Clostridium difficile: Pathogenesis and Host Response

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Pathogenesis of *Clostridium difficile* associated diarrhea (CDAD)

Antibiotic therapy

Disturbed colonic microflora

C. difficile exposure & colonization

Toxin A & Toxin B

Diarrhea & colitis

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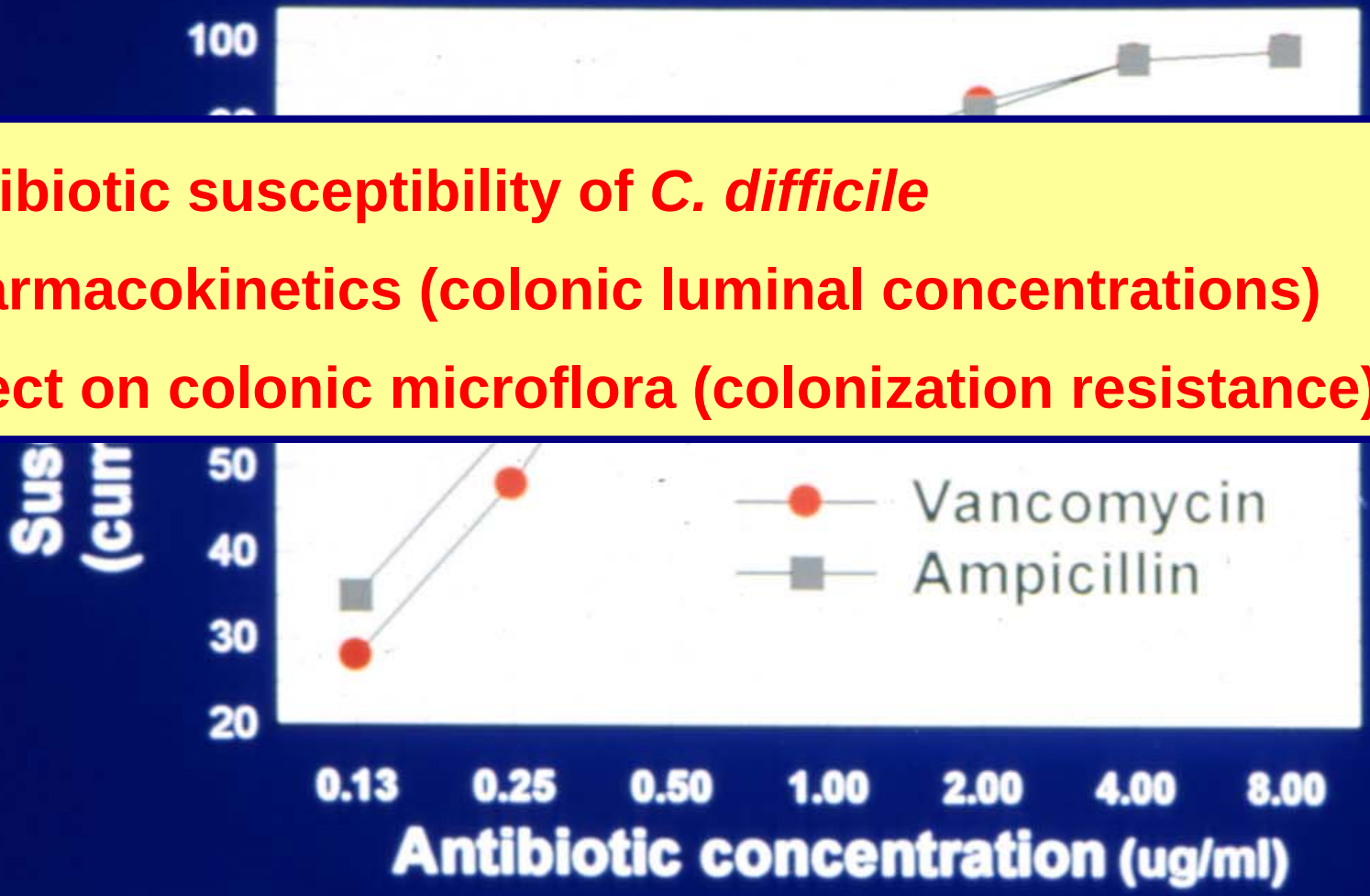
Antibiotic therapy

Disrupt "colonization resistance"

of colonic microflora

Antibiotic susceptibility of *C. difficile* isolates



- Antibiotic susceptibility of *C. difficile*
- Pharmacokinetics (colonic luminal concentrations)
- Effect on colonic microflora (colonization resistance)

Bartlett et al, Am J Clin Nut 1980

Antimicrobial agents that induce *C. difficile*-associated diarrhea and colitis

Frequent	Infrequent	Rare
Ampicillin /amoxicillin	Chloramphenicol	Metronidazole
Cephalosporins	Macrolide	Parenteral aminoglycoside
Clindamycin	Sulfonamide	Vancomycin
Quinolones	Tetracycline	
	Trimethoprim	

- Cytotoxic chemotherapy
- Colon preparation
- IBD (esp. Ulcerative colitis)

Adapted from Kelly et. al. NEJM 1994;330:257

Onset of *Clostridium difficile* associated diarrhea

- **> 80%** **During antibiotic treatment**

  (typically after 4 - 5 days of therapy)

- **< 20%** **After inciting antibiotic discontinued**

  most within 4 weeks

  almost all within 12 weeks

Non-antibiotic associated *Clostridium difficile* induced diarrhea

- **Nosocomial: Very rare**

Community acquired CDAD

- **Less common than nosocomial**
- **Undocumented Abx use in community-based studies?**

versus

- **"Spontaneous" CDAD more evident?**

JID 1994, 169:127 J Clin Microbiol, 2004, 42:3635 JAMA 2005, 294:2989

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***C. difficile* exposure & colonization**

Clostridium difficile: Environmental sources

- Hospital:

  linens, toilet, bathroom floor, telephone

- Personnel:

  hands, fingernails, rings, stethoscopes

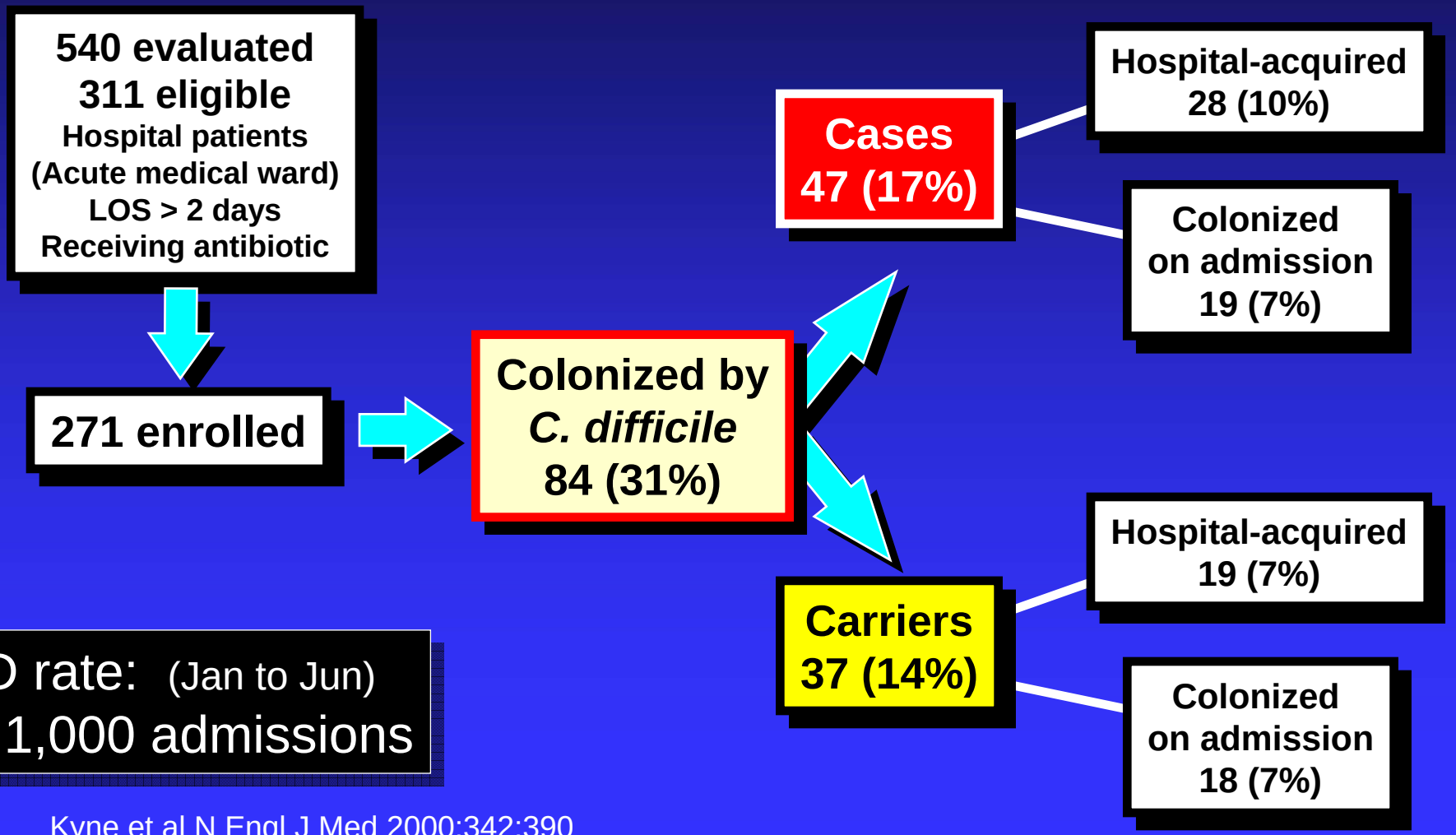
- Home:

  toilet, infant's room, diaper pail, backyard

- Other:

  infants, adult carriers, animals

Nosocomial *C. difficile* associated diarrhea and asymptomatic carriage are common



CDAD rate: (Jan to Jun)
7 per 1,000 admissions

Kyne et al N Engl J Med 2000;342:390

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***C. difficile* exposure & colonization**

Toxin A & Toxin B

Clostridium difficile toxins: Is A=B?

Toxin A

- "The Enterotoxin"
  - Enterotoxic to animal intestine (>> toxin B)
  - Toxin A immunization protective in animals (toxin B not)

Toxin B

- Not an enterotoxin?
  - In animals - correct
  - BUT: Enterotoxic in humans!
    - Colonic explants
    - Intestinal zenografts
    - ToxA-/ToxB+ strains

- Toxin A important
- Toxin B probably also important

Pathogenesis of *Clostridium difficile* associated diarrhea (CDAD)

Antibiotic therapy

↓

Disturbed colonic microflora

↓

C. difficile exposure & colonization

↓

Toxin A & Toxin B

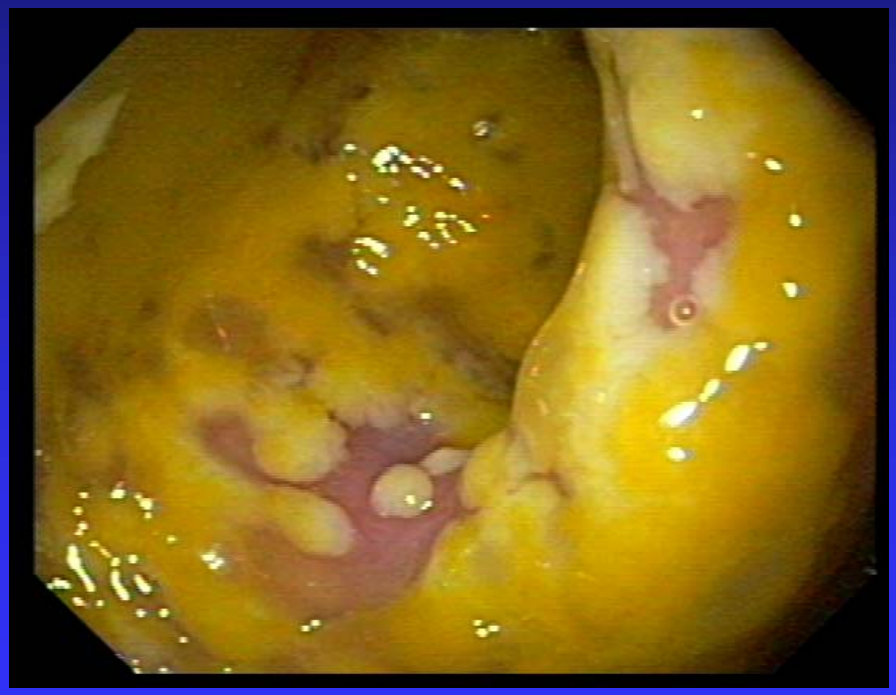
↓

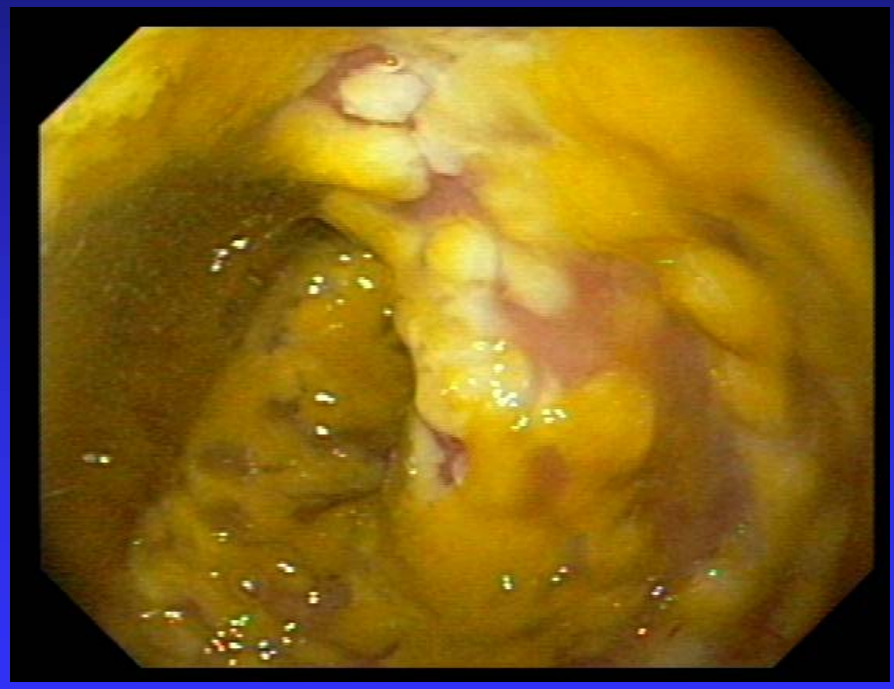
Diarrhea & colitis

CDAD: Host factors

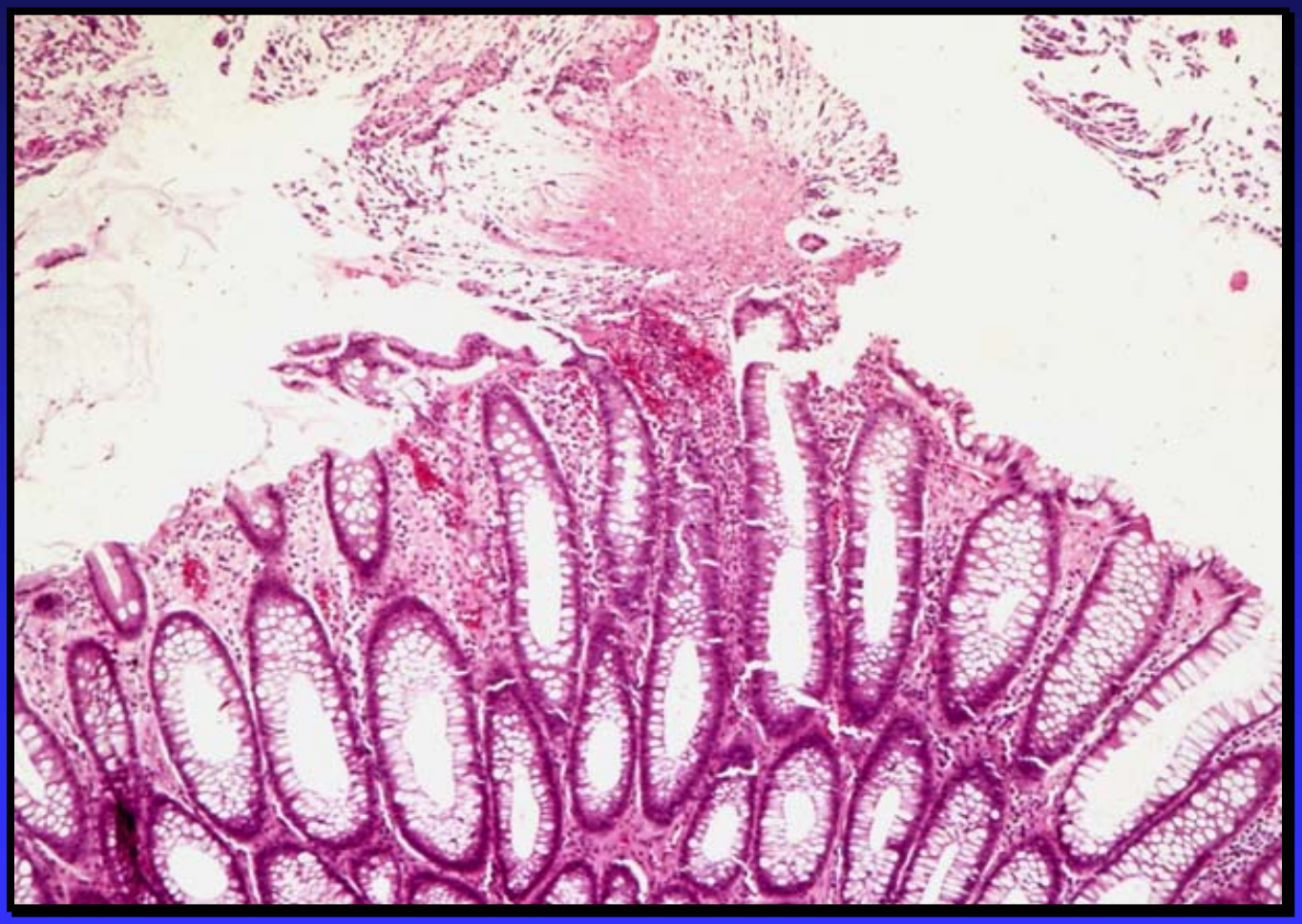
- Age
- Co-morbidity / disease severity
- Immune response
  - Innate e.g. IL-8 SNPs
  - Adaptive e.g. Anti-toxin IgG response

C. difficile toxin-induced Pseudomembranous colitis





Histopathology of pseudomembranous colitis



“Volcano” lesion in PMC

Kelly et al, N Engl J Med 1994;330:257-262

CDAD: Host innate immune response

- PMN leukocytosis characteristic & prognostic
- Blocking PMN recruitment (anti-CD18 mAb) prevents toxin-mediated intestinal injury in animals
- Toxins activate phagocytes
  - PMN & Macrophage activation
  - NF-kB & MAP kinase signal induction
  - Cytokine release (IL-8, IL-1β)
- IL-8 promoter SNP assoc with symptomatic CDAD
- Role for corticosteroid [or other immunosuppressive Rx] in severe CDAD?

CDAD: Adaptive immune response

- ~ 60% of humans have serum IgG and colonic IgA anti-toxin antibody
- Animals protected by anti-toxin immunization

Hypothesis:

The host immune response plays a pivotal role in determining the clinical outcome of infection with toxigenic *Clostridium difficile*

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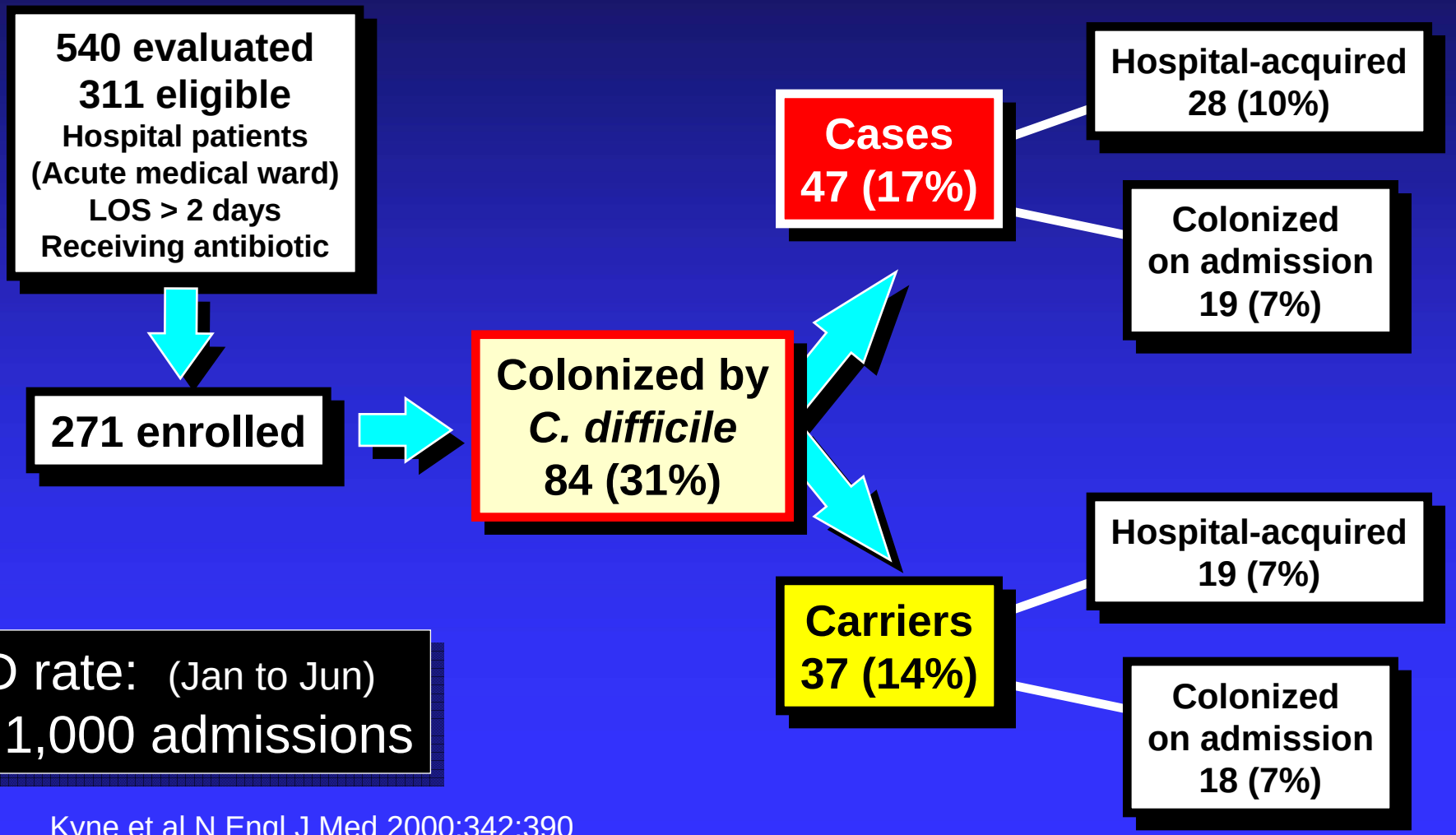

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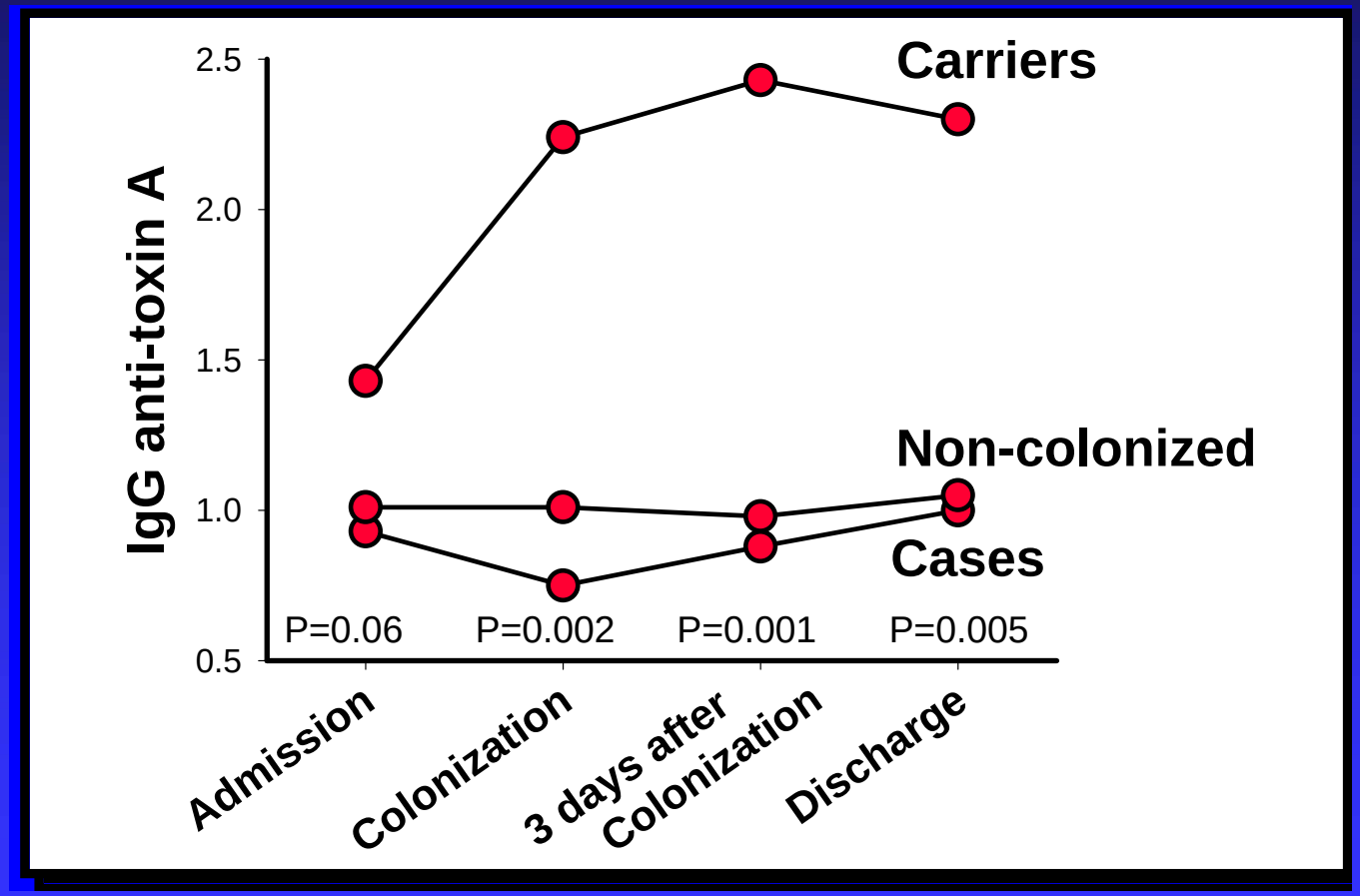
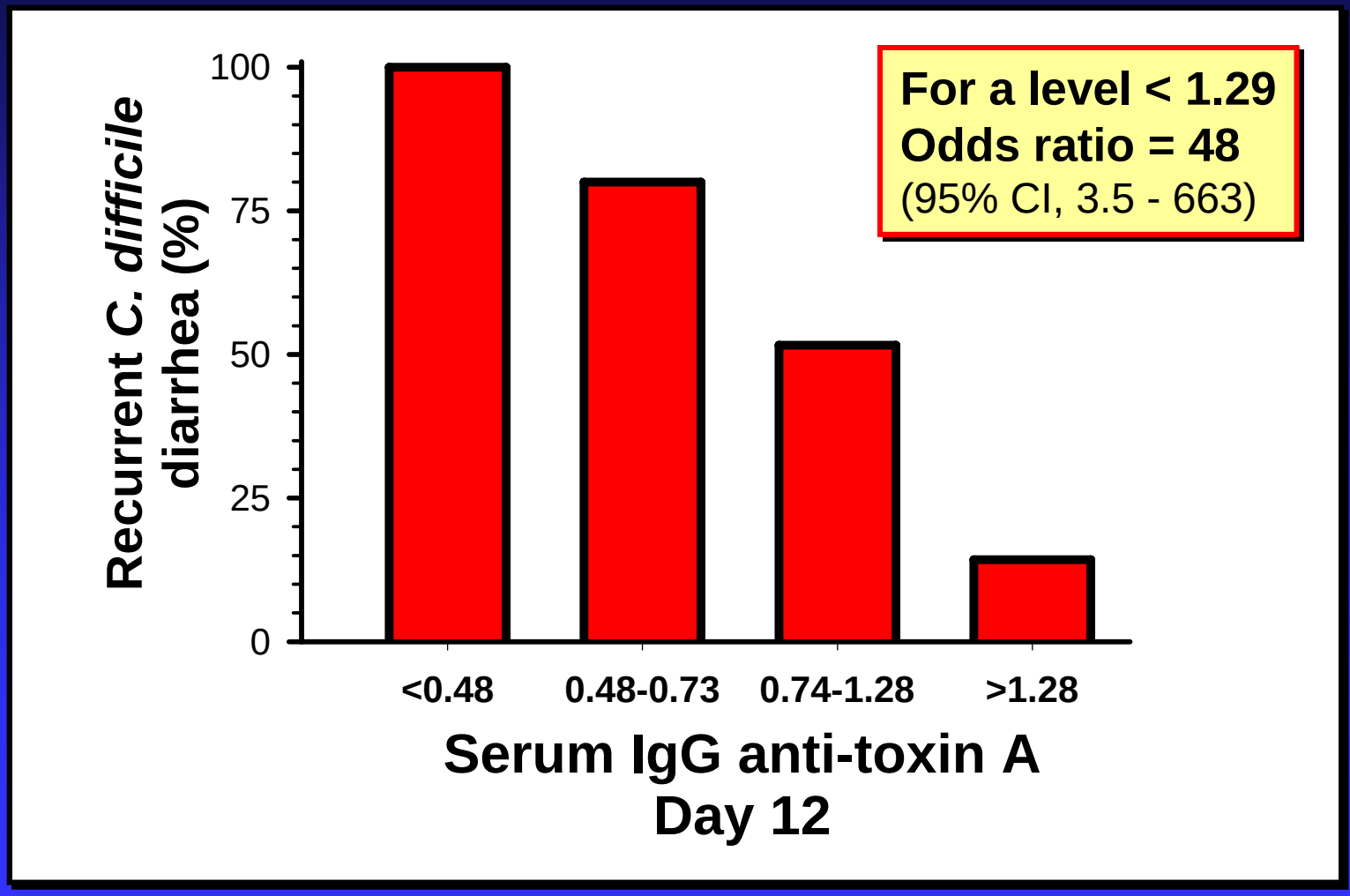
Serum IgG anti-toxin A levels are high in asymptomatic carriers of *C. difficile*



Kyne et al N Engl J Med 2000;342:390

High serum IgG anti-toxin A levels are associated with a lower risk for recurrent *C. difficile* diarrhea



Kyne et al, Lancet 2001

Treatment approaches for *C. difficile* associated diarrhea