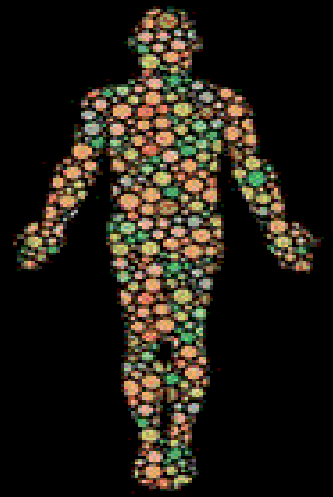
ANTIBIOTICI
QUANDO USARLI O NON USARLI ?

Roberto Luzzati

SC Malattie Infettive,

Ospedale Maggiore, Trieste

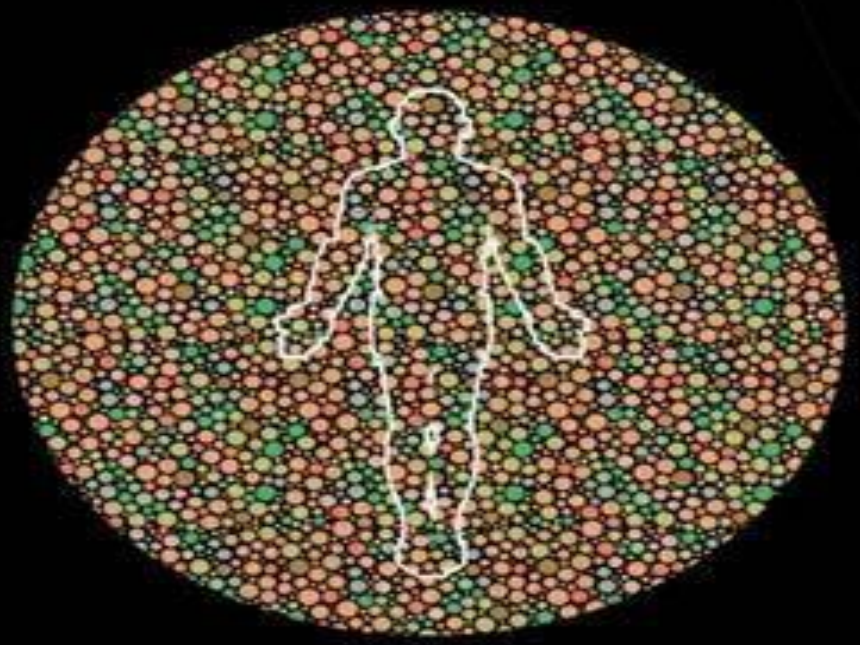
CORPO UMANO = 1.000 miliardi cellule umane



CORPO UMANO = 1.000 MILIARDI CELLULE UMANE

+

10.000 MILIARDI DI CELLULE BATTERICHE



BATTERI: LA MAGGIORANZA INVISIBILE

@ UBIQUITARI: CAPACI DI COLONIZZARE GLI HABITAT PIÙ ESTREMI
@ DIVERSI: 10^7-10^9 SPECIE (STIMATE)
@ RAPIDI NEL CRESCERE: TEMPO DI GENERAZIONE MINUTI, ORE
@ NUMEROSI: 10^{30} CELLULE (2/3 DELL'INTERA BIOMASSA TERRESTRE)

Complications of Antibiotic Therapy

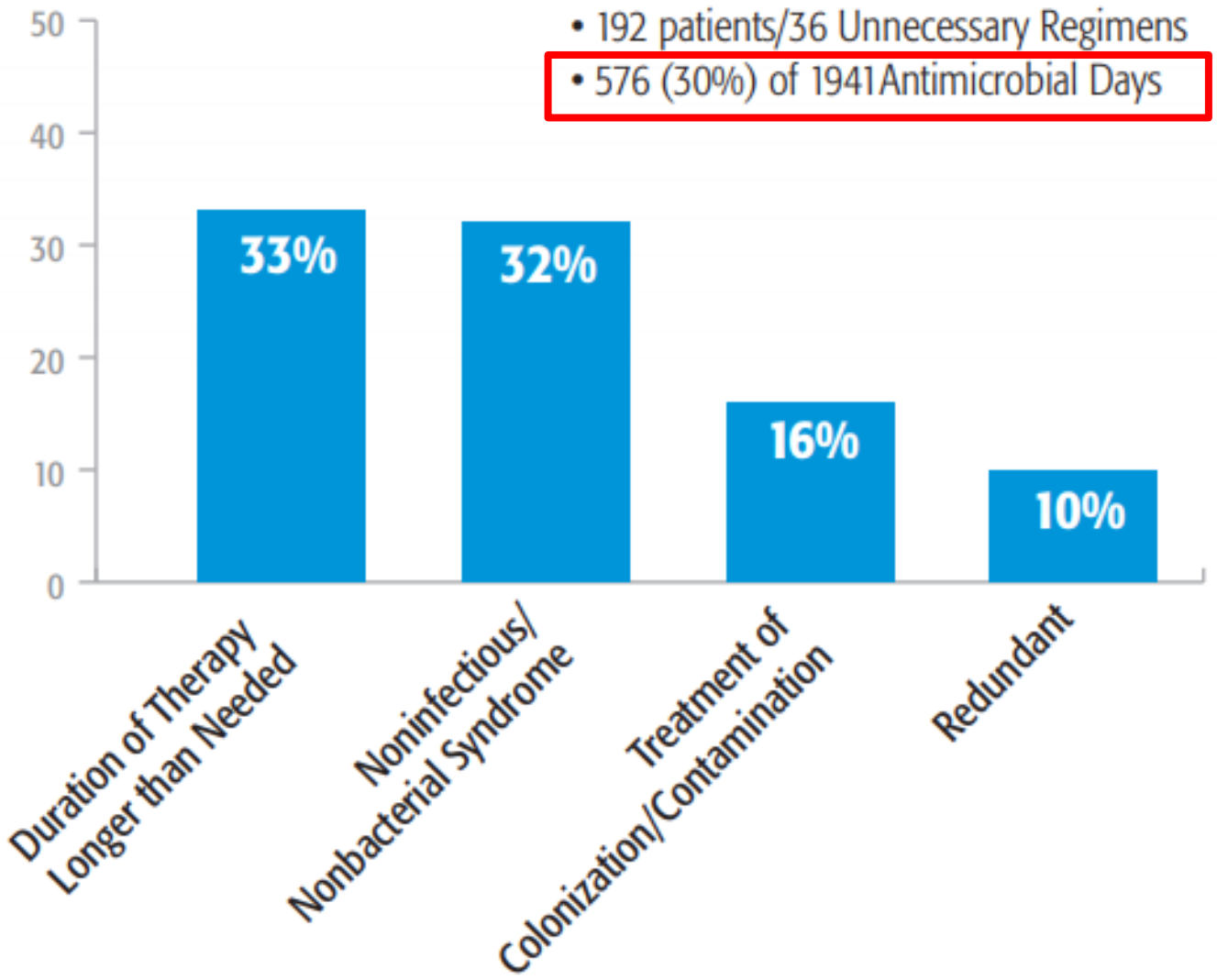
- **Resistance –** inappropriate use of antibiotics
- **Hypersensitivity** – penicillin
- **Direct toxicity** – aminoglycosides = ototoxicity
- **Super infections** – broad spectrum antimicrobials cause alteration of the normal flora; often difficult to treat

Unnecessary use of Antimicrobials in hospitalized patients

- Prospective, observational study in a 650-bed, university-affiliated hospital
- All adults nonintensive care in patients for whom a new antimicrobials were precribed during a 2-week period
- OBJECTIVE: How often antimicrobials, in particular those with antianaerobic activity, were used unnecessarily.

Hecker MT et al Arch Int Med 2003

Figure 2. "Unnecessary" Antimicrobial Therapy.



Adapted from Hecker MT. et al. Arch Intern Med. 2003;162:972-978.

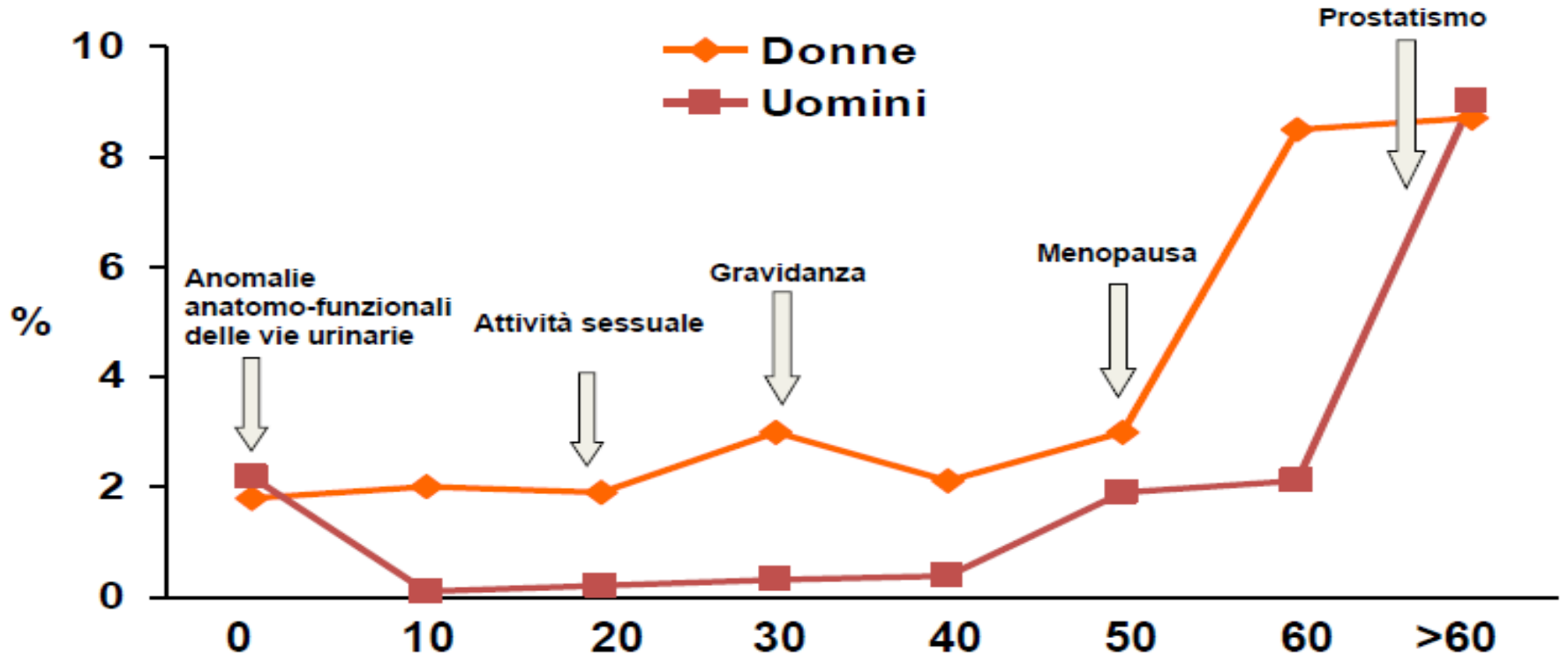
DURATA SUGGERITA DELLA TERAPIA ANTIBIOTICA (MODIF. DA SANFORD GUIDE 2019)

Sito anatomico	diagnosi	durata
Sangue	Batteriemia (focus infettivo rimosso)	10-14 giorni
Osso	Osteomielite	42 giorni
SNC-Meningi	*N. meningitis/H.influenzae*	7 giorni
	S. pneumoniae	10-14 giorni
	L. monocytogenes	21 giorni
Intestino	*C. difficile*	10 giorni
Cuore-endocardio	Endocardite /valvola nativa	14-42 giorni
Articolazione	Artrite	14-28 giorni
Rene	Pielonefrite	14 giorni (ciprofloxacina 7 gg, levofloxacina 5 gg)
Polmone	Polmonite comunitaria (CAP)	5-7 giorni (a-febbrile e stabile per 3-5 giorni)
	Polmonite (HAP/VAP)	7-8 giorni se buona risposta clinica ab-initio
	Ascesso polmonare	42 giorni
Peritoneo	Peritonite (focus infettivo rimosso)	4-8 giorni
Prostata	Prostatite (cronica)	30 (90) giorni
Cute/sottocute	Cellulite	3 giorni dopo scomparsa della flogosi

INFEZIONI DELLE VIE URINARIE

- tra le più comuni infezioni batteriche
- nel mondo 150 milioni/anno di persone colpite
- circa il 50% delle donne presentano almeno 1 episodio di cistite, in particolare prima della menopausa

Epidemiologia



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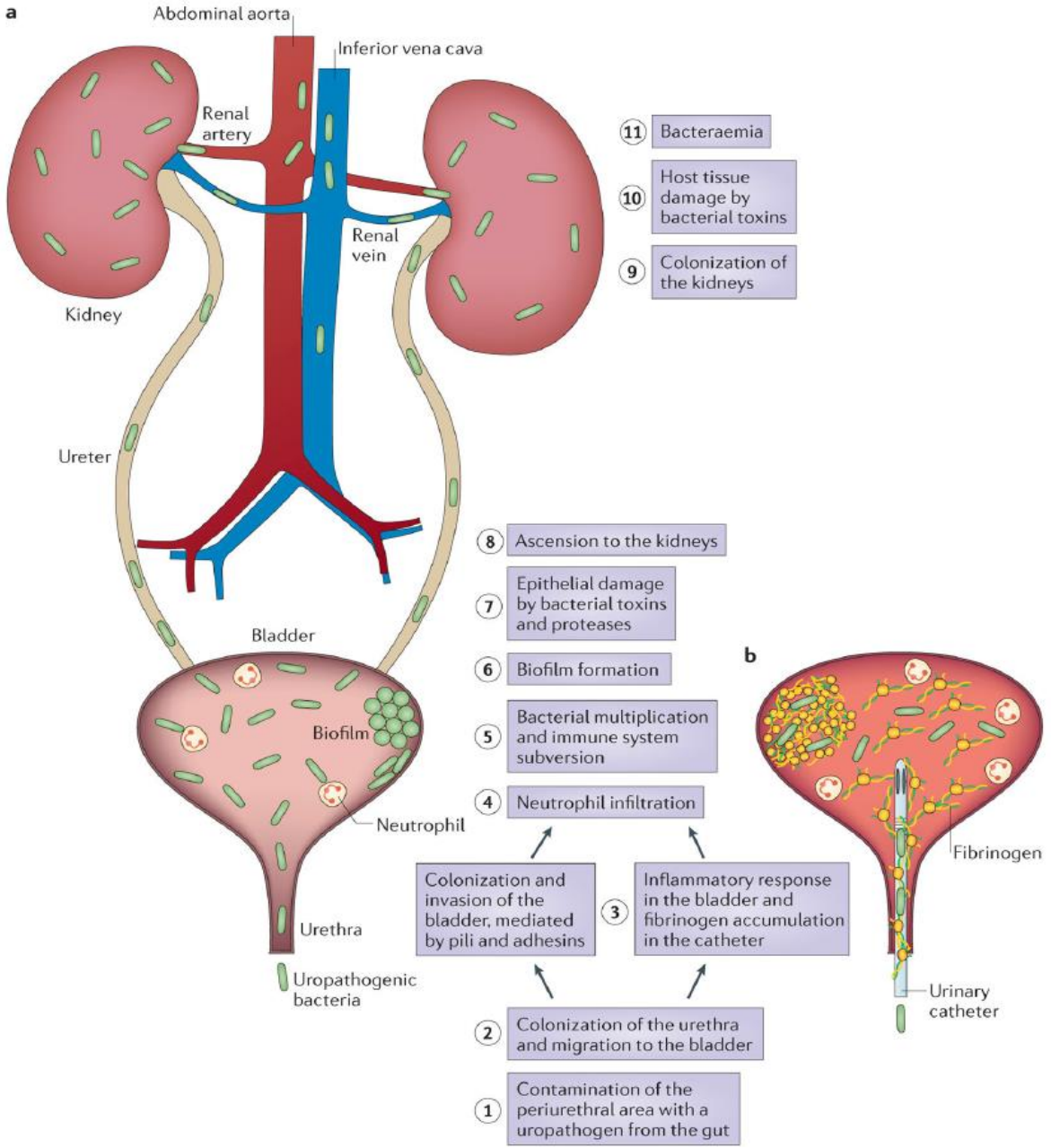


Figure 2. Pathogenesis of urinary tract infections

BATTERIURIA ASINTOMATICA

- 1-2 urinocolture (mitto intermedio)= ≥ 100.000 UFC/ml (= germe)

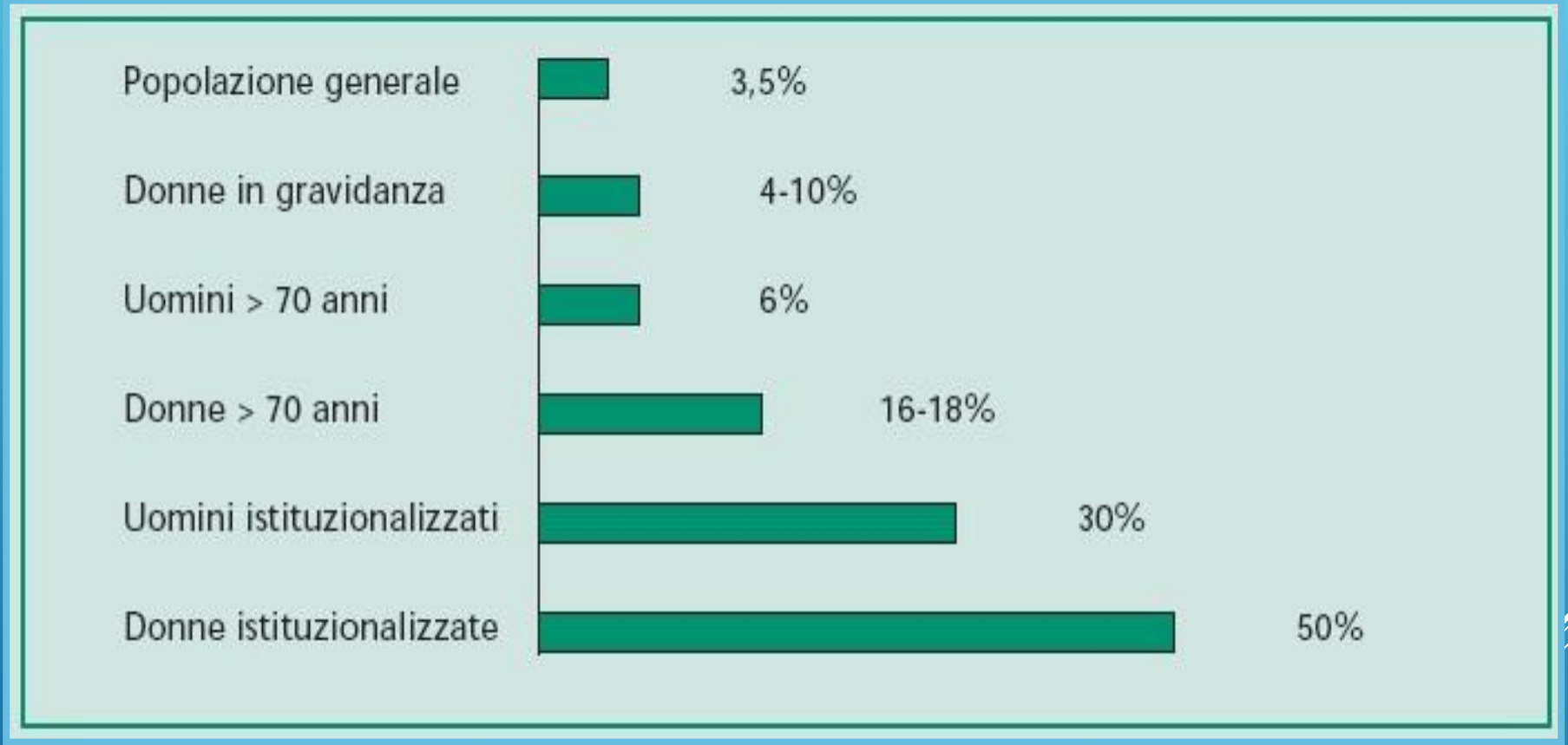
- 1 urinocoltura (cateterismo estemp.)= ≥ 100 UFC/ml

N.B. IN ASSENZA DI SINTOMI il controllo dell'urocoltura è indicato

1. prima di manovre urologiche
2. in gravidanza (Ia visita e 28 a settimana).

La presenza o meno di piuria non è specifica per IVU (in particolare nell'anziano e nel paziente con catetere urinario)

PREVALENZA DELLA BATTERIURIA ASINTOMATICA IN DIVERSE POPOLAZIONI



- Foxman B., Am J Med 2002,113(1A): 5S-13S
- Gruppo Multdisciplinare; Italian J Internal Med 2003, Vol2; N°1.

Table 1. Prevalence of Asymptomatic Bacteriuria Reported for Different Populations

Population	Prevalence, %	Reference
Children		
Boys	<1	[7]
Girls	1–2	[8–10]
Healthy women		
Premenopausal	1.0–5.0	[11]
Pregnant	1.9–9.5	[11]
Postmenopausal (age 50–70 y)	2.8–8.6	[11]
Persons with diabetes		
Women	10.8–16	[12]
Men	0.7–11	[12]
Elderly persons in the community (age ≥70 y)		
Women	10.8–16	[13]
Men	3.6–19	[13]
Elderly persons in a long-term care facility		
Women	25–50	[13]
Men	15–50	[13]
Persons with spinal cord injury		
Intermittent catheter use	23–69	[14]
Sphincterotomy/condom catheter	57	[15]
Persons with kidney transplant		
First month posttransplant	23–24	[16, 17]
1 mo–1 y post-transplant	10–17	[16]
>1 y post-transplant	2–9	[16]
Persons with indwelling catheter use		
Short-term	3%–5%/day catheter	[18]
Long-term	100	[19]

IDSA, CID 2019

Inappropriate Management of Asymptomatic Patients With Positive Urine Cultures: A Systematic Review and Meta-analysis

Myrto Eleni Flokas,[1,a] Nikolaos Andreatos,[1,a] Michail Alevizakos,[1] Alireza Kalbasi,[2] Pelin Onur,[1] and Eleftherios Mylonakis[1]

Background. Mismanagement of asymptomatic patients with positive urine cultures (referred to as asymptomatic bacteriuria [ASB] in the literature) promotes antimicrobial resistance and results in unnecessary antimicrobial-related adverse events and increased health care costs.

Methods. We conducted a systematic review and meta-analysis of studies that reported on the rate of inappropriate ASB treatment published from 2004 to August 2016. The appropriateness of antimicrobial administration was based on guidelines published by the Infectious Diseases Society of America.

Results. A total of 2142 nonduplicate articles were identified, and among them 30 fulfilled our inclusion criteria. The pooled

Open Forum ID 2017

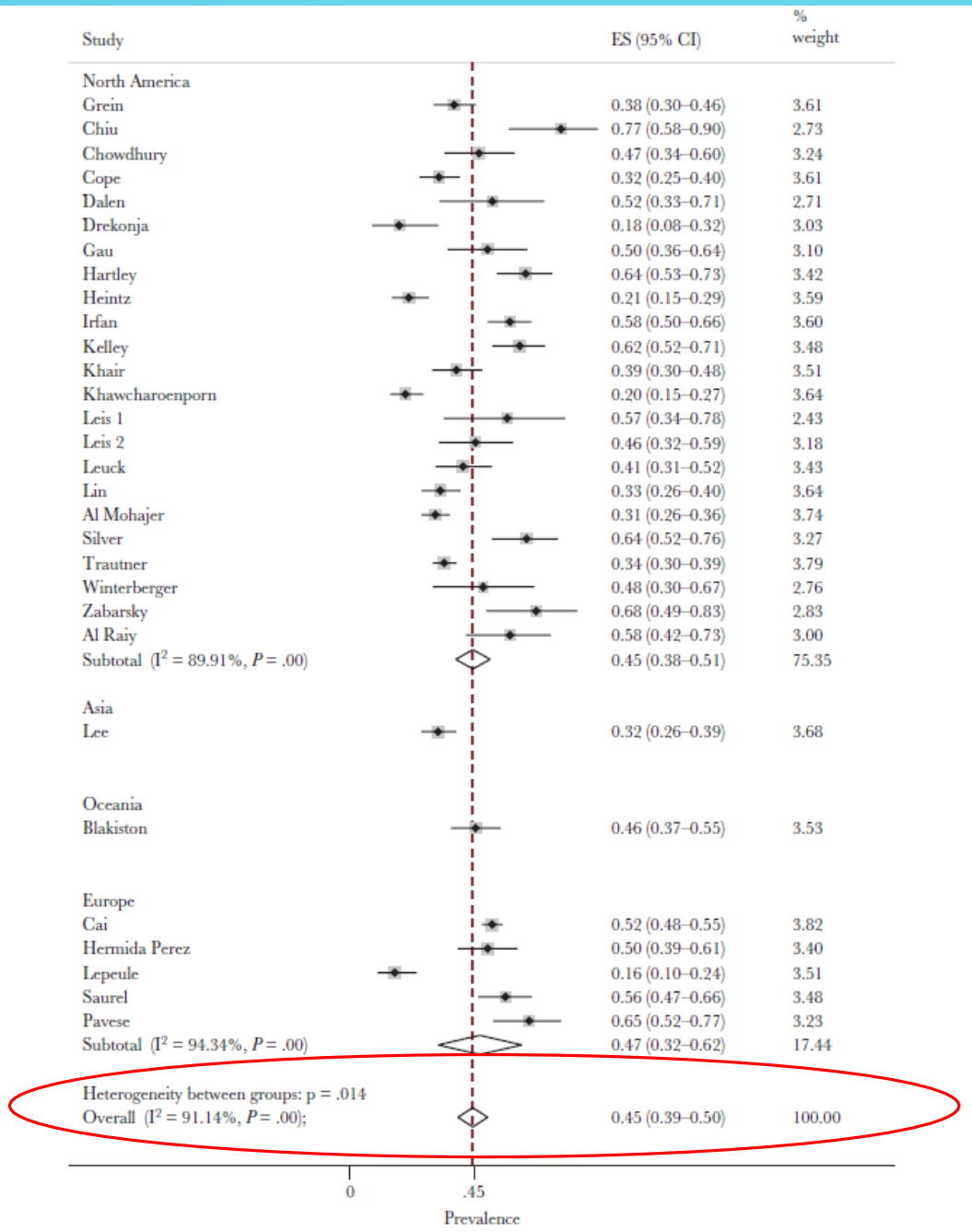


Figure 2. Forest plot of included studies. Rates of overtreatment of asymptomatic bacteriuria stratified by region. ES, effect size.

Results. A total of 2142 nonduplicate articles were identified, and among them 30 fulfilled our inclusion criteria. The pooled prevalence of antimicrobial treatment among 4129 cases who did not require treatment was 45% (95% CI, 39–50). Isolation of gram-negative pathogens (odds ratio [OR], 3.58; 95% CI, 2.12–6.06), pyuria (OR, 2.83; 95% CI, 1.9–4.22), nitrite positivity (OR, 3.83; 95% CI, 2.24–6.54), and female sex (OR, 2.11; 95% CI, 1.46–3.06) increased the odds of receiving treatment. The rates of treatment were higher in studies with ≥100 000 cfu/mL cutoff values compared with <10 000 cfu/mL for bacterial growth (*P*, .011). The implementation of educational and organizational interventions designed to eliminate the overtreatment of ASB resulted in a median absolute risk reduction of 33% ($range_{ARR}$, 16–36%, $median_{RRR}$, 53%; $range_{RRR}$, 25–80%).

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

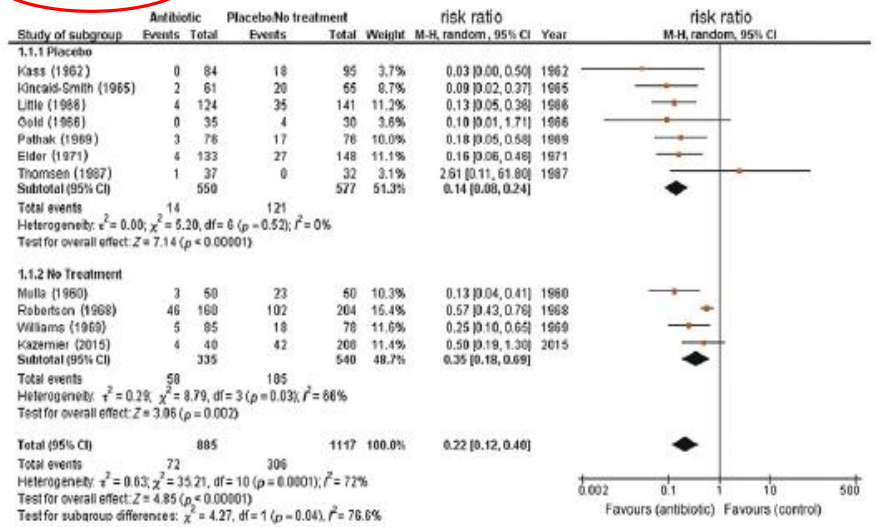
Brief Correspondence

Benefits and Harms of Treatment of Asymptomatic Bacteriuria: A Systematic Review and Meta-analysis by the European Association of Urology Urological Infection Guidelines Panel

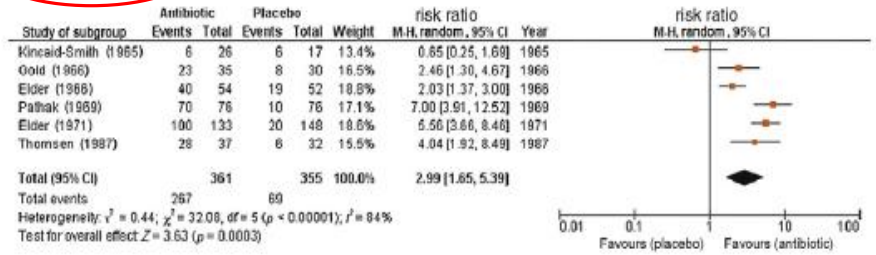
People with asymptomatic bacteriuria (ABU) are often unnecessarily treated with antibiotics risking adverse effects and antimicrobial resistance. We performed a systematic review to determine any benefits and harms of treating ABU in particular patient groups. Relevant databases were searched and eligible trials were assessed for risk-of-bias and Grading of Recommendations, Assessment, Development and Education quality. Where possible, a meta-analysis of extracted data was performed or a narrative synthesis of the evidence was presented. After screening 3626 articles, 50 studies involving 7088 patients were included. Overall, quality of evidence ranged from very low to low. There was no

ABU treatment vs. no treatment/placebo in pregnant women

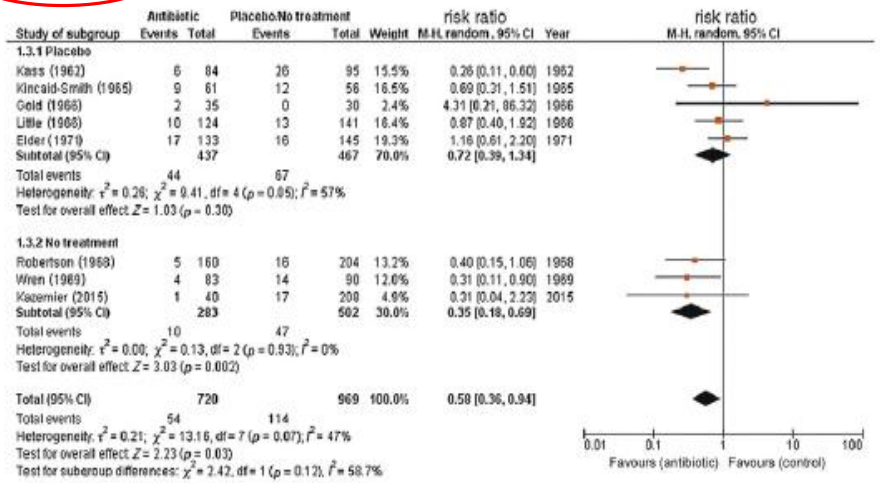
A. Symptomatic UTI



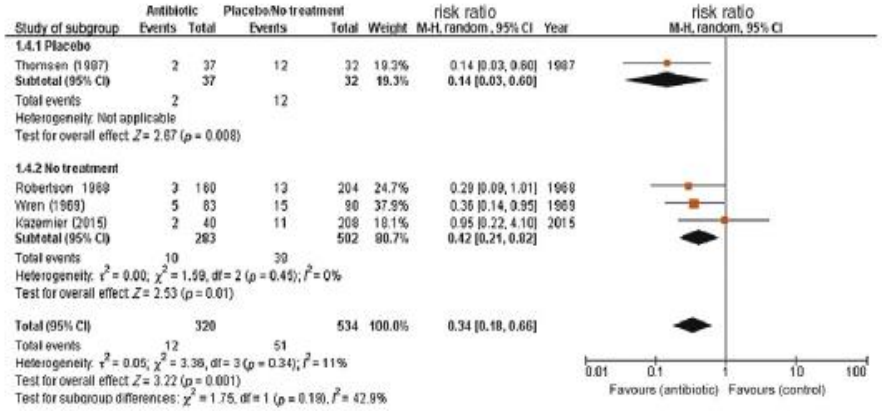
B. Resolution of ABU



C. Low birthweight



D. Preterm delivery



Clinical Infectious Diseases

IDSA FEATURES

Clinical Practice Guideline for the Management of Asymptomatic Bacteriuria: 2019 Update by the Infectious Diseases Society of America[a]

Lindsay E. Nicolle,[1] Kalpana Gupta,[2] Suzanne F. Bradley,[3] Richard Colgan,[4] Gregory P. DeMuri,[5] Dimitri Drekonja,[6] Linda O. Eckert,[7] Suzanne E. Geerlings,[8] Béla Köves,[9] Thomas M. Hooton,[10] Manisha Juthani-Mehta,[11] Shandra L. Knight,[12] Sanjay Saint,[13] Anthony J. Schaeffer,[14] Barbara Trautner,[15] Bjorn Wullt,[16] and Reed Siemieniuk[17]

2. In pregnant women with ASB, we suggest 4–7 days of antimicrobial treatment rather than a shorter duration (*weak recommendation, low-quality evidence*). **Remarks:** The optimal duration of therapy will vary depending on the antimicrobial given; the shortest effective course should be used.

IDSA, CID 2019

Recommendations	Strength rating
Do not screen or treat asymptomatic bacteriuria in the following conditions:	
• women without risk factors;	Strong
• patients with well-regulated diabetes mellitus;	Strong
• post-menopausal women;	Strong
• elderly institutionalised patients;	Strong
• patients with dysfunctional and/or reconstructed lower urinary tracts;	Strong
• patients with renal transplants;	Strong
• patients prior to arthoplasty surgeries;	Strong
• patients with recurrent urinary tract infections.	Strong
Screen for and treat asymptomatic bacteriuria prior to urological procedures breaching the mucosa.	Strong
Screen for and treat asymptomatic bacteriuria in pregnant women with standard short course treatment.	Weak

EAU 2018/IDSA 2019

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DIARREA (INFETTIVA)

alterazione dell'alvo caratterizzata da un'aumento del contenuto d'acqua e quindi del volume e/o della frequenza delle scariche: emissione di > 3 scariche di feci liquide nell'arco delle 24 ore

Dissenteria

diarrea con emissione di feci muco-ematiche, tenesmo, dolori addominali e febbre

Diaree infettive

CLASSIFICAZIONE PATOGENETICA ed ETIOLOGICA

CARATTERISTICHE	TIPO1	TIPO 2	TIPO 3
meccanismo	secretorio	infiammatorio	invasività
localizzazione	tenue prossimale	colon	tenue distale
patogeni	*Vibrio cholerae* *E. coli (ETEC)* *Clostridium perfrigens* *Bacillus cereus* *S. aureus* *Giardia lamblia* ***Rotavirus*** ***Norwalk-like virus*** *Astrovirus - Calicivirus* *Cryptosporidium parvum* *E. coli (EPEC)* *Microsporidia* *Cyclospora cayetanensis*	*Shigella spp.* ***E. coli (EHEC)*** ***E. coli (EIEC)*** *V. parahaemolyticus* ***Clostridium difficile*** ***Campylobacter jejuni*** *Entamoeba histolytica* *Balantidium coli* ***Salmonella spp***	*Salmonella typhi* *Salmonella paratypi A* *Salmonel.schottmuelleri* *Salmonella hirschfeldii* ***Yersinia enterocolitica*** ***Campylobacter fetus***

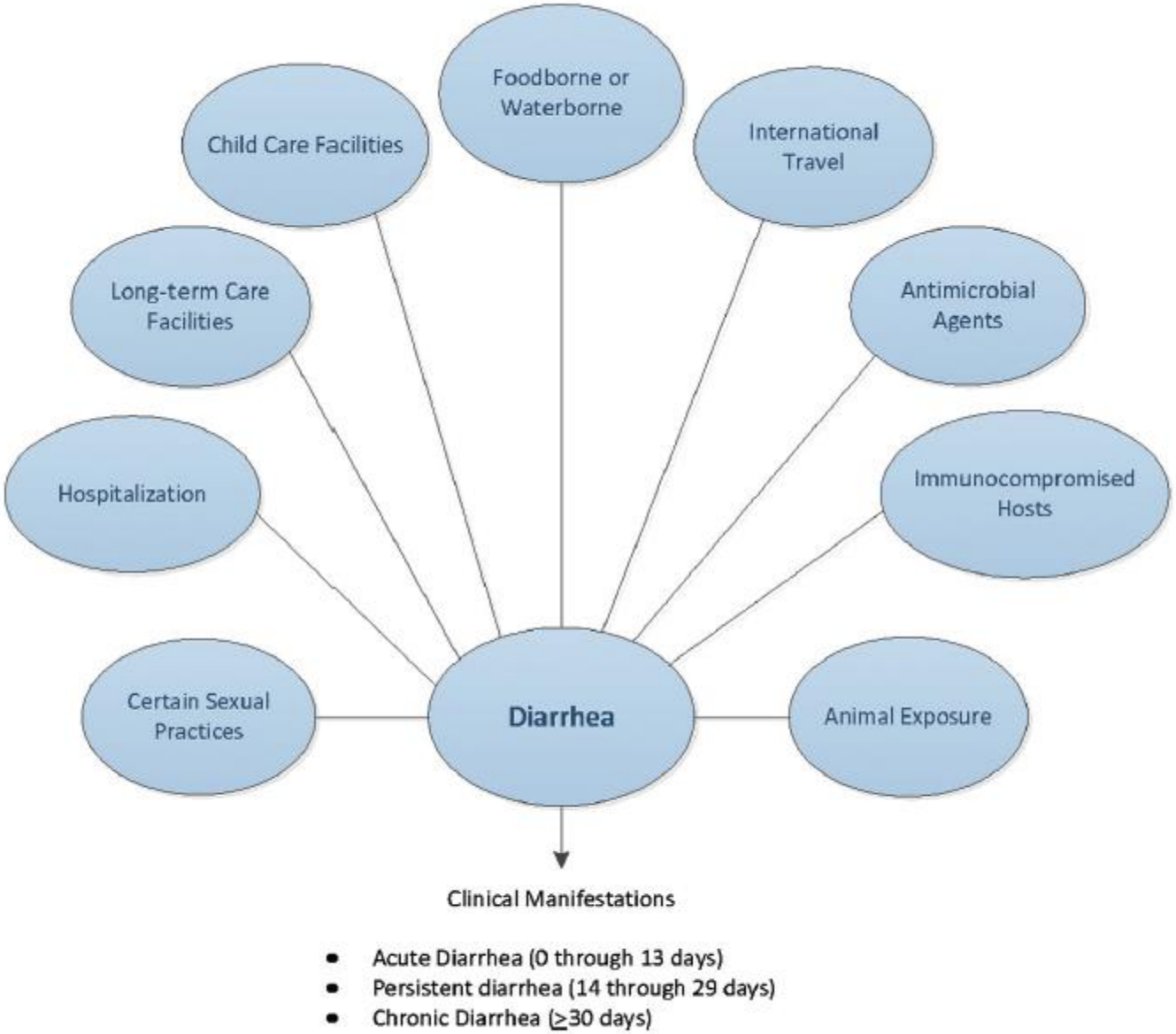

Figure 1. Considerations when evaluating people with infectious diarrhea. Modified from Long SS, Pickering LK, Pober CG, eds. Principles and Practice of Pediatric Infectious Diseases, 4th ed. New York: Elsevier Saunders, 2012.

Table 3. Clinical Presentations Suggestive of Infectious Diarrhea Etiologies

Finding	Likely Pathogens
Persistent or chronic diarrhea	*Cryptosporidium* spp, *Giardia lamblia*, *Cyclospora cayetanensis*, *Cystoisospora belli*, and *Entamoeba histolytica*
Visible blood in stool	STEC, *Shigella*, *Salmonella*, *Campylobacter*, *Entamoeba histolytica*, noncholera *Vibrio* species, *Yersinia*, *Balantidium coli*, *Plesiomonas*
Fever	Not highly discriminatory—viral, bacterial, and parasitic infections can cause fever. In general, higher temperatures are suggestive of bacterial etiology or *E. histolytica*. Patients infected with STEC usually are not febrile at time of presentation
Abdominal pain	STEC, *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, noncholera *Vibrio* species, *Clostridium difficile*
Severe abdominal pain, often grossly bloody stools (occasionally nonbloody), and minimal or no fever	STEC, *Salmonella*, *Shigella*, *Campylobacter*, and *Yersinia enterocolitica*
Persistent abdominal pain and fever	*Y. enterocolitica and Y. pseudotuberculosis*; may mimic appendicitis
Nausea and vomiting lasting ≤24 hours	Ingestion of *Staphylococcus aureus* enterotoxin or *Bacillus cereus* (short-incubation emetic syndrome)
Diarrhea and abdominal cramping lasting 1–2 days	Ingestion of *Clostridium perfringens* or *B. cereus* (long-incubation emetic syndrome)
Vomiting and nonbloody diarrhea lasting 2–3 days or less	Norovirus (low-grade fever usually present during the first 24 hours in 40% if infections)
Chronic watery diarrhea, often lasting a year or more	Brainerd diarrhea (etiologic agent has not been identified); postinfectious irritable bowel syndrome

Abbreviation: STEC, Shiga toxin–producing *Escherichia coli*.

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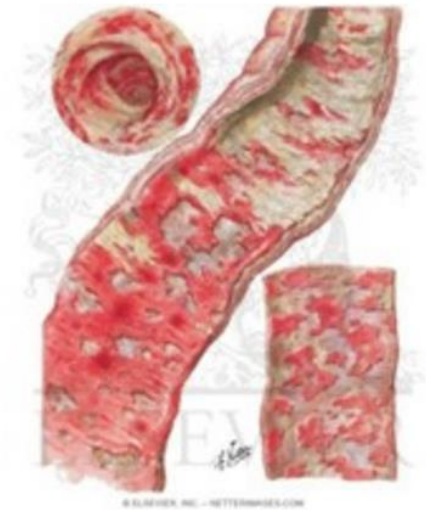
Acute Bloody Diarrhea (dysentery)

1). *Shigella* species
2). Campylobacter species (may be non bloody)
3). Enterohemorrhagic *E.coli* (EHEC)
4). Enteroinvasive *E.coli* (EIEC)
5). Nontyphoidal Salmonella
6). Entamoeba histolytica



COPROCOLTURA: cosa cercare ?

-***Salmonella***

-***Shigella***

-***Campylobacter***

-***Yersinia*** **(se assunzione di carne di maiale cruda/poco cotta)**

-***C. difficile*** **(se storia di assunzione di antibiotici)**

-**Shiga toxin-producing *E. coli*** **(se dissenteria)**

-***Vibrio*** **(se viaggio in area endemica fino a 3 giorni prima dell'esordio diarroico)**

Complications of Bacterial Diarrhea

Complication	Associated Bacterial Agents	Clinical Considerations
Dehydration	Any bacterial pathogen	Most important complication of watery diarrhea
Bacteremia	*Salmonella* spp., *C. fetus*	Certain conditions predispose to systemic *Salmonella* infection
Hemolytic-uremic syndrome (HUS)	STEC, *S. dysenteriae* type 1	Pathogenesis due to shiga toxin absorption and damage
Guillain-Barré syndrome	*Campylobacter jejuni*	40% cases of GBS caused by *C. jejuni;* molecular mimicry LOS
Reactive arthritis	*C. jejuni, Salmonella, S. flexneri*	Occurs in 2.1 per 100 000 *Campylobacter* infections
Irritable bowel syndrome	Most bacterial pathogens	≤ 10% incidence following bacterial enteric infection

Terapia antibiotica

- Nei paesi sviluppati il 58% delle gastroenteriti è sostenuta dai rotavirus/norovirus → virus → non batteri → nessun beneficio dell'antibioticoterapia

- La terapia antibiotica provoca disbiosi anche della flora batterica intestinale > diarrea 'da antibiotici' > colite pseudomembranosa

Among immunocompetent children and adults, empiric antimicrobial therapy for bloody diarrhea while waiting for results of investigations is not recommended, except for the followings:

- **a. Infants (< 3 mesi con sospetta infezione batterica)**
- **b. Ill immunocompetent people with fever documented in a medical setting, abdominal pain, bloody diarrhea, and bacillary dysentery (frequent scant bloody stools, fever, abdominal cramps, tenesmus) presumptively due to *Shigella*.**
- **c. People who have recently travelled internationally with body temperatures ≥38.5°C and/or signs of sepsis**

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Terapia antibiotica empirica

- Considerare trattamento empirico anche in:
- Pazienti immunodepressi con malattia grave e diarrea con sangue
- Sospetti per febbre tifoide (dopo aver prelevato emocolture, coprocolture ed urinocoltura)

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Terapia antibiotica empirica

- Fluorochinolone (es. ciprofloxacina) o
- Azitromicina
- Se sintomi neurologici o infanti (< 3 mesi) utilizzare cefalosporina di 3° generazione (es. ceftriaxone)

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Batterio	1° scelta	2° scelta
Campylobacter	Azitromicina	Ciprofloxacina
Clostridium difficile	Vancomicina per os	Metronidazolo
Salmonella enterica	Non indicata	
Salmonella typhi o *paratyphi*	Ceftriaxone, ciprofloxacina	Ampicillina, cotrimossazolo, azitromicina
Shigella	Azitromicina, ciprofloxacina, ceftriaxone	Cotrimossazolo, ampicillina
Vibrio cholerae	Doxiciclina	Ciprofloxacina, azitromicina, ceftriaxone
Yersinia enterocolitica	Cotrimossazolo	Cefotaxime, ciprofloxacina

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Terapia antimicrobica delle infezioni sostenute da *Clostridium difficile*

Manifestazione clinica	Esempi/note	Terapia	Alternative/Commenti
CDI lieve/moderata	GB < 15000/mmc Creatininemia nella norma	Metronidazolo PO 500 mg x 3 ore per 10-14 giorni Vancomicina PO 125 mg x 4 per 10-14 giorni	Fidaxomicina PO 200 mg x 2 per 10 giorni
CDI grave	GB > 15000/mmc Aumento creatininemia ≥ 50% Ipoalbuminemia (< 2.5 g/dl)	Vancomicina PO 125 mg x 4 per 10-14 giorni	Fidaxomicina PO 200 mg x 2 per 10 giorni
CDI grave, complicata	Ipotensione/shock Megacolon Alterazione stato mentale	Vancomicina PO 125 mg x 4 per 10-14 giorni Ileostomia ad ansa con irrigazione anterograda del colon con vancomicina	Aggiungere metronidazolo EV 500 mg x 3 Non dati su fidaxomicina Richiedere consulenza chirurgica
Prima recidiva (non complicata)	Valuta fattori di rischio per ulteriori recidive	Trattare come il primo episodio di CDI	Valutare costo/beneficio di fidaxomicina
≥ 2 recidiva (non complicata)	-	Vancomicina PO a scalare (125 mg x 4 per 10 gg, poi 125 mg x 2 per 1 sett, poi 125 mg x 1 per 1 sett, poi 125 mg ogni 2-3 gg per 2-8 sett) Fidaxomicina PO a scalare (200 mg x 2 nei giorni 1-5, poi 200 mg ogni 48 h nei giorni 7-25) Trapianto di microbiota fecale (efficacia ~ 90%)	Considerare aggiunta alla terapia standard (vancomicina o fidaxomicina) di bezlotoxumab EV 10 mg/kg in dose singola
Recidiva (complicata)	-	Trattare come CDI grave o grave/complicata	
Commenti	Evitare agenti antiperistaltici. Buone evidenze dall'uso concomitante di probiotici. Limitare antibiotici sitemici allo stretto necessario e se usati prediligere quelli con minor impatto su microbiota (es. doxiciclina) o con azione anti Clostridium (es. linezolid, tigeciclina)		

Chi non trattare?

- Evitare terapia per Shiga-toxin *E. coli* O157 e altri *E. coli* che producono Shiga toxin 2 (se trattati aumenta il rischio di sviluppare sindrome emolitico-uremica)
- Evitare terapia empirica in pazienti con diarrea acquosa persistente da ≥ 14 giorni (se dura così tanto verosimilmente non è batterica o comunque non è clinicamente urgente).

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Consigli ‘REALF LIFE’

-Mettere in diagnosi differenziale esordio di IBD (inflammatory bowel disease)

-Evitare uso di antiperistaltici (es. loperamide) salvo in situazioni contingenti (es. In viaggio) e sempre in età pediatrica

-Infezioni da *Yersinia* possono mimare appendiciti