# Colonic neoplasms and *S. gallolyticus and E. faecalis* endocarditis

JM Pericàs, MD, MPH, PhD

16TH SYMPOSIUM

ISCVID

BARCELONA

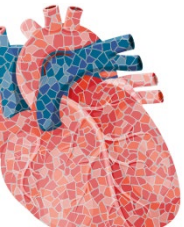
JUNE 18TH - 20TH

2022

INTERNATIONAL SOCIETY FOR CARDIOVASCULAR INFECTIOUS DISEASES

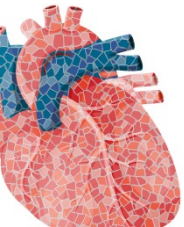
# Disclosures

- **Educational, consultory, and research or travel grants:** Gilead, NovoNordisk, Novartis, Boehringer-Ingelheim, Intercept, BMS, Pfizer, Accelerate, Astellas, ViiV, Janssen, MSD, Abbvie
- **European Commission/EFPIA:** IMI2 853966-2, IMI2 777377, H2020 847989
- **ISCIII:** PI19/01898

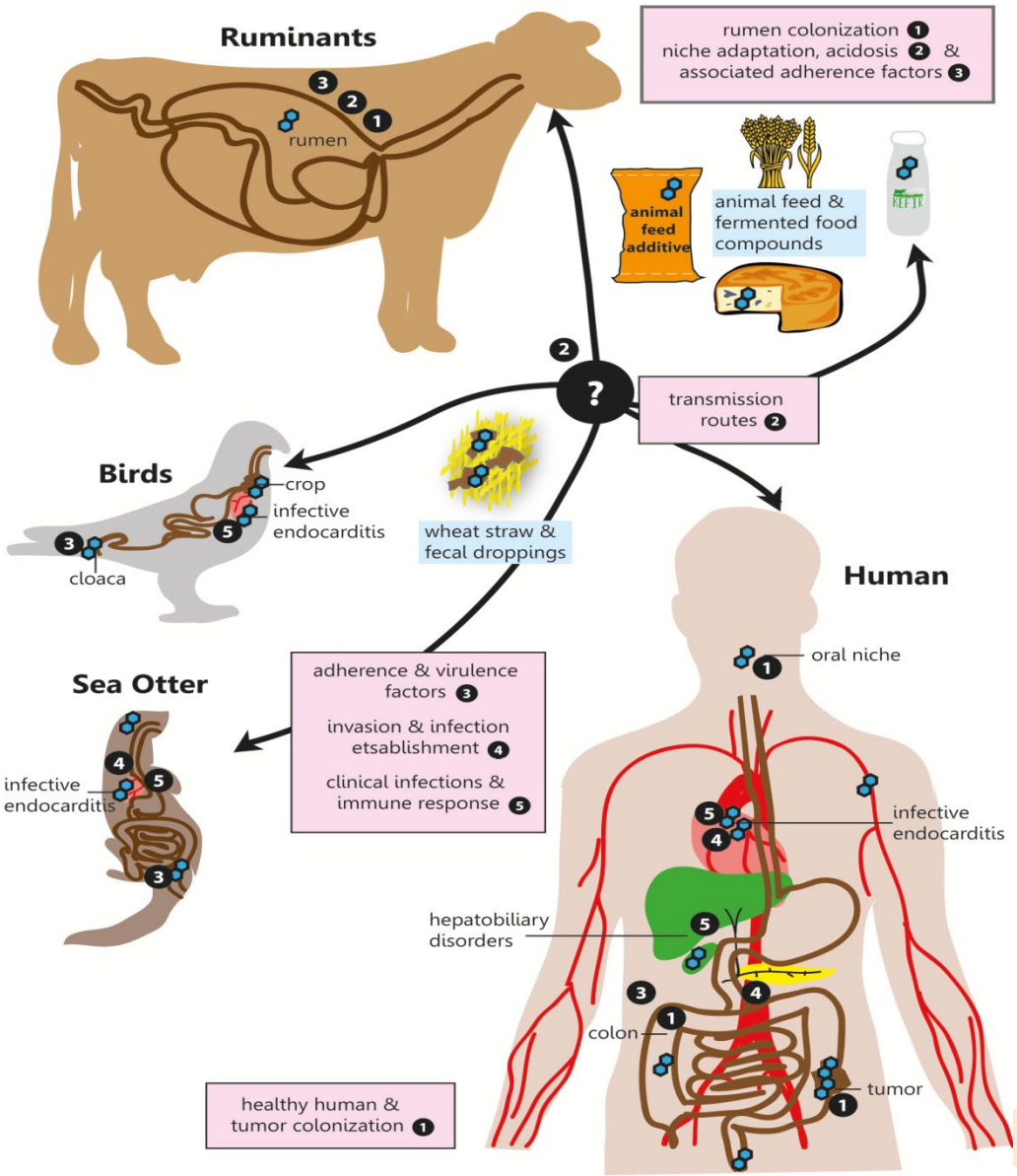


# Ground to be covered

- SGG IE and CRN: strenght of the association
- SGG and CRN: causation?
- EFIE and CRN: still preliminary evidence?
- Any translational evidence linking EF and CRN? Active role or mere bystander?
- SGG and EF often dance together
- Colonoscopy: to whom and when?



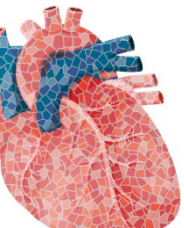
# *S. bovis/S. equinus* complex: the road to infection




Jans & Boleij. *Front Microbiol.* 2018

# S. Bovis: new nomenclature

| New name | Former phenotypic designation | Synonym |
|---|---|---|
| *Streptococcus gallolyticus* subsp *gallolyticus* | *S. bovis* biotype I | *S. gallolyticus* |
| *Streptococcus infantarius* subsp *infantarius* | *S. bovis* biotype II/1 | *S. infantarius* |
| *S. infantarius* subsp *coli* | *S. bovis* biotype II/1 | *Streptococcus lutiensis* |
| *S. gallolyticus* subsp *pasteurianus* | *S. bovis* biotype II/2 | *Streptococcus pasteurianus* |



Boleij et al. *Clin Infect Dis*. 2011

# Current guidelines

## 2015 ESC Guidelines for the management of infective endocarditis

In the setting of *S. bovis* IE, there is a need for proper microbiological classification. In case of *S. bovis*/*S. gallolyticus* IE, it is recommended to rule out occult colon cancer during hospitalization. In the absence of any tumour, scheduling an annual colonoscopy is highly suggested.[482]

European Heart Journal (2015) **36**, 3075–3123

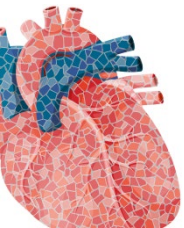
## Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications

**A Scientific Statement for Healthcare Professionals From the American Heart Association**

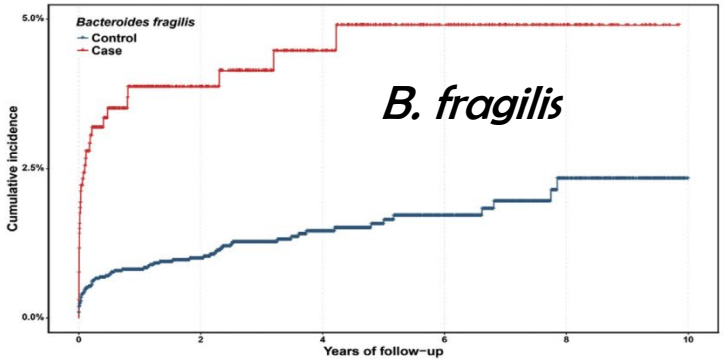
*Endorsed by the Infectious Diseases Society of America*

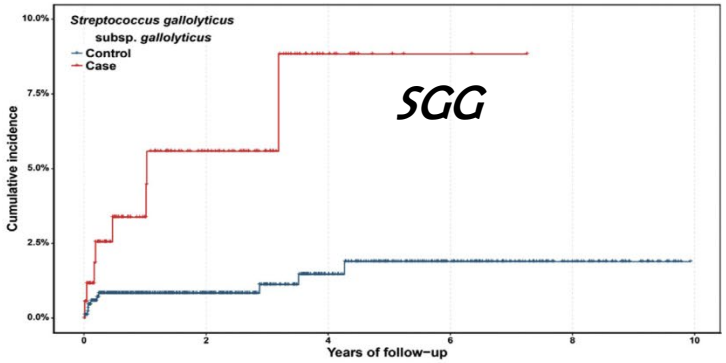
*Enterococcus* by appropriate biochemical tests. Patients with either *S gallolyticus (bovis)* bacteremia or IE should undergo a colonoscopy to determine whether malignancy or other mucosal lesions are present.

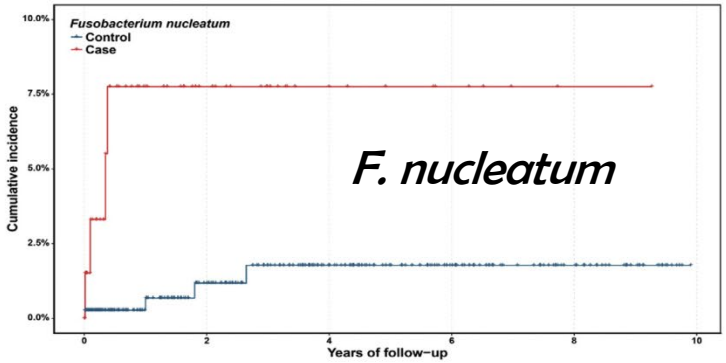
***Circulation*. 2015;132:1435-1486.**

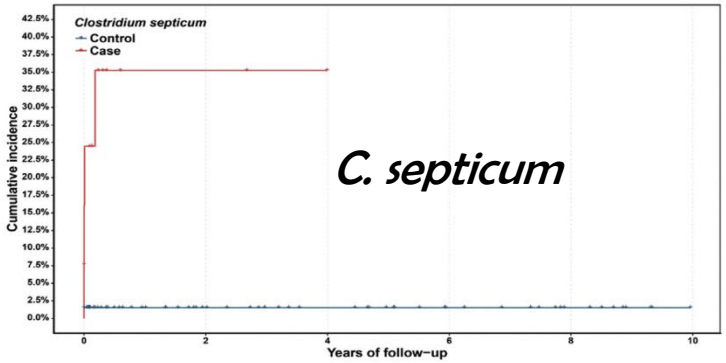


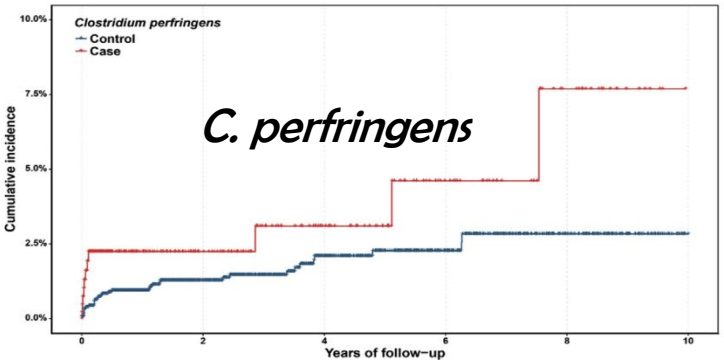
# Bacteremia and subsequent diagnosis of CRC

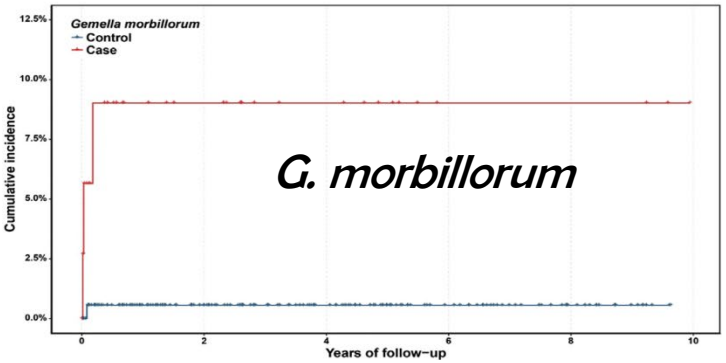


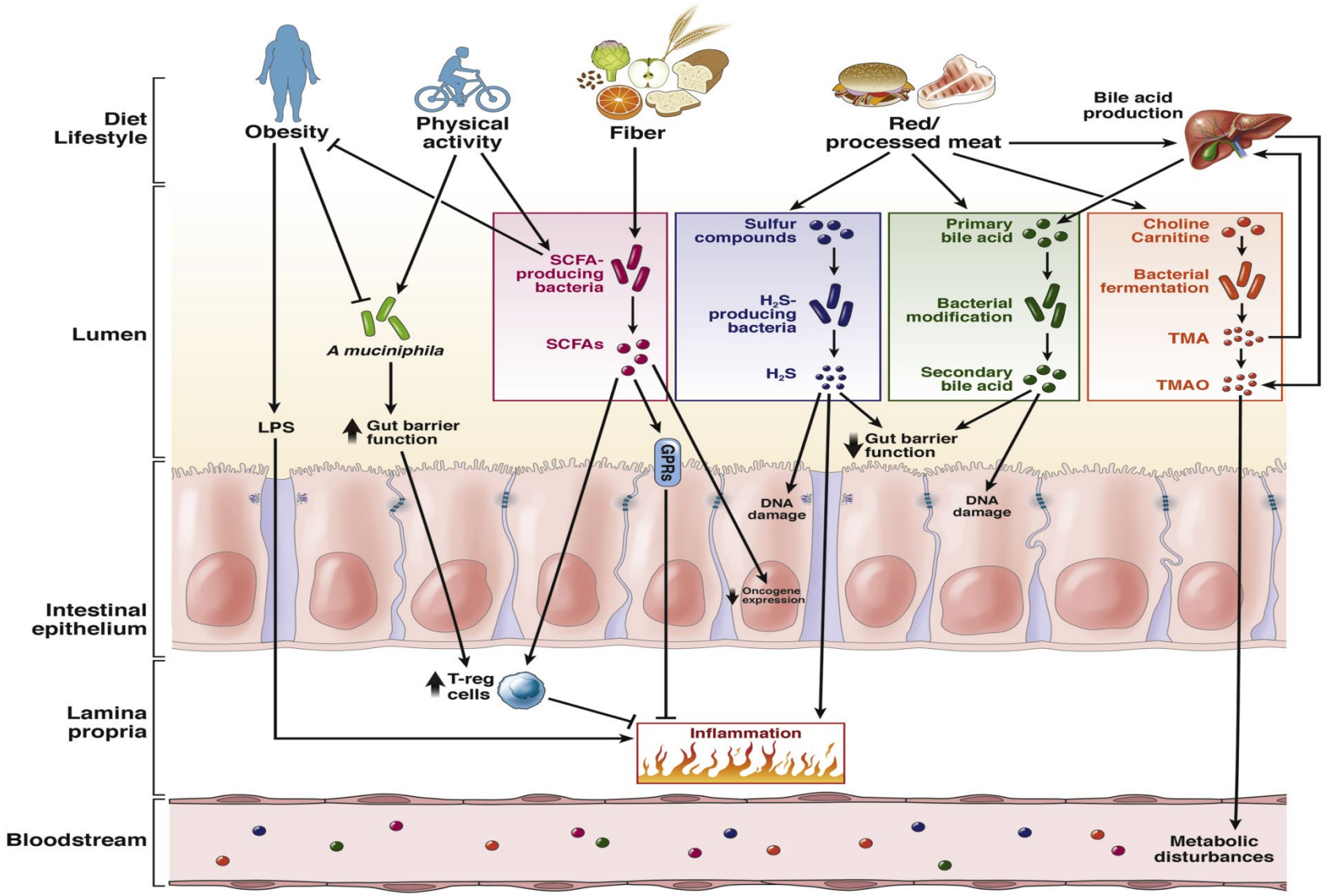



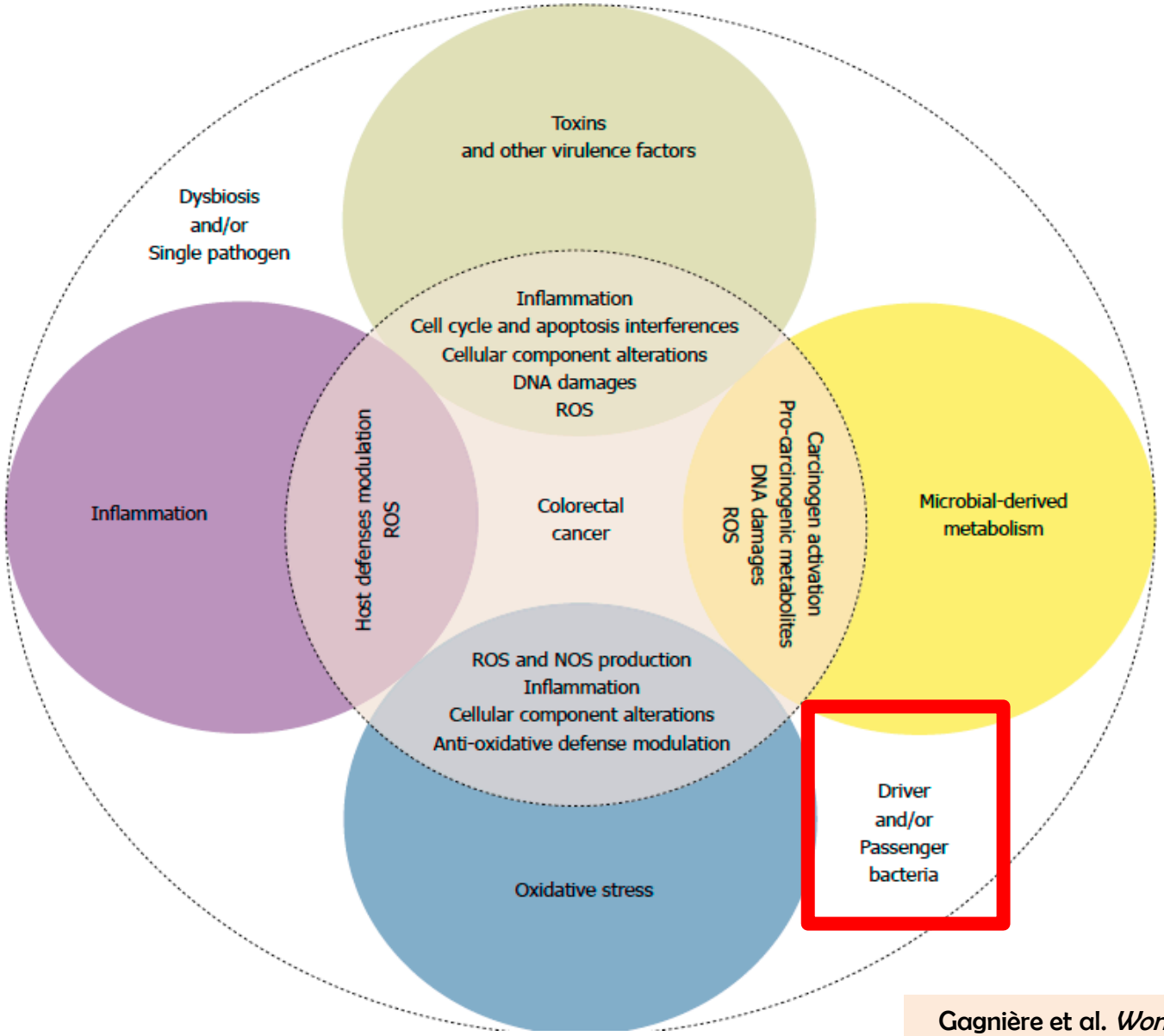

Kwong et al. *Gastroenterology* 2018

# Gut microbiota and CRC



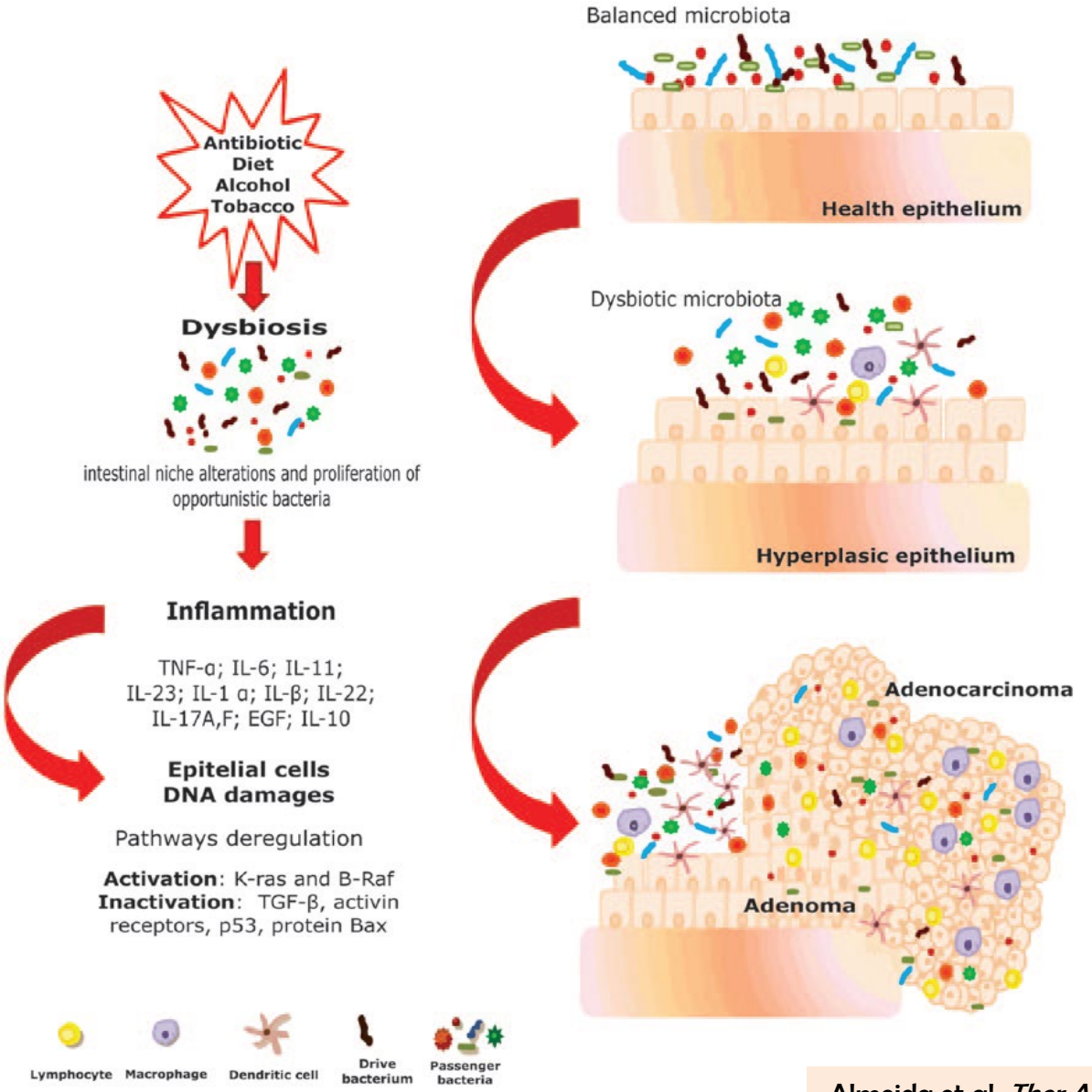

Song et al. *Gastroenterology*. 2020

# Mechanisms gut microbiota→CRC



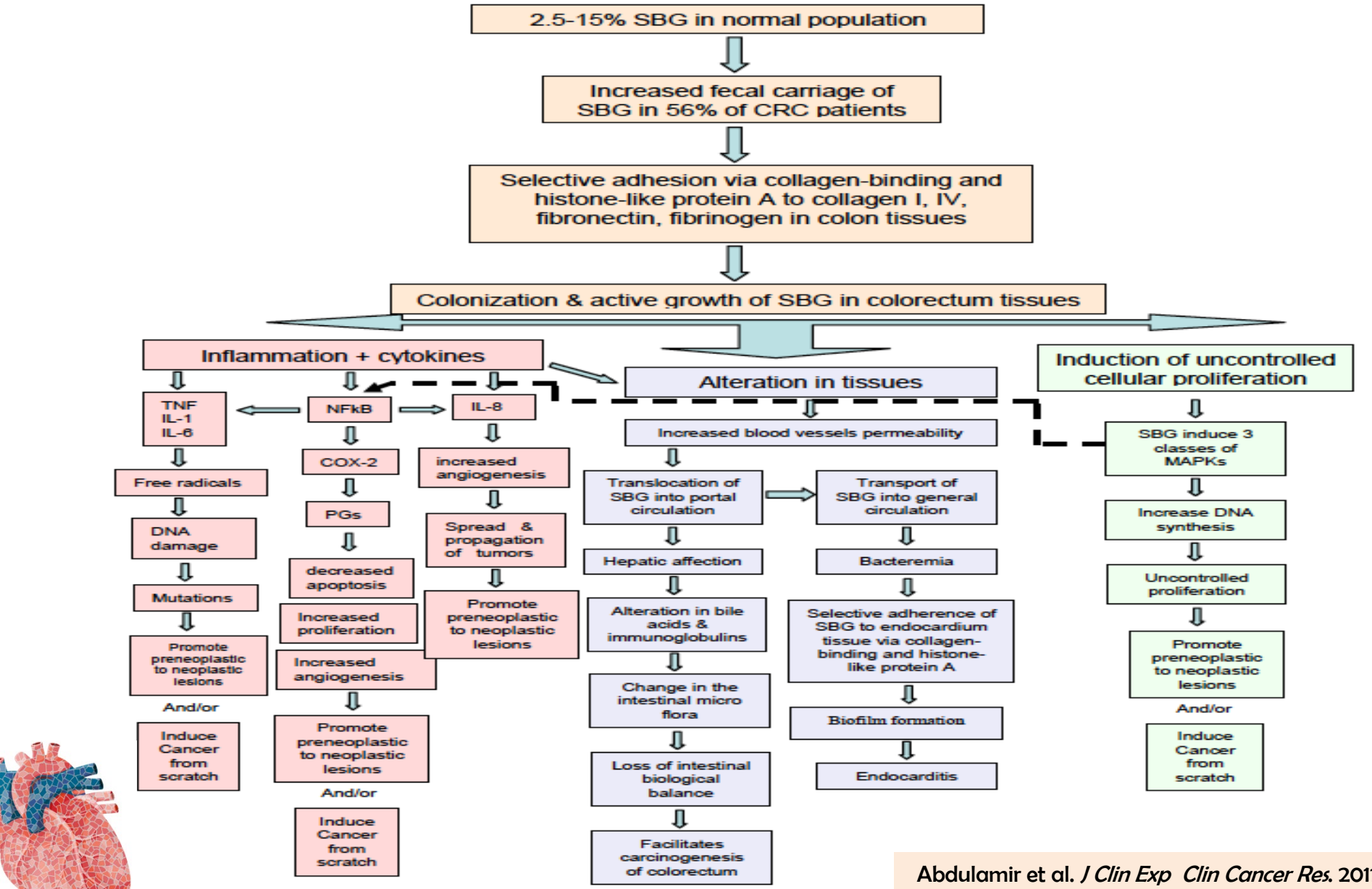

Gagnière et al. *World J Gastroenterol.* 2016

# The "adenoma-carcinoma sequence"




Almeida et al. *Ther Adv Gastroenterol*. 2018

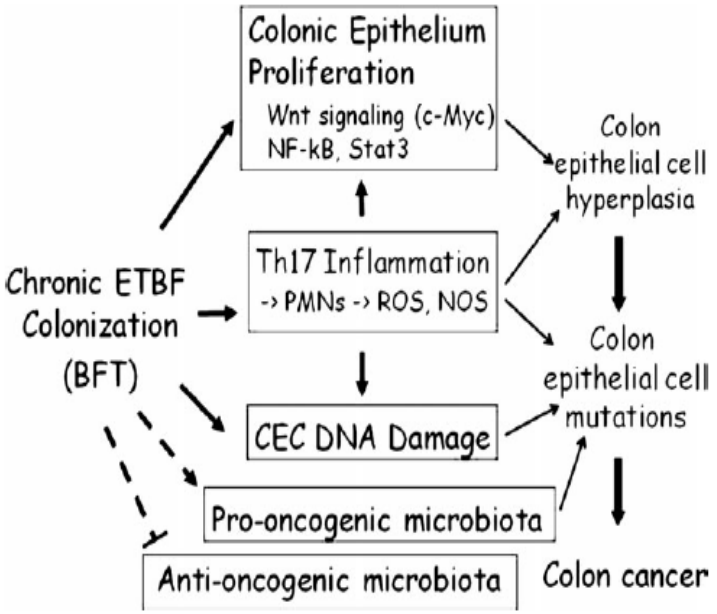
# SGG: Proposed mechanisms of carcinogesis

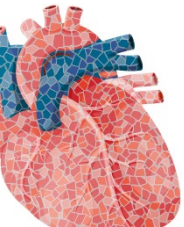



Abdulamir et al. *J Clin Exp Clin Cancer Res.* 2011

# "Alpha" bugs

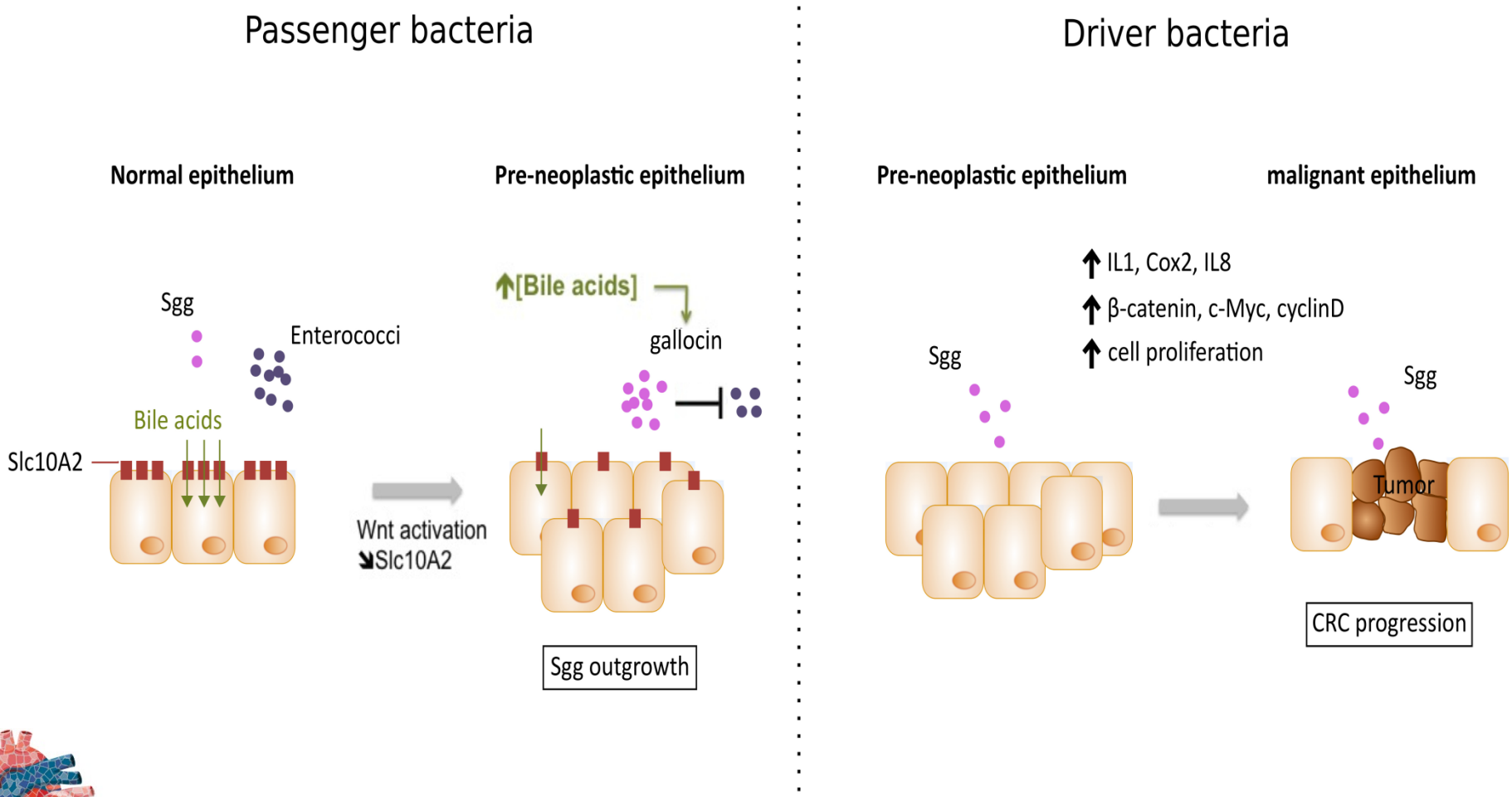
- Certain gut bacteria acquire oncogenic capacity through **direct or indirect mechanisms**
- SGG terminal ileum, not colon, but CRN induce carbohydrate-rich microenvironments
- **Remodeling** the colonic flora, **favoring** development of other oncogenesis-contributing bacteria, and **preventing** the development of anti-oncogenic microbiota
- Unknown whether these bacteria **persist** in advanced phases of neoplasia or are rather **progressively replaced** as the CRN advances



Sears & Pardoll. *J Infect Dis*. 2011

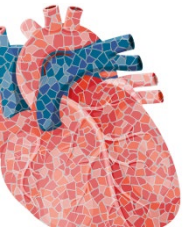
# "Passenger" and "driver" bacteria toward CRC




Pasquereau-Kotula et al. *Front Microbiol.* 2018

# Pathophysiology keys

| Microorganism | Phylum | Natural habitat | Characteristics in CRC | Effectors | References |
|---|---|---|---|---|---|
| *Streptococcus bovis* | Firmicutes | GI tract | Early sign for CRC | | (38–40) |
| Enterotoxigenic *Bacteroides fragilis* | Bacteroidetes | GI tract | Detected in ~90% of CRC patients | BFT | (41–44) |
| *Fusobacterium nucleatum* | Fusobacteria | Oral cavity | Increased in CRC patients, indicate a worse prognosis | Adhesin FadA, Fap2 | (45–49) |
| *Enterococcus faecalis* | Firmicutes | GI tract | Increased in CRC patients | Production of superoxide | (31, 50–52) |
| *Escherichia coli* | Proteobacteria | GI tract | Increased in CRC patients | Colibactin | (53, 54) |
| *Peptostreptococcus anaerobius* | Firmicutes | GI tract | Increased in CRC patients | PCWBR2 | (55, 56) |



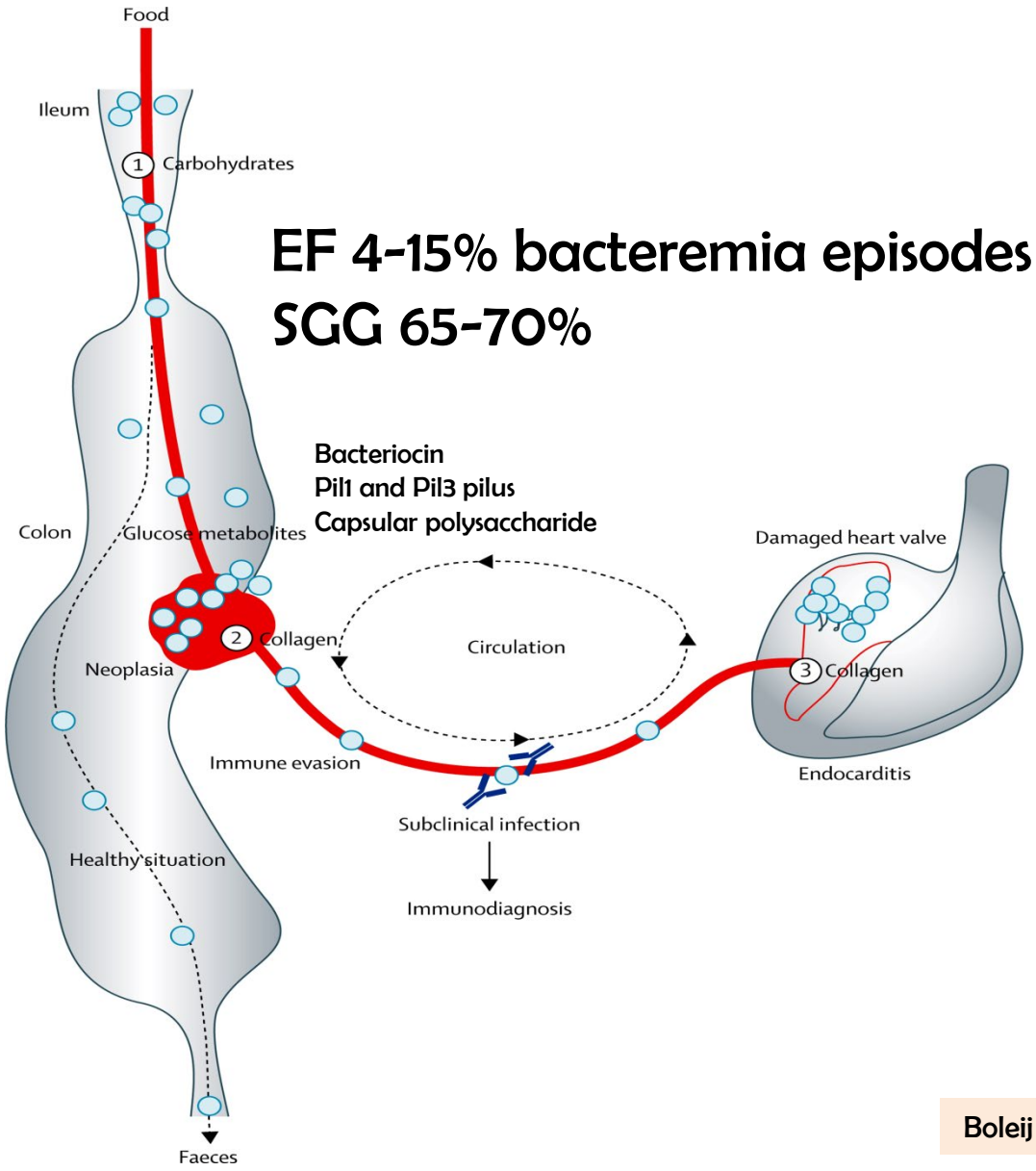
Cheng, Ling, Li. *Front Immunol.* 2020

# Experimental evidence of *E. faecalis*-induced carcinogesis

| | IBD Associated | Immuno-Suppressive | Pro-Inflammatory | CHROMOSOMAL instability | MSI Associated | CIMP Associated | DNA Damage Induction in Cultured Colonocytes | Proliferation Influence over Cultured Colonocytes | Metastasis Influencing |
|---|---|---|---|---|---|---|---|---|---|
| *Streptococcus gallolyticus* | | | ++ | | | | | ++ | |
| *Enterococcus faecalis* | ++ | | ++ | ++ | | | ++ | ++ | + |
| CIF +ve *Escherichia coli* | ++ | | | | | | | ++ | |
| CNF +ve *Escherichia coli* | | | | + | | | | ++ | |
| Colibactin +ve *Eschericia coli* | ++ | | | | | | ++ | ++ | |
| BFT+ve *Bacteroides fragilis* | ++ | | ++ | | | | ++ | ++ | |
| *Fusobacterium nucleatum* | | ++ | | | ++ | ++ | | ++ | |

Alhinai et al. *Int J Mol Sci* 2019

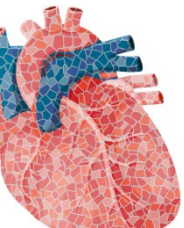
# The journey of SGG from gut to heart




EF 4-15% bacteremia episodes associated to IE

SGG 65-70%

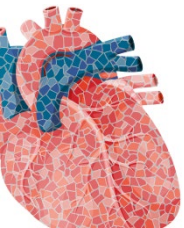
**Bacteriocin**
**Pil1 and Pil3 pilus**
**Capsular polysaccharide**



Boleij & Tjalsma. *Lancet Infect Dis.* 2013

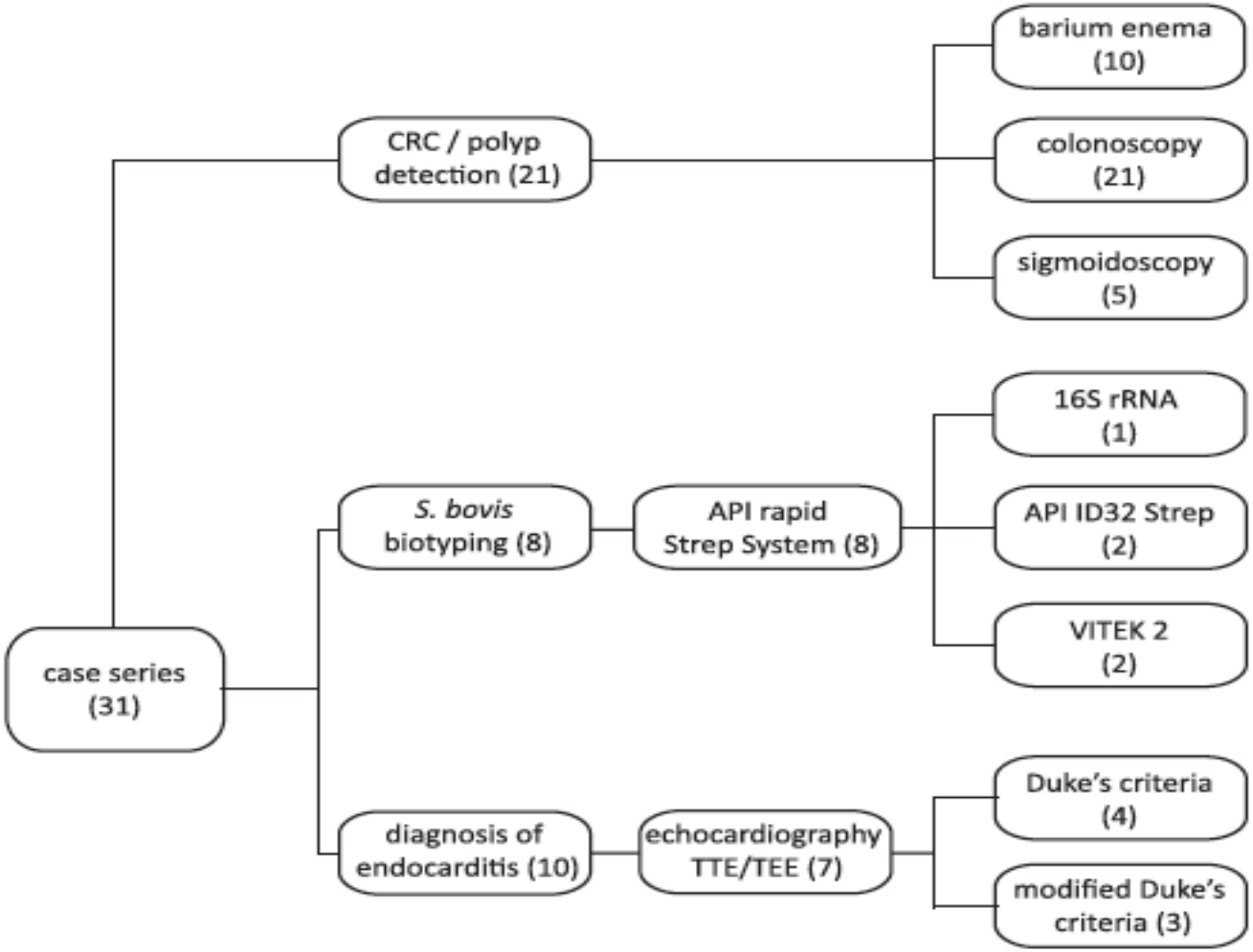
# Clinical evidence: SGG IE and CRN

| | *S. bovis* |
|---|---|
| Strength | ORs for detection of *S. bovis* in stool range from 1.0 to 10.7<br>+ |
| Temporality | Not evaluated<br>0 |
| Consistency | *S. bovis* endocarditis studies consistently show elevated risks for colorectal neoplasia. However, stool studies of colorectal cancer cases and controls are not consistent.<br>++ |
| Specificity | *S. bovis* is a cause of septicemia and endocarditis.<br>+ |
| Biological plausibility | *S. bovis* is known to inhabit the colon, and molecular studies indicate that *S. bovis* proteins have carcinogenic properties.<br>+++ |
| Coherence | Many colorectal cancers exhibit overexpression of cyclooxygenase-2. *S. bovis* proteins up-regulate cyclooxygenase-2 *in vitro*.<br>+++ |



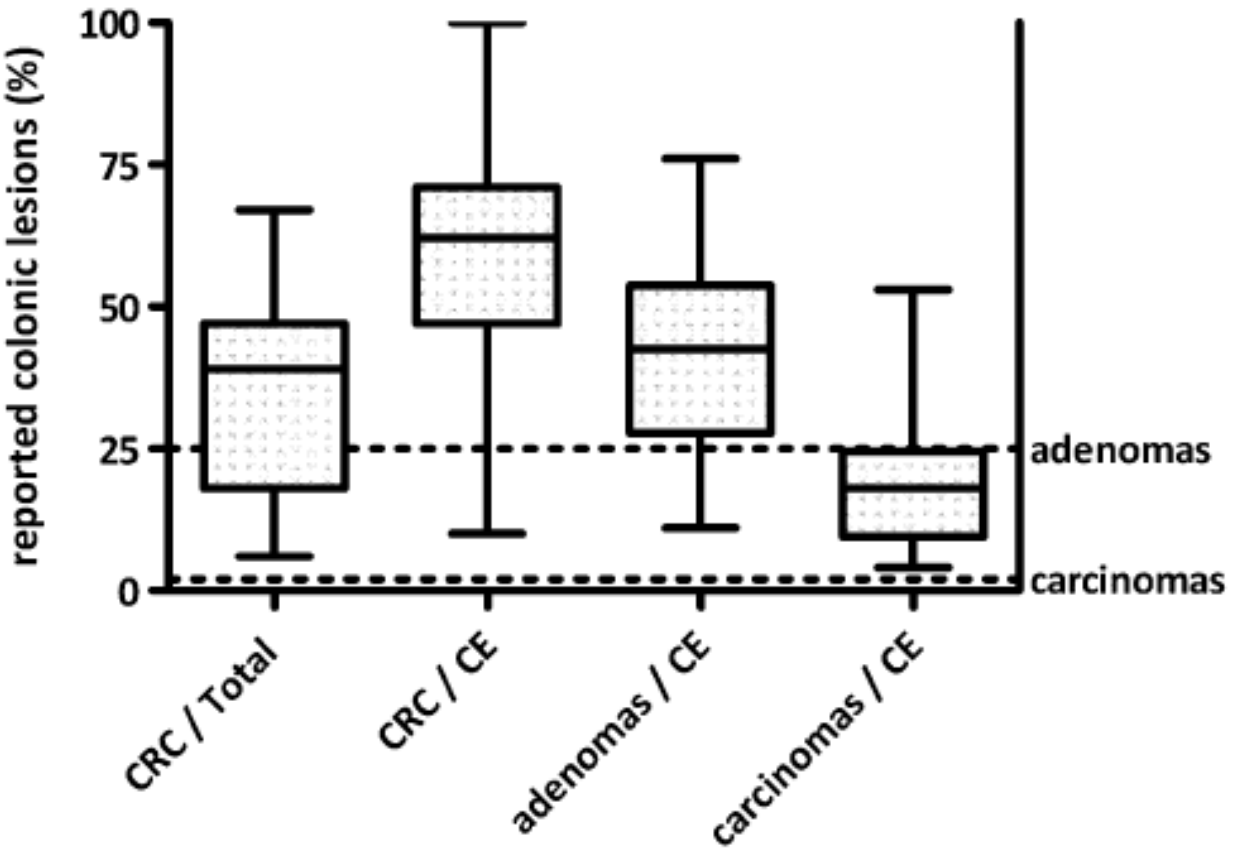
Burtnett-Hartman et al. *Cancer Epidemiol Biomarkers Prev*. 2008

# Clinical evidence: SGG IE and CRN




Boleij et al. *Clin Infect Dis.* 2011

# Clinical evidence: SGG IE and CRN



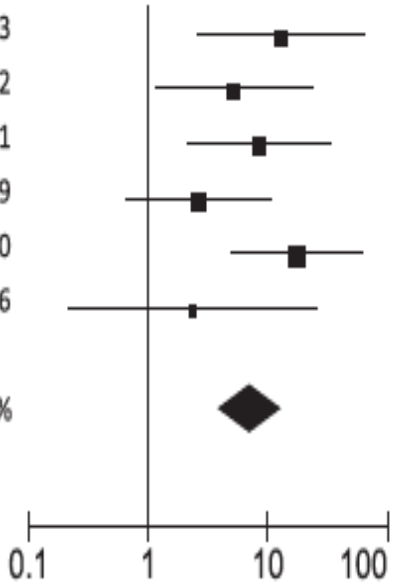

Boleij et al. *Clin Infect Dis.* 2011

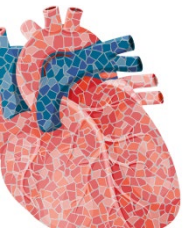
# Clinical evidence: SGG IE and CRN

| | Biotype I | | | Biotype II | | | | |
|---|---|---|---|---|---|---|---|---|
| | # CRC | # Total | Rate | # CRC | # Total | Rate | Odds Ratio (95% CI) | Weight % |
| **Colorectal cancer** | | | | | | | | |
| 18 Ruoff (1989) | 12 | 17 | 0.71 | 3 | 19 | 0.16 | 12.80 (2.55, 64.37) | 14.3 |
| 31 Jean (2004) | 5 | 10 | 0.50 | 6 | 37 | 0.16 | 5.17 (1.13, 23.55) | 16.2 |
| 32 Corredoira (2005) | 24 | 42 | 0.57 | 3 | 22 | 0.14 | 8.44 (2.16, 32.98) | 20.1 |
| 8 Beck (2008) | 7 | 21 | 0.33 | 4 | 25 | 0.16 | 2.63 (0.65, 10.67) | 18.9 |
| 35 Corredoira (2008a) | 51 | 90 | 0.57 | 3 | 43 | 0.07 | 17.44 (5.02, 60.56) | 24.0 |
| 37 Vaska (2009) | 7 | 9 | 0.78 | 3 | 5 | 0.60 | 2.33 (0.22, 25.24) | 6.6 |
| | 106 | 189 | | 22 | 151 | | 7.26 (3.94, 13.36) | 100% |

Heterogeneity: $I^2 = 9.0\%$; $P = 0.36$

Overall (fixed effect): $p < 0.00001$



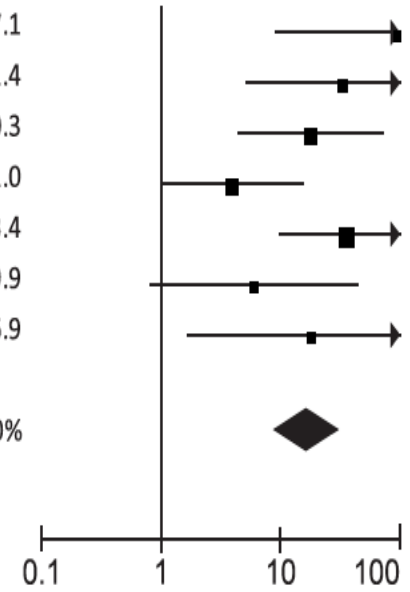
Boleij et al. *Clin Infect Dis.* 2011

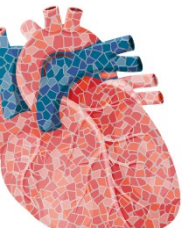
# Clinical evidence: SGG IE and CRN

| | Biotype I | | | Biotype II | | | | |
|---|---|---|---|---|---|---|---|---|
| | # IE | # Total | Rate | # IE | # Total | Rate | Odds Ratio (95% CI) | Weight % |
| **Endocarditis** | | | | | | | | |
| 18 Ruoff (1989) | 16 | 17 | 0.94 | 3 | 21 | 0.14 | 96.00 (9.05, 1017.99) | 7.1 |
| 31 Jean (2004) | 8 | 10 | 0.80 | 4 | 37 | 0.11 | 33.00 (5.11, 213.02) | 11.4 |
| 32 Corredoira (2005) | 31 | 42 | 0.74 | 3 | 22 | 0.14 | 17.85 (4.41, 72.27) | 20.3 |
| 8 Beck (2008) | 9 | 21 | 0.43 | 4 | 25 | 0.16 | 3.94 (1.00, 15.57) | 21.0 |
| 36 Corredoira (2008b) | 52 | 69 | 0.75 | 3 | 38 | 0.08 | 35.69 (9.73, 130.95) | 23.4 |
| 37 Vaska (2009) | 6 | 10 | 0.60 | 2 | 10 | 0.20 | 6.00 (0.81, 44.35) | 9.9 |
| 38 Fernandez-Ruiz (2010) | 8 | 12 | 0.67 | 1 | 10 | 0.10 | 18.00 (1.65, 196.31) | 6.9 |
| | 130 | 181 | | 20 | 163 | | 16.61 (8.85, 31.16) | 100% |

Heterogeneity: $I^2 = 35.0\ \%$; $P = 0.16$

Overall (fixed effect): $p < 0.00001$



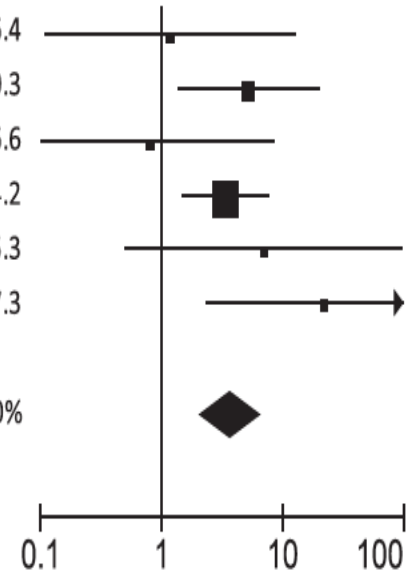
Boleij et al. *Clin Infect Dis.* 2011

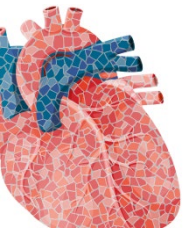
# Clinical evidence: SGG IE and CRN

| | Endocarditis | | | Other locations | | | | |
|---|---|---|---|---|---|---|---|---|
| | # CRC | # Total | Rate | # CRC | # Total | Rate | Odds Ratio (95% CI) | Weight % |
| **Colorectal cancer** | | | | | | | | |
| 10 Murray (1978) | 3 | 26 | 0.12 | 1 | 10 | 0.10 | 1.17 (0.11, 12.82) | 6.4 |
| 19 Zarkin (1990) | 11 | 19 | 0.58 | 5 | 24 | 0.21 | 5.22 (1.37, 19.99) | 20.3 |
| 23 Gonzalez-Quintela (2001) | 4 | 9 | 0.44 | 2 | 4 | 0.50 | 0.80 (0.08, 8.47) | 6.6 |
| 36 Corredoira (2008b) | 29 | 55 | 0.53 | 13 | 52 | 0.25 | 3.35 (1.47, 7.61) | 54.2 |
| 37 Vaska (2009) | 7 | 8 | 0.88 | 3 | 6 | 0.50 | 7.00 (0.50, 97.75) | 5.3 |
| 38 Fernandez-Ruiz (2010) | 14 | 15 | 0.93 | 7 | 18 | 0.39 | 22.00 (2.34, 206.48) | 7.3 |
| | 68 | 132 | | 31 | 114 | | 3.72 (2.03, 6.81) | 100% |

Heterogeneity: $I^2 = 9.0\ \%$; $P = 0.36$

Overall (fixed effect): $p < 0.0001$

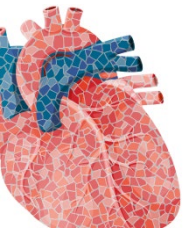


Boleij et al. *Clin Infect Dis.* 2011

# Clinical evidence: SGG bacteremia and CRN

| | *S. gallolyticus* subsp. *gallolyticus* Bacteremia (n = 98)[a] | Control Group (n = 196) | OR (95% CI) | *P* Value |
|---|---|---|---|---|
| Age, mean ± SD | 66.2 ± 11.7 | 66.3 ± 11.9 | | NS |
| Sex, % male | 89 (91%) | 178 (91%) | 1.0 (.4–2.3) | NS |
| Born in Spain | 98 (100%) | 192 (98%) | 4.6 (.2–86.4) | NS |
| Symptoms[b] | 11 (11%) | 143 (73%) | 0.05 (.02–.1) | .0001 |
| Colorectal neoplasia[c] | 69 (70%) | 62 (32%) | 5.1 (3.0–8.6) | .0001 |
| Nonadvanced adenoma | 18 (19%) | 23 (12%) | 1.7 (.9–3.3) | NS |
| Advanced adenoma | 39 (40%) | 31 (16%) | 3.5 (2.0–6.1) | .0001 |
| Invasive carcinoma | 12 (12.5%) | 9 (5%) | 2.9 (1.2–6.9) | .03 |
| Benign colorectal pathology[c] | 44 (45%) | 107 (55%) | 0.7 (.4–1.1) | NS |
| Diverticular disease | 35 (36%) | 63 (32%) | 1.2 (.7–1.9) | NS |
| Internal hemorrhoids | 14 (14%) | 37 (19%) | 0.7 (.4–1.4) | NS |
| Hyperplasic polyps | 10 (10%) | 15 (8%) | 1.4 (.6–3.2) | NS |
| Angiodysplasia | 4 (4%) | 5 (3%) | 1.7 (.5–6.0) | NS |
| Lipoma | 2 (2%) | 1 (0.5%) | 3.4 (.4–25.9) | NS |
| Leiomyoma | 2 (2%) | 1 (0.5%) | 3.4 (.4–25.9) | NS |
| Melanosis coli | 2 (2%) | 0 | 10.2 (.5–214.2) | NS |
| Rectal fistula | 1 (1%) | 0 | 6.0 (.2–149.8) | NS |
| Ischemic colitis | 1 (1%) | 6 (3%) | 0.5 (.1–2.7) | NS |
| Noncolorectal cancer | 5 (5%) | 12 (6%) | 0.9 (.3–2.4) | NS |



Corredoira et al. *Clin Infect Dis* 2012

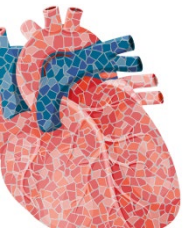
# What about *E. faecalis* IE?

## Enterococcal Endocarditis

An Analysis of 38 Patients Observed at the
New York Hospital-Cornell Medical Center

While in the majority of cases enterococcal endocarditis is associated with organic heart disease, the infection may be engrafted on normal heart valves. This aspect of enterococcal endocarditis will be commented on later.

Enterococcal endocarditis may complicate urologic instrumentation[29, 30] such as cystoscopy, urethral dilatation or transurethral resection. This infection has been associated with or complicated carcinoma of the sigmoid colon,[28] so-called Blalock-Taussig operation,[31] abortion[32] and normal pregnancy.[33] Periapical dental abscesses have also been implicated.[34]

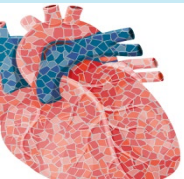


Mandell et al. *Arch Intern Med.* 1978

# Enterococcal IE in ICE cohort

| | Enterococci *n* = 500 30.9% | Oral streptococci *n* = 823 51.0% | Group D streptococci *n* = 293 18.1% | p value |
|---|---|---|---|---|
| Age (years), mean [SD] | 65.5 (15.3) | 54.6 (18.4) | 65.2 (12.4) | <0.0001 |
| Male sex, *N* (%) | 361 (72.6) | 584 (71.0) | 218 (74.7) | 0.46 |
| History of IE, *N* (%) | 62 (12.5) | 86 (10.5) | 21 (7.2) | 0.07 |
| Admission delay > 1 month, *N* (%) | 172 (36.8) | 350 (44.9) | 142 (51.4) | <0.0001 |
| Haemodialysis, *N* (%) | 41 (8.4) | 11 (1.4) | 6 (2.1) | <0.0001 |
| Diabetes, *N* (%) | 110 (22.4) | 90 (11.1) | 56 (19.3) | <0.0001 |
| Cancer, *N* (%) | 55 (11.2) | 67 (8.3) | 34 (11.7) | 0.11 |
| Charlson index, mean [SD] | 1.7 (1.8) | 1.0 (1.5) | 1.3 (1.5) | <0.0001 |
| Place of acquisition, *N* (%) | | | | <0.0001 |
| Community | 352 (70.4) | 758 (92.1) | 280 (95.6) | |
| Healthcare, nosocomial | 65 (13.0) | 12 (1.5) | 3 (1.0) | |
| Healthcare, non-nosocomial | | | 4 (1.4) | |
| Multiple, unknown, missing | | | 6 (2.0) | |
| Intracardiac device, *N* (%) | | | 1 (7.2) | <0.0001 |
| Type of IE, *N* (%) | | | | <0.0001 |
| Native valve | 324 (66.4) | 641 (80.9) | 216 (75.8) | |
| Prosthetic valve | 142 (29.1) | 130 (16.4) | 62 (21.8) | |
| Other | 22 (4.5) | 21 (2.7) | 7 (2.5) | |
| Location of vegetation, *N* (%) | | | | 0.18 |
| Left-sided only | 380 (80.3) | 643 (83.0) | 241 (87.6) | |
| Right-sided only | 26 (5.5) | 27 (3.5) | 6 (2.2) | |
| Left + right | 11 (2.3) | 14 (1.8) | 4 (1.5) | |
| Elsewhere | 16 (3.4) | 18 (2.3) | 4 (1.5) | |
| No vegetation | 40 (8.5) | 73 (9.4) | 20 (7.3) | |
| Missing information | 27 (5.4) | 48 (5.8) | 18 (6.1) | |
| Stroke, *N* (%) | 78 (16.0) | 118 (14.7) | 38 (13.3) | 0.59 |
| Embolic event, *N* (%) | 94 (19.3) | 147 (18.3) | 70 (24.4) | 0.08 |
| Heart failure, *N* (%) | 94 (18.8) | 139 (16.9) | 56 (19.1) | 0.90 |
| Intracardiac abscess, *N* (%) | 57 (11.8) | 110 (13.6) | 33 (11.5) | 0.51 |
| Paravalvular complications in prosthetic valve IE, *N* (%) | 53 (10.8) | 41 (5.1) | 15 (5.2) | 0.0002 |
| Valve surgery within 60 days, *N* (%) | 209 (42.1) | 380 (46.5) | 137 (47.2) | 0.22 |
| One-year mortality, *N* (%) | 144 (28.9) | 120 (14.6) | 52 (17.8) | <0.0001 |

No information on the source of infection

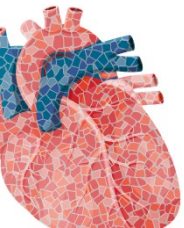


Chirouze et al. *Clin Microbiol Infect* 2013

# Enterococcal IE in GAMES cohort

| | ococcal IE ,308) | p Value |
|---|---|---|
| Median time of symptoms dur | -18) | 0.549 |
| Source | | |
| Oral | 6.7) | <0.001 |
| Respiratory | 1.2) | 0.096 |
| Genitourinary | 3.2) | <0.001 |
| Gastrointestinal | 5.2) | <0.001 |
| Vascular | 19.3) | <0.001 |
| Cutaneous | 7.9) | <0.001 |
| Other | 6.3) | 0.031 |
| Unknown | (51.6) | 0.734 |

- **Overall: either retrospective data or sources of infection not systematically studied / large differences accross sites**
- **Loose definition of gastrointestinal source: most times refers to biliary tract**



Pericàs et al. *JACC* 2020

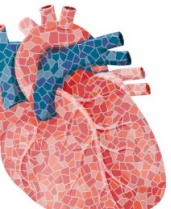
# First comparison of SGG vs. EF IE

## First admission

| Endocarditis | *S. bovis* N=109 | *Enterococcus* spp. N=36 | p-value |
|---|---|---|---|
| Spondylodiscitis | 15 (13.8 %) | 6 (16.7 %) | ns |
| Arthritis | 5 (4.6 %) | 3 (8.3 %) | ns |
| Colon tumour | 70 (64.2 %) | 9 (25 %) | 0.0000 |
| Duke's criteria endocarditis | | | |
| - Definitive | 102 (93.6 %) | 30 (83.3 %) | ns |
| - Possible | 7 (6.4 %) | 6 (16.7 %) | ns |
| Antibiotic treatment | | | |
| - β-lactamic | 54 (49.5 %) | 0 | 0.0000 |
| - Double β-lactamic | 0 | 19 (52.8 %) | 0.0000 |
| - β-lactamic+ aminoglycoside | 54 (49.5 %) | 12 (33.3 %) | ns |
| - Others | 1 (0.9 %) | 5 (13.9 %) | 0.0007 |
| Early cardiac surgery | 16 (14.7 %) | 4 (11.1 %) | ns |
| Early mortality | 14 (12.8 %) | 8 (22.2 %) | ns |

## Follow-up

| Endocarditis | *S. bovis* | *Enterococcus* spp. | p-value |
|---|---|---|---|
| Number of cases | 95 | 28 | |
| Follow-up (months) | 71.2±59.5 | 47.8±46.6 | ns |
| Range (months) | (2–216) | (3–192) | |
| Relapses | 0 | 3 (10.7 %) | 0.015 |
| Recurrences | 8 (8.4 %) | 3 (10.7 %) | ns |
| Cardiac surgery | | | |
| In the first year | 10 (10.5 %) | 2 (7.1 %) | ns |
| After the first year | 12 (10.5 %) | 3 (10.7 %) | ns |
| Mortality | | | |
| First 6 months | 10 (10.5 %) | 2 (7.1 %) | ns |
| 6–12 months | 2 (2.1 %) | 1 (3.6 %) | ns |
| 1–2 years | 9 (9.4 %) | 3 (10.7 %) | ns |
| >2 years | 26 (27.3 %) | 6 (21.4 %) | ns |
| Colorectal neoplasia | 43 (45.2 %) | 6 (21.4 %) | 0.01 |

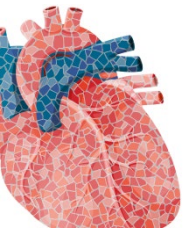


Corredoira et al. *EJCMID* 2015

# Geographical variation?

**EFIE with available colonoscopy= 58**

A total of 44 patients (76%) received a new diagnosis of colonic disease, including colorectal adenoma in 20 patients (34%) and colorectal cancer in 5 (9%) (1 patient received a diagnosis dur-

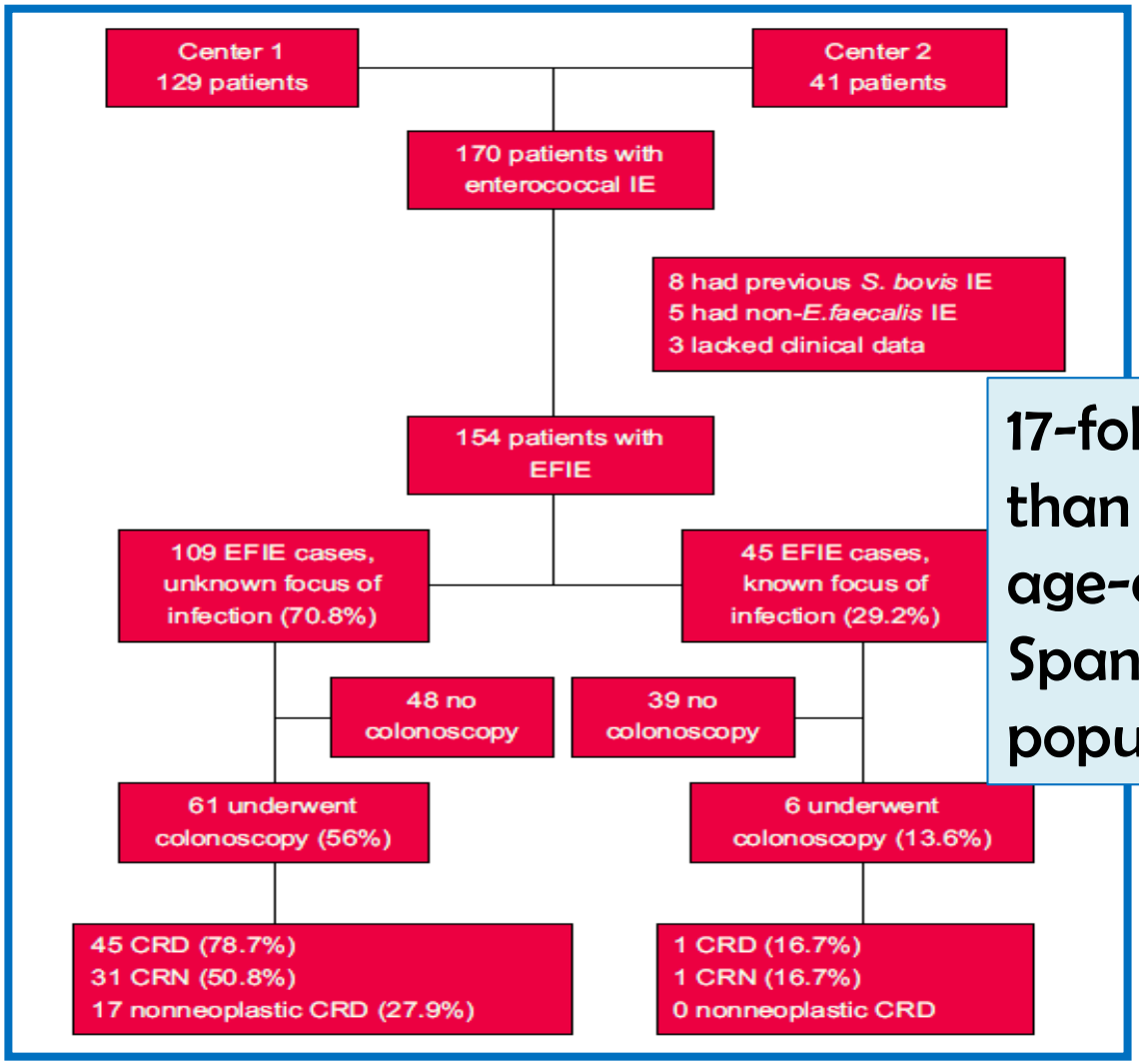


Pericàs, Corredoira, Miró. *NEJM* 2016

# Clinical evidence: EFIE and CRN

**1979-2015**

**154 pts**




17-fold higher than that of the age-adjusted Spanish general population

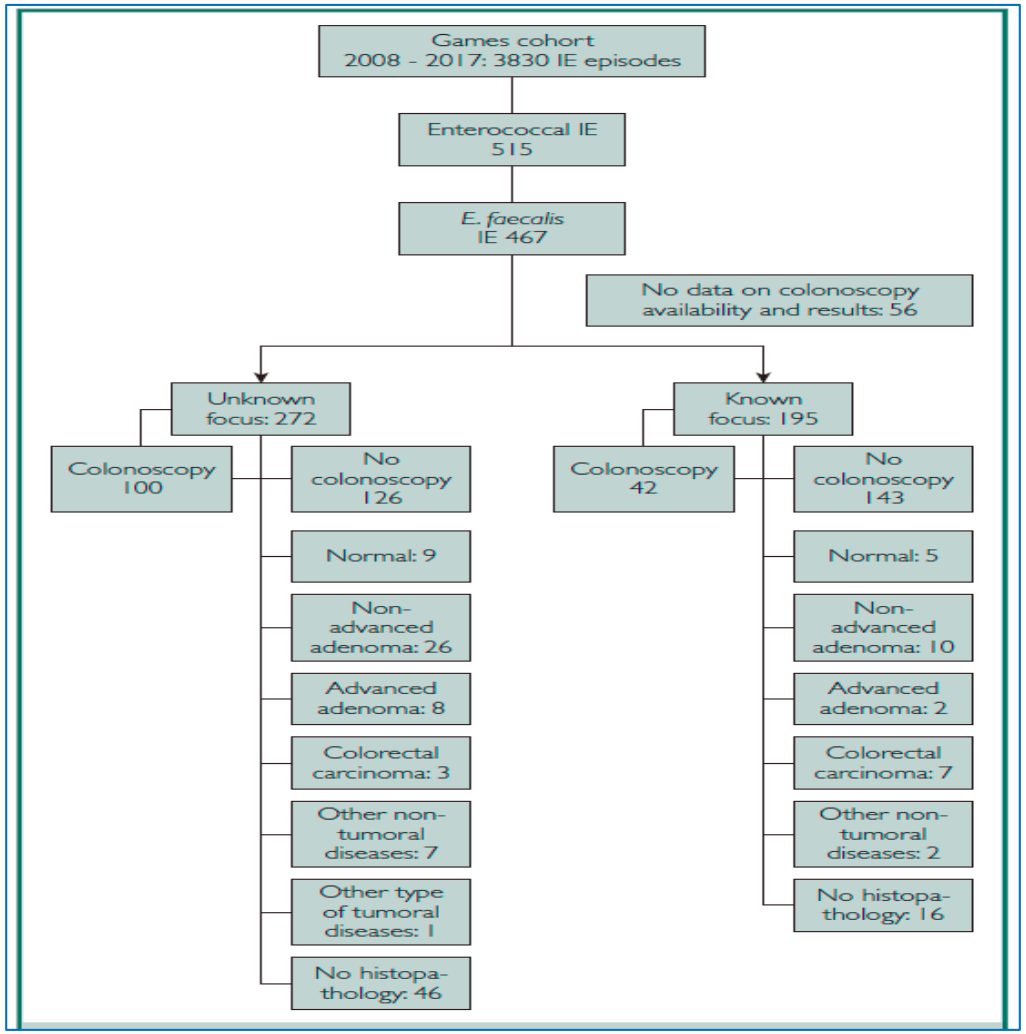
Pericàs et al. *REC* 2017

# Clinical evidence: EFIE and CRN

| | All EFIE N = 103 | Unknown source n = 63 | Known source excluding colorectal disease[a] n = 32 |
|---|---|---|---|
| *Colonoscopy performed* | 78/103 (76) | 45/63 (71) | 25/32 (78) |
| *Endoscopic findings being potential portal of entry*[b] | 47/78 (60) | 29/45 (64) | 11/25 (44) |
| *Colorectal neoplasms* | 39/47 (83) | 26/29 (90) | 9/11 (82) |
| Nonadvanced colorectal adenoma | 19 | 12 | 6 |
| Advanced colorectal adenoma | 18 | 13 | 3 |
| Colorectal carcinoma[c] | 2 | 1 | 0 |
| *Nonneoplastic colorectal disease* | 8/47 (17) | 3/29 (10) | 2/11 (18) |
| Colorectal ulcer[d] | 3 | 1 | 1 |
| Mucosal inflammation | 2 | 1 | 0 |
| Bleeding vascular lesion | 2 | 0 | 1 |
| Polyp without histopathological report[e] | 1 | 1 | 0 |

Escolà-Vergé et al. *REC* 2019

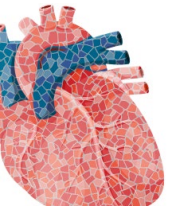
# Clinical evidence: EFIE and CRN




Pericàs et al. *Mayo Clin Proc.* 2021

# Clinical evidence: EFIE and CRN

| | No colonoscopy (N=269) | Colonoscopy (N=142) | P |
|---|---|---|---|
| Source | | | |
| Urinary | 54 (20.1) | 22 (15.5) | .287 |
| Vascular | 46 (17.1) | 14 (9.9) | .048 |
| Biliary | 36 (13.4) | 0 | <.001 |
| Respiratory | 0 | 1 (0.7) | .345 |
| Cutaneous | 3 (1.1) | 3 (2.1) | .420 |
| Other | 18 (6.7) | 7 (4.9) | .477 |
| Unknown | 112 (41.6) | 95 (66.9) | <.001 |
| Treatment characteristics | | | |
| Antibiotics properly indicated | 259 (96.3) | 138 (97.2) | .633 |
| Median length of antibiotic treatment, days (IQR) | 42 (28-45) | 42 (31-46) | .139 |
| Antibiotic treatment | | | |
| Double beta-lactam combination[c] | 180 (66.9) | 103 (72.5) | .290 |
| Beta-lactam + aminoglycoside | 54 (20.1) | 27 (19) | .899 |
| Other | 35 (13) | 12 (8.5) | .223 |
| Cardiac surgery | | | |
| Indicated | 174 (64.9) | 81 (57) | .144 |
| Operated | 109 (40.5) | 60 (42.3) | .734 |
| Outcomes | | | |
| In-hospital mortality | 78 (29) | 20 (14.1) | .001 |
| Mortality at 1 year | 96 (35.7) | 31 (21.8) | .005 |
| Recurrences at 1 year | 5 (1.8) | 8 (5.6) | .074 |



Pericàs et al. *Mayo Clin Proc.* 2021

# Clinical evidence: EFIE and CRN

| | Known focus (n=42) | Unknown focus (n=100) | P | Overall (N=142) |
|---|---|---|---|---|
| Median age, years (IQR) | 69 (65-78) | 71 (65-78) | .545 | 70 (65-78) |
| Male (%) | 27 (64.3) | 68 (68) | .815 | 95 (66.9) |
| Diagnosis of colorectal disease (n, %) | 33 (78.6) | 67 (67) | .167 | 100 (70.4) |
| During admission | 6 (18.2) | 22 (32.8) | .544 | 28 (28) |
| Before IE admission | 12 (36.4) | 10 (14.9) | | 22 (22) |
| During follow-up | 15 (45.4) | 35 (52.2) | | 50 (50) |
| Results of index colonoscopy | | | .088 | |
| Normal | 9 (21.4) | 32 (32) | | 41 (28.9) |
| Findings suggestive of non-neoplastic disease | 15 (35.7) | 22 (22) | | 37 (26) |
| Findings suggestive of CRN | 12 (28.6) | 39 (39) | | 51 (35.9) |
| Findings highly suspicious of CRN | 6 (14.3) | 6 (6) | | 12 (8.5) |
| Not conclusive due to bad preparation | 0 | 1 (1) | | 1 (0.7) |
| Histopathology findings | | | .139 | |
| Not performed | 16 (38) | 46 (46) | | 62 (43.7) |
| Benign polyps | 5 (11.9) | 9 (9) | | 14 (9.9) |
| Nonadvanced adenoma | 10 (23.8) | 26 (26) | | 36 (25.3) |
| Advanced adenoma | 2 (4.8) | 8 (8) | | 10 (7) |
| Colorectal carcinoma[c] | 7 (16.7) | 3 (3) | | 10 (7) |
| Other type of colorectal cancer | 0 | 1 (1) | | 1 (0.7) |
| Other non-neoplastic disease | 2 (4.8) | 7 (7) | | 9 (6.3) |

Pericàs et al. *Mayo Clin Proc.* 2021

# Recent comparison of SGG vs. EF IE

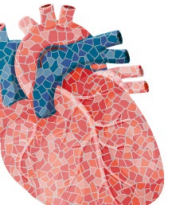
| | *Enterococcus* IE ($n$ = 85) | *S. gallolyticus* IE ($n$ = 81) | p value |
|---|---|---|---|
| Underwent colonoscopy (any time) | | | 0.203 |
| *Yes* | 42 (49.4) | 48 (59.2) | |
| *No* | 43 (50.6) | 33 (40.8) | |
| Timing of colonoscopy | | | **<0.001** |
| *During the acute phase of IE* | 18 (42.9) | 37 (75) | |
| *After IE* | 13 (30.9) | 10 (18.7) | |
| *Before IE* | 11 (26.2) | 1 (6.3) | |
| **Endoscopy-proven intestinal disease*** | 30 (71.4) | 40 (83.3) | 0.174 |
| Non-neoplastic disease** | 15 (35.7) | 22 (45.8) | |
| - *Unspecific Colitis, Ulcerative colitis* | 2 (4.7) | 1 (2.1) | |
| - *Diverticulosis/Diverticulitis* | 7 (16.6) | 11 (22.9) | |
| - *Non-neoplastic polyposis* | 6 (14.3) | 10 (20.8) | |
| Colorectal neoplasia** | 22 (52.4) | 27 (56.2) | |
| - *Adenoma* | 15 (35.7) | 20 (41.6) | |
| - *Adenocarcinoma* | 7 (16.6) | 7 (14.6) | |
| No intestinal disease (negative colonoscopy) | 12 (28.6) | 8 (16.6) | |

Ursi et al. *Eur J Intern Med* 2021

# SGG and EF in relapsing IE

| First IE Episode | | | | | Second IE Episode | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Patients | Date (M/Y) | Age/sex, comorbidities | Type of IE, microorganism, complications | Colonos-copy * | Date (M/Y) | Type of IE, micro-organism, complica-tions | Colonoscopy | Follow-up, status | Comments |
| Case 1 | 8/2002 | 68/M, DM, CKD. | NVE Ao | Not performed (due | | PVE Ao | Tubular adenomas | 8/2015 deceased | 2007, 2009, 2010, and 2013 advanced adenomas |
| Case 2 | 6/2004 | 67/M, IHD, COPD | | | | | | | |
| Case 3 | 7/2008 | 73/M Renal and prostate cancer | | | | | | | 4/2017 *S. sanguis* IE; 2013, 2017, and 2020 advanced adenomas |
| Case 4 | 4/2004 | 71/M DM, IHD, renal carcinoma. | | | | | | | 8/2008 SGG IE; 3/2009 *S. salivarius* IE |
| Case 5 | 6/2016 | 83/M DM, acute myeloid leukemia, COPD, CKD. | | | | | | | 2002 EF IE T013 tubulovillous adenoma |
| Case 6 | 1/2011 | 80/F DM, PCM. | | | | | | | |
| Case 7 | 10/2011 | 65/M Liver cirrhosis, IHD, PCM. | | | | | | | Four SGG IE episodes in total (2011, 2012, 2013, 2015); 9/2014 Gastric cancer |
| Case 8 | 2/2005 | 53/M DM, COPD. | | | | | | | 4/2012 Multiple polyps, not biopsied; 2/2013 Tubular adenomas (3); 1/2020 Tubular adenomas (7) |
| Case 9 | 8/2007 | 57/M CHD. | | | | | | | 2003 *S. mitis* IE 6/2020 normal colonoscopy |
| Case 10 | 3/2011 | 79/F DM, IHD, CKD. | PVE M SGG | Normal | 10/2013 | PVE M EF | Not performed (volvuli in sigma) | 1/2014 deceased during IE episode (heart failure) | |

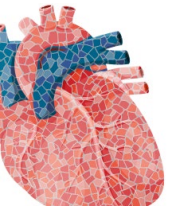
- 1552 IE episodes, 1979-2019
- 204 (13.1%) EF, 197 (12.7%) SGG
- 155 episodes of recurrent IE (10%)
- 20 (12.9%) due to a succession of EF/SGG or vice versa (2/8)
- All patients diagnosed with CRN either during the initial or recurrent episodes



Romay et al. *J Clin Med* 2022

# Gaps in potential underlying mechanisms of SGG-EF coupling

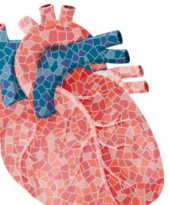
- Aging population in Western societies; CRN in younger patients growing; changes in diet; metabolic syndrome
- Role of SGG in early phases of tumor development ("non-oncogenic" strains, approx. 30%)→ second or subsequent CRN?
- EF as a "passenger" re SGG ("driver")?
- If EF in the bloodstream, increased risk of leaked gut mucosa through prior SGG or EF/SGG damage?
- Genomic and proteomic studies on clinical samples needed for EF at early stages, alone and in combination with SGG if overgrowth or associated BSI found
- Sequential gut microbiota changes
- Host-immune responses



Corredoira et al. *submitted*

# Further hypotheses for EFIE and CRN

- Patients with EFIE have higher rates of CRN than individuals from the general population of the same age and sex, as well as **distinct microbiome profiles**, both in patients with known and unknown source of infection
- *E. faecalis* strains associated to EFIE and CRN have also a **distinct genotypic repertoire**, potentially related to antimicrobial resistance profiles
- These features might also apply to *E. faecalis* bacteremia
- **Sistematically performing a colonoscopy** in patients with EF BSI (older than 50 y or younger with history of familiar poliposis/CRC) might be indicated



# EnteroColonus GAMES Project

**Multicenter (25s), prospective, matched, interventional cohort**

**Length of follow-up: 1 year**

**Group 1:** ***E. faecalis*** **bacteremia/IE with a suspected focus other than colonic (N=124)**

**Group 2:** ***E. faecalis*** **bacteremia/IE of unknown/potentially colonic origin (N=124)**

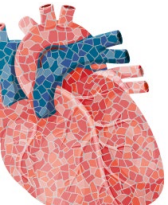
**Group 3: healthy subjects undergoing a CRC screening colonoscopy (N=124)**

**Tests performed:**

**Group 1: colonoscopy, feces sample for microbiome studies, whole genome analysis & resistance profile studies on** ***E. faecalis*** **strains, RT-PCR 16S in colon biopsies.**

**Group 2: same than Group 1 plus follow-up colonoscopy at 1-year.**

**Group 3: colonoscopy and feces sample**



# How to manage enterococcal bacteremia?

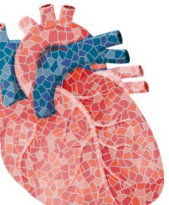
**Enterococcal bacteraemia should be suspected if**

a patient presents a clinical picture of sepsis or worsening general clinical condition in association with - advanced age and/or hospitalization and/or immunosuppression

- Nosocomial infection under broad-spectrum antibiotics
- Prior enterococcal infections or colonization
- Comorbidities, in particular related to urogenital and intra-abdominal organs, and neoplasms (both solid and haematological)
- Recent surgery, mainly urinary or gastro-intestinal tract procedures (including hepato-biliary structures)
- Intravascular devices and/or indwelling urinary catheters

**The initial work-up should include**

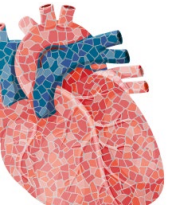
- Physical examination to identify potential sources of bacteraemia (catheter-related phlebitis, murmurs, indwelling urinary catheters, biliary tract, surgical wounds, etc.) or related complications such as emboli, abscesses or osteomyelitis
- Blood cultures obtained before initiating antibiotic treatment (at least 2 sets; 3 sets separated by 30–60 min each in case IE is suspected[a])
- If available, use rapid identification methods for blood samples (e.g. MALDI-TOF)
- Perform antibiotic susceptibility tests tailored according to the enterococcal species and the local epidemiology. Usually, at least the following should be included: ampicillin, gentamicin, vancomycin, linezolid and daptomycin[b]
- Other cultures: catheter tips, urine, biliary fluid, peritoneal liquid, abscesses, deep surgical wound swab
- Potential additional studies: genitourinary and hepatobiliary ultrasound, abdominal CT scan, muscle-skeletal MRI, colonoscopy, $^{18}$FDG-PET scan



Rosselli Del Turco et al. *Clin Microbiol Infect*. 2021

# "Expert opinion" on colonoscopy

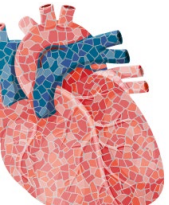
- SGG BSI (both IE and bacteremia) during first episode and follow-up (yearly; age?)
- EF IE during first episode (irrespective of the "known" source, if any; if feasible/sensible)
- EF IE: age and follow-up need further data
- EF bacteremia needs further data



Corredoira et al. *EJIM* 2021

# Future perspectives

- Ellucidating the role of the colon as a source/"paraphenomenon" of EF-BSI
- SGG and EF might not act alone
- *E. faecalis* bacteremia yet to be thoroughly investigated
- Relevance of prospective designs and external validity
- Further data on epidemiological/geographical variability needed (aging, diet, cows' density…)
- Clinical relevance: indication of colonoscopy, interpretation of potential CRN risk





# Thanks for your attention!