Debate – Selective Decontamination of the Gut
Prof. Jan Kluytmans and Dr. Cliff McDonald
Broadcast live from the 2015 Infection Prevention Society conference

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Stewardship

- Optimal treatment of patients while
  - limiting side effects
  - limiting antimicrobial resistance

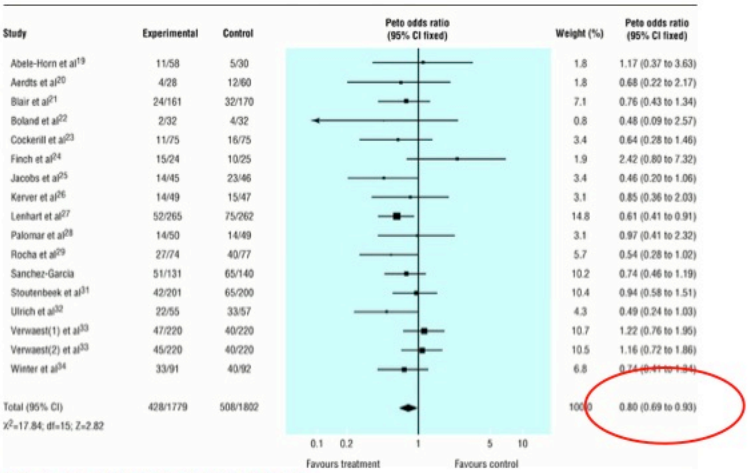
What is SDD?

- Intravenous prophylaxis
  - cefotaxim
- Oropharyngeal decontamination
  - tobramycin and colistin
- Gastric and intestinal decontamination
  - tobramycin and colistin
- Avoiding the use of anti-anaerobic antibiotics
- Surveillance cultures twice weekly
- High level of hygiene

Arguments for SDD

- Does it affect the outcome?
  - Mortality
  - Length of stay
- Does it prevent nosocomial infections?
- Does it affect the use of antibiotics?
- What is the effect on the development of resistance?

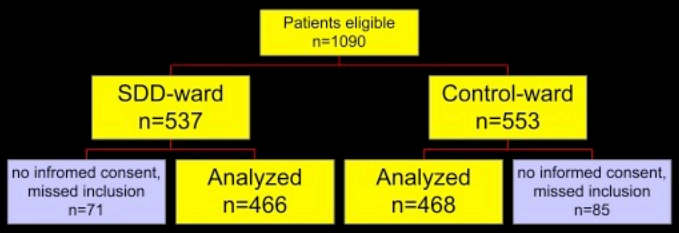
Meta-analysis: effect on ICU-mortality systemic and topical prophylaxis



D'Amico, R. et al. BMJ 1998;316:1275-1285

Effects of SDD on mortality

E. de Jonge et al. Lancet 2003; 362: 1011-1016



	SDD	Controls	RR (95%CI)	p-value
IC-mortality	14.8 %	22.9 %	0.65 (0.44 – 0.85)	
Hospital-mortality	24.2 %	31.2 %	0.78 (0.63 – 0.96)	
Duration ICU-stay (d)	11.6	13.4		< 0.01

COMMENTARY

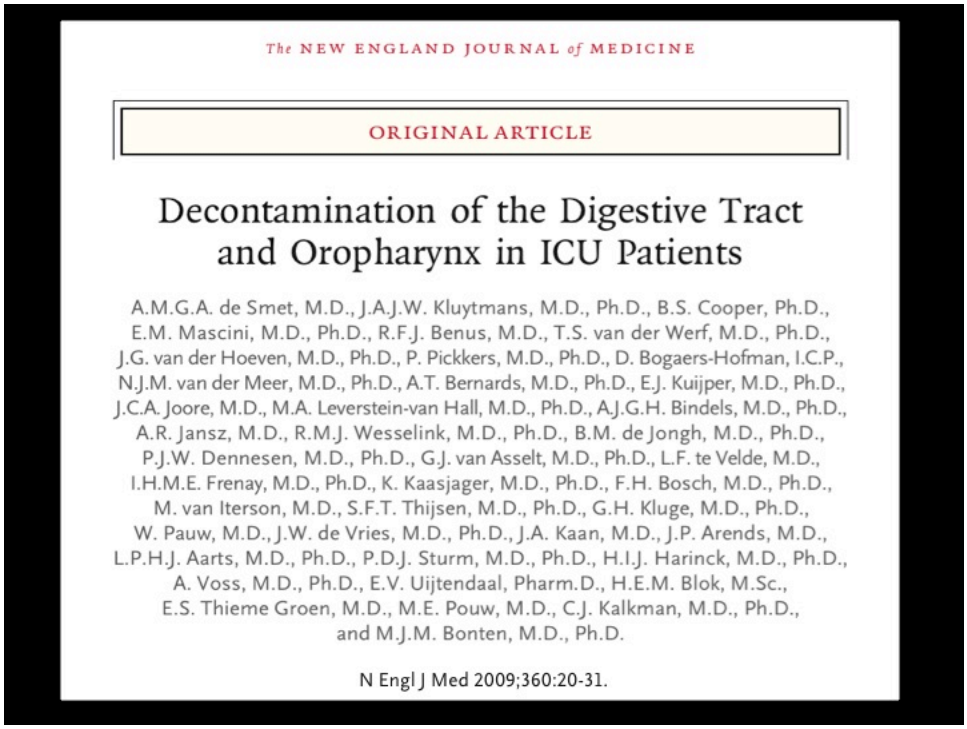
COMMENTARY

Selective digestive decontamination: for everyone, everywhere?

THE LANCET • Vol 362 • September 27, 2003

So should SDD be applied routinely in all ICUs? To the question does SDD work, the answer now must definitely be yes—SDD reduces mortality. But, do the data apply to

?



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Decontamination of the Digestive Tract and Oropharynx in ICU Patients

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N Engl J Med 2009;360:20-31.

Study design

- Cluster-randomized controlled multi-centre cross-over trial (ICUs in 13 hospitals)
  - 2 non-teaching; 7 teaching; 4 university
- Study periods: SDD, SOD and standard care
- Six months per study period
- 1 month wash in/wash out before and between study periods
- Order of study periods randomized per study centre

Endpoints

- ICU-mortality (primary)
- Hospital-mortality (primary)
- Resistance (secundary)
- Duration of intubation (secundary)
- LOS ICU (secundary)
- Antibiotic use (secundary)
- Costs (secundary)

Patients

- Inclusion criteria:
  - Expected stay in ICU >72 hours
  - and/or expected duration of ventilation >48 hours
- Exclusion criteria:
  - Documented allergy for study medication
  - Pregnancy

End Point	Adjusted Odds Ratio or Hazard Ratio (95% CI)†		
	Standard Care	SDD	SOD
Death — no. (%)			
During the first 28 days	1.00	0.83 (0.72–0.97)	0.86 (0.74–0.99)
In the ICU	1.00	0.81 (0.69–0.94)	0.87 (0.74–1.02)
In the hospital	1.00	0.88 (0.76–1.01)	0.85 (0.74–0.98)
Time to outcome for survivors at day 28 — days			
Cessation of mechanical ventilation	1.00	1.10 (0.99–1.22)	1.03 (0.90–1.17)
Median			
Interquartile range			
Discharge from ICU	1.00	1.09 (0.99–1.21)	1.06 (0.94–1.19)
Median			
Interquartile range			
Discharge from hospital	1.00	1.13 (1.01–1.25)	1.13 (0.96–1.32)
Median			
Interquartile range			

Arguments

- Does it affect the outcome?
  - Mortality
  - Length of stay

YES

- Does it prevent nosocomial infections?
- Does it affect the use of antibiotics?
- What is the effect on the development of resistance?

Arguments

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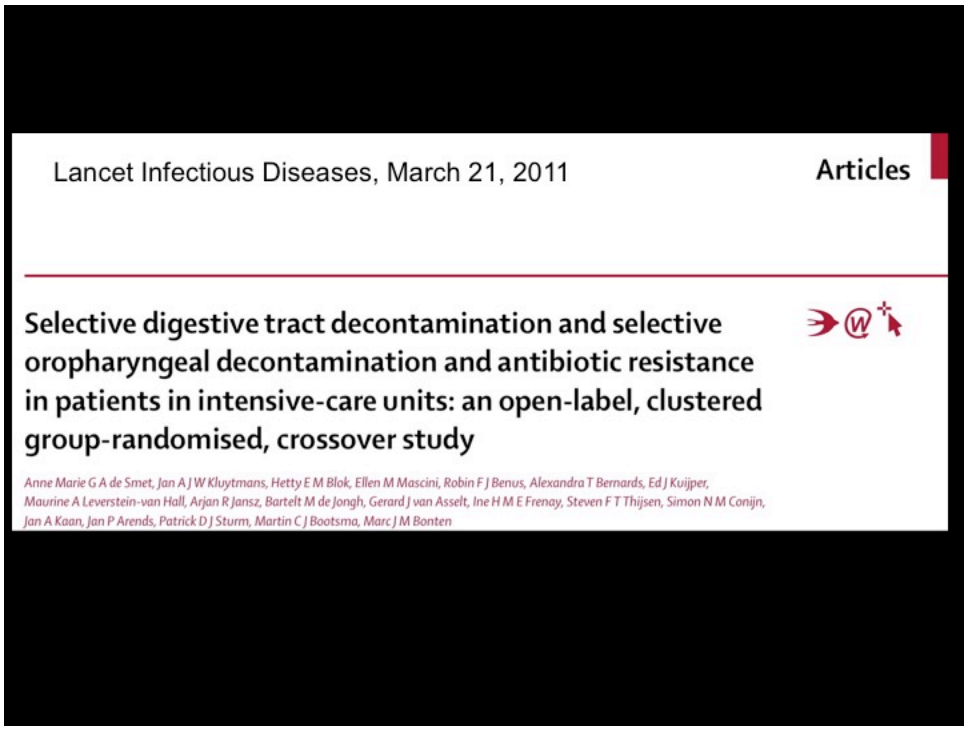

ICU-acquired bacteremia and candidemia

	Standard care (n=1837)	SOD (n=1758)	SDD (n=186	Crude odds ratio (95% CI)		
				SDD vs standard care	SOD vs standard care	SDD vs SOD
Any microorganism, apart from coagulase-negative staphylococci	239 (13%)	158 (9%)	124 (7%	0·48 (0·38–0·60); ARR 6·4%; NNT 16	0·66 (0·53–0·82); ARR 4·0%; NNT 25	0·72 (0·56–0·92); ARR 2·4%; NNT 43
Candida spp and other yeasts*	18 (1%)	20 (1%)	6 (<1	0·33 (0·13–0·82); ARR 0·7%; NNT 152	1·16 (0·61–2·21)	0·28 (0·11–0·70); ARR 0·8%; NNT 127
HRMO†	19 (1%)	20 (1%)	8 (<1	0·41 (0·18–0·94); ARR 0·6%; NNT 170	1·10 (0·59–2·07)	0·37 (0·16–0·85); ARR 0·7%; NNT 145

-selective oropharyngeal decontamination. SI ARR=absolute risk reduction. NNT=number needed to treat. HRMO=highly resistant microorganism. *One case of *Saccharomyces cerevisiae* in the standard-care group. †One patient in the control group had two episodes of bacteraemia with HRMOs (one episode on day 9 with *Enterobacter cloacae* and *Escherichia coli* and one on day 30 with *Acinetobacter baumanii*).

Table 3: **Patients with bacteraemia and candidaemia acquired in intensive-care units**

	Crude odds ratio (95% CI)
	SDD *vs* standard care
Any microorganism, apart from coagulase-negative staphylococci	0·48 (0·38–0·60); ARR 6·4%; NNT 16
Candida spp and other yeasts*	0·33 (0·13–0·82); ARR 0·7%; NNT 152
HRMO†	0·41 (0·18–0·94); ARR 0·6%; NNT 170

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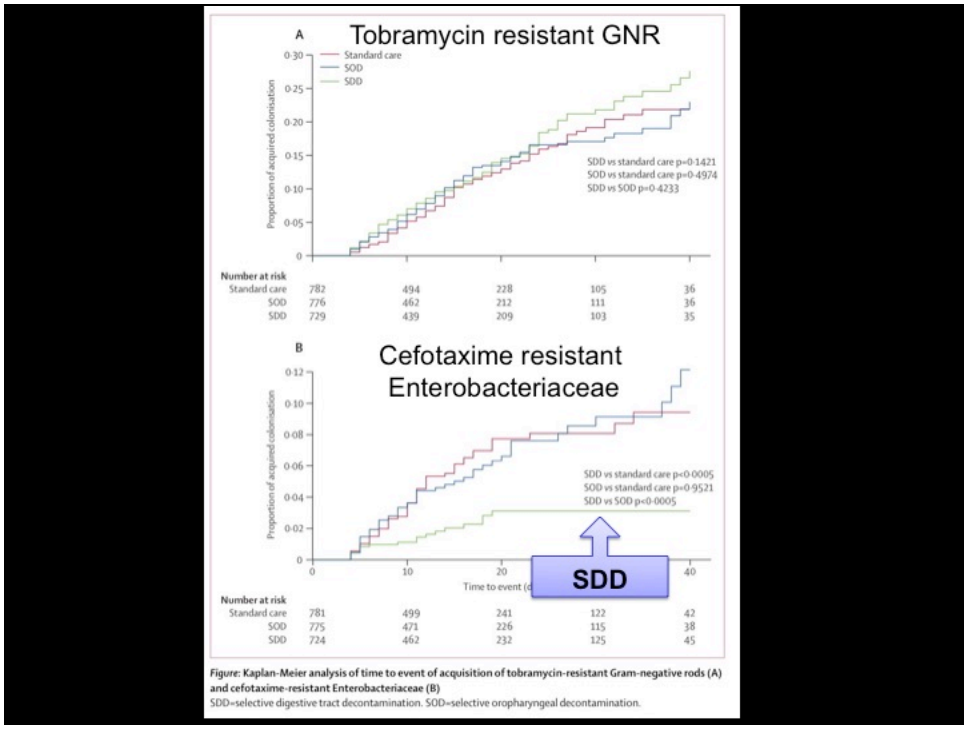

Figure: Kaplan-Meier analysis of time to event of acquisition of tobramycin-resistant Gram-negative rods (A) and cefotaxime-resistant Enterobacteriaceae (B)
SDD=selective digestive tract decontamination. SOD=selective oropharyngeal decontamination.

Arguments

- Does it affect the outcome?
  - Mortality
  - Length of stay

YES

- Does it prevent nosocomial infections?
- Does it affect the use of antibiotics?
- What is the effect on the development of resistance?

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Arguments

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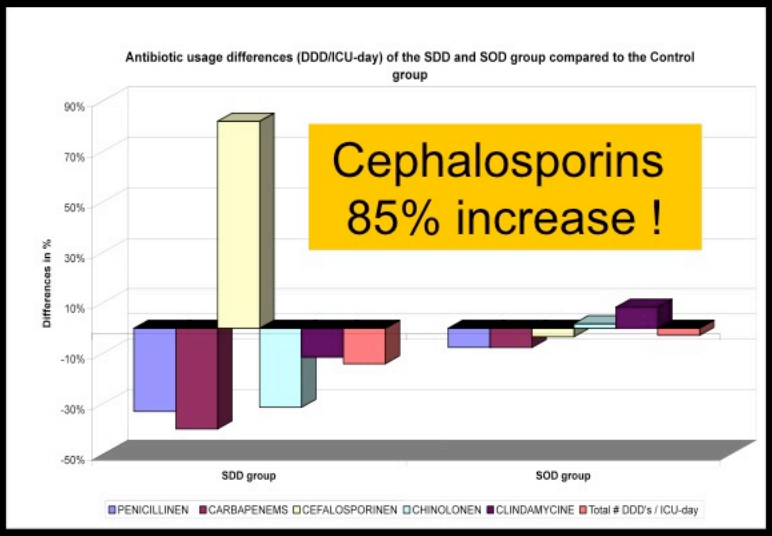
LESS

Systemic antibiotic use (totals in DDD)

Antibiotics	SDD group Total DDD use (Δ SDD vs Control)	SOD group Total DDD use (Δ SOD vs Control)	Standard care Total DDD use
Penicillins	9,767 (-27.8%)	12,805 (+5.3%)	13,523
Carbapenems	724 (-45.7%)	995 (-25.4%)	1,334
Cefalosporins	8,473 (+86.6%)	3,935 (-13.3%)	4,541
Quinolones	2,637 (-31.4%)	3,291 (-14,4%)	3,846
Clindamycins	473 (-11.6%)	553 (+3.4%)	535
Other antibiotics	7,589 (- 23.4%)	8,720 (-12.0%)	9,909
All Systemic antibiotics	29,663 (-12.0%)	30,299 (-10.1%)	33,688

N ENGL J MED 360;1 NEJM.ORG JANUARY 1, 2009

Effects on antbiotic use in ICU



Arguments

- Does it affect the outcome?
  - Mortality
  - Length of stay
- Does it prevent nosocomial infections?
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- What is the effect on development of resistance?

YES

Conclusions

- SDD is an evidence based intervention
  - Reduced mortality
  - Reduced ICU acquired infection rates
  - Lower rates of resistance
  - Alters the use of systemic antibiotics
- Should be accompanied by
  - Careful monitoring of surveillance cultures
  - Good infection control

the proof of the pudding
IS IN THE EATING

- My own hospital uses SDD for >25 year
- 30 bed ICU
- No MRSA, VRE, CRE, C. diff etc.
- ESBL is often found on admission but disappears rapidly
- Extremely low rates of ICU-acquired bacteremia
- Long term use is not associated with increased resistance rates


SDD in 2025?


O VER

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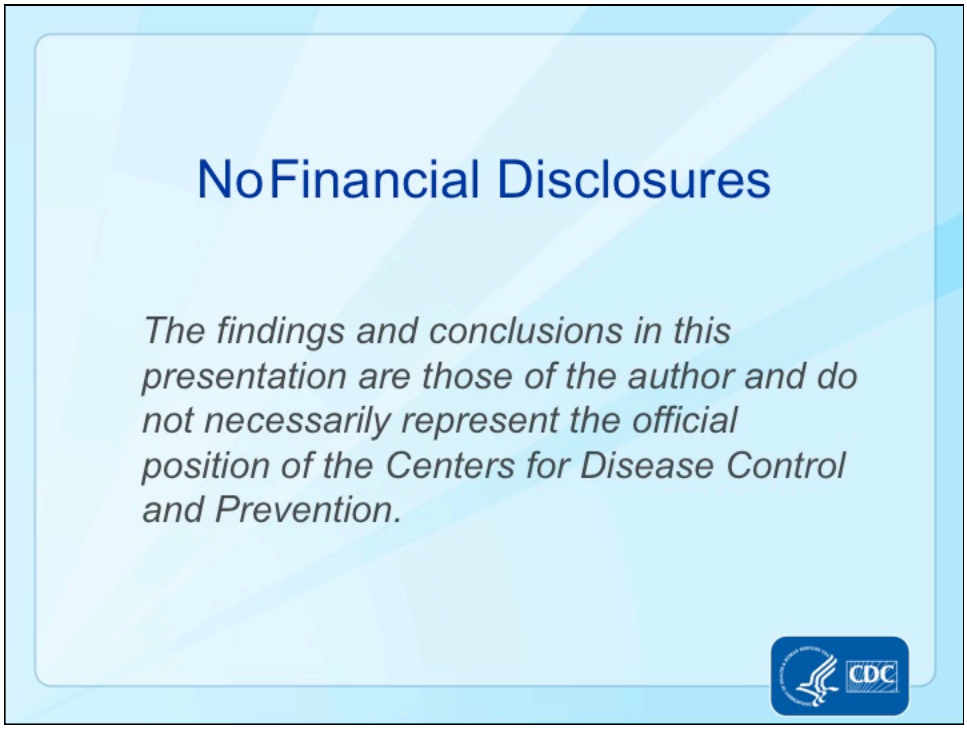
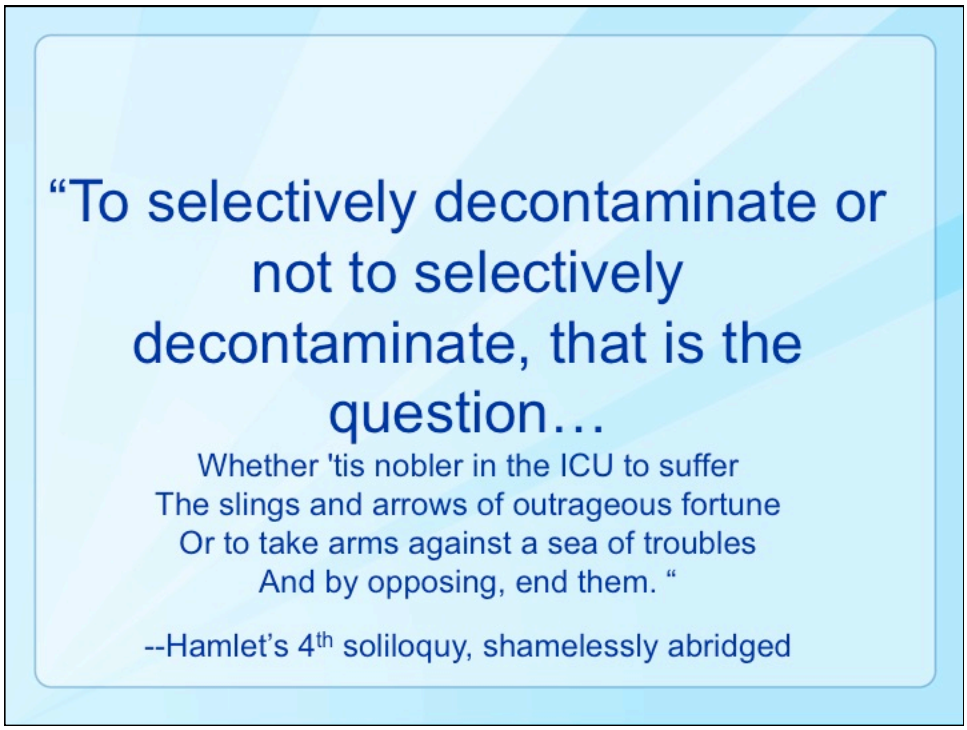
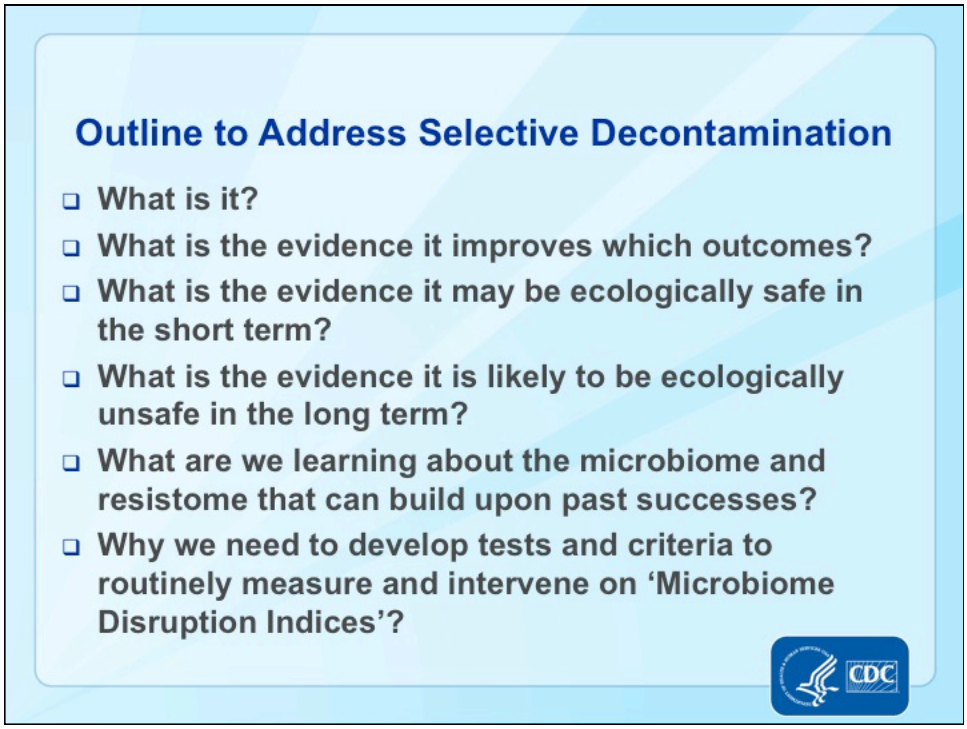

No Financial Disclosures
The findings and conclusions in this presentation are those of the author and do not necessarily represent the official position of the Centers for Disease Control and Prevention.
CDC


"To selectively decontaminate or not to selectively decontaminate, that is the question…
Whether 'tis nobler in the ICU to suffer
The slings and arrows of outrageous fortune
Or to take arms against a sea of troubles
And by opposing, end them. "
--Hamlet's 4th soliloquy, shamelessly abridged


Outline to Address Selective Decontamination
What is it?
What is the evidence it improves which outcomes?
What is the evidence it may be ecologically safe in the short term?
What is the evidence it is likely to be ecologically unsafe in the long term?
What are we learning about the microbiome and resistome that can build upon past successes?
Why we need to develop tests and criteria to routinely measure and intervene on 'Microbiome Disruption Indices'?
CDC

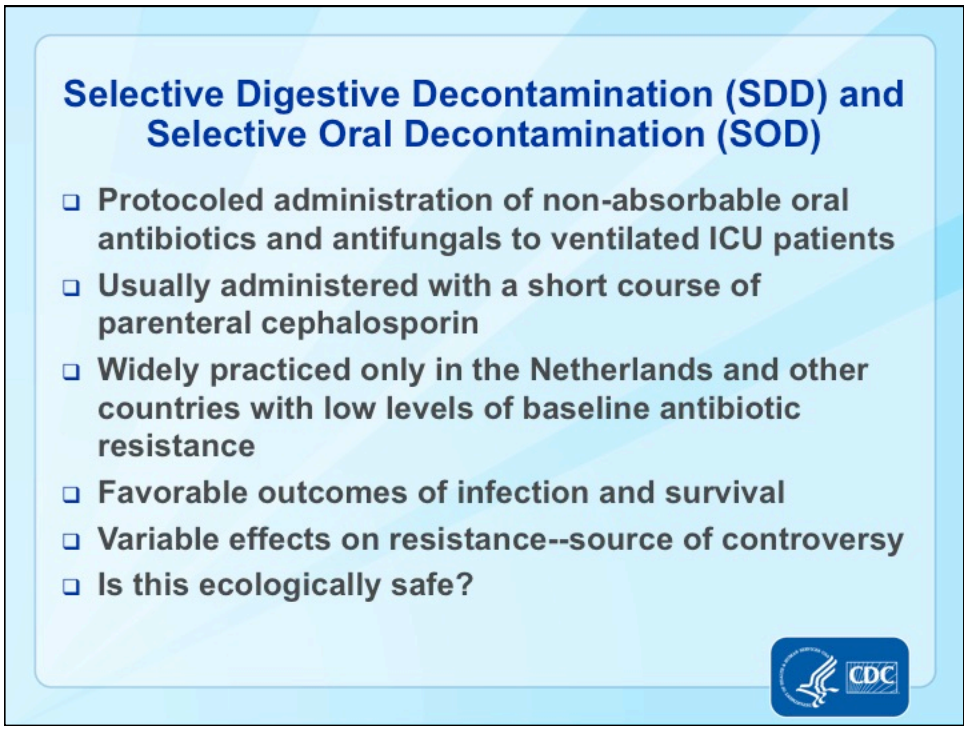

Selective Digestive Decontamination (SDD) and Selective Oral Decontamination (SOD)
Protocoled administration of non-absorbable oral antibiotics and antifungals to ventilated ICU patients
Usually administered with a short course of parenteral cephalosporin
Widely practiced only in the Netherlands and other countries with low levels of baseline antibiotic resistance
Favorable outcomes of infection and survival
Variable effects on resistance--source of controversy
Is this ecologically safe?
CDC

Table 1. Description of selective decontamination of the digestive tract and selective oropharyngeal decontamination regimens

Intervention	Timing	Purpose
SDD and SOD regimens		
0.5 g of a paste containing polymyxin E, tobramycin and amphotericin B each in a 2% concentration applied in oropharynx	Four times daily until ICU discharge	Selective decontaminaton of the oropharynx
10 ml of a suspension containing 100 mg polymyxin E, 80 mg tobramycin and 500 mg amphotericin B via the nasogastric tube	Four times daily until ICU discharge	Selective decontaminaton of the gut from stomach to rectum
Cefotaxime 1 g i.v. during the first 4 days of study (or other third-generation cephalosporins)	Four times daily during the first 4 days	Preemptive treatment of primary infections
Avoidance of (systemic) antibiotics that might impair the colonization resistance, that is, with antianaerobic activity	During treatment with SDD, until ICU discharge	Avoidance of penicillins, carbapenems and so on
		No addition of antibiotics for patients with colonization without clinical signs suggestive for infection
Oropharyngeal endotracheal, and rectal cultures	On admission and twice weekly	Determination of colonization pattern at admission and during treatment, including monitoring of effectiveness of SDD
		Detection of infection

de Smet AM. Curr Opin Infect Dis 2012, 25:211–217

SDD and SOD in Crossover Study Among 13 Dutch ICUs (N=5,939)

Table 2. Primary and Secondary End Points.*

End Point	Study Group			Unadjusted Odds Ratio or Hazard Ratio (95% CI)†			Adjusted Odds Ratio or Hazard Ratio (95% CI)†		
	Standard Care (N=1990)	SDD (N=2045)	SOD (N=1904)	Standard Care	SDD	SOD	Standard Care	SDD	SOD
Death — no. (%)									
During the first 28 days	544 (27.5)	546 (26.9)	502 (26.6)	1.00	0.94 (0.82–1.08)	0.95 (0.82–1.10)	1.00	0.83 (0.72–0.97)	0.86 (0.74–0.99)
In the ICU	443 (22.3)	440 (21.5)	416 (21.8)	1.00	0.91 (0.79–1.06)	0.97 (0.83–1.13)	1.00	0.81 (0.69–0.94)	0.87 (0.74–1.02)
In the hospital	632 (31.8)	665 (32.6)	584 (30.7)	1.00	0.99 (0.86–1.13)	0.94 (0.82–1.08)	1.00	0.88 (0.76–1.01)	0.85 (0.74–0.98)
Time to outcome for survivors at day 28 — days									
Cessation of mechanical ventilation				1.00	1.06 (0.96–1.18)	1.01 (0.89–1.15)	1.00	1.10 (0.99–1.22)	1.03 (0.90–1.17)
Median	8	7	8						
Interquartile range	3–17	4–15	4–15						
Discharge from ICU				1.00	1.02 (0.92–1.12)	1.00 (0.89–1.11)	1.00	1.09 (0.99–1.21)	1.06 (0.94–1.19)
Median	9	9	9						
Interquartile range	6–19	6–18	6–17						
Discharge from hospital				1.00	1.04 (0.91–1.19)	1.05 (0.91–1.22)	1.00	1.13 (1.01–1.25)	1.13 (0.96–1.32)
Median	29	28	28						
Interquartile range	16–48	16–45	16–47						

de Smet. N Engl J Med 2009;360:20-31.

SDD and SOD in Crossover Study Among 13 Dutch ICUs (N=5,939)

Table 3. Cumulative Incidence of ICU-Acquired Bacteremia and Candidemia.*

Type of Infection	Study Group			Crude Odds Ratio (95% CI)		
	Standard Care (N=1990)	SOD (N=1904)	SDD (N=2045)	SDD vs. Standard Care	SOD vs. Standard Care	SDD vs. SOD
		no. (%)				
Staphylococcus aureus	22 (1.1)	9 (0.5)	9 (0.4)	0.40 (0.18–0.86)	0.43 (0.20–0.93)	0.93 (0.37–2.40)
Streptococcus pneumoniae	3 (0.2)	1 (0.1)	1 (0.0)	0.32 (0.03–3.12)	0.35 (0.04–3.35)	0.93 (0.06–14.90)
GNF-GNR species†	36 (1.8)	17 (0.9)	16 (0.8)	0.43 (0.24–0.77)	0.49 (0.27–0.87)	0.88 (0.44–1.74)
Enterobacteriaceae	87 (4.4)	59 (3.1)	18 (0.9)	0.19 (0.12–0.32)	0.70 (0.50–0.98)	0.28 (0.16–0.47)
Enterococcus species	55 (2.8)	49 (2.6)	48 (2.3)	0.85 (0.57–1.25)	0.93 (0.63–1.37)	0.91 (0.61–1.36)
Candida species	16 (0.8)	14 (0.7)	8 (0.4)	0.49 (0.21–1.11)	0.91 (0.45–1.85)	0.53 (0.23–1.24)
Patients with at least one episode of bacteremia or candidemia — no. (%)	186 (9.3)	124 (6.5)	88 (4.3)	0.44 (0.34–0.57)	0.68 (0.53–0.86)	0.65 (0.49–0.85)

de Smet. N Engl J Med 2009;360:20-31.

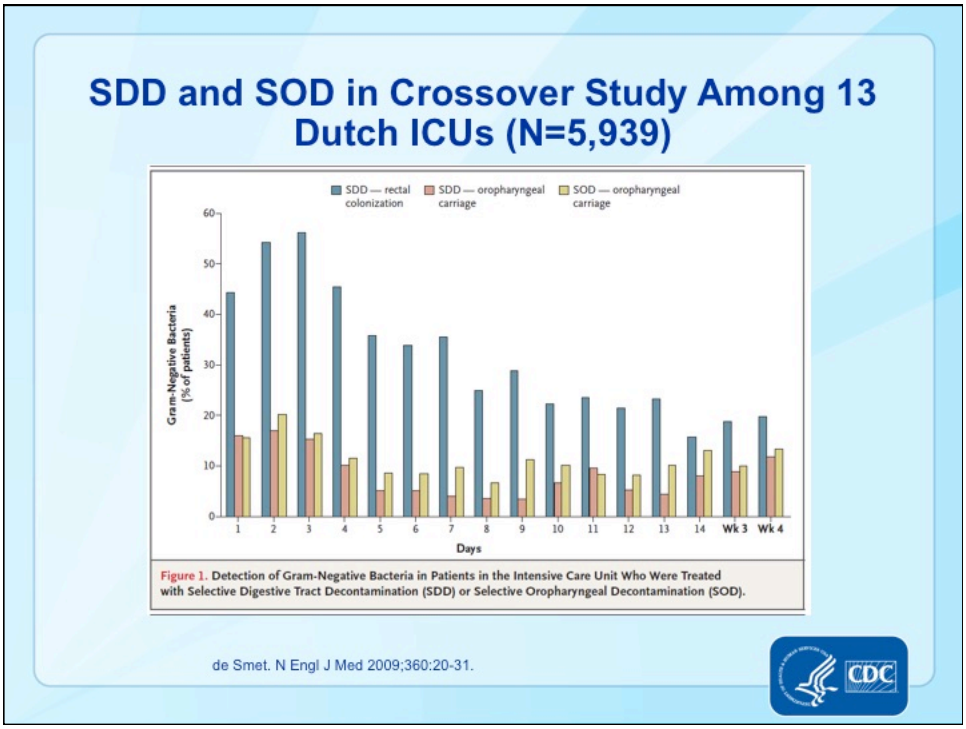


Figure 1. Detection of Gram-Negative Bacteria in Patients in the Intensive Care Unit Who Were Treated with Selective Digestive Tract Decontamination (SDD) or Selective Oropharyngeal Decontamination (SOD).

de Smet. N Engl J Med 2009;360:20-31.

SDD and SOD in Crossover Study Among 13 Dutch ICUs (N=5,939)

Table 4. Detection of Antibiotic-Resistant, Gram-Negative Bacteria in Rectal and Respiratory Tract Samples during Point-Prevalence Surveys.*

Organism	Resistant to Aminoglycosides†			Resistant to Ciprofloxacin			Resistant to Ceftazidime			Multiresistant A‡			Multiresistant B§		
	Standard Care	SOD	SDD	Standard Care	SOD	SDD	Standard Care	SOD	SDD	Standard Care	SOD	SDD	Standard Care	SOD	SDD
	percentage of patients														
Rectal samples															
Escherichia coli	4.5¶	4.9¶	1.8	4.9¶	4.5	2.9	3.3¶	2.3	1.3	2.2¶	2.3¶	0.5	1.4	1.0	0.5
Klebsiella pneumoniae	2.6¶	1.4	1.0	3.0¶‖	1.4	0.7	2.2¶	1.1	0.4	0.6	1.0	0.6	1.9¶‖	0.3	0.3
Enterobacter cloacae	1.7¶	1.8¶	0.6	1.3	1.6	0.5	4.7¶	4.2¶	1.7	1.0	1.1	0.5	0.6	1.0	0.2
Pseudomonas aeruginosa	1.2	1.0	0.7	1.6	1.6	0.7	2.6¶	1.8¶	0.7	1.3¶	0.8	0.4	0.4	0.3	0.4
Respiratory tract samples															
E. coli	1.3¶	0.5	0	1.0	0.2	0.4	1.0¶	0.5	0	0.4	0.1	0	0.4	0.2	0
K. pneumoniae	2.0¶‖	0.5	0.2	2.4¶‖	0.4	0.2	1.9¶‖	0.6	0.2	0.1	0.2	0.1	2.0	0.2	0.1
E. cloacae	1.5¶	0.5	0.4	1.1‖	0.2	0.4	3.8¶‖	0.6	1.2	0.6	0.2	0	0.6	0.1	0.3
P. aeruginosa	2.6¶	1.8	1.0	3.7¶‖	1.8	0.9	3.5¶‖	1.1	0.4	2.2	1.2	0.4	0.8	0.1	0.1

¶ P<0.05 for the comparison with SDD.
‖ P<0.05 for the comparison with SOD.

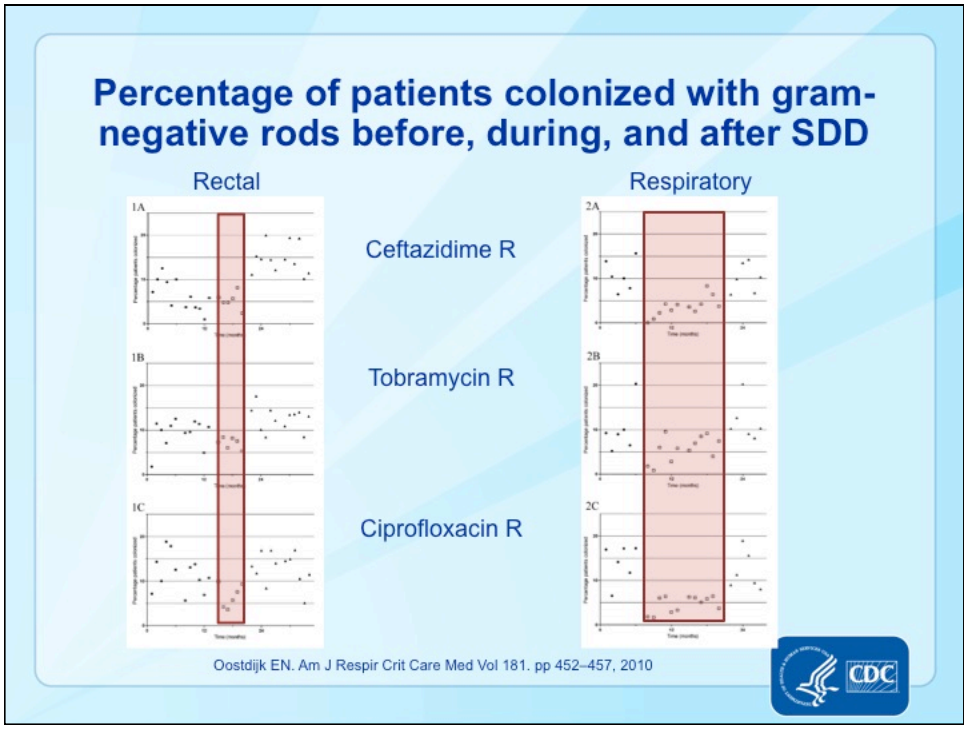
de Smet. N Engl J Med 2009;360:20-31.

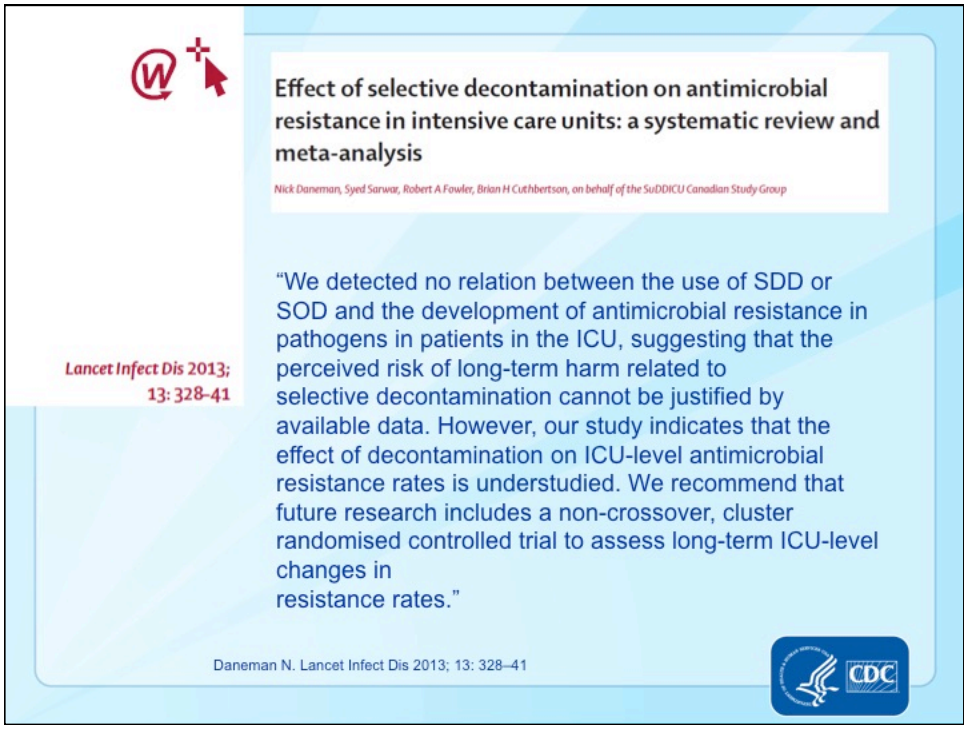
Persisting Survival Benefit of SDD and SOD at One Year (N=5,403)

TABLE 3. STRATIFIED ANALYSIS FOR AGE WITH ADJUSTED ODD RATIOS FOR 1-YEAR MORTALITY FOR PATIENTS IN QUARTILES 1 AND 2, IN QUARTILES 3 AND 4, AND FOR ALL PATIENTS

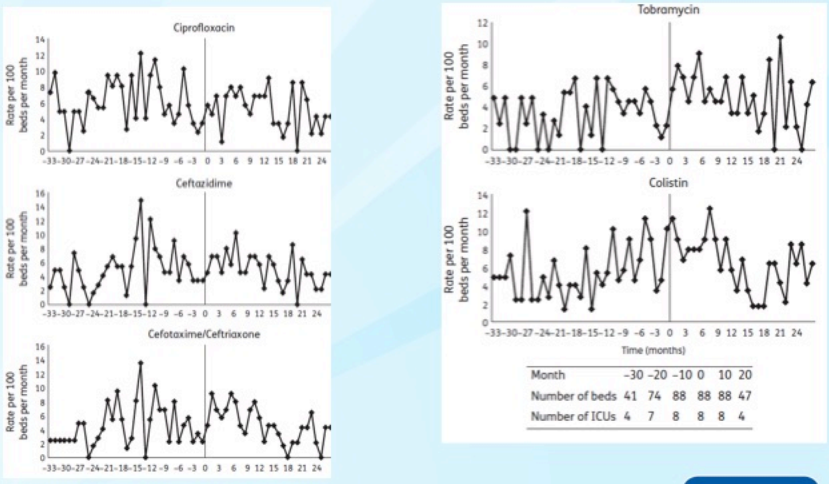
	SC	SOD	SDD
Median age (IQR) Q 1, 2	53 (17)	53 (18)	54 (17)
Median age (IQR) Q 3, 4	74 (8)	74 (8)	75 (8)
One-year survival vs. SC			
aOR (95% CI) age, lower quartiles (Q 1, 2)	Reference	0.81 (0.65–1.00)	1.00 (0.82–1.22)
aOR (95% CI) age, upper quartiles (Q 3, 4)	Reference	0.97 (0.79–1.18)	0.88 (0.72–1.07)
aOR (95% CI) total (Q 1–4)	Reference	0.89 (0.77–1.02)	0.93 (0.81–1.07)

Oostdijk EA. AM J RESP CRIT CARE MED VOL 188 2013


Percentage of patients colonized with gram-negative rods before, during, and after SDD
Rectal
Respiratory
Ceftazidime R
Tobramycin R
Ciprofloxacin R
Oostdijk EN. Am J Respir Crit Care Med Vol 181. pp 452–457, 2010
CDC

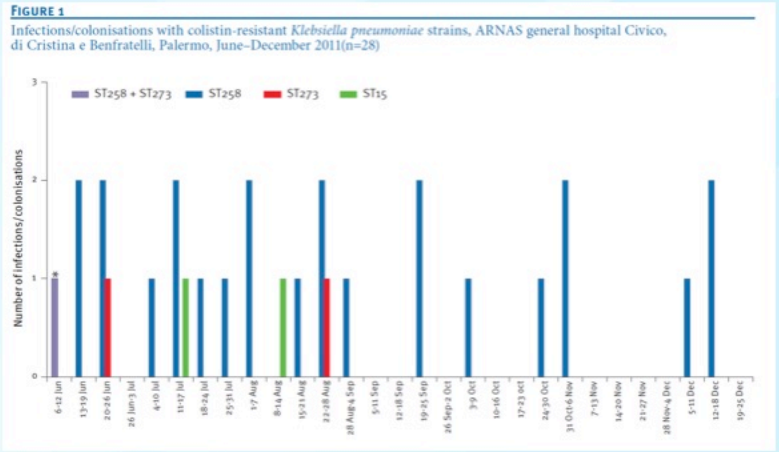

Effect of selective decontamination on antimicrobial resistance in intensive care units: a systematic review and meta-analysis
Nick Daneman, Syed Sarwar, Robert A Fowler, Brian H Cuthbertson, on behalf of the SuDDICU Canadian Study Group
Lancet Infect Dis 2013; 13: 328-41
"We detected no relation between the use of SDD or SOD and the development of antimicrobial resistance in pathogens in patients in the ICU, suggesting that the perceived risk of long-term harm related to selective decontamination cannot be justified by available data. However, our study indicates that the effect of decontamination on ICU-level antimicrobial resistance rates is understudied. We recommend that future research includes a non-crossover, cluster randomised controlled trial to assess long-term ICU-level changes in resistance rates."
Daneman N. Lancet Infect Dis 2013; 13: 328–41
CDC

A 4 Year Ecological Study in 38 Intensive Care Units in the Netherlands

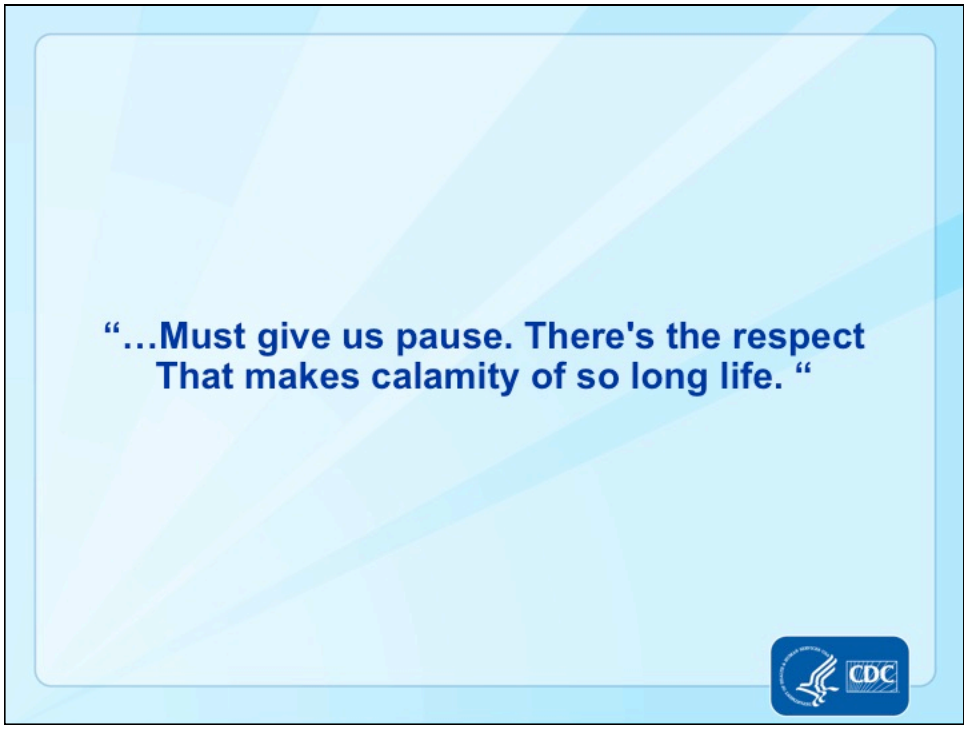


Houben AJM. J Antimicrob Chemother 2014; 69: 797–804

Crumbling Last Lines of Defense: Colistin-resistant *K. pneumoniae* in an Italian Hospital



Mammina C. Euro Surveill. 2012;17(33)



An Extended Outbreak of Colistin and Tobramycin Resistant Enterobacteriaceae Driven by SDD

TABLE 1 Susceptibilities of ESBL-producing *K. pneumoniae* isolates to colistin as determined by disc diffusion, Vitek, and Etest

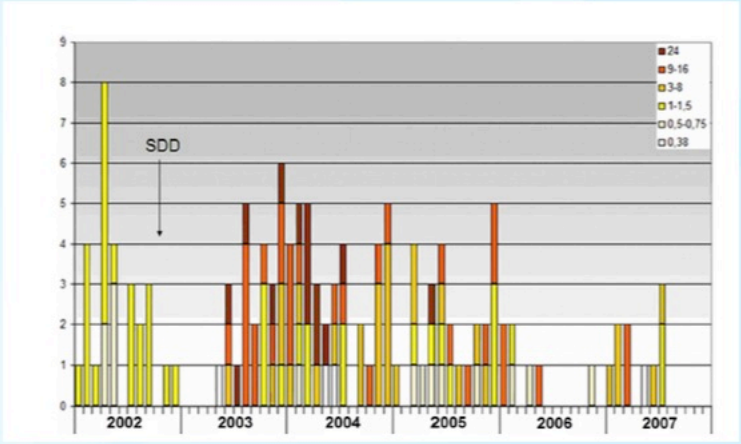
Isolate group[a]	No. of isolates[b]								
	Disc diffusion (n = 89)			Vitek (n = 134)			Etest (n = 134)		
	S	I	R	S	I	R	S	I	R
Before SDD	12	0	0	28	0	0	28	0	0
After SDD	45	28	4	31	0	75	32	0	74

[a] Isolates are grouped according to whether they were identified before or after the introduction of SDD on the ICU in October 2002.
[b] S, susceptible; I, intermediate; R, resistant.

Halaby T. Antimicrobial Agents and Chemotherapy 2013; 57 (7); 3224-9

CDC

An Extended Outbreak of Colistin and Tobramycin Resistant Enterobacteriaceae Driven by SDD



Halaby T. Antimicrobial Agents and Chemotherapy 2013; 57 (7); 3224-9

Introduction of SDD and Tobramycin Resistance Among Colistin-Resistant Enterobacteriaceae

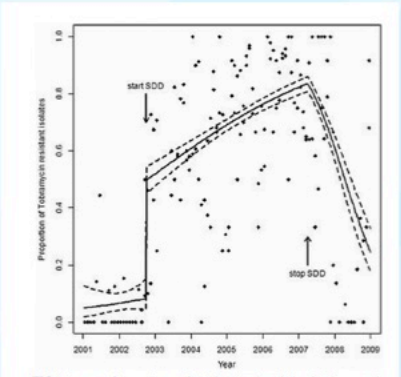
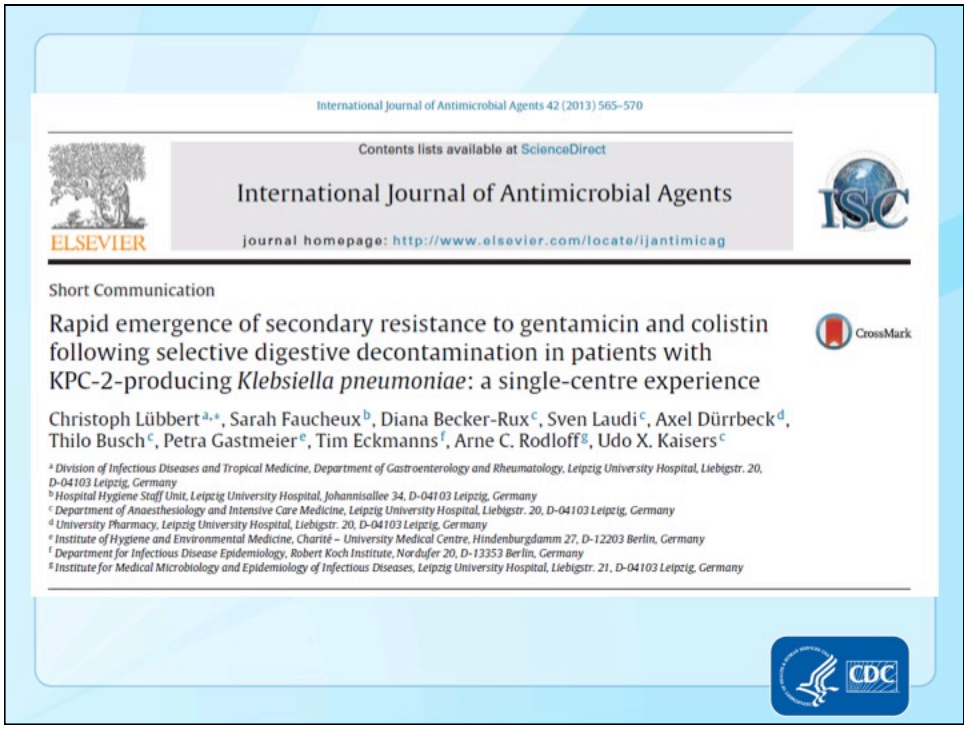


FIG 4 Segmented regression analysis showing the relationship between the introduction of SDD and tobramycin resistance among CIR isolates (black dots). The logistic regression model fit (solid lines) is shown, together with its 95% confidence interval (dashed lines).

Halaby T. Antimicrobial Agents and Chemotherapy 2013; 57 (7); 3224-9



International Journal of Antimicrobial Agents 42 (2013) 565–570

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

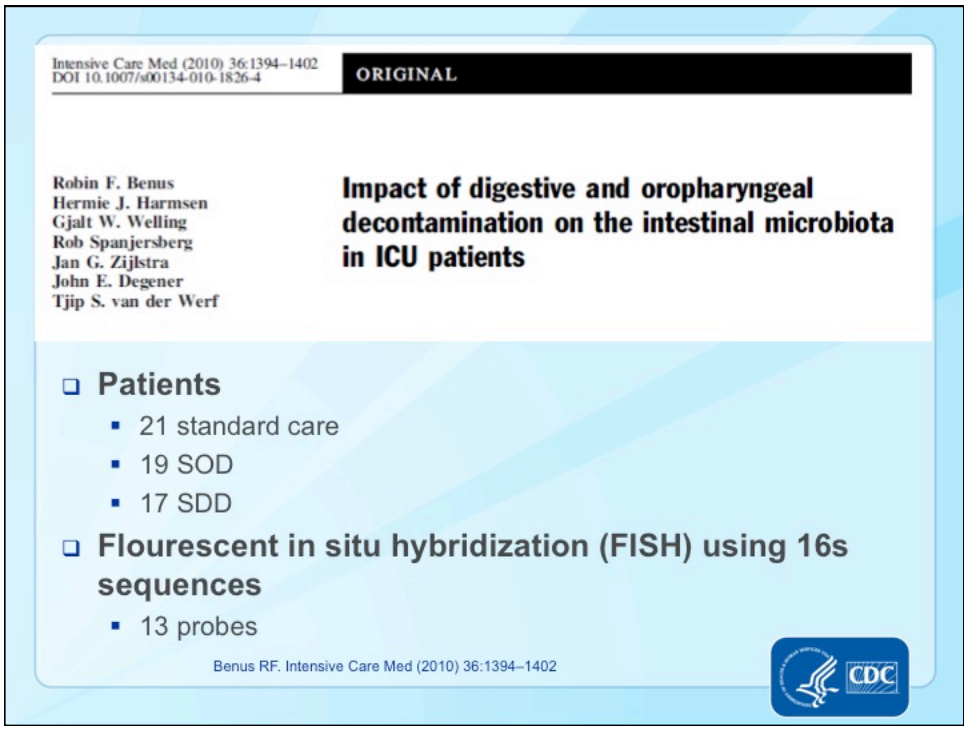
journal homepage: http://www.elsevier.com/locate/ijantimicag

Short Communication

Rapid emergence of secondary resistance to gentamicin and colistin following selective digestive decontamination in patients with KPC-2-producing *Klebsiella pneumoniae*: a single-centre experience

Christoph Lübbert[a,*], Sarah Faucheux[b], Diana Becker-Rux[c], Sven Laudi[c], Axel Dürrbeck[d], Thilo Busch[c], Petra Gastmeier[e], Tim Eckmanns[f], Arne C. Rodloff[g], Udo X. Kaisers[c]

[a] Division of Infectious Diseases and Tropical Medicine, Department of Gastroenterology and Rheumatology, Leipzig University Hospital, Liebigstr. 20, D-04103 Leipzig, Germany
[b] Hospital Hygiene Staff Unit, Leipzig University Hospital, Johannisallee 34, D-04103 Leipzig, Germany
[c] Department of Anaesthesiology and Intensive Care Medicine, Leipzig University Hospital, Liebigstr. 20, D-04103 Leipzig, Germany
[d] University Pharmacy, Leipzig University Hospital, Liebigstr. 20, D-04103 Leipzig, Germany
[e] Institute of Hygiene and Environmental Medicine, Charité – University Medical Centre, Hindenburgdamm 27, D-12203 Berlin, Germany
[f] Department for Infectious Disease Epidemiology, Robert Koch Institute, Nordufer 20, D-13353 Berlin, Germany
[g] Institute for Medical Microbiology and Epidemiology of Infectious Diseases, Leipzig University Hospital, Liebigstr. 21, D-04103 Leipzig, Germany



Intensive Care Med (2010) 36:1394–1402
DOI 10.1007/s00134-010-1826-4

ORIGINAL

Robin F. Benus
Hermie J. Harmsen
Gjalt W. Welling
Rob Spanjersberg
Jan G. Zijlstra
John E. Degener
Tjip S. van der Werf

Impact of digestive and oropharyngeal decontamination on the intestinal microbiota in ICU patients

- **Patients**
  - 21 standard care
  - 19 SOD
  - 17 SDD
- **Flourescent in situ hybridization (FISH) using 16s sequences**
  - 13 probes

Benus RF. Intensive Care Med (2010) 36:1394–1402

Table 3 Numbers and statistical analysis of the main intestinal microbiota groups

Variable	Regimen:					
	SC (21[a])		SOD (19[a])		SDD (17[a])	
	Mean	95% CI	Mean	95% CI	Mean	95% CI
Probe						
Total bacteria	3.7×10^9	2.2×10^9–6.2×10^9	1.6×10^9	7.8×10^8–3.4×10^9	1.9×10^9	8.7×10^8–4.3×10^9
Bacteroides	6.5×10^8	3.5×10^8–1.2×10^9	3.6×10^8	1.4×10^8–9.5×10^8	4.2×10^8	2.1×10^8–8.1×10^8
E. rectale[b]	5.1×10^8	3.0×10^8–8.5×10^8	1.4×10^8	5.4×10^7–3.4×10^8	6.2×10^7	2.6×10^7–1.4×10^8
R. intestinalis[b]	6.8×10^7	3.7×10^7–1.3×10^8	1.8×10^7	7.0×10^6–4.8×10^7	1.1×10^7	4.9×10^6–2.7×10^7
F. prausnitzii[c]	5.5×10^7	2.3×10^7–1.3×10^8	4.0×10^7	1.6×10^7–9.9×10^7	2.9×10^6	1.4×10^6–6.0×10^6
Atopobium	1.3×10^8	6.6×10^7–2.3×10^8	3.5×10^7	1.3×10^7–9.2×10^7	4.2×10^7	1.4×10^7–1.2×10^8
Bifidobacteria	4.4×10^7	1.6×10^7–1.2×10^8	1.6×10^7	5.4×10^6–4.6×10^7	5.8×10^7	1.8×10^7–1.8×10^8
Ruminococci	2.0×10^8	1.3×10^8–3.3×10^8	8.6×10^7	3.8×10^7–2.0×10^8	7.8×10^7	3.1×10^7–1.7×10^8
Enterobacteriaceae[c]	7.2×10^7	3.6×10^7–1.4×10^8	4.8×10^7	1.7×10^7–1.4×10^8	4.1×10^6	2.0×10^6–8.3×10^6

ANOVA test was used for statistical analysis
[a] Number of study subjects
[b] Indicates a significant difference between the SDD and SC regimens only
[c] Indicates a significant difference between SDD and both SC and SOD regimens

Table 4 Numbers and statistical analysis of enterococci per gram faeces

	SC ($n = 21$)	SOD ($n = 19$)	SDD ($n = 17$)	SC vs. SOD[a]	SC vs. SDD[a]	SOD vs. SDD[a]
E. faecalis	2.6×10^6	7.6×10^6	6.9×10^7	0.002	0.000	0.000
E. faecium	6.3×10^6	9.8×10^6	5.4×10^7	0.142	0.000	0.000

[a] Mann–Whitney U-tests, p values

Benus RF. Intensive Care Med (2010) 36:1394–1402

Impact of SOD and SDD on the Intestinal Microbiota in ICU Patients

- Total number of bacteria unchanged
- Reduction in Enterobacteriaceae
- Reduction in *Faecalibacterium prausnitzii* –group bacteria (Clostridiaceae)
  - Also *Roseburia intestinalis (Lachnospiraceae/Clostridiales)*
  - Butyrate producers important for bowel health
- Increase in ***Enterococcus*** **spp.**

Benus RF. Intensive Care Med (2010) 36:1394–1402

Debate – Selective Decontamination of the Gut
Prof. Jan Kluytmans and Dr. Cliff McDonald
Broadcast live from the 2015 Infection Prevention Society conference

J Antimicrob Chemother 2014; **69**: 2215–2223
doi:10.1093/jac/dku092 Advance Access publication 7 April 2014

Journal of Antimicrobial Chemotherapy

Effects of selective digestive decontamination (SDD) on the gut resistome

Elena Buelow[1], Teresita Bello Gonzalez[2], Dennis Versluis[2], Evelien A. N. Oostdijk[1], Lesley A. Ogilvie[3,4], Maaike S. M. van Mourik[1], Els Oosterink[1], Mark W. J. van Passel[5], Hauke Smidt[2], Marco Maria D'Andrea[6], Mark de Been[1], Brian V. Jones[3,7], Rob J. L. Willems[1], Marc J. M. Bonten[1] and Willem van Schaik[1]*

- Metagenomic and resistome dynamics in one patient
  - Neurotrauma, 30d ICU stay, 47d hospital stay
  - SOD, SDD, cefotaxime IV x 4 days
- 16S HITChip and shotgun sequencing/assembly
- Fosmid libraries
- Quantitative PCR (qPCR) for *aph(2'')-Ib* and the *aadE*-like gene in 12 ICU patients

Buelow E. J Antimicrob Chemother 2014; 69: 2215–2223

Effects of SDD on the Gut Resistome

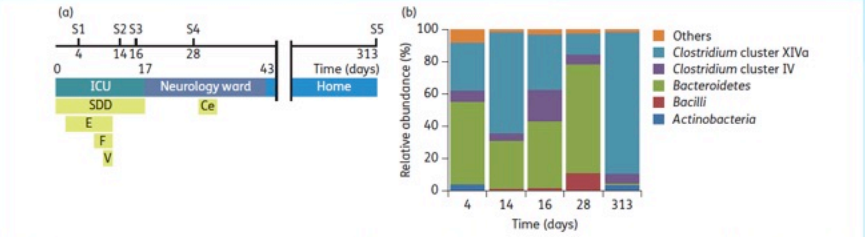


Figure 1. Patient history and gut microbiota composition. (a) The timeline indicates the major events throughout the patient's hospital stay and the times at which faeces were collected. Light green boxes indicate the antibiotics (E, erythromycin; F, flucloxacillin; V, vancomycin; Ce, cefazolin) that were administered to the patient. Further details are provided in the Methods section. Diagnostic culturing was performed for rectum, sputum, throat, urine

Buelow E. J Antimicrob Chemother 2014; 69: 2215–2223

Debate – Selective Decontamination of the Gut
Prof. Jan Kluytmans and Dr. Cliff McDonald
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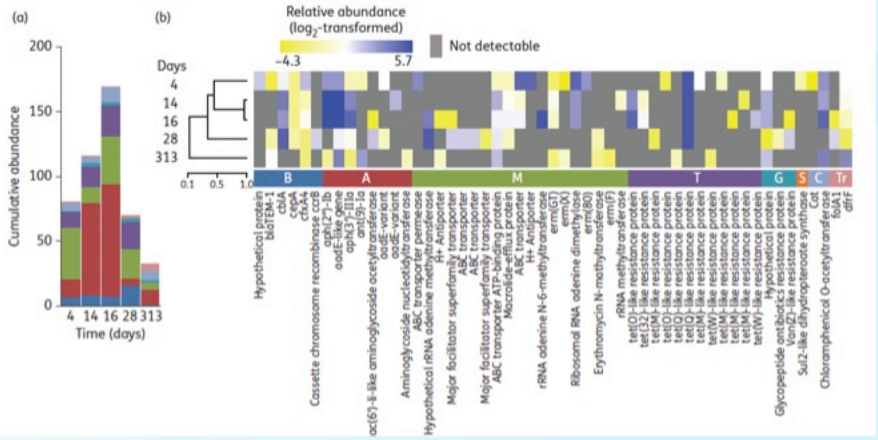
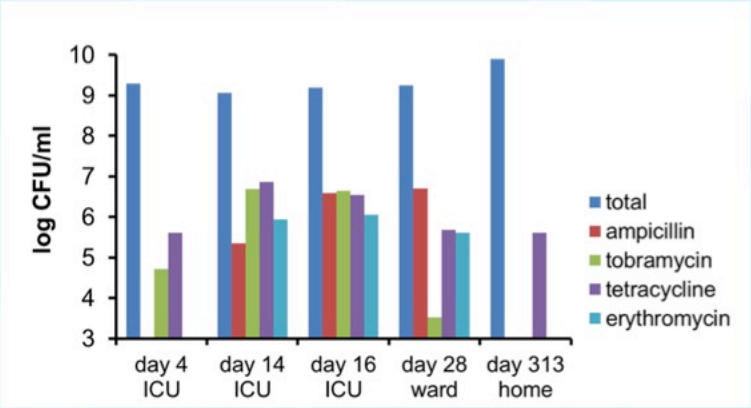
Effects of SDD on the Gut Resistome



Buelow E. J Antimicrob Chemother 2014; 69: 2215–2223

Quantification of Antibiotic-resistant Fosmid Clones

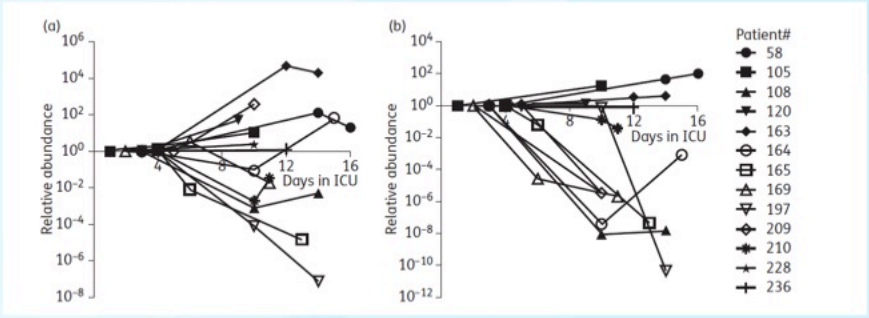


"…cloned resistance genes were harboured by anaerobes from the phyla Firmicutes (Subdoligranulum, Clostridia), Bacteroidetes (Bacteroides uniformis) and Actinobacteria"

Buelow E. J Antimicrob Chemother 2014; 69: 2215–2223

A Webber Training Teleclass
www.webbertraining.com

Relative Abundance of the Aminoglycoside Resistance Genes aph(2″)-Ib and aadE-like in ICU Patients Receiving SDD



Buelow E. J Antimicrob Chemother 2014; 69: 2215–2223

Profound Ecological Impact of SOD and SDD

- While on SOD and SDD the resistome is, in at least some patients, expanding, not contracting
- This resistome is expanding in obligate anaerobes that form the core of the human microbiome
- The resistance genes that variably expand (like aph(2″)-Ib and aadE-like genes) may have heretofore unrecognized selective advantage for anaerobes
- The variable expansion of the resistome during SOD/SDD may be what drives the 'blooming' of resistance in aerobes after withdrawal of SOD/SDD

Buelow E. J Antimicrob Chemother 2014; 69: 2215–2223

Debate – Selective Decontamination of the Gut
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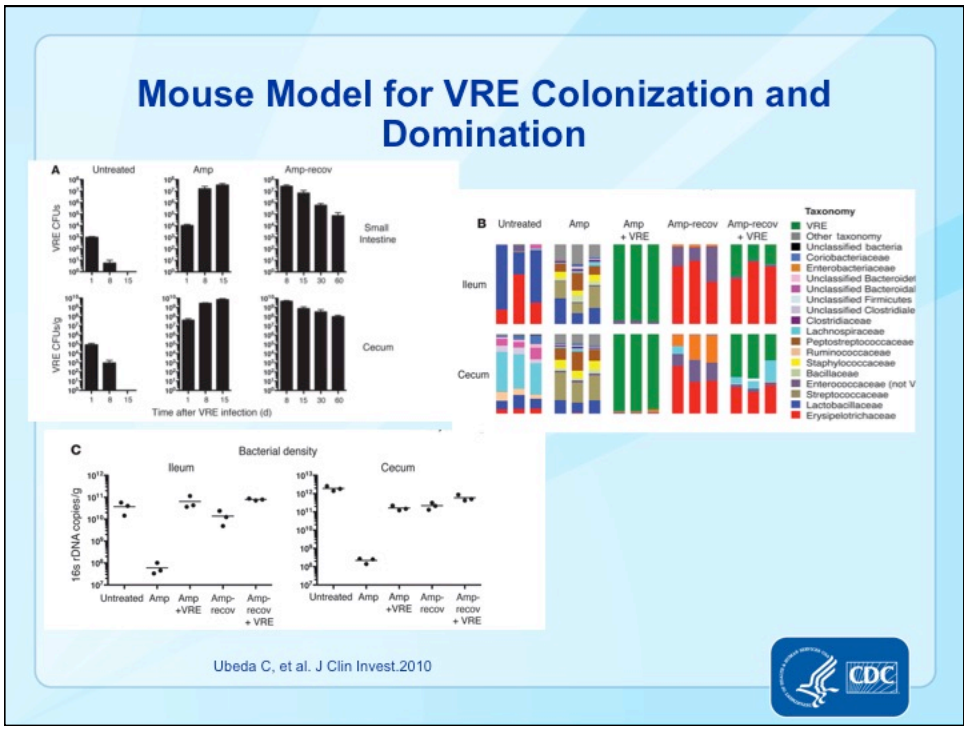

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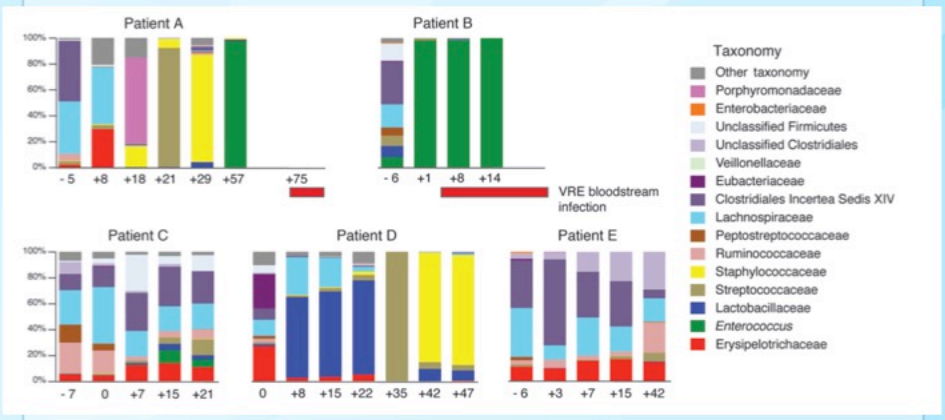
VRE Intestinal Domination Precedes Bacteremia in Human Cancer Patients



Ubeda C, et al. J Clin Invest.2010

Intestinal Domination and the Risk of Bacteremia in Patients Undergoing Allogeneic Hematopoietic Stem Cell Transplantation

Ying Taur,[1,2] Joao B. Xavier,[2,3] Lauren Lipuma,[2] Carles Ubeda,[5] Jenna Goldberg,[4] Asia Gobourne,[2] Yeon Joo Lee,[1] Krista A. Dubin,[2] Nicholas D. Socci,[3] Agnes Viale,[6] Miguel-Angel Perales,[4] Robert R. Jenq,[4] Marcel R. M. van den Brink,[4,5] and Eric G. Pamer[1,2,5]

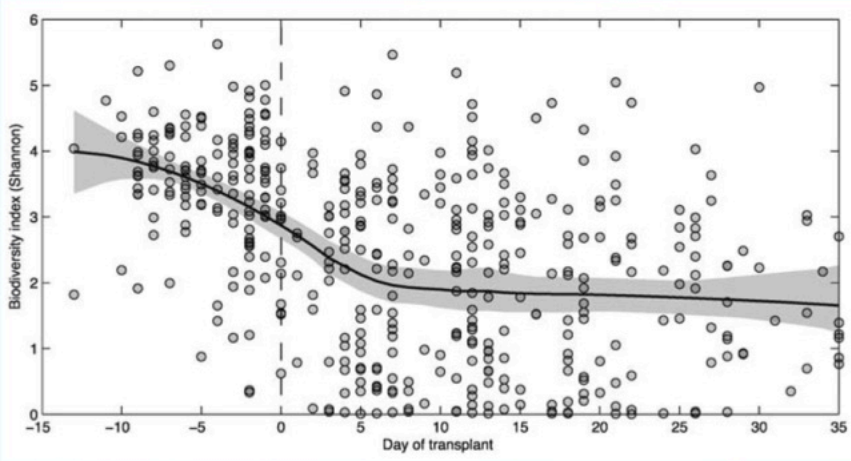
[1]Infectious Disease Service, Department of Medicine, [2]Lucille Castori Center for Microbes, Inflammation and Cancer, [3]Computational Biology Center, and [4]Bone Marrow Transplant Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, and [5]Immunology Program, and [6]Genomics Core Laboratory, Sloan-Kettering Institute, New York, New York

- **N=94**
- **Intestinal domination:**
  - >30% of composition by single genus

Parameter	No. (%) of Patients
Bloodstream infection[b,e]	
Vancomycin-resistant *Enterococcus*	9 (9.6)
Gram-negative bacilli, aerobic	10 (10.6)
Other organism	3 (3.2)
None	72 (76.6)
Vital status[b]	
Alive	92 (97.9)
Dead	2 (2.1)
Total	94 (100)

Taur Y et al. Clin Infect Dis 2012

Decrease in Biodiversity among Hematopoeitic Stem Cell Transplant Patients



Taur Y et al. Clin Infect Dis 2012

Clinical Predictors of Intestinal Domination

	Enterococcus Domination		*Streptococcus* Domination		Proteobacteria Domination	
Predictor	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age, years	1.00 (.98–1.04)	.790	0.99 (.97–1.03)	.681	1.00 (.95–1.05)	.978
Female sex	0.84 (.42–1.64)	.611	1.07 (.50–2.27)	.852	1.12 (.33–3.78)	.854
Underlying diagnosis (leukemia vs other)	3.22 (1.60–6.94)	.001	0.71 (.32–1.51)	.375	0.66 (.18–2.19)	.498
Prior antibiotics (14 days)[a]	1.49 (.77–2.94)	.237	1.03 (.48–2.17)	.945	1.31 (.39–4.44)	.651
Conditioning regimen (myeloablative or reduced intensity vs non-myeloablative)	1.01 (.44–2.84)	.977	0.61 (.25–1.75)	.329	0.98 (.22–9.25)	.983
T-cell depleted graft	0.81 (.40–1.61)	.551	0.91 (.39–2.00)	.812	1.07 (.29–3.62)	.910
Stem cell source (cord vs other)	1.22 (.55–2.52)	.607	0.54 (.19–1.34)	.196	1.36 (.36–4.69)	.633
Fever[b]	1.68 (.78–3.74)	.182	0.90 (.36–2.39)	.826	1.28 (.30–6.34)	.747
Antibiotics[b]						
Vancomycin	2.12 (.67–10.21)	.222	0.95 (.33–3.77)	.938	5.17 (.52–707.15)	.192
Metronidazole	3.38 (1.65–6.73)	.001	1.94 (.81–4.30)	.131	1.73 (.41–6.03)	.426
Fluoroquinolones[c]	1.09 (.49–2.24)	.832	1.19 (.51–2.60)	.677	0.09 (.00–.75)	.020
Beta-lactam[d]	1.64 (.74–3.99)	.232	1.69 (.62–5.64)	.319	1.23 (.27–7.50)	.800

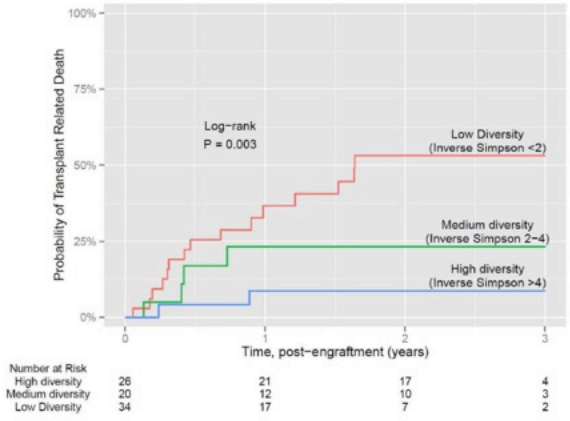
Taur Y et al. Clin Infect Dis 2012

Association of Preceding Intestinal Domination with Bacteremia

	VRE Bacteremia		Gram-negative Bacteremia	
Dominating Taxon[b]	HR (95% CI)	*P*	HR (95% CI)	*P*
Enterococcus	9.35 (2.43–45.44)	.001	1.35 (.25–5.08)	.690
Streptococcus	0.21 (.00–1.75)	.184	0.82 (.09–3.65)	.823
Proteobacteria	0.75 (.01–6.14)	.837	5.46 (1.03–19.91)	.047

Taur Y et al. Clin Infect Dis 2012

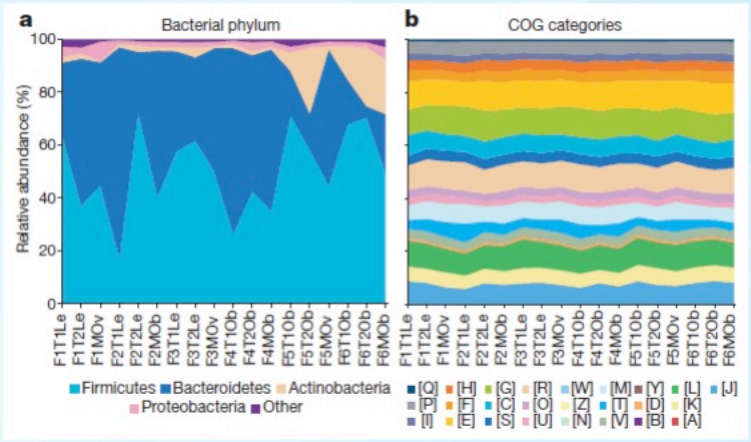
Transplant-related mortality is reduced in patients with a diverse microbiota following engraftment



Taur et al. (2014) Blood 124:1174-82.

Slide courtesy of Dr. Eric Pamer

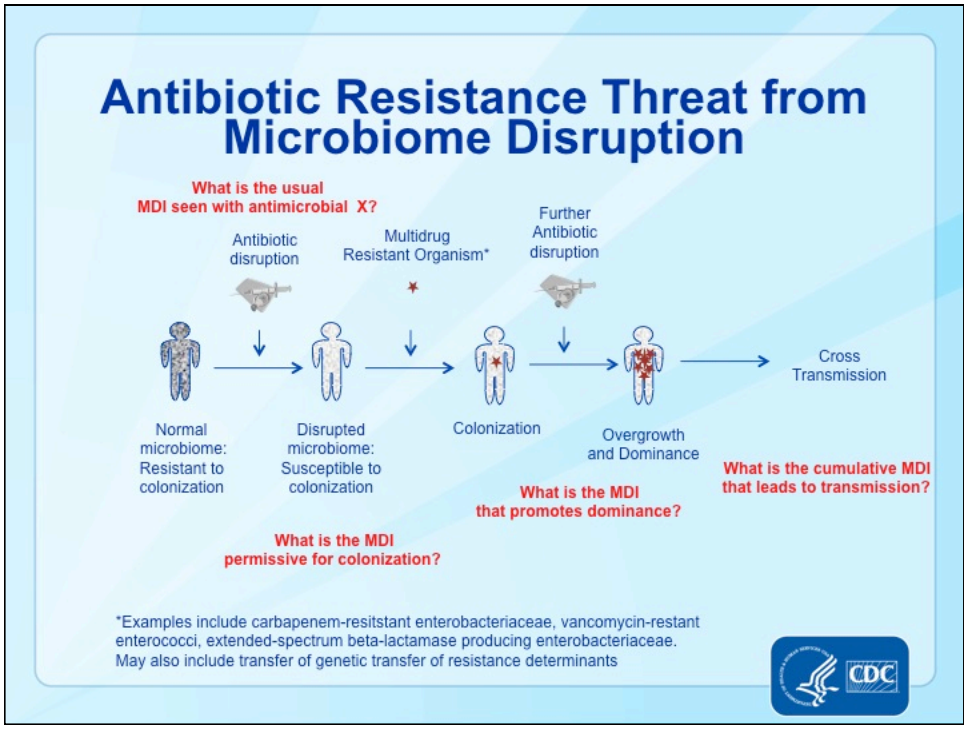
Comparison of Taxonomic and Functional Variations in the Human Gut Microbiome

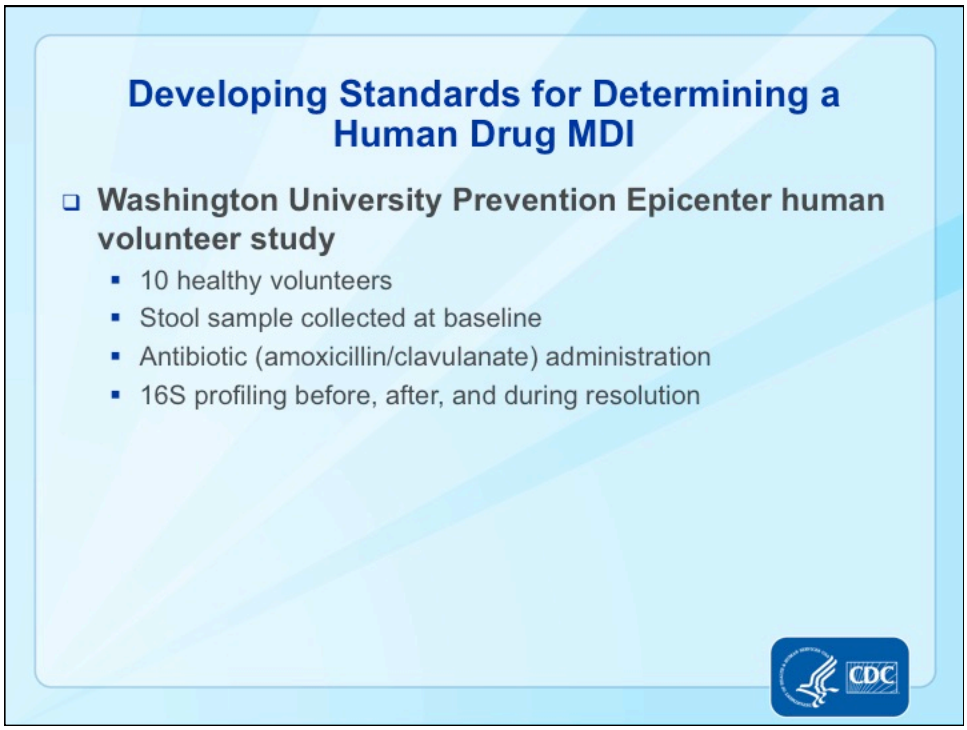


Turnbaugh PJ et al. Nature Vol 457|22 January 2009 Supplementary Info

CDC Developing Microbiome Disruption Indices (MDI)

- **Uses**
  - Monitor patients before, during, and after antibiotic therapy
    - Alert when disruption reaches critical level or if colonization or dominance is detected
    - Stage patient need for microbiome restoration
  - Characterize risk of specific antibiotics
    - Rating system to gauge relative risks of different agents
    - MDIs determined during approval process and included in package insert


Antibiotic Resistance Threat from Microbiome Disruption
What is the usual MDI seen with antimicrobial X?
Antibiotic disruption
Multidrug Resistant Organism*
Further Antibiotic disruption
Cross Transmission
Normal microbiome: Resistant to colonization
Disrupted microbiome: Susceptible to colonization
Colonization
Overgrowth and Dominance
What is the MDI permissive for colonization?
What is the MDI that promotes dominance?
What is the cumulative MDI that leads to transmission?
*Examples include carbapenem-resitstant enterobacteriaceae, vancomycin-restant enterococci, extended-spectrum beta-lactamase producing enterobacteriaceae. May also include transfer of genetic transfer of resistance determinants
CDC

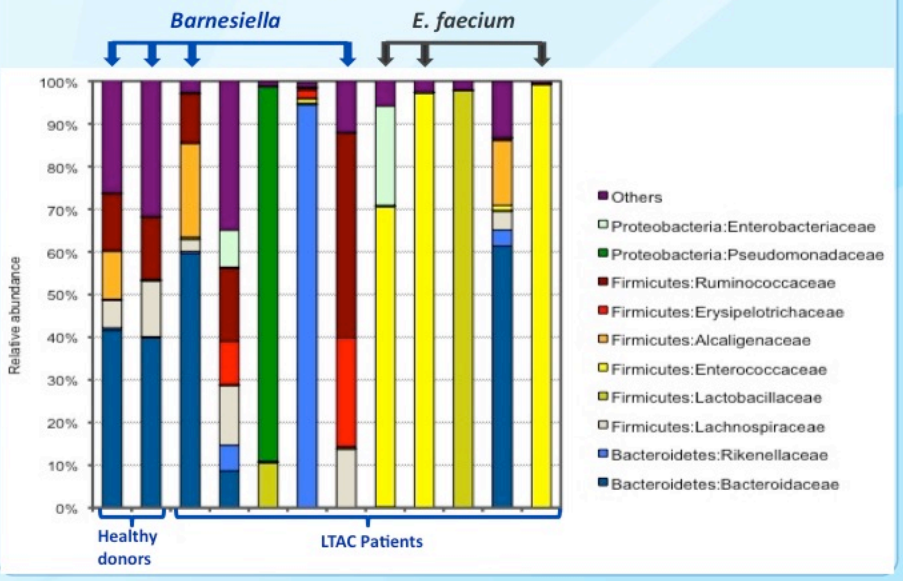

Developing Standards for Determining a Human Drug MDI
Washington University Prevention Epicenter human volunteer study
10 healthy volunteers
Stool sample collected at baseline
Antibiotic (amoxicillin/clavulanate) administration
16S profiling before, after, and during resolution
CDC

Understanding Candidate MDIs in Patients with Major Antibiotic Exposure Histories

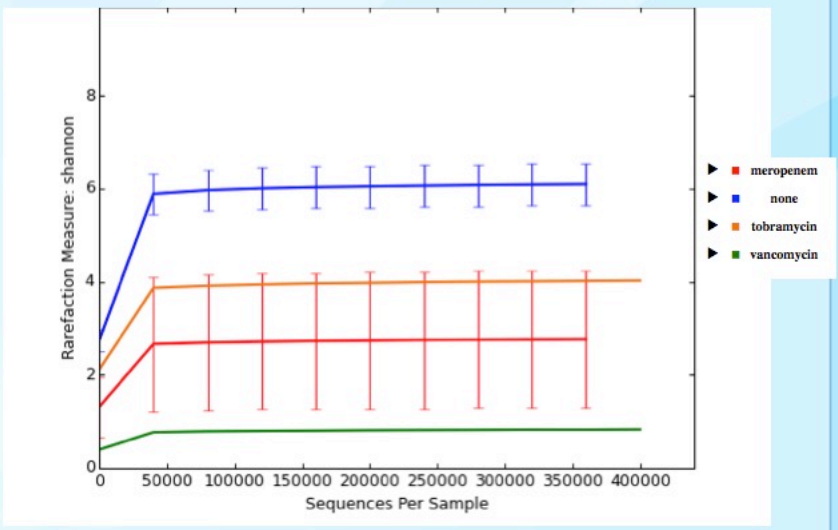
- **Cross-sectional pilot with Emory in long-term acute care hospital (LTACH) inpatients**
  - Admission 'screening' for *C. difficile* infection, waste specimens
  - 16S ribosomal RNA encoding DNA amplification and sequencing
  - Association with antibiotic exposure histories and MDRO colonization
- **Chicago Prevention Epicenter microbiome studies prior to and following CRE colonization**
  - Begin to fill key need for natural history studies

CDC

Microbial Community Composition in Emory LTAC Patients

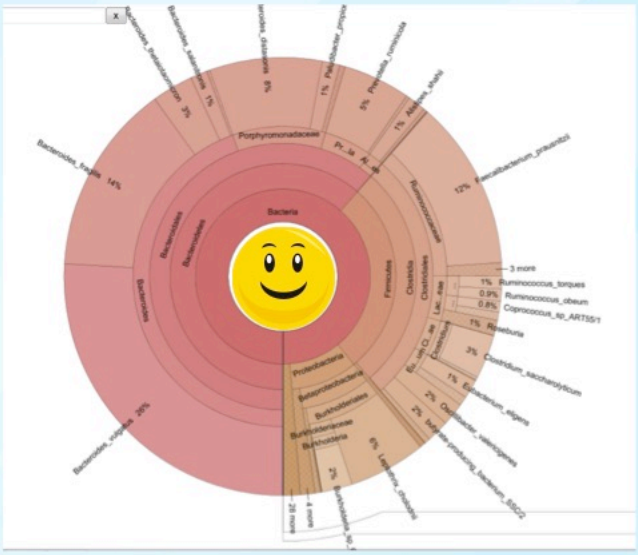


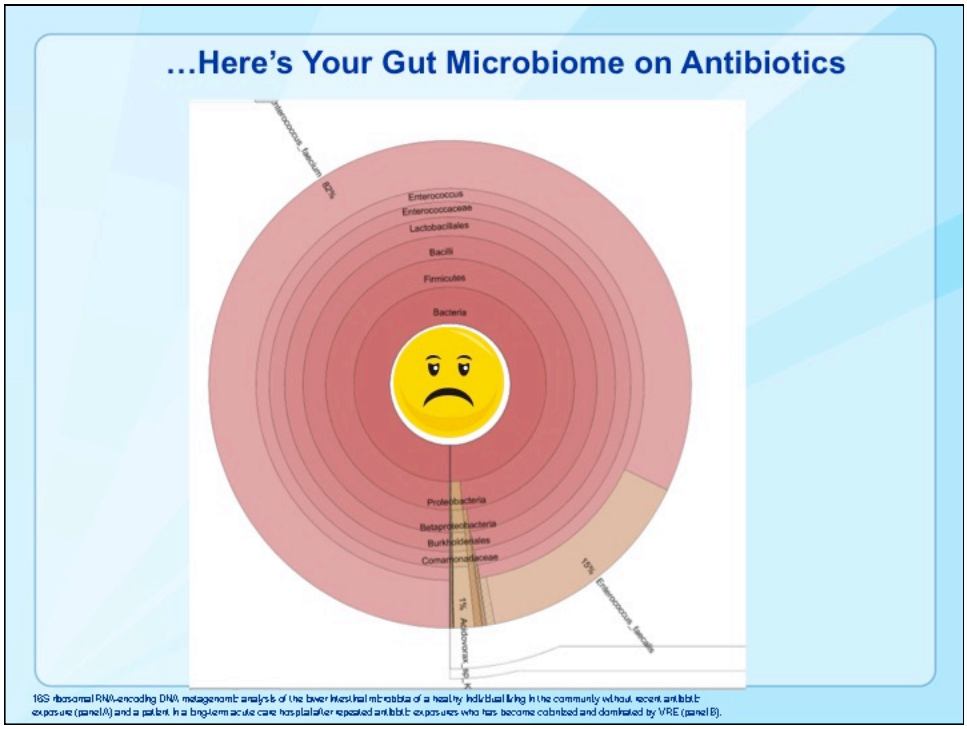
Another MDI Metric: Loss of Diversity as Measured by the Shannon Diversity Index

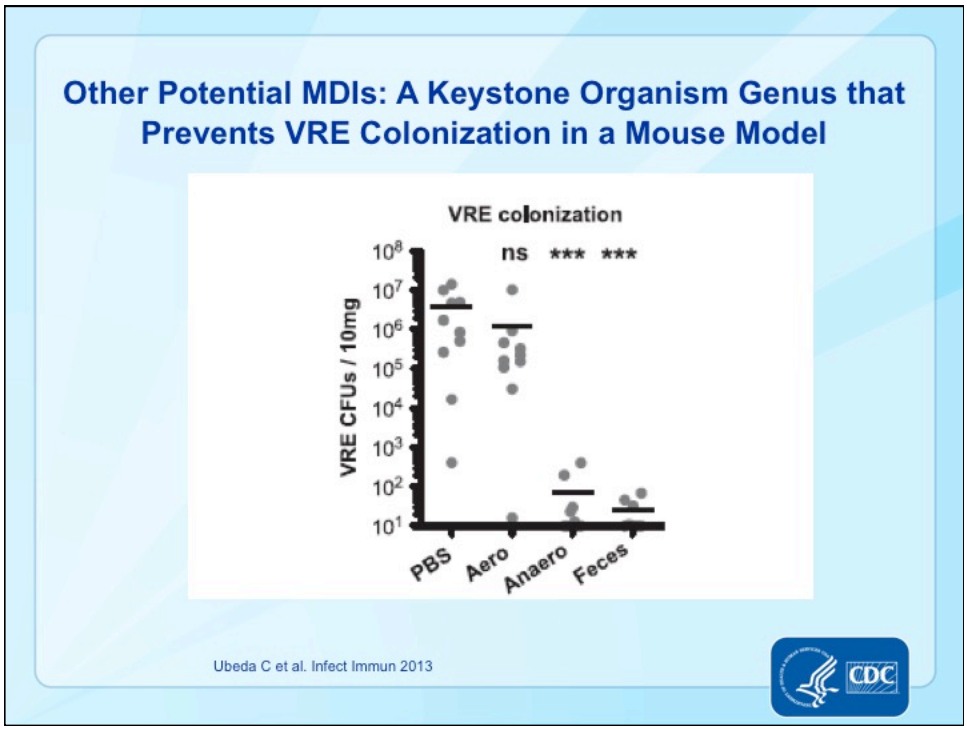


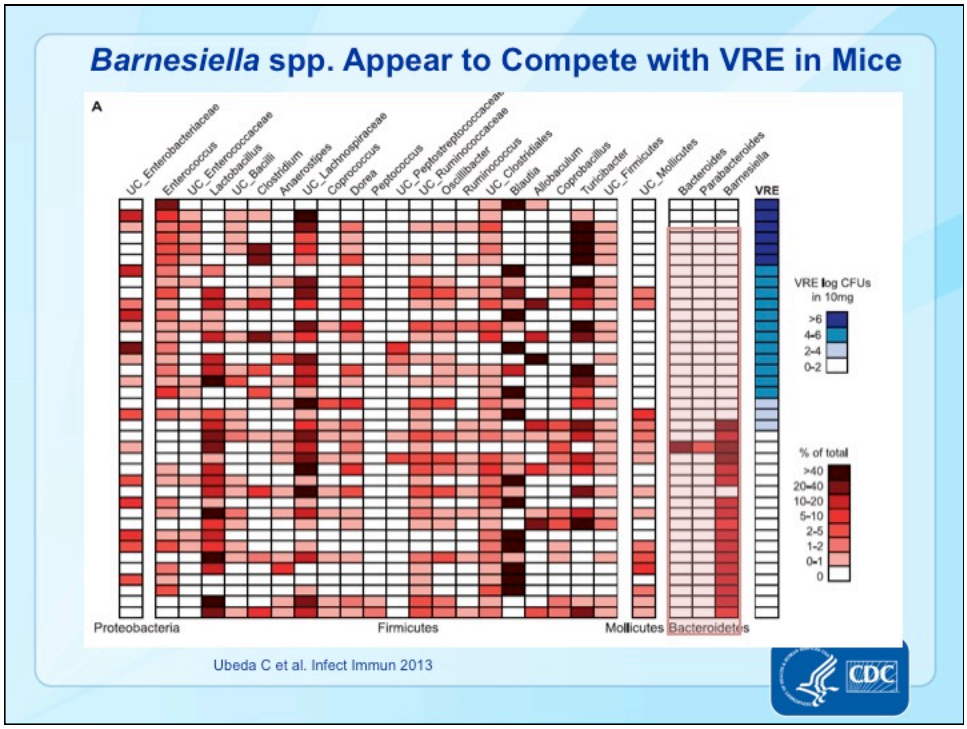
De Man T, et al. Keystone Symposia on Molecular and Cellular Biology, Big Sky, MT. April, 2014

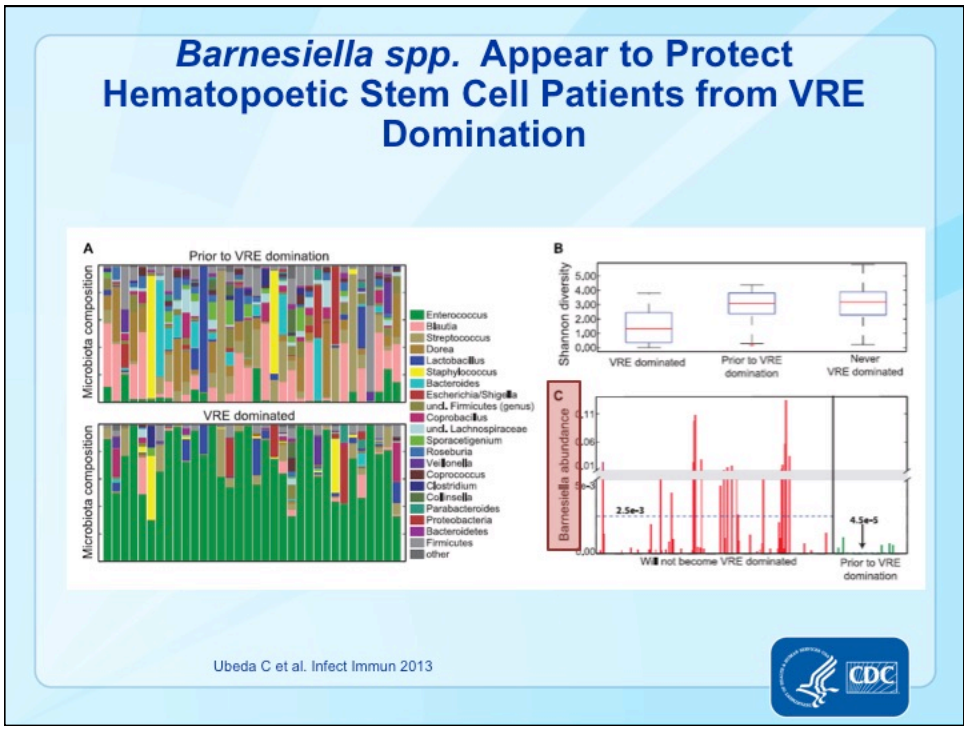
Here's Your Gut Microbiome…



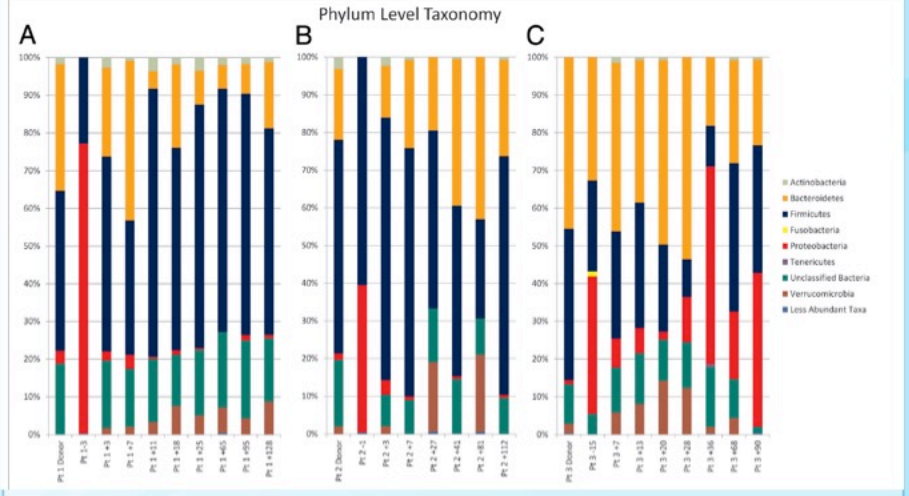

…Here's Your Gut Microbiome on Antibiotics
Enterococcus
Enterococcaceae
Lactobacillales
Bacilli
Firmicutes
Bacteria
Proteobacteria
Betaproteobacteria
Burkholderiales
Comamonadaceae
16S ribosomal RNA-encoding DNA metagenomic analysis of the bowel intestinal microbiota of a healthy individual living in the community without recent antibiotic exposure (panel A) and a patient in a long-term acute care hospital after repeated antibiotic exposures who has become colonized and dominated by VRE (panel B).


Other Potential MDIs: A Keystone Organism Genus that Prevents VRE Colonization in a Mouse Model
VRE colonization
ns *** ***
VRE CFUs / 10mg
PBS
Aero
Anaero
Feces
Ubeda C et al. Infect Immun 2013
CDC


Barnesiella spp. Appear to Compete with VRE in Mice
A
UC_Enterobacteriaceae
Enterococcus
UC_Enterococcaceae
Lactobacillus
UC_Bacilli
Clostridium
Anaerostipes
UC_Lachnospiraceae
Coprococcus
Dorea
Peptococcus
UC_Peptostreptococcaceae
Oscillibacter
Ruminococcus
UC_Ruminococcaceae
UC_Clostridiales
Blautia
Allobaculum
Coprobacillus
Turicibacter
UC_Firmicutes
UC_Mollicutes
Bacteroides
Parabacteroides
Barnesiella
VRE
VRE log CFUs in 10mg
>6
4-6
2-4
0-2
% of total
>40
20-40
10-20
5-10
2-5
1-2
0-1
0
Proteobacteria
Firmicutes
Mollicutes
Bacteroidetes
Ubeda C et al. Infect Immun 2013
CDC


Barnesiella spp. Appear to Protect Hematopoetic Stem Cell Patients from VRE Domination
A
Prior to VRE domination
VRE dominated
Microbiota composition
Enterococcus
Blautia
Streptococcus
Dorea
Lactobacillus
Staphylococcus
Bacteroides
Escherichia/Shigella
und. Firmicutes (genus)
Coprobacillus
und. Lachnospiraceae
Sporacetigenium
Roseburia
Veillonella
Coprococcus
Clostridium
Collinsella
Parabacteroides
Proteobacteria
Bacteroidetes
Firmicutes
other
B
Shannon diversity
VRE dominated
Prior to VRE domination
Never VRE dominated
C
Barnesiella abundance
2.5e-3
4.5e-5
Will not become VRE dominated
Prior to VRE domination
Ubeda C et al. Infect Immun 2013
CDC

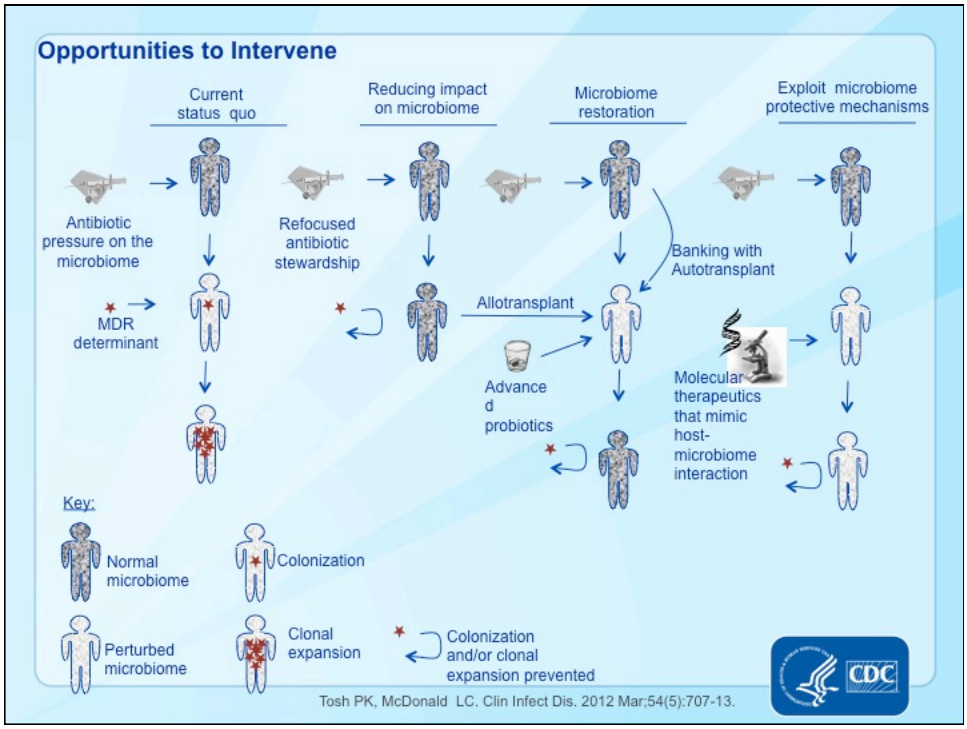
Fecal Microbiota Transplant Engraftment



Hamilton et al. Gut Microbes 4:2;125-35. 2013

Provide Proof of Concept: Microbiome Restoration to Ameliorate MDRO Dominance or Colonization and Improve the Resistome

- **Washington University Prevention Epicenter**
  - Auto-transplant subset of human volunteers with FMT following antibiotic administration
    - Investigational New Drug number obtained from FDA
    - Enrollment beginning by end of summer
  - Assess how the intestinal resistome shrinks
- **CDC has been in discussions with companies developing advanced probiotics that may ameliorate MDRO dominance or colonization**


Opportunities to Intervene
Current status quo
Reducing impact on microbiome
Microbiome restoration
Exploit microbiome protective mechanisms
Antibiotic pressure on the microbiome
MDR determinant
Refocused antibiotic stewardship
Allotransplant
Advanced probiotics
Banking with Autotransplant
Molecular therapeutics that mimic host-microbiome interaction
Key:
Normal microbiome
Colonization
Perturbed microbiome
Clonal expansion
Colonization and/or clonal expansion prevented
Tosh PK, McDonald LC. Clin Infect Dis. 2012 Mar;54(5):707-13.
CDC


Strategic Public Health Priorities for Microbiome Research to Address AR
Natural history or longitudinal studies in healthcare settings
Understanding the MDIs associated with MDRO colonization, dominance, and infection
Larger cross-sectional studies
Understand major MDI fluxes around healthcare
Impact of AR determinants in food on the resistome
Assess the health and presence of AR determinants in the collective U.S. microbiome
Nationally representative cross-sectional sampling to assess microbiome health and its association with exposures
CDC

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  - Director of Clinical Microbiology Laboratory
  - Co-director of FMT program
  - Investigator on several FMT translational projects
  - Member of DHQP MWG via CDC Interpersonal Agreement
- **Mary Hayden, Vince Young, Robert Weinstein**
  - Chicago-Rush Prevention Epicenter

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National Center for Emerging and Zoonotic Infectious Diseases
Division of Healthcare Quality Promotion

Debate – Selective Decontamination of the Gut
Prof. Jan Kluytmans and Dr. Cliff McDonald
Broadcast live from the 2015 Infection Prevention Society conference

Thanks to Teleclass Education

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