Prevention and control of infection risk in nephrology

Pr Jean Ralph Zahar, MD, PhD
Infection Control Unit
Department of Clinical Microbiology
Université Paris13 – GH Paris Seine Saint-Denis

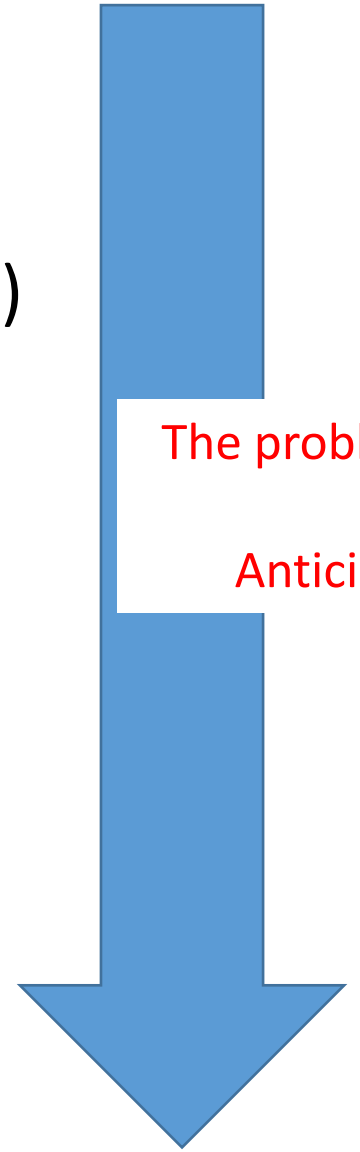
It is a major subject

- **Infection is the second leading cause of death among**
    - Patients with end-stage renal disease
    - Those who have undergone renal transplantation
- **Several reasons**
    - Presence of indwelling catheters
    - Higher antimicrobial resistance
    - Multiple hospitalisation and multiple surgeries
    - Immunodepression
- **Prolonged survival**

Wang TZ, Kodiyanplakkal RPL, Calfee DP. Antimicrobial resistance in nephrology. Nat Rev Nephrol. 2019 May 13.
Saran R, *et al*. US Renal Data System 2018 Annual Data Report: Epidemiology of Kidney Disease in the United States. Am J Kidney Dis. 2019 Mar;73(3S1):A7-A8

Renal diseases: what does it mean ?

- Several hospitalisation (ie, several comorbidities)
- Invasive procedures (urinary and vascular catheters)
- Immunodepression (related to different treatment)
- Hemodialysis
- Kidney transplantation
    - Hospitalisation
    - Transplant kidney
    - Invasive procedures
    - Immunodepression



How can we assess the infectious risk?

- **Patients-related risk**
    - Comorbidities
    - Age of patients
    - Conditions of living (promiscuity, young children,traveling)

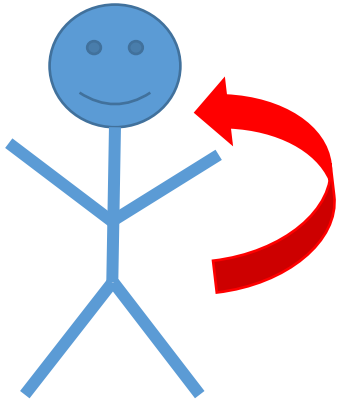
- **Risk related to disease**
    - Duration of disease (ie, several hospitalisation…)
    - Immunosuppression related to different therapeutics
        - During the initial disease
        - During transplantation

        } Cumulative risk

What are the risks?

Endogenous risk

Urinary tract infection
Bloodstream infection



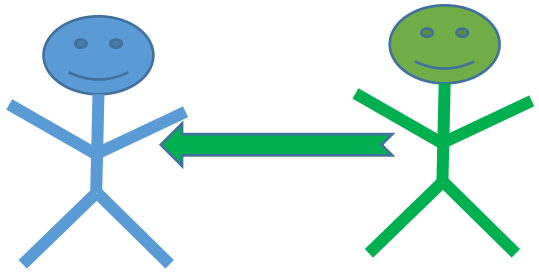
Exogenous risk

Humans

Viral infection
Fungal infections

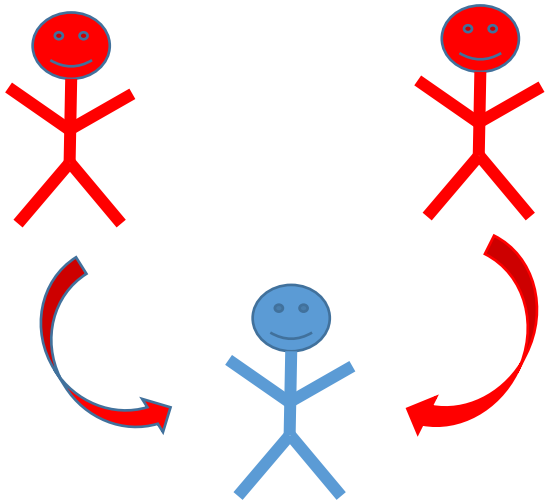
Environmental

Healthcare workers

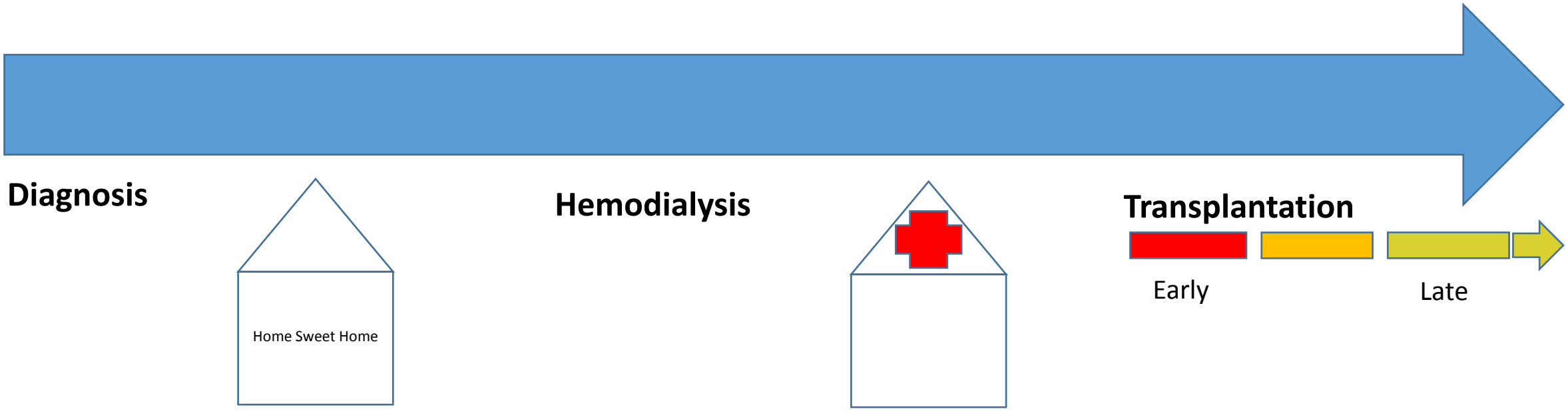


Relatives

Family **Others**



The risk throughout a lifetime



Like other patients
Unlike immunosupression treatment

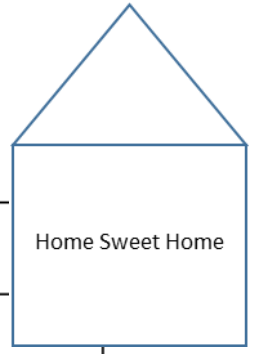
Bloodstream infection
Urinary tract infection
Like other patients
Unlike immunosupression treatment

Bloodstream infection
Urinary tract infection
Post operative infection
Like other patients
Unlike immunosupression treatment

Infection control

- **Basic infection control practices**
  - Horizontal strategies
    - Hand hygiene
    - Standard precautions
    - Cleaning
    - Desinfection
  - Vertical strategies
    - Search and isolate
- **Specific and novel approach**
  - Defining target populations
  - Define the specific risks
  - Introduce specific strategies

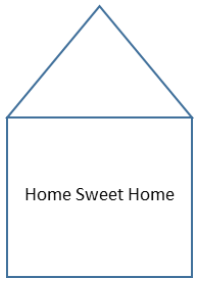
Infectious risks and solutions

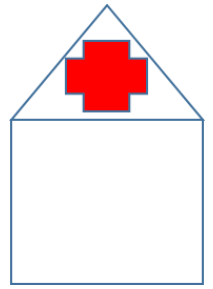


Traitement	Risque infectieux	Facteurs de risque et Comorbidités accentuant le risque
Glucocorticoides	*Pneumocystis jirovecii* *Mycobacterium tuberculosis* Hepatite B et C	Dose journalière (> 20mg/J) Diabète Hypoalbuminémie Traitements associés : azathioprine, cyclophosphamide
Mycophenolate mofetil	Infections virales : herpès, CMV, VZV	leucopénie
Cyclophosphamide	Pneumocytis jirovecii Leuco encéphalopathie progressive multifocale	Dose et durée d'administration (dose cumulative) Lymphopénie
Inhibiteur de la calcineurine Cyclosporine Tacrolimus	Pneumocystis jirovecii	Lymphopenie Infection à CMV Rejet Age
Rituximab	Pneumocystis jirovecii Leuco encéphalopathie progressive multifocale Réactivation de l'hépatite B	Age, comorbidités Effets cumulatifs des immunosuppresseurs associés Corticothérapie associée Hypogammaglobulinémie Neutropénie tardive
Eculizimab	Infections à *Streptococcus pneumoniae* Infections *Neisseria meningitidis* Infections à *Haemophilus influnezae*	
Anti TNF α	*Mycobacterium tuberculosis* Infections à bactéries encapsulées *Listeria monocytogenes* *Legionella pneumophila* VZV Hepatite B et Hepatite C	Leucopénie Première année de traitement Age>45 ans, traitement avec de la thiopurine, corticoides > 2 mois

Zahar JR.: [Prevention of infectious diseases in patients with chronic renal failure]. Nephrol Ther. 2019 Apr;15 Suppl 1:S21-S26

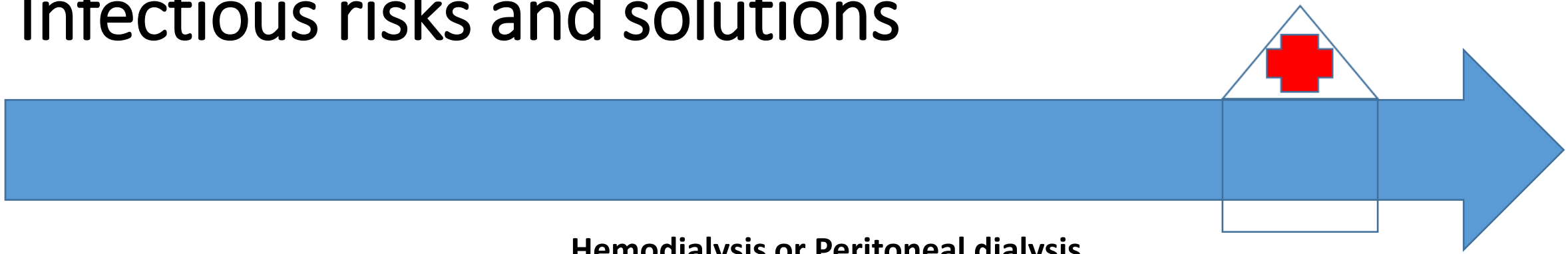
Infectious risks and solutions





The risk of viral infection Immune statuts (Measle, chickenpox) Vaccination (influenzae, Measle, chickenpox) Standard precautions	Check the patients statuts Patients and household members	Check the HCW statuts Vaccination HCW Single bed Room
The risk of bacterial infection Vaccination (*Streptococcus pneumoniae, Bordetella pertusis)* Standard or specific precautions	Patients and household members Reduce invasive procedures	Vaccination HCW Single bed room Single bed room Cleaning desinfection
Other risks ? I**mmunosuppression ?** Tuberculosis	Identify at risk populations	Single bed room Standard precautions

Infectious risks and solutions



Hemodialysis or Peritoneal dialysis

Bloodstream infections

Peritonitis

- Select the vascular access (AVF < vascular catheter)
- Standard precautions (hand hygiene, desinfection)
- Decolonisation ? (nasal, insertion site)
- Lock interdialytic solution

Nguyen DB,. Completeness of Methicillin-Resistant Staphylococcus aureus Bloodstream Infection Reporting From Outpatient Hemodialysis Facilities to the National Healthcare Safety Network, 2013. Infect Control Hosp Epidemiol. 2016 Feb;37(2):205-7.

Dalgaard LS,. Risk and Prognosis of Bacteremia and Fungemia Among Peritoneal Dialysis Patients: A Population-Based Cohort Study. Perit Dial Int. 2016 11-12;36(6):647-654.

Akoh JA. Peritoneal dialysis associated infections: An update on diagnosis and management. World J Nephrol. 2012 Aug 6;1(4):106-22.

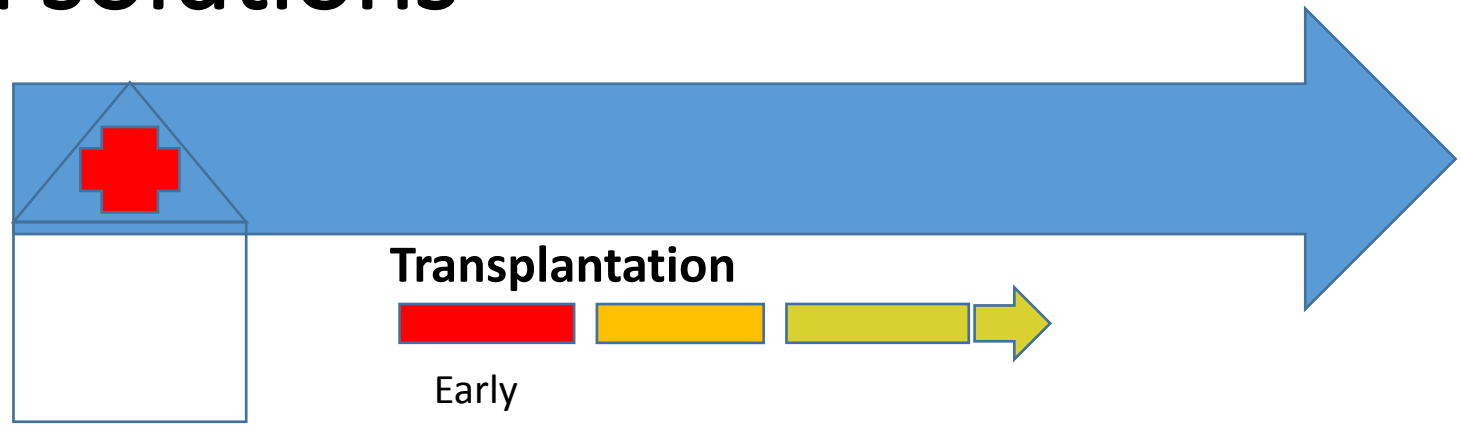
Infectious risks and solutions

Hemodialysis or Peritoneal dialysis

Vaccin	Type	Indications membre de la famille	Indication chez les patients transplantés	Modalités	Suivre les taux sériques
Hepatite B	Inactivé	OUI	OUI	Avant EER, Vérifier la séro conversion	NON
Streptoccoque pneumoniae *PCV-13* *PPSV-23*	Inactivé	OUI	OUI	Vaccin conjugué 13 valences suivi 8 semaines plus tard par le 23 valences	 OUI OUI
Influenza	Inactivé	OUI	OUI	Injection annuelle	OUI
Coqueluche	Inactivé	OUI	OUI	Mettre à jour (population non vaccinée dans l'enfance) Rappel tous les 10 ans (coqueluche)	NON
Diphtérie Tetanos	Inactivé Inactivé	OUI	OUI OUI		NON OUI
Neisseria meningitidis	Inactivé	OUI	OUI	Effectuer avant triatement par Eculizimab	NON
Rougeole-Oreillons-Rubéole	Vivant atténué	OUI	NON	Mettre à jour avant tout traitement immunosuppresseurs Chez l'adulte vérifier préalablement la sérologie	OUI
Varicelle	Vivant atténué	OUI	NON		OUI

Zahar JR.: [Prevention of infectious diseases in patients with chronic renal failure]. Nephrol Ther. 2019 Apr;15 Suppl 1:S21-S26

Infectious risks and solutions

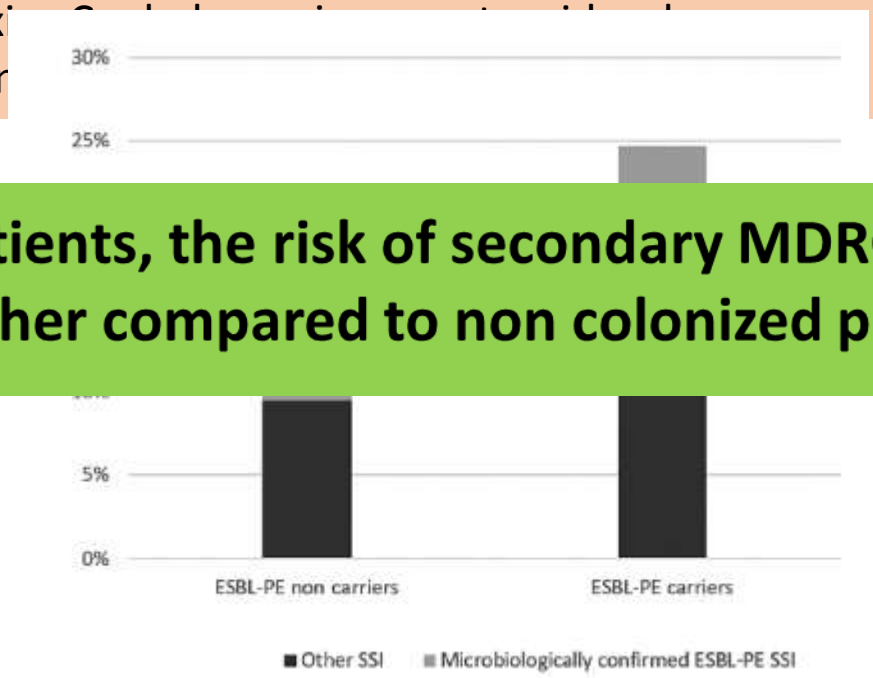


Patients colonized with MDRO	Identifying at risk patients Rectal sampling
Numerous invasive procedures	Reduce duration
High care load	Standard precautions Single bed room
High immunosuppression	Standard precautions Enhance cleaning Environmental control

Infectious risks and solutions

- Reduce the risk of post operative MDRO infection
- Adapt antibiotic prophylaxis to previous MDRO colonisation ?

Prospective cohort study
Patients undergoing colorectal surgery (2012-2017)
Exposed pouplation : ESBL-PE carriers; Unexposed population : Non –carriers
Antibiotic prophylax
3626 patients screen



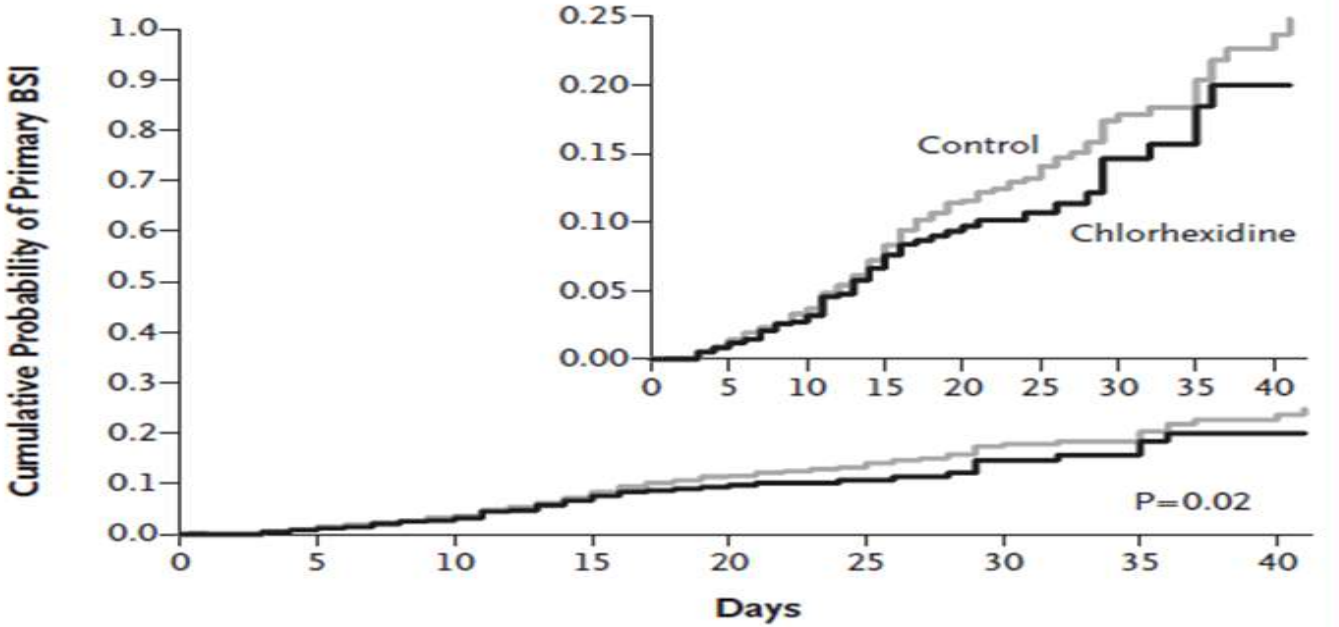
In previous colonized patients, the risk of secondary MDRO related infection seems to be higher compared to non colonized patients !!

Dubinsky-Pertzov B,; R-GNOSIS WP4 study group. Carriage of extended-spectrum beta-lactamase-producing Enterobacteriaceae and the risk of surgical site infection after colorectal surgery: a prospective cohort study. Clin Infect Dis. 2018 Sep 10.

How can we reduce the risk in previous colonized patients ?

- **Reducing the risk means**
  - Reducing the risk of MDRO translocation — adapting antibio prophylaxis ?
  - Reducing the risk of MDRO HAI — reducing invasive procedures? reducing MDRO colonization ?
  - Reducing the MDRO relative abondance (ie, [MDRO]) — Using SDD ?

Effect of Daily Chlorhexidine Bathing on Hospital-Acquired Infection

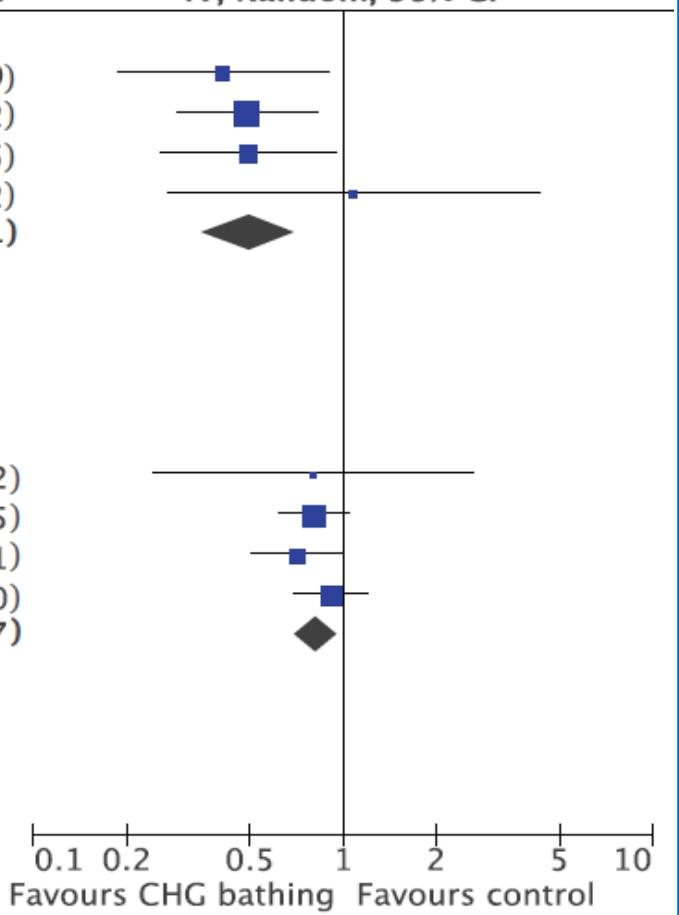


No. at Risk								
Control	1398	582	346	218	143	94	59	37
Chlorhexidine	1410	616	391	242	151	95	60	36
Total Cumulative No. of Primary BSIs								
Control	33	55	80	101	114	119	122	127
Chlorhexidine	26	44	64	73	75	80	83	84

Climo *et al,* New Eng J Med 2013

Use of antiseptic bathing to reduce the risk of HAI

Study or subgroup	CHG bathing Events	Total	Control Events	Total	Weight	Odds ratio IV, Random, 95% CI
1.7.1 CLABSI						
Bleasdale 2007	9	2,210	21	2,119	20.1%	0.41 (0.19−0.89)
Climo 2013	21	24,931	43	25,000	45.1%	0.49 (0.29−0.82)
Milstone 2013	13	15,057	28	16,024	28.4%	0.49 (0.26−0.95)
Noto 2015	4	19,202	4	20,721	6.4%	1.08 (0.27−4.32)
Subtotal		**61,400**		**63,864**	**100.0%**	**0.50 (0.35−0.71)**
Total events	47		96			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.45$, df = 3 ($p = 0.69$); $I^2 = 0\%$						
Test for overall effect: $Z = 3.90$ ($p < 0.0001$)						
1.7.2 Non-central line BSI						
Bleasdale 2007	5	2,210	6	2,119	1.9%	0.80 (0.24−2.62)
Climo 2013	98	24,931	122	25,000	38.6%	0.80 (0.62−1.05)
Milstone 2013	53	15,057	79	16,024	22.6%	0.71 (0.50−1.01)
Noto 2015	96	19,202	113	20,721	36.9%	0.92 (0.70−1.20)
Subtotal		**61,400**		**63,864**	**100.0%**	**0.82 (0.70−0.97)**
Total events	252		320			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.28$, df = 3 ($p = 0.73$); $I^2 = 0\%$						
Test for overall effect: $Z = 2.33$ ($p = 0.02$)						
Test for subgroup differences: $Chi^2 = 6.41$, df = 1 ($p = 0.01$), $I^2 = 84.4\%$						

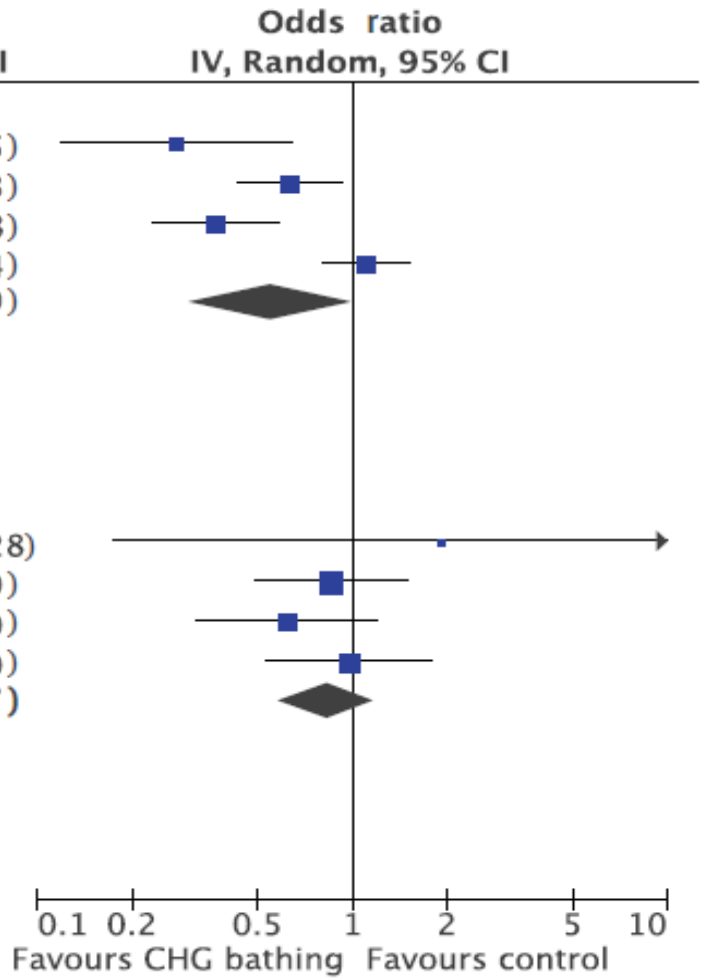


Afonso *et al,* Eurosurevillance 2016

Use of antiseptic bathing to reduce the risk of HAI

Subgroup analysis of rates of hospital-acquired Gram-positive and Gram-negative bloodstream infections per patient days (n = 4 studies)

Study or subgroup	CHG bathing Events	Total	Control Events	Total	Weight	Odds ratio IV, Random, 95% CI
1.1 Gram-positive BSI						
Bleasdale 2007	7	2,195	24	2,115	18.8%	0.28 (0.12–0.65)
Climo 2013	43	24,931	68	25,000	27.2%	0.63 (0.43–0.93)
Milstone 2013	25	15,057	72	16,024	25.9%	0.37 (0.23–0.58)
Noto 2015	74	19,202	72	20,721	28.1%	1.11 (0.80–1.54)
Subtotal		**61,385**		**63,860**	**100.0%**	**0.55 (0.31–0.99)**
Total events	149		236			
Heterogeneity: $Tau^2 = 0.29$; $Chi^2 = 20.09$, df = 3 (p = 0.0002); $I^2 = 85\%$						
Test for overall effect: Z = 1.99 (p = 0.05)						
1.2 Gram-negative BSI						
Bleasdale 2007	2	2,195	1	2,115	2.1%	1.93 (0.17–21.28)
Climo 2013	23	24,931	27	25,000	38.3%	0.85 (0.49–1.49)
Milstone 2013	14	15,057	24	16,024	27.3%	0.62 (0.32–1.20)
Noto 2015	20	19,202	22	20,721	32.3%	0.98 (0.54–1.80)
Subtotal		**61,385**		**63,860**	**100.0%**	**0.83 (0.59–1.17)**
Total events	59		74			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.52$, df = 3 (p = 0.68); $I^2 = 0\%$						
Test for overall effect: Z = 1.04 (p = 0.30)						



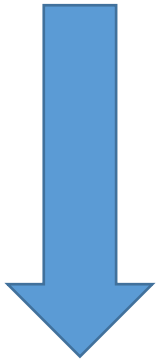
Afonso *et al,* Eurosurevillance 2016

SDD: how does it (theorically) work ?

Control of gut overgrowth

- Eradicating potentially pathogenic micro organisms
  - Oral, gastric and intestinal « flora »
- Sparing anaerobes species
- Topical application of non absorbable antibiotics

High rate carriage (>10^5 pathogens/g digestive tract secretions



Increase the risk of infections

Soutenbeek *et al,* Intensive Care Med 1984
Van Saene *et al,* J Hosp Inf 1996
Silvestri *et al,* Intensive Care Med 2012

SDD/SOD: any results ?

Selective digestive tract decontamination and selective oropharyngeal decontamination and antibiotic resistance in patients in intensive-care units: an open-label, clustered group-randomised, crossover study

- Open label clustered group randomized study
- 13 ICU's included, 5927 patients

BACTEREMIA

adapted and constantly reassesse

	Standard care (n=1837)	SOD (n=1768)	SDD (n=1868)	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

Data are n (%), unless otherwise stated. SOD=selective oropharyngeal decontamination. SDD=selective digestive tract decontamination. 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*).

Smet *et al,* Lancet inf Dis 2011

Health acquired infection : The mechanical hypothesis

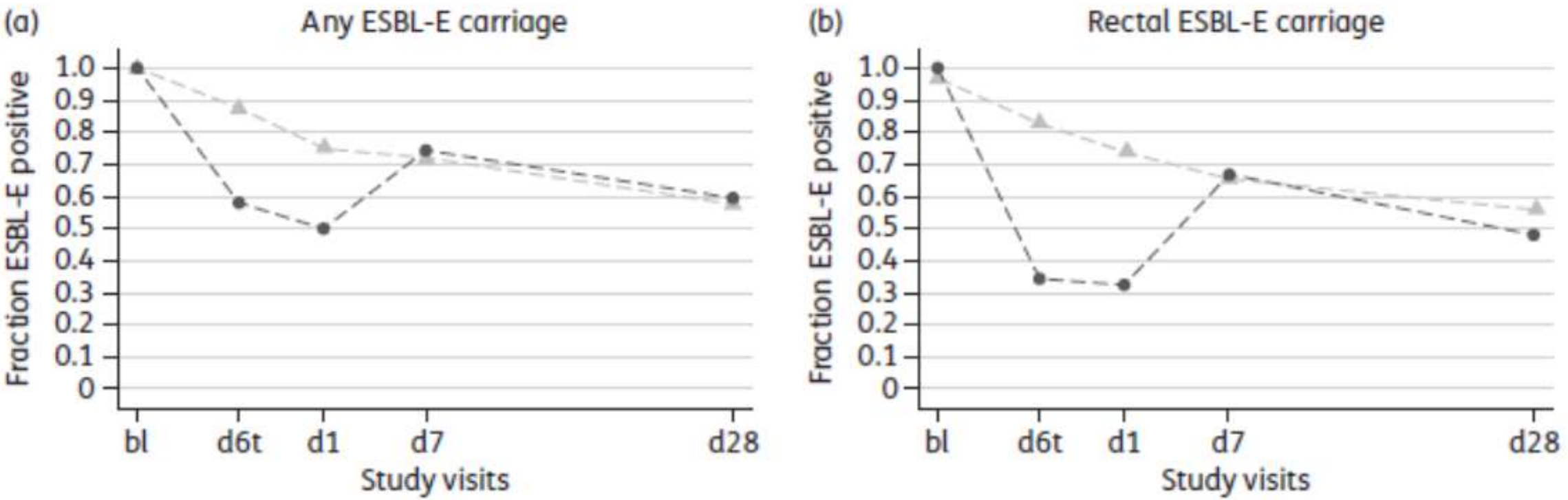
Relative Fecal Abundance of Extended-Spectrum-β-Lactamase-Producing *Escherichia coli* Strains and Their Occurrence in Urinary Tract Infections in Women

TABLE 3 ESBL-RA as a predictor of UTI caused by ESBL *E. coli* for the 31 women not exposed to antibiotics

	Concordance determined according to[a]:			
ESBL-RA value (%)	Sens	Spec	PPV	NPV
10–100	0.57	0.77	0.57	0.88
1–10	0.57	0.61	0.33	0.84
0.1–1	0.86	0.45	0.35	0.93
0.01–0.1	1.00	0.10	0.26	1.00
0.001–0.01	1.00	0.03	0.23	1.00

Ruppé *et al,* Antimicrob Agents Chemother 2013

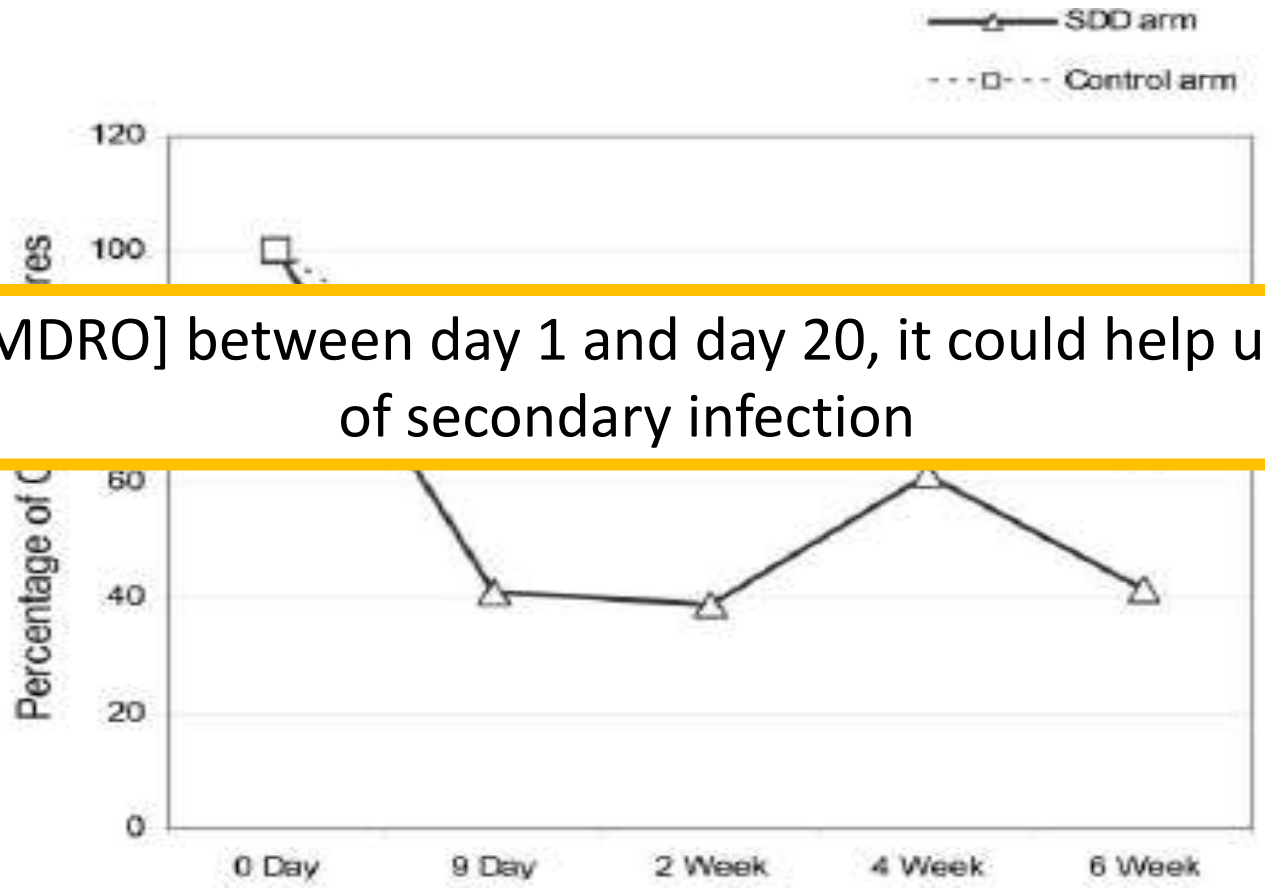
Reducing the bacterial concentration ?



Huttner *et al,* J Antimicrob Chemotherapy 2013

Reducing the bacterial concentration ?

A Randomized, Double-Blind, Placebo-Controlled Trial of Selective Digestive Decontamination Using Oral Gentamicin and Oral Polymyxin E for Eradication of Carbapenem-Resistant *Klebsiella pneumoniae* Carriage



If SDD reduce the [MDRO] between day 1 and day 20, it could help us to reduce the risk of secondary infection

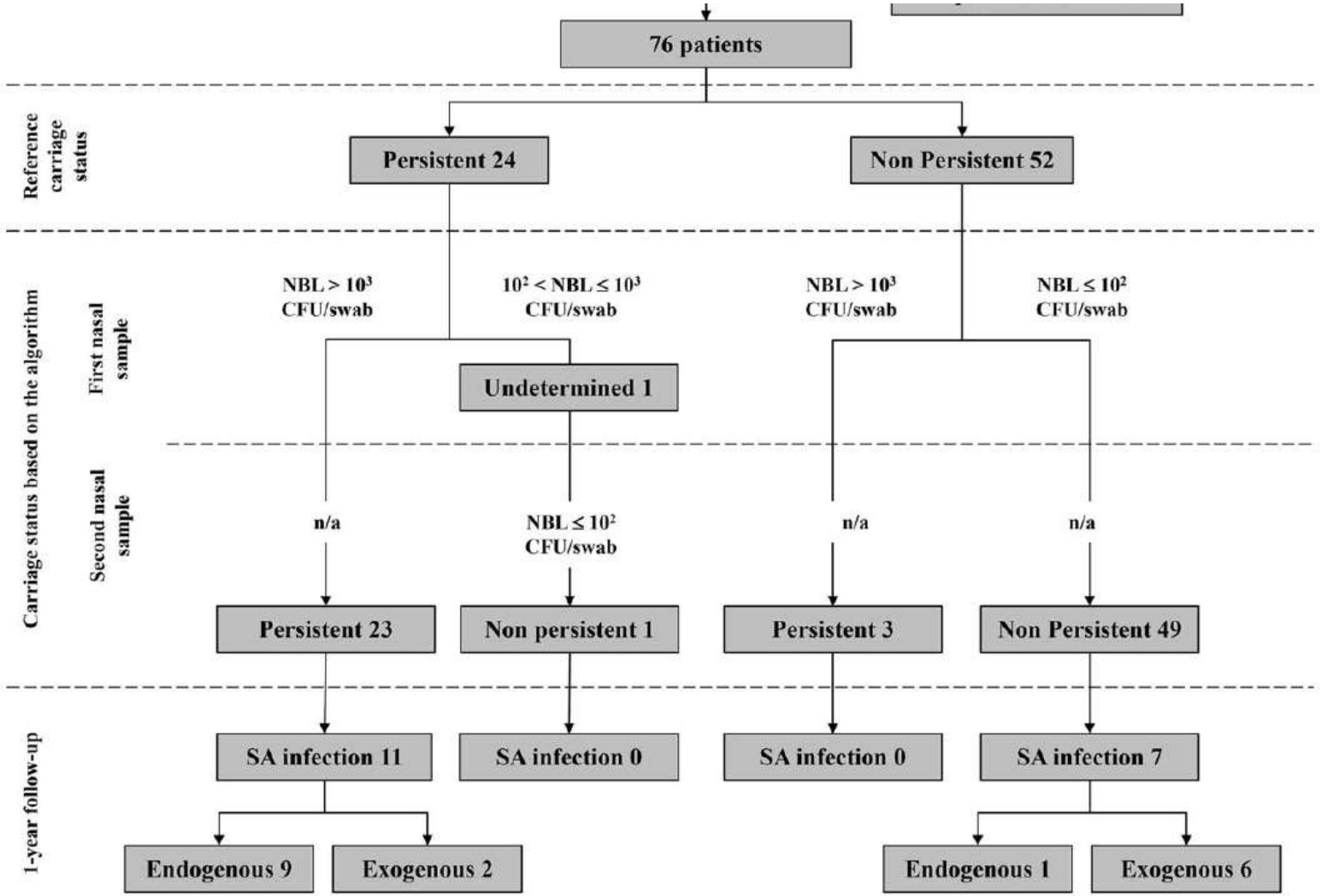
Saidel-Odes *et al*, ICHE 2014

Fecal microbial transplantation (FMT)?

- Proven to be an effective treatment for *Clostridium difficile* infections
- Several case reports in patients with recurrent MDRO infections
- Animal models, suggesting that FMT could be an effective treatment for reducing MDRO carriage
- Impact of immunosuppression is not evaluated: FMT is usually discouraged in immunocompromised patients due to possible septic complications

And the future ?

Identifying Hemodialysis Patients With the Highest Risk of *Staphylococcus aureus* Endogenous Infection Through a Simple Nasal Sampling Algorithm



Verhoeven PO, Identifying Hemodialysis Patients With the Highest Risk of Staphylococcus aureus Endogenous Infection Through a Simple Nasal Sampling Algorithm. Medicine (Baltimore). 2016 Apr;95(14):e3231

Identifying Hemodialysis Patients With the Highest Risk of *Staphylococcus aureus* Endogenous Infection Through a Simple Nasal Sampling Algorithm

TABLE 5. Bacterial Infections in Hemodialysis Patients According to the Nasal Carriage Status Determined by the Reference Definition or by the Algorithm Based on 1 or 2 Nasal Samples

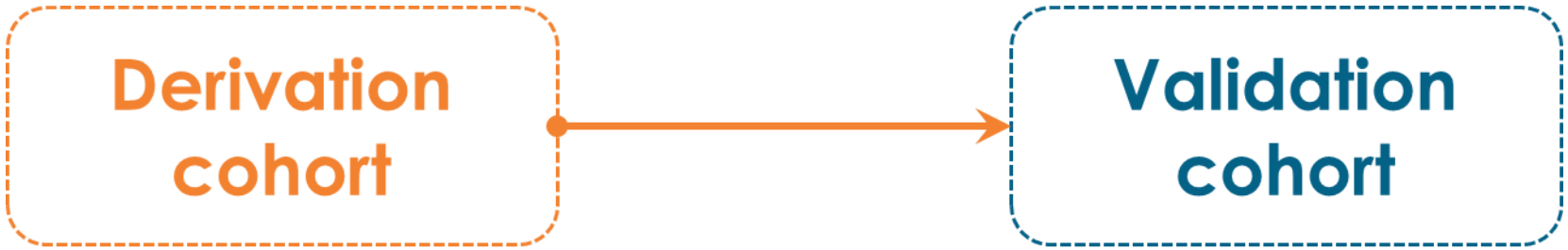
	***S. aureus* Carriage State Based on the Reference Definition**			***S. aureus* Carriage State Based on the Algorithm**		
Episodes of Bacterial Infections	**Persistent (n = 24)**	**Nonpersistent (n = 52)**	***P****	**Persistent (n = 26)**	**Nonpersistent (n = 50)**	***P****
Episodes of *S. aureus* infection (incidence in %)	11 (45.8)	7 (13.5)	<0.01	11 (42.3)	7 (14.0)	<0.05
With a strain similar to that of the nose†	9 (37.5)	1 (1.9)	<0.001	9 (34.6)	1 (2.0)	<0.001
With a strain different to that of the nose†	2 (8.3)	6 (11.5)‡	NS	2 (7.7)	6 (12.0)‡	NS
Episodes of non-*S. aureus* infection (incidence in %)	13 (54.2)	25 (48.1)	NS	11 (45.8)	27 (51.9)	NS

Verhoeven PO, Identifying Hemodialysis Patients With the Highest Risk of Staphylococcus aureus Endogenous Infection Through a Simple Nasal Sampling Algorithm. Medicine (Baltimore). 2016 Apr;95(14):e3231

A simple immunological risk score to predict infection in kidney transplant recipients (the SIMPLICITY score): derivation and multi-centre external validation

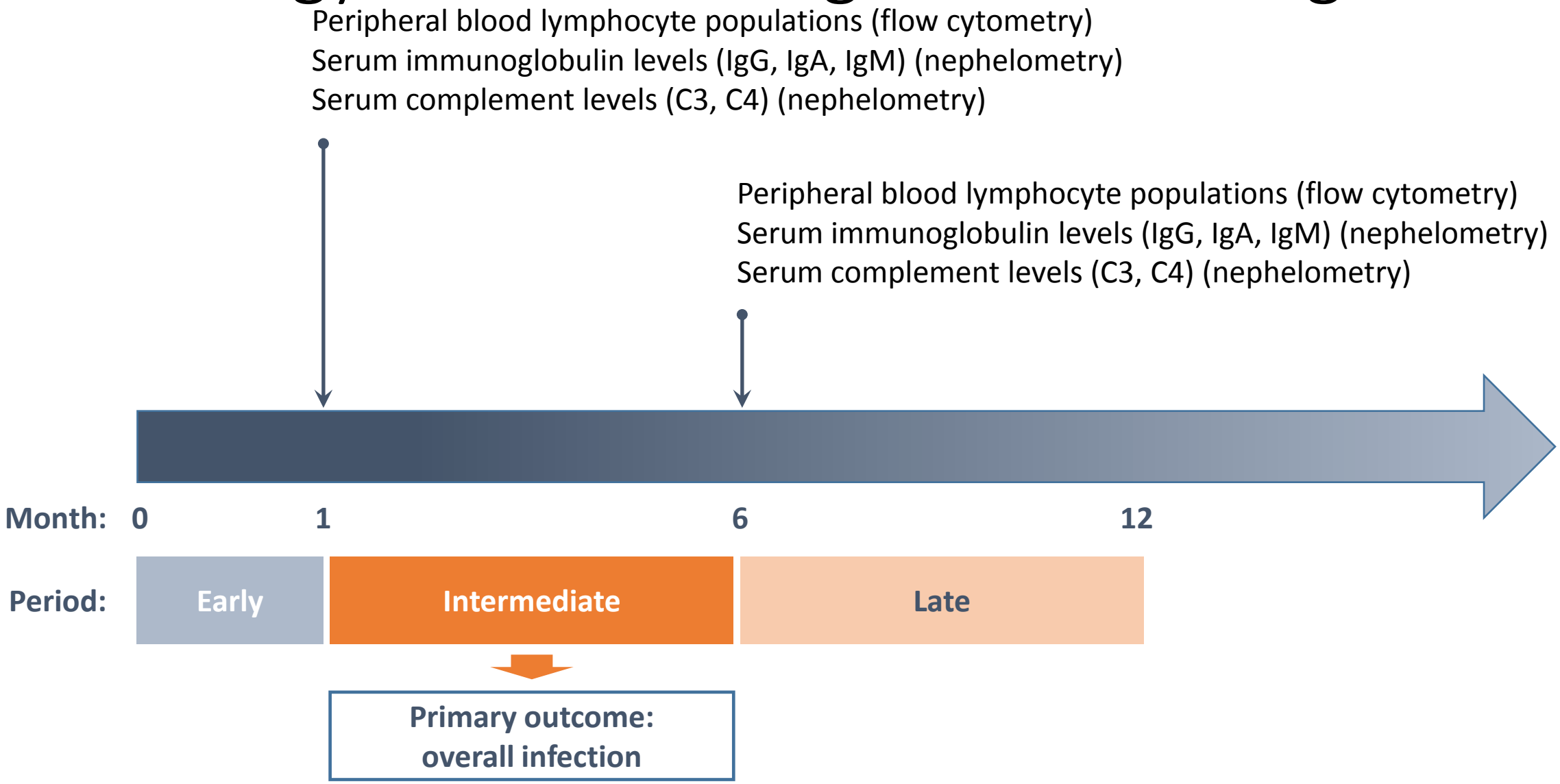
To develop a **weighted risk score** based on **simple immune parameters** and **clinical variables** to predict the occurrence of infection among KT recipients recruited in **a single-center cohort**

To **externally validate** the resulting score in a **prospective multicentre cohort**



M. Fernandez. A simple immunological risk score to predict infection in kidney transplant recipients (the SIMPLICITY score): derivation and multi-centre external validation. O0702, ESCMID 2019

Strategy for immunological monitoring

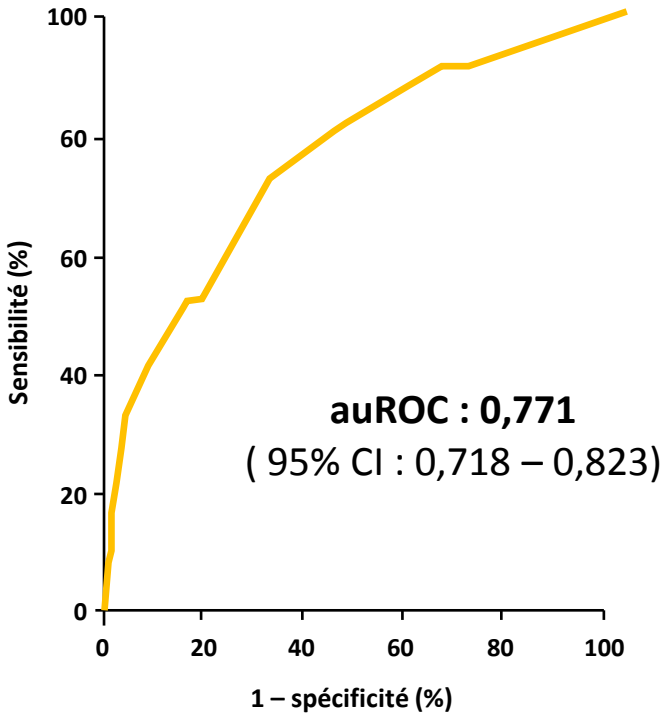


Derivation cohort: incidence of infection between 1 and 6 months = 33.2%.
Validation cohort: incidence of infection between 1 and 6 months = 19.6%.

Variable	ß regression coefficient (95% CI	Score
Âge du bénéficiaire ≥ 62 ans	0.94 (0.36 – 1.50)	3
DFG * (à 1 mois) < 37 ml/min	0.69 (0.18 – 1.23)	3
InFection au cours du 1er mois après la transplantation	0.85 (0.25 – 1.46)	3
Taux de CD4 < 40 cells/µL	0.94 (0.17 – 1.70)	3
Taux de CD8 < 155 cells/µL	0. 56 (-0.07 – 1.18)	2
Taux sérique IgG < 500 mg/dL	0.71 (-0.03 – 1.44)	3
Taux sérique C3 < 78 mg/dL	1.14 (0.39 – 1.88)	4

M. Fernandez. A simple immunological risk score to predict infection in kidney transplant recipients (the SIMPLICITY score): derivation and multi-centre external validation. O0702 ESCMID 2019

Performance du score pour la prédiction du risque d'infection entre 1 et 6 mois



Valeur diagnostique du score pour la survenue d'infection entre 1 et 6 mois

Cohorte de dérivation

SIMPLICITY score	Pourcentage de patients (%)	Sensibilité (95% CI)	Spécificité(95% CI)	VPP (95% CI)	VPN (95% CI)
Score ≥0	100.0	100. 0 (97.0 - 100.0)	0.0 (0.0 -1.5)	32.5 (32.5 – 32.5)	NA
Score 2	**32.9%**	91.8 (85.4 – 96.0)	30.0 (24.5 – 36.1)	38.8 (36.5 – 41.1)	**VPN: 88.4%**
Score ≥4	56.8	81.9 (73.9 – 88.3)	55.3 (48.9 – 61.6)	46.9 (42.9 – 50.9)	86.4 (81.1 - 90.4)
Score ≥6	44.5	72.9 (64.2 – 80.6)	69.2 (63.1 – 74.8)	53.3 (47.9 – 58.6)	84.1 (79.7 – 87.8)
Score ≥8	27.5	52.5 (43.2 – 61.6)	84.6 (79.5 – 88.8)	62.1 (54.0 – 69.6)	78.7 (75.3 – 81.8)
Score 10	**15.5%**	36.9 (28.3 – 46.1)	94.9 (91.4 – 97.2)	**VPP: 77.6%**	75.7 (73.1 – 78.2)
Score ≥12	7.2	19.7 (13.0 – 27.8)	98.8 (96.6 – 99.8)	88.9 (71.1 – 96.3)	71.8 (70.0 – 73.6)
Score ≥14	3.7	9.8 (5.2 – 16.6)	99.2 (97.2 – 99.9)	85.7 (57.7 – 96.4)	69.5 (68.3 – 70.8)

M. Fernandez. A simple immunological risk score to predict infection in kidney transplant recipients (the SIMPLICITY score): derivation and multi-centre external validation. O0702 ESCMID 2019

Conclusion

- Infection control can and should start by prevention

- To prevent we have to take into account three parameters
  - The individual one : Comorbidities, other diseases, age
  - The one due to kidney disease : treatment, duration (the cumulative risk)
  - The one due to risk exposure (type, duration, frequency)

- The prevention should be adapted and and constantly reassessed