 µg/g</td>
<td>1433.3 µg/g</td>
</tr>
<tr>
<td>MIC&lt;sub&gt;90&lt;/sub&gt;</td>
<td>0.75-2 µg/ml</td>
<td>0.2-2 µg/ml</td>
<td>0.125 µg/ml</td>
</tr>
<tr>
<td>Resistance</td>
<td>3% Spanish strains (MIC 4-16 µg/ml)</td>
<td>6.3% MIC &gt;16 µg/ml (heteroresistance)</td>
<td>Exceptionnel</td>
</tr>
<tr>
<td>Cost (10 days)</td>
<td>172-260 CHF</td>
<td>8-16 CHF</td>
<td>2186 CHF</td>
</tr>
<tr>
<td>-----------</td>
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<td>----------</td>
<td>-------------------</td>
</tr>
<tr>
<td>- Leukocytosis with WBC ≥15000 cells/mL Or - serum creatinine level &gt;1.5 mg/dL</td>
<td>Physical examination Fever, Rigors, Haemodynamic instability Respiratory failure Signs and symptoms of peritonitis. Signs and symptoms of colonic ileus. Laboratory investigations Marked leucocytosis (leucocyte count &gt;15 9 109/L). Marked left shift Rise in serum creatinine Elevated serum lactate (≥5 mM). Markedly reduced serum albumin (&lt;30 g/L). Colonoscopy Pseudomembranous colitis. Imaging Distension of large intestine (&gt;6 cm in transverse width of colon). Colonic wall thickening including low-attenuation mural thickening. Pericolonic fat stranding. Ascites not explained by other causes.</td>
<td>- Serum albumin &lt;3g/dl plus ONE of the following: - WBC ≥15,000 cells/mm3, - Abdominal tenderness</td>
<td>One point each for - age &gt;60 years, - temperature &gt;38.3° C, - albumin level &lt;2.5 mg/dL, - peripheral white blood cell count &gt;15,000 cells/mm³ within 48 hours of enrolment. Two points were given for endoscopic evidence of pseudomembranous colitis or treatment in an ICU. Patients with ≥2 points were considered to have severe CDI</td>
</tr>
</tbody>
</table>
Severe CDI

The issue is to identify prognosis markers that can be used to determine (increased risk of developing) severe *Clostridium difficile* infection

Target Population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>SoR</th>
<th>QoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (≥65 years)</td>
<td>A</td>
<td>IIr</td>
</tr>
<tr>
<td>Marked leucocytosis (leucocyte count &gt; 15 × 10⁹/L)</td>
<td>A</td>
<td>IIrht</td>
</tr>
<tr>
<td>Decreased blood albumin (&lt;30 g/L)</td>
<td>A</td>
<td>IIr</td>
</tr>
<tr>
<td>Rise in serum creatinine level (≥133 μM or ≥1.5 times the premorbid level)</td>
<td>A</td>
<td>IIht</td>
</tr>
<tr>
<td>Comorbidity (severe underlying disease and/or immunodeficiency)</td>
<td>B</td>
<td>IIht</td>
</tr>
</tbody>
</table>

Debast et al, CMI 2014
Recurrent CDI

✓ The issue is to identify prognosis markers that can be used to determine (increased risk of developing) recurrent *Clostridium difficile* infection

Target Population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>SoR</th>
<th>QoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (&gt;65 years)</td>
<td>A</td>
<td>Iirh</td>
</tr>
<tr>
<td>Continued use of (non-CDI) antibiotics after diagnosis of CDI and/or after CDI treatment</td>
<td>A</td>
<td>Iirh</td>
</tr>
<tr>
<td>Comorbidity (severe underlying disease) and/or renal failure</td>
<td>A</td>
<td>Iih</td>
</tr>
<tr>
<td>A history of previous CDI (more than one recurrence)</td>
<td>A</td>
<td>Iit</td>
</tr>
<tr>
<td>Concomitant use of antacid medications (proton pump inhibitors)</td>
<td>B</td>
<td>Iirh</td>
</tr>
<tr>
<td>Initial disease severity</td>
<td>B</td>
<td>Iitch</td>
</tr>
</tbody>
</table>
A Comparison of Vancomycin and Metronidazole for the Treatment of Clostridium difficile–Associated Diarrhea, Stratified by Disease Severity

Note: patients were stratified by mild or severe disease based on a severity assessment score developed for this study. Patients received one point each for age >60 years, temperature >38.3°C, albumin level <2.5 mg/dL, or peripheral white blood cell count >15,000 cells/mm³ within 48 hours of enrolment. Two points were given for endoscopic evidence of pseudomembranous colitis or treatment in an ICU. Patients with ≥2 points were considered to have severe CDI.

Two multicentric prospective randomized double blinded studies
- 289 pts MTZ 375 mgx4/j
- 266 pts Va 125 mgx4/j

Primary endpoint: clinical success

Conclusion
- Tolevamer was inferior to antibiotic treatment of CDI
- Metronidazole was inferior to vancomycin.
629 patients were enrolled, of whom 548 (87.1%) could be evaluated for the per-protocol analysis.

1st recurrence: F 16.7%/V 17.5%

Follow up 4 weeks
Fidaxomicin versus vancomycin for infection with *Clostridium difficile* in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial

Oliver A Conolly, Derric W Crook, Roberto Españo, André Parier, Michael S Somers, Karl Weiss, Pamela Sears, Sherwood Gorbach, for the OPT-80-004 Clinical Study Group
Extended-pulsed fidaxomicin versus vancomycin for *Clostridium difficile* infection in patients 60 years and older (EXTEND): a randomised, controlled, open-label, phase 3b/4 trial

Benno Guery, Francesco Menichetti, Veli-Jukka Anttila, Nicola Askomakoh, Jose Maria Aguado, Karen Bosnaugh, Arnd Georgopoul, Simon D. Goldberg, Andreas Koura, Gilberta Kariem, Chris Longshaw, Jose Alejandro Pardo-Foligno, Oliver A. Cordly, Maria A. G. T. Vetherschiff, for the EXTEND Clinical Study Group*

- Open-label, randomised, active-comparator controlled, parallel-group, phase IIIb/IV study conducted at 86 centres in 21 countries
- Follow up 90 days
- Patients
  - aged ≥60 years with clinically confirmed CDI
  - Severe 46%
  - Use of antibiotics 72%

Lancet Inf Dis 2018;18:296-307
Efficacy and safety of ridinilazole compared with vancomycin for the treatment of *Clostridium difficile* infection: a phase 2, randomised, double-blind, active-controlled, non-inferiority study

- Phase 2, randomised, double-blind, active-controlled, non-inferiority study
- 33 centres in the USA and Canada
  - oral ridinilazole (200 mg every 12 h)
  - oral vancomycin (125 mg every 6 h) for 10 days.
- Primary endpoint: achievement of a sustained clinical response
  - clinical cure at the end of treatment
  - and no recurrence within 30 days.
Two-year prospective observational study
- First episode or first recurrence of CDI
- Severe or severe-complicated CDI

287 patients
- 107 teicoplanin 100 mg q12h, 10 days
- 180 vancomycin 125 mg q6h, 10 days

Severe complicated disease
- T: 23/107 (21.5%)
- V: 42/180 (23.3%)

No statistically significant difference in time to resolution of diarrhea between two treatment arms (vs days, p = 0.672)

Clinical cure severe and complicated: T 73.9 vs V 41.6%
In development

✓ Cadazolid
  - Oxazolidinone
  - Phase 2 RCT \(^1\)
  - Clinical cure rate equivalent to Vancomycin
  - Lower recurrence rate than vanco (18.2 to 25% vs 50%)
  - Phase 3 on the road...

✓ Surotomycin
  - Lipopeptide
  - But unfavourable efficacy data from a late stage clinical trial \(^2\)
  - In danger....

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1. Boix et al, Open Forum Inf Dis 2017
2. Louie et al, AAC 2015
Comparative efficacy of treatments for *Clostridium difficile* infection: a systematic review and network meta-analysis

Tumas Beinortas*, Nicholas E Burr*, Mark H Wilcox, Venkataraman Subramanian

- 23004 studies screened
- 24 trials with 5361 patients and 13 treatments
- Quality of evidence: moderate to low
- Conclusion
  - For non multiply-recurrent infections Fidaxomicin (Fdx) provides SCC most frequently
  - Fdx better than vancomycin for all but severe patients
  - MTZ should not be recommended for treatment

The size of the circle is proportional to the number of patients assigned to receive the treatment

*Lancet Inf Dis* 2018;18:1035-44
Duodenal Infusion of Donor Feces for Recurrent Clostridium difficile

Els van Nood, M.D., Anne Vrieze, M.D., Max Nieuwdorp, M.D., Ph.D., Susana Fuentes, Ph.D., Erwin G. Zoetendal, Ph.D., Willem M. de Vos, Ph.D., Caroline E. Visser, M.D., Ph.D., Ed J. Kuijper, M.D., Ph.D., Joep F.W.M. Bartelsman, M.D., Jan G.P. Tijssen, Ph.D., Peter Speelman, M.D., Ph.D., Marcel G.W. Dijkstra, Ph.D., and Josbert J. Keller, M.D., Ph.D.

Figure 2. Rates of Cure without Relapse for Recurrent Clostridium difficile Infection.

Figure 3. Microbiota Diversity in Patients before and after Infusion of Donor Feces, as Compared with Diversity in Healthy Donors.
Noninferiority, unblinded, randomized trial conducted in 3 academic centers in Alberta, Canada.

116 adult patients with RCDI were enrolled between October 2014 and September 2016

- 57 patients randomized to the capsule group
- 59 to the colonoscopy group

Results: prevention of RCDI after a single treatment was achieved in 96.2% in both the capsule group (51/53) and the colonoscopy group (50/52).
Patients who received FMT for RCDI at Emory Hospital between 1 July 2012 and 31 December 2016 were contacted via telephone for a follow-up survey.

Of 190 eligible patients, 137 (72%) completed the survey.

Median time of follow up: 22 months

Results
- 82% no recurrence
- Antibiotic exposure more frequent in recurrent patients
- Underscore the need for thoughtful antibiotic use to reduce recurrence
Proof of concept trial

Six hospitals in Norway, 21 patients with acute CDI

Randomized to
- MTZ 400mg x 3/d, 10g
- FMT: 60 mL enema

Primary endpoint
- Clinical cure at D70

Overall response to
- seven patients in the transplantation group (78%; 95% CI, 40 to 97)
- five in the metronidazole group (45%; 95% CI, 17 to 77) (P = 0.20)

A phase 3 trial is under way.
Humanized Mab anti-\textit{C. difficile} toxins A and B
- Anti toxin A (ACTO or MK3415)
- Anti-toxin B (BEZLO MK 6072)

2 Phase 3 randomized double-blind clinical trials versus placebo (Modify I and II)
- Acto+Bezlo: 773 patients
- Bezlo: 781 patients
- Placebo: 773 patients

Primary endpoint: recurrent CDI in the following 3 months.

Secondary endpoint: rate of global cure, sub-group analysis

N Engl J Med 2017;376:4
Risk factors for rCDI prespecified in the statistical analysis plan:

- age ≥65 years
- history of CDI
- compromised immunity
- severe CDI
- ribotype 027/078/244

Participants with ≥3 risk factors had the greatest reduction of rCDI with bezlotoxumab, those with 1 or 2 risk factors may also benefit.
## Vaccines in clinical development

<table>
<thead>
<tr>
<th>Vaccine product</th>
<th>Antigen</th>
<th>Clinical status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanofi Pasteur</td>
<td>Formalin-inactivated toxins A and B from VPI 10463</td>
<td>Phase III</td>
</tr>
<tr>
<td>Valneva Austria</td>
<td>Recombinant fusion protein of toxin A and B binding regions</td>
<td>Phase II</td>
</tr>
<tr>
<td>Pfizer</td>
<td>Genetically modified and chemically treated recombinant vaccine</td>
<td>Phase II</td>
</tr>
</tbody>
</table>
The schizophrenic brain of the ID physician

What I want

- I’m scientific: Double blind randomized studies
- Recurrence?
- Best place for a new molecule
- Best treatment for my patient
- Cost effectiveness studies

What I do….

- My experience, »MY patients do well with MTZ…", not my patients, not my ecology
- I never had a recurrence….
  - 15% Rec and 90 days follow up….
- It’s new, preserve it, don’t prescribe in case we need it in the future…
- Price is an issue (hospital cost, insurances….)
- Yes but they are not from my country…. So it’s different
<table>
<thead>
<tr>
<th>Clinical Definition</th>
<th>Supportive Clinical Data</th>
<th>Recommended Treatment(^a)</th>
<th>Strength of Recommendation/Quality of Evidence</th>
</tr>
</thead>
</table>
| Initial episode, non-severe         | Leukocytosis with a white blood cell count of ≤15000 cells/mL and a serum creatinine level <1.5 mg/dL | • VAN 125 mg given 4 times daily for 10 days, OR  
• FDX 200 mg given twice daily for 10 days  
• Alternate if above agents are unavailable: metronidazole, 500 mg 3 times per day by mouth for 10 days | Strong/High  
Strong/High  
Weak/High |
| Initial episode, severe\(^b\)       | Leukocytosis with a white blood cell count of ≥15000 cells/mL or a serum creatinine level >1.5 mg/dL | • VAN, 125 mg 4 times per day by mouth for 10 days, OR  
• FDX 200 mg given twice daily for 10 days | Strong/High  
Strong/High |
| Initial episode, fulminant          | Hypotension or shock, ileus, megacolon    | • VAN, 500 mg 4 times per day by mouth or by nasogastric tube. If ileus, consider adding rectal instillation of VAN. Intravenously administered metronidazole (500 mg every 8 hours) should be administered together with oral or rectal VAN, particularly if ileus is present. \(\text{oral VAN} \); Weak/Low (rectal VAN); Strong/Moderate (intravenous metronidazole) | Strong/Moderate (oral VAN); Weak/Low (rectal VAN); Strong/Moderate (intravenous metronidazole) |
| First recurrence                    | ...                                      | • VAN 125 mg given 4 times daily for 10 days if metronidazole was used for the initial episode, OR  
• Use a prolonged tapered and pulsed VAN regimen if a standard regimen was used for the initial episode (eg, 125 mg 4 times per day for 10–14 days, 2 times per day for a week, once per day for a week, and then every 2 or 3 days for 2–3 weeks), OR  
• FDX 200 mg given twice daily for 10 days if VAN was used for the initial episode | Weak/Low  
Weak/Low  
Weak/Moderate |
| Second or subsequent recurrence     | ...                                      | • VAN in a tapered and pulsed regimen, OR  
• VAN, 125 mg 4 times per day by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days, OR  
• FDX 200 mg given twice daily for 10 days, OR  
• Fecal microbiota transplantation\(^c\) | Weak/Low  
Weak/Low  
Weak/Low  
Strong/Moderate |
CDI

No RF for severity or recurrence
- Vancomycin per os 125 mg x 4/d, 10 days

1st recurrence or RF for recurrence
- Fidaxomicine per os 200mg x 2/d, 10 days or tapered 25 days
- Alternative: Vancomycin per os 125 mg x 4/d, 10 days
  - +/- Bezlol
  - Teicoplanin?
  - Cadazolid?
  - NTCD
  - FMT?

>1 recurrence
- Fecal microbiota transplantation/vancomycin pretreatment
  - Capsule
  - GT
  - Colonoscopy
  - Enema

Severe
- Vancomycin
- Alternative: Fidaxomicine per os
- Teicoplanin?
- FMT

Complicated
- Vancomycin enema +/- metronidazole IV or Tigecycline IV
- FMT

Severity risks factors
- Leucocytosis > 15,000
- Albumin < 30g/L
- Renal insufficiency (creat >133mM or x1.5)

Recurrence risks factors
- Concomitant antibiotic therapy
- Age >65
- Immunosuppression
- Renal insufficiency (GF< 30-40 ml/mn)