Enfeksiyon Hastalıkları Tanısında Sendromik Yaklaşım: Avantaj ve Dezavantajları: İshal

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İshal

- Frekans: ≥3 dışkı/gün
  veya
- Hacim: ≥200 ml/gün

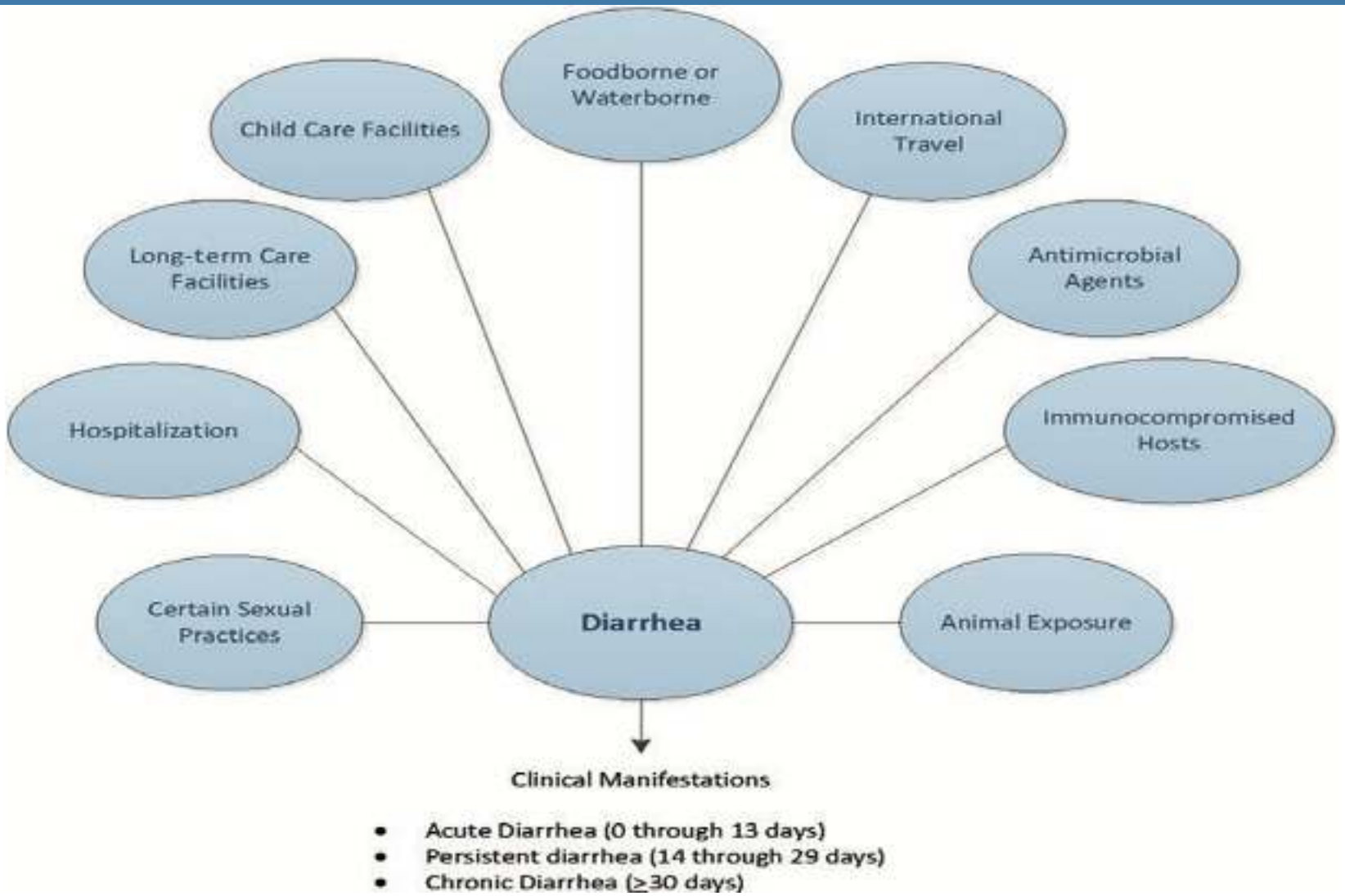
DuPont HL (2009) Bacterial diarrhea. New Engl J Med

İshal epidemiyoloji I

- ABD'de ishal yıllık yaklaşık 500.000 yatışa ve >5000 ölüme neden olmakta
- Hayat boyu gastroenterit tanısı ile taburcu olma 1/8
- Görülme sıklığı 5 yaşın altındaki çocuklarda fazla, ancak yatış ve ölüm 65 yaş üstünde fazla

Shane AL etal (2017) *IDSA clinical practice guidelines for the diagnosis and management of infectious diarrhea* Clin Infect Dis

İshal epidemiyoloji II



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İshal epidemiyoloji III

- Kabuklu deniz ürünleri
- Çiğ süt
- Az pişmiş et, balık, yumurta
- Kontamine meyve ve sebzeler
- Kontamine içme ve havuz suyu
- Hayvan dışkısı ile temas
- Yakın zamanda antimikrobiyal tedavi
- Uluslararası yolculuk
- Anal veya oral seksüel temas

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Epidemiyoloji

Enteric Illness			
Shigellosis	*Clostridium difficile*–assoc diarrhea	Cryptosporidiosis	Enzyme immunoassay of stool specimen
Salmonellosis	First or second bout	Intestinal amebiasis	Fecal antigen-detection enzyme immunoassay, stool culture plus isoenzyme assay, or PCR-based assay
Nontyphoidal sal		Cyclosporiasis	Stool acid-fast assay to detect oocysts, which appear as large cryptosporidia
	Recurrent (≥3 bouts)	*Cystoisospora belli* infection	Stool acid-fast assay to detect oocysts, which are larger than cyclospora oocysts
	Travelers' diarrhea and e toxigenic *E. coli* di	*Enterocytozoon bieneusi* or *Encephal-itozoon intestinalis* infection	Light-microscopic examination of stool specimen with Weber's chromotrope-based stain or aniline blue stain to detect small spores
Enteric fever, bac nellosis (inclu fever)		Strongyloidiasis	Light-microscopic examination of stool specimen to detect larvae
Chronic carriage salmonella	Gastroenteritis	*Dientamoeba fragilis* diarrhea	Light-microscopic examination and conventional and real-time PCR assay of stool specimen
Intestinal campyloba	Norovirus		
Infection with Shiga t *Escherichia col*		*Blastocystis hominis* diarrhea	Light-microscopic examination of stool specimen
	Rotavirus		
Noncholeraic vibrio	Enteric adenoviruses, or 41		
Vibrio cholerae infecti	Giardiasis	Cytomegalovirus colitis in immunocompromised persons	Mucosal biopsy or serologic test

DuPont HL 2014 *Acute infectious diarrhea* New Engl J Med

- Semptom tek
- Tanı yöntemleri çeşitli
- Hastayı gören hekim hangi testi isteyeceğine karar veremiyor

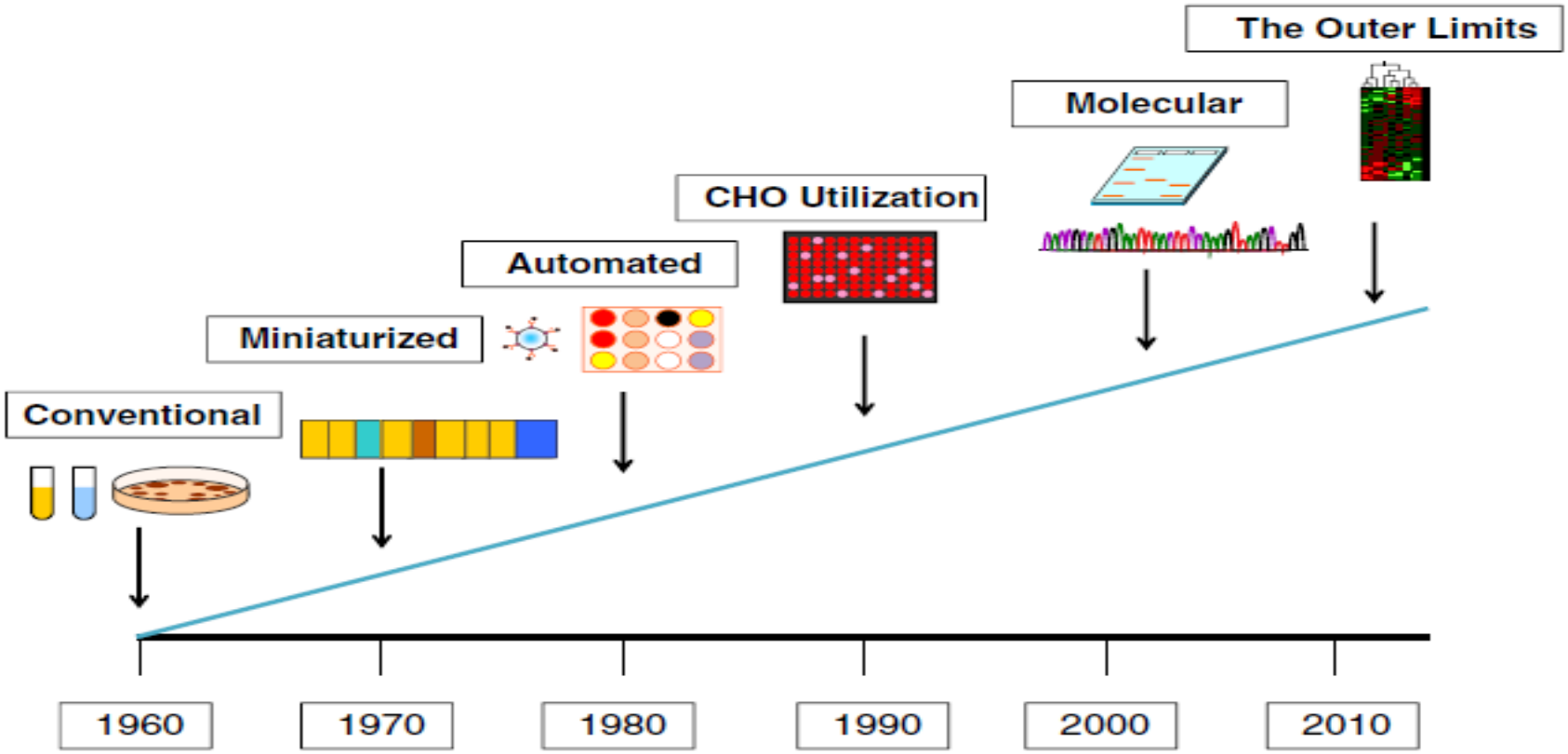
Riddle MS etal (2016) *ACG Clinical Guideline: Diagnosis, Treatment and Prevention of Acute Diarrheal Infections in Adults* Am J Gastroenterol

Risk faktörüne göre epidemiyoloji

Foodborne	
Foodborne outbreaks in hotels, cruise ships, resorts, restaurants, catered events	Norovirus, nontyphoidal *Salmonella*, *Clostridium perfringens*, *Bacillus cereus*, *Staphylococcus aureus*, *Campylobacter* spp, ETEC, STEC, *Listeria*, *Shigella*, *Cyclospora cayetanensis*, *Cryptosporidium* spp
Consumption of unpasteurized milk or dairy products	*Salmonella*, *Campylobacter*, *Yersinia enterocolitica*, *S. aureus* toxin, *Cryptosporidium*, and STEC. *Listeria* is infrequently associated with diarrhea, *Brucella* (goat milk cheese), *Mycobacterium bovis*, *Coxiella burnetii*
Consumption of raw or undercooked meat or poultry	STEC (beef), *C. perfringens* (beef, poultry), *Salmonella* (poultry), *Campylobacter* (poultry), *Yersinia* (pork, chitterlings), *S. aureus* (poultry), and *Trichinella* spp (pork, wild game meat)
Consumption of fruits or unpasteurized fruit juices, vegetables, leafy greens, and sprouts	STEC, nontyphoidal *Salmonella*, *Cyclospora*, *Cryptosporidium*, norovirus, hepatitis A, and *Listeria monocytogenes*
Consumption of undercooked eggs	*Salmonella*, *Shigella* (egg salad)
Consumption of raw shellfish	*Vibrio* species, norovirus, hepatitis A, *Plesiomonas*
Exposure or contact	
Swimming in or drinking untreated fresh water	*Campylobacter*, *Cryptosporidium*, *Giardia*, *Shigella*, *Salmonella*, STEC, *Plesiomonas shigelloides*
Swimming in recreational water facility with treated water	*Cryptosporidium* and other potentially waterborne pathogens when disinfectant concentrations are inadequately maintained
Healthcare, long-term care, prison exposure, or employment	Norovirus, *Clostridium difficile*, *Shigella*, *Cryptosporidium*, *Giardia*, STEC, rotavirus
Child care center attendance or employment	Rotavirus, *Cryptosporidium*, *Giardia*, *Shigella*, STEC
Recent antimicrobial therapy	*C. difficile*, multidrug-resistant *Salmonella*
Travel to resource-challenged countries	*Escherichia coli* (enteroaggregative, enterotoxigenic, enteroinvasive), *Shigella*, Typhi and nontyphoidal *Salmonella*, *Campylobacter*, *Vibrio cholerae*, *Entamoeba histolytica*, *Giardia*, *Blastocystis*, *Cyclospora*, *Cystoisospora*, *Cryptosporidium*
Exposure to house pets with diarrhea	*Campylobacter*, *Yersinia*
Exposure to pig feces in certain parts of the world	*Balantidium coli*
Contact with young poultry or reptiles	Nontyphoidal *Salmonella*
Visiting a farm or petting zoo	STEC, *Cryptosporidium*, *Campylobacter*
Exposure or condition	
Age group	Rotavirus (6–18 months of age), nontyphoidal *Salmonella* (infants from birth to 3 months of age and adults >50 years with a history of atherosclerosis), *Shigella* (1–7 years of age), *Campylobacter* (young adults)
Underlying immunocompromising condition	Nontyphoidal *Salmonella*, *Cryptosporidium*, *Campylobacter*, *Shigella*, *Yersinia*
Hemochromatosis or hemoglobinopathy	*Y. enterocolitica*, *Salmonella*
AIDS, immunosuppressive therapies	*Cryptosporidium*, *Cyclospora*, *Cystoisospora*, microsporidia, *Mycobacterium avium*-intercellulare complex, cytomegalovirus
Anal-genital, oral-anal, or digital-anal contact	*Shigella*, *Salmonella*, *Campylobacter*, *E. histolytica*, *Giardia lamblia*, *Cryptosporidium* as well as sexually transmitted infections

Shane AL etal (2017) *IDSA clinical practice guidelines for the diagnosis and management of infectious diarrhea* Clin Infect Dis

Tanı



Janda JM etal (2014) Culture-independent diagnostic testing: have we opened Pandora's box for good? Diagn Microbiol Infect Dis

Epidemiyolojik tanı

Etiologic Agent	Diagnostic Procedures	Optimal Specimen
Clostridium difficile	NAAT	Stool
	GDH antigen with or without toxin detection followed by cytotoxin or *Clostridium difficile* toxin or toxigenic *C. difficile* strain	
Salmonella enterica, *Shigella* spp, *Campylobacter* spp	Routine stool enteric pathogen culture[a] or NAAT	Stool
Salmonella enterica serovars Typhi and Paratyphi (enteric fever)	Routine culture	Stool, blood, bone marrow, and duodenal fluid
Shiga toxin–producing *Escherichia coli*	Culture for *E. coli* O157:H7[b] and Shiga toxin immunoassay or NAAT for Shiga toxin genes	Stool
Yersinia spp, *Plesiomonas* spp, *Edwardsiella tarda*, *Staphylococcus aureus*, *E. coli* (enterotoxigenic, enteroinvasive, enteropathogenic, enteroaggregative)	Specialized stool culture or molecular assays[c] or NAAT	Stool
Clostridium perfringens	Specialized procedure for toxin detection[d]	Stool
Bacillus cereus, *S. aureus*	Specialized procedure for toxin detection[d]	Food
Clostridium botulinum	Mouse lethality assay (performed at a state public health laboratory, or CDC) [e,f,g]	Serum, stool, gastric contents, vomitus
Entamoeba histolytica; *Blastocystis hominis*[h]; *Dientamoeba fragilis*h; *Balantidium coli*; *Giardia lamblia*; nematodes (generally not associated with diarrhea) including *Ascaris lumbricoides*, *Strongyloides stercoralis*[i], *Trichuris trichiura*, hookworms; cestodes (tapeworms); trematodes (flukes)	Ova and parasite examination including permanent stained smear[i] or NAAT	Stool Duodenal fluid for *Giardia* and *Strongyloides*
E. histolytica	*E. histolytica* species-specific immunoassay or NAAT	Stool
G. lamblia[i]	EIA or NAAT	Stool
Cryptosporidium spp [121][j]	Direct fluorescent immunoassay, EIA, or NAAT	Stool
Cyclospora cayetanensis, *Cystoisospora belli*[k]	Modified acid-fast stain[k] performed on concentrated specimen, ultraviolet fluorescence microscopy, or NAAT	Stool
Microsporidia (now classified as a fungus)	Modified trichrome stain[k] performed on concentrated specimen	Stool
	Histologic examination with electron microscopic confirmation	Small bowel biopsy
Calicivirus (norovirus, sapovirus)[k]; enteric adenovirus; enterovirus/parechovirus[k]; rotavirus	NAAT	Stool
Rotavirus, enteric adenovirus	EIA	Stool
Enteric adenovirus[l]; enterovirus/parechovirus	Viral culture	Stool
Cytomegalovirus	Histopathological examination	Biopsy
	Cytomegalovirus culture	Biopsy

Shane AL etal (2017) *IDSA clinical practice guidelines for the diagnosis and management of infectious diarrhea* Clin Infect Dis

Multipleks yöntemler, avantaj

- Yüksek duyarlılık ve özgüllük
- Hızlı sonuç
- Aynı anda birden fazla ajanı araştırabilme
- Zenginleştirme ihtiyacı yok
- Farklı besi yeri ihtiyacı yok
- Biyokimyasal tanımlama testlerine gerek yok
- İleri tanımlama yöntemlerine gerek yok
- Bilgili ve deneyimli yorum yapan kişiye ihtiyaç yok
- Seroloji kitlerine ihtiyaç yok

Gray J etal (2014) *The increasing application of multiplex nucleic acid detection tests to the diagnosis of syndromic infections* Epidemiol. Infect
Janda JM etal (2014) Culture-independent diagnostic testing: have we opened Pandora's box for good? Diagn Microbiol Infect Dis

Multipleks yöntemler, dezavantaj

- Sadece gen varlığını gösterir
- Pahalı
- Özellikle bu işe ayrılmış laboratuvar ihtiyacı
- Kolonizasyon / invaziv hastalık ayrımı yapamaz
- Canlı ölü bakteri ayrımı yapamaz
- Polimikrobiyal sinyal

Gray J etal (2014) *The increasing application of multiplex nucleic acid detection tests to the diagnosis of syndromic infections* Epidemiol. Infect
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Multipleks yöntem avantaj / dezavantaj II

- 4-23 arası hedefle çalışır
- Antibiyotik duyarlılık profili olmaz
- Morbidite ve morbiditeye daha çok neden olacak tipleri saptayamaz
- Serolojik ve moleküler metotlarla tiplendirmeye izin vermez

- Bazı etkenler gözden kaçabilir
- Değişen direnç paterni fark edilmez
- Salgın analizinde kullanılamaz

Platformlar

Reddington K etal (2014) *A current overview of commercially available nucleic acid diagnostics approaches to detect and identify human gastroenteritis pathogens* Biomol Detect Quantif

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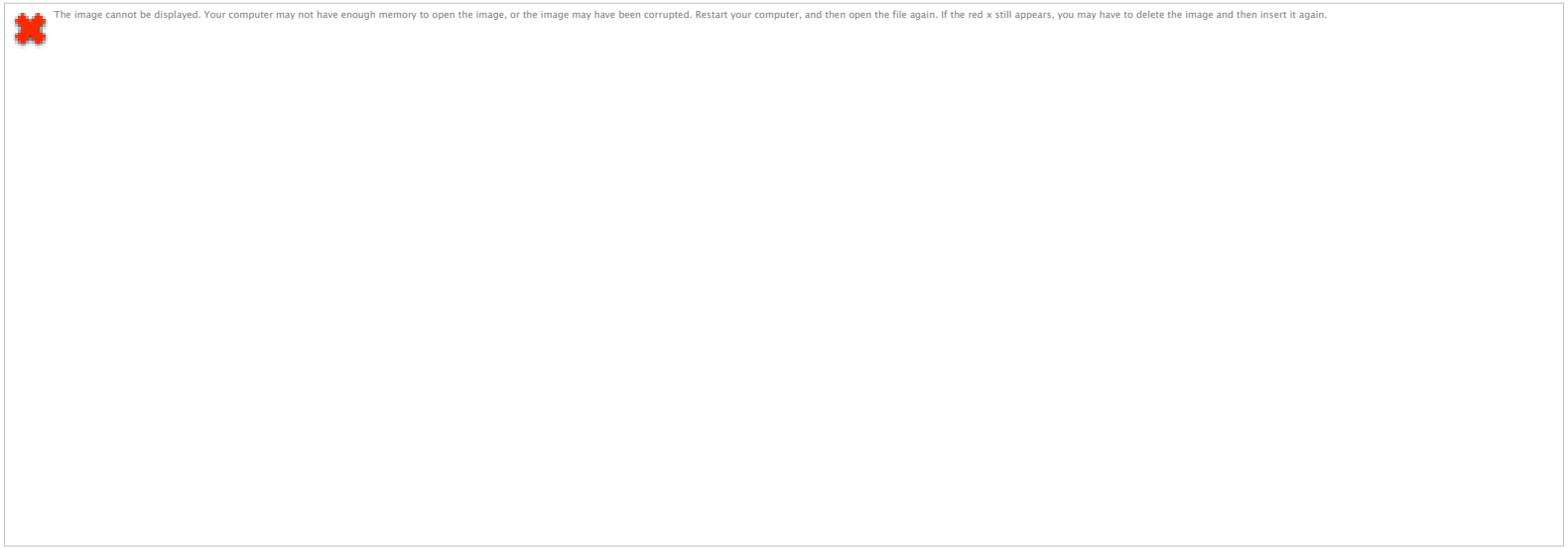
Turist İshali I

Zboromyrska Y etal (2014) *Aetiology of traveller's diarrhoea: evaluation of a multiplex PCR tool to detect different enteropathogens* Clin Microbiol Infect

Turist İshali II

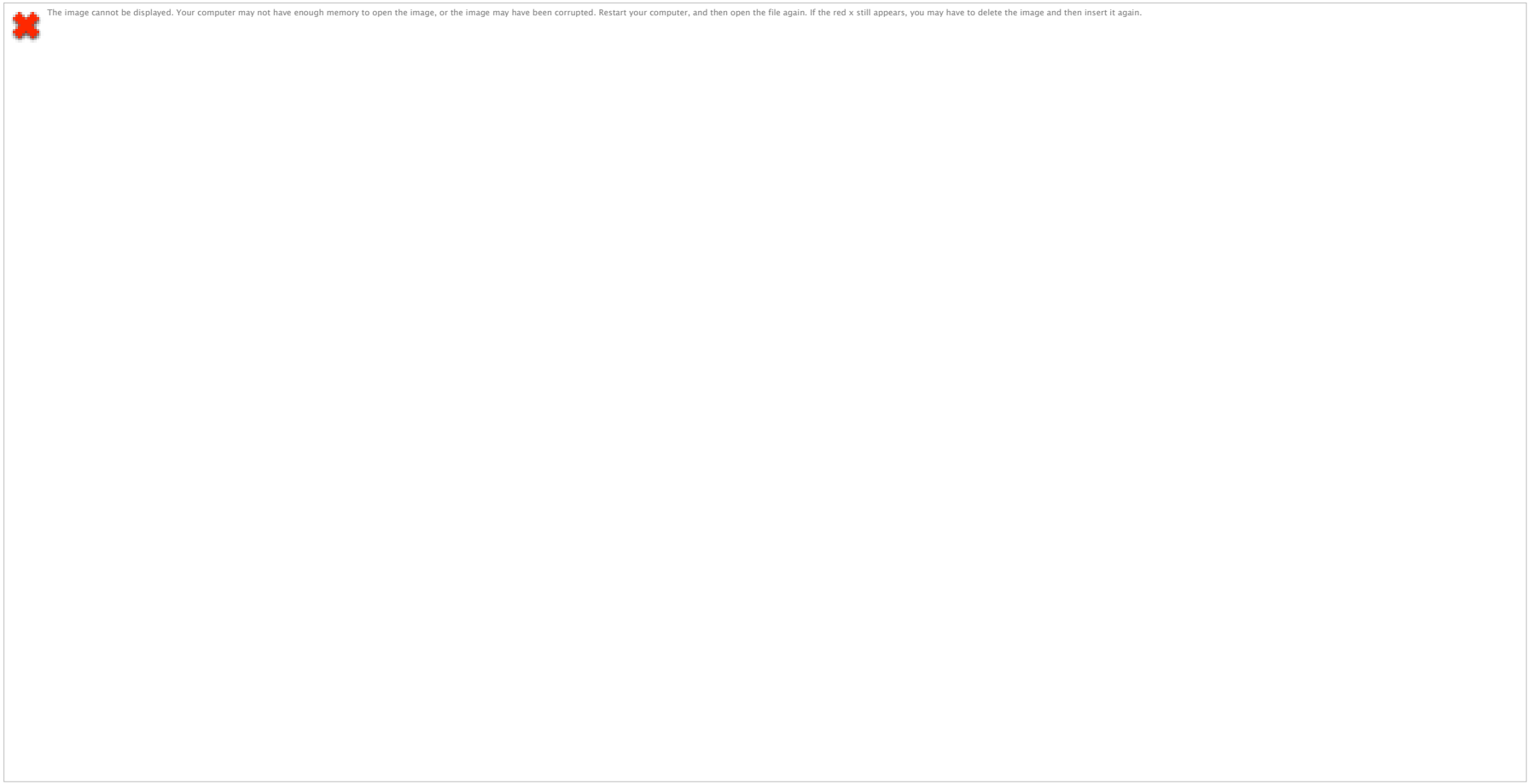
Zboromyrska Y etal (2014) *Aetiology of traveller's diarrhoea: evaluation of a multiplex PCR tool to detect different enteropathogens* Clin Microbiol Infect

Multipleks platformlar koenfeksiyonları da saptar



Buss SN etal (2015) *Multicenter Evaluation of the BioFire FilmArray Gastrointestinal Panel for Etiologic Diagnosis of Infectious Gastroenteritis* J Clin Microbiol

Turist İshali III



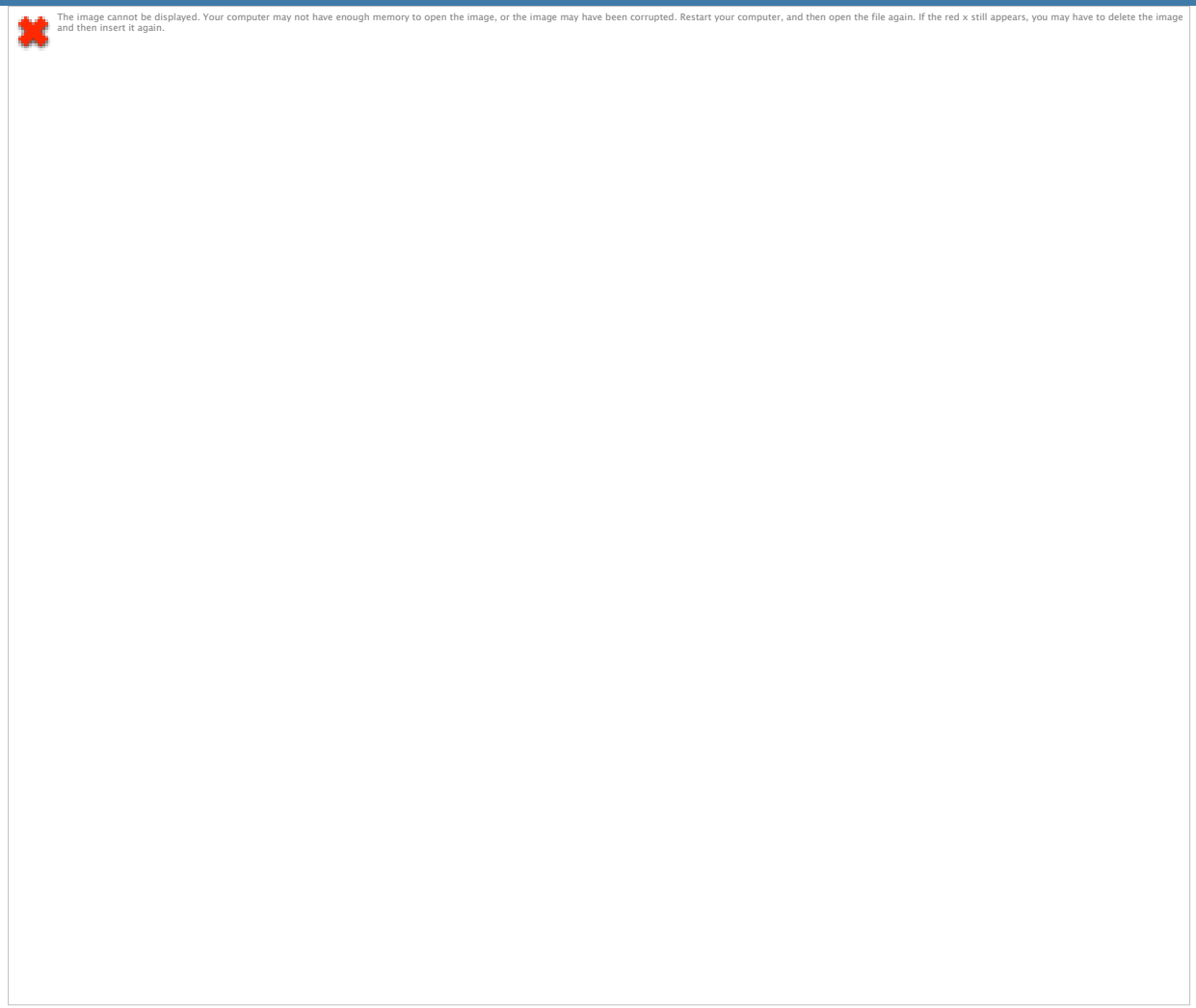
Zboromyrska Y etal (2014) *Aetiology of traveller's diarrhoea: evaluation of a multiplex PCR tool to detect different enteropathogens* Clin Microbiol Infect

Pediatri grubunda hekimler doğru test istiyor mu?

- Her bir ishal atağı için laboratuvar medyan 3 (1-10) test yapıyor
- Sadece *C.difficile* testi istenen epizodların %28'inde farklı bir patojen var
- *C.difficile* istenmeyen ishal ataklarının %8'inde *C.difficile* var

Stockmann C etal (2015) *How well does physician selection of microbiologic tests identify Clostridium difficile and other pathogens in paediatric diarrhoea? Insights using multiplex PCR-based detection* Clin Microbiol Infect

Pediatri grubunda etkenler



Stockmann C etal (2015) *How well does physician selection of microbiologic tests identify Clostridium difficile and other pathogens in paediatric diarrhoea? Insights using multiplex PCR-based detection* Clin Microbiol Infect

Enfeksiyon kontrol için

- 35/158 (%22.2) olgu konvansiyonel olarak enfeksiyöz ajan negatif (C. difficile ve rotavirus)
- Bunların 21'i (%60) izole edilmemiş
- Negatif GPP sonucu ile izolasyon kalkabilir
- Multiplex panel kullanarak erken izolasyon mümkün olabilir

Rand KH etal (2015) *Multiplex gastrointestinal pathogen panels: implications for infection control* Diagn Microbiol Inf Dis

Tekrar test gerekir mi?

Başlangıçta negatifler

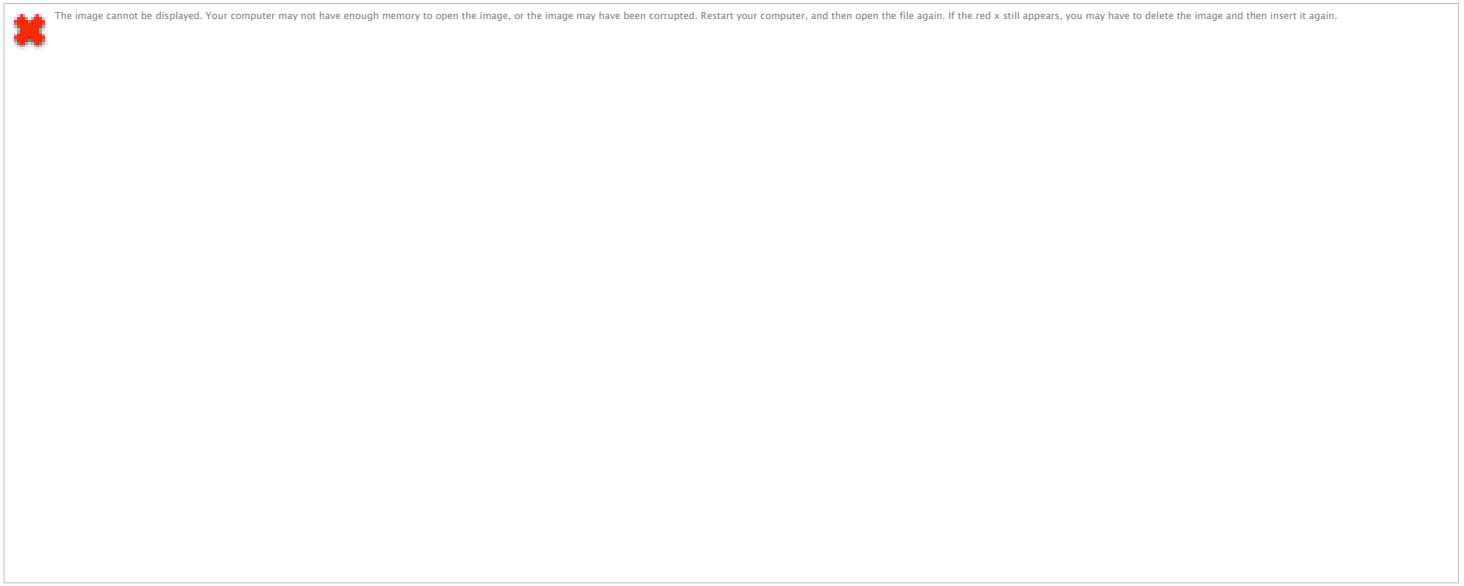
Başlangıçta pozitifler

Park S etal (2017) Is Follow-Up Testing with the FilmArray Gastrointestinal Multiplex PCR Panel Necessary? J Clin Microbiol

- Konvansiyonel yöntemlere nazaran daha duyarlı
- Klinisyenlerin tahmin etmediği patojenleri saptar
- Tek bir dışkıdan çalışır
  - Endoskopi ihtiyacı
- Refleks kültür ihtiyacı
  - *Salmonella*, *Shigella*, *Campylobacter* spp. ve *Escherichia coli* O157:H7
- Akılcı antibiyotik kullanımı
  - STEC
  - *Salmonella*, *Shigella*, *Campylobacter* spp.

Fang FC etal (2017) 2017 Infectious Diseases Society of America Infectious Diarrhea Guidelines: A View From the Clinical Laboratory Clin Inf Dis

Eksikler



Gray J etal (2014) *The increasing application of multiplex nucleic acid detection tests to the diagnosis of syndromic infections* Epidemiol. Infect

Teşekkürler