MANAGEMENT OF INFECTIONS IN MULTIPLE MYELOMA

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Multiple myeloma patients have **an increased risk** for infections

- population based study from Sweden
- n = 9,253 MM patients diagnosed between 1988 and 2004 and 34,931 matched controls (follow-up till 2007)
- MM patients had a **7-fold** increased risk for developing any infection compared to matched controls
- type of infections:
  - **bacterial: 7-fold** increased risk
  - **viral: 10-fold** increased risk

Disease	Myeloma (n=9 253)	Total Controls (n=34 931)	HR* (95%CI)
Any infection (combined)**	3781	6519	7.1 (6.8-7.4)
Specific infections			
Bacterial***	3361	5792	7.1 (6.8-7.4)
Pneumonia	2150	3504	7.7 (7.2-8.1)
Osteomyelitis	37	100	3.5 (2.4-5.2)
Septicemia	1336	960	15.6 (14.3-17.1)
Pyelonephritis	152	570	2.9 (2.4-3.5)
Cellulitis	164	564	3.0 (2.5-3.6)
Meningitis	51	28	16.6 (10.2-27.1)
Endocarditis	35	73	5.3 (3.4-8.1)
Viral****	607	556	10.0 (8.9-11.4)
Influenza	150	245	6.1 (4.9-7.6)
Herpes zoster	282	171	14.8 (12.1-18.2)

Blimark et al. Haematologica 2015;100:107

Causes of immune dysfunction in MM

HOST FACTORS

MYELOMA

TREATMENT

Hypogammaglobulinaemia, leukopenia, organ damage (renal, bone)

comorbidities: renal, respiratory, cardiac

neutropenia

B- and T-cell lymphopenia

(NK-, dendritic cell deficiency)

age, frailty

mucosal barrier damage

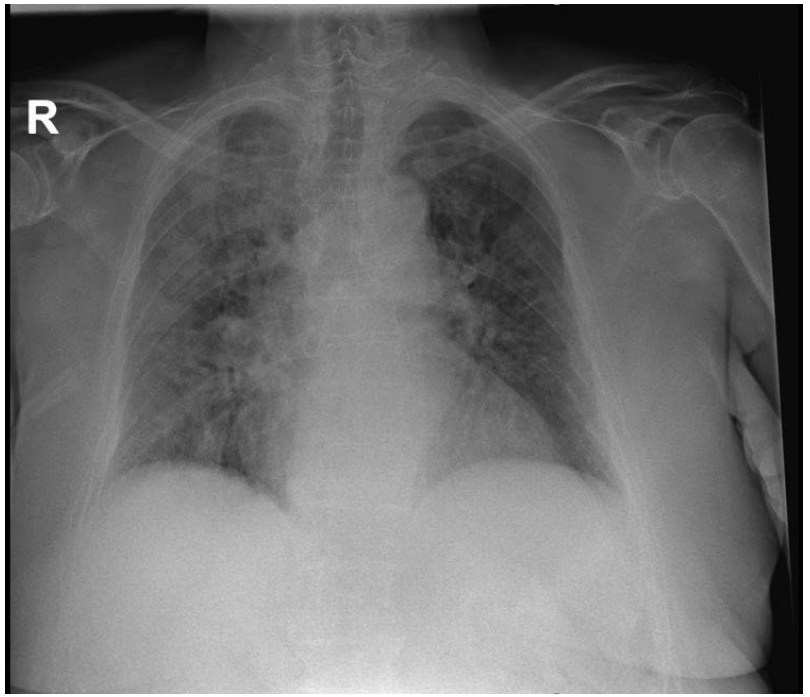
Immune suppression according to drug classes

	Neutropenia	Lymphopenia	Hypogammaglobulinemia
Chemotherapy	XX	X	X
Steroids		X	
IMiDs	X		
PI	X	X	
Anti-CD38 MoAb	X	X	XX
Anti-BCMA	XX	X	XX

IMiDs: Immmunomodulatory Drugs
PI: Proteasome inhibitors
MoAb: Monoclonal Antibody
BCMA: B-Cell Maturation Antigen

Most common pathogens in multiple myeloma

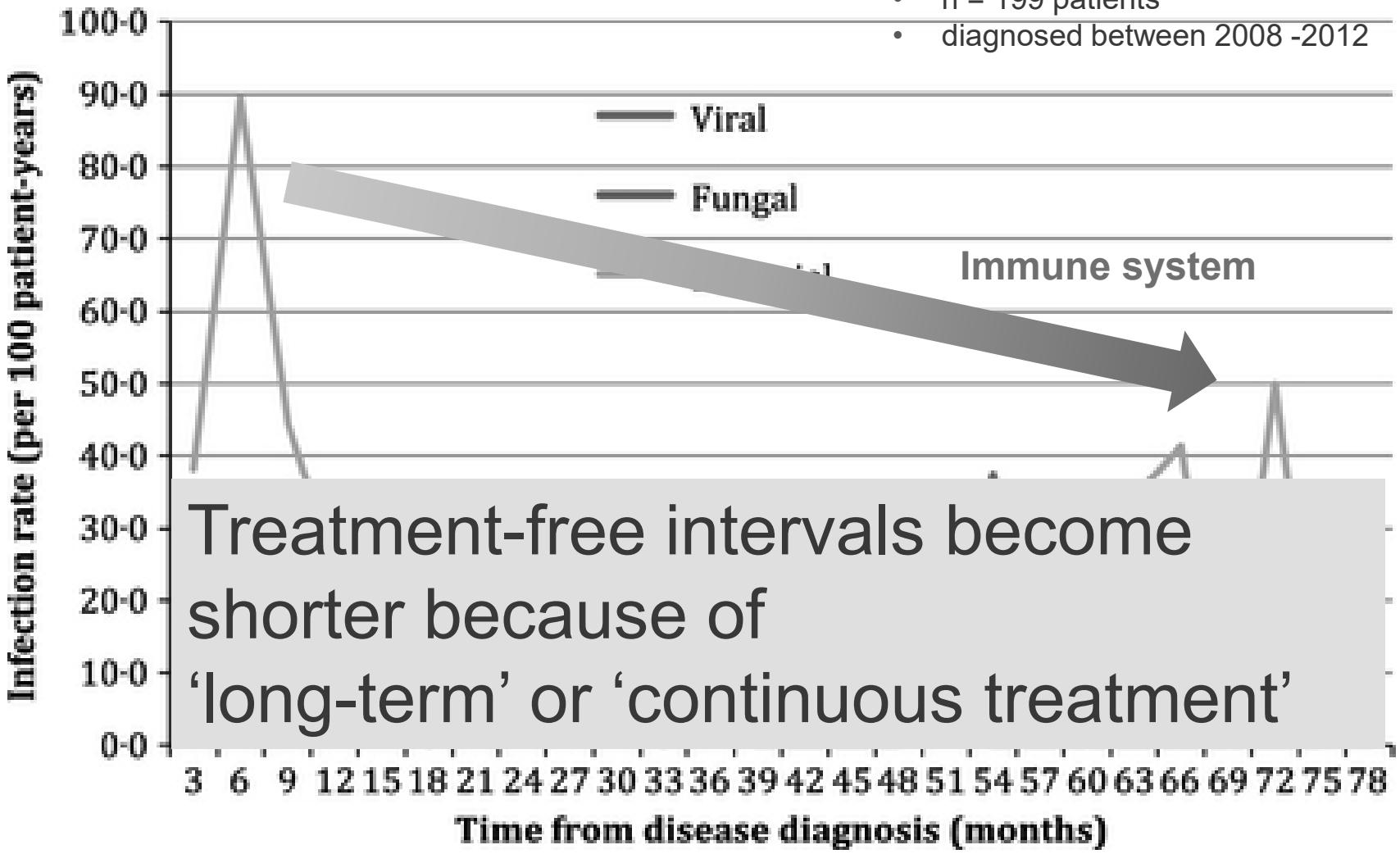
- **Bacterial**
  - Germs:
    - Gram-positive (S. pneumoniae, S. aureus, coagulase-negative staphylococci),
    - Gram-negative (H. influenzae, Enterobacteriaceae)
- **Viral**
  - Varicella-zoster virus, cytomegalovirus
  - Influenza
  - Hepatitis B or C
  - SARS-CoV-2
- **Opportunistic**
  - Pneumocystis jirovecii
  - invasive aspergillosis



Nucci & Anaissie. Clin Infect Dis 2009;49:1211
Delforge & Ludwig. Blood 2017;129:2359
Ludwig et al. Leukemia 2021;35:31

Infections during the course of myeloma

- n = 199 patients
- diagnosed between 2008 -2012

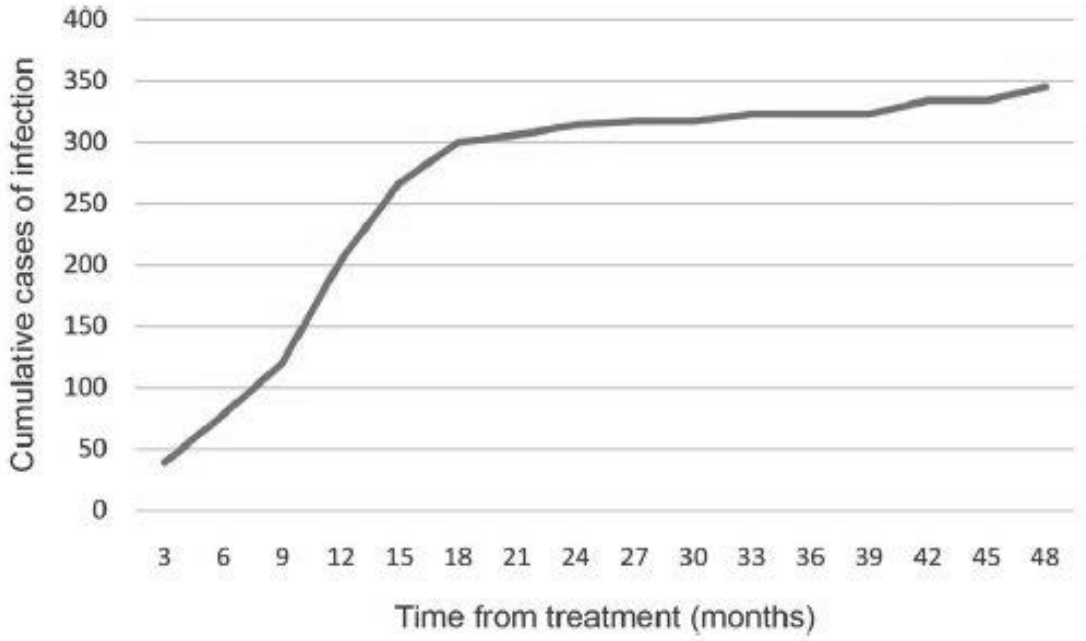


Treatment-free intervals become shorter because of 'long-term' or 'continuous treatment'

adapted from Teh at al. Br J Haematol 2015;17:100

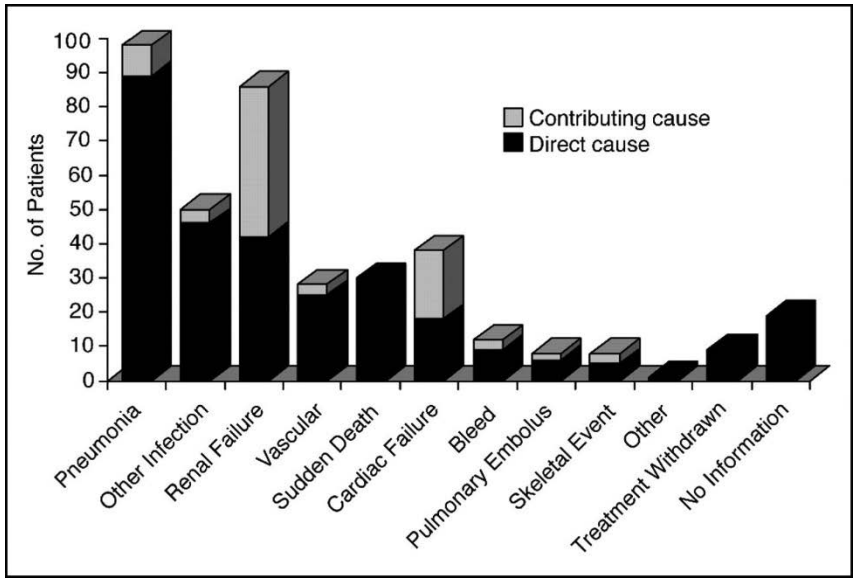
Impact of evolving treatment on infection in MM

Cumulative cases of infection



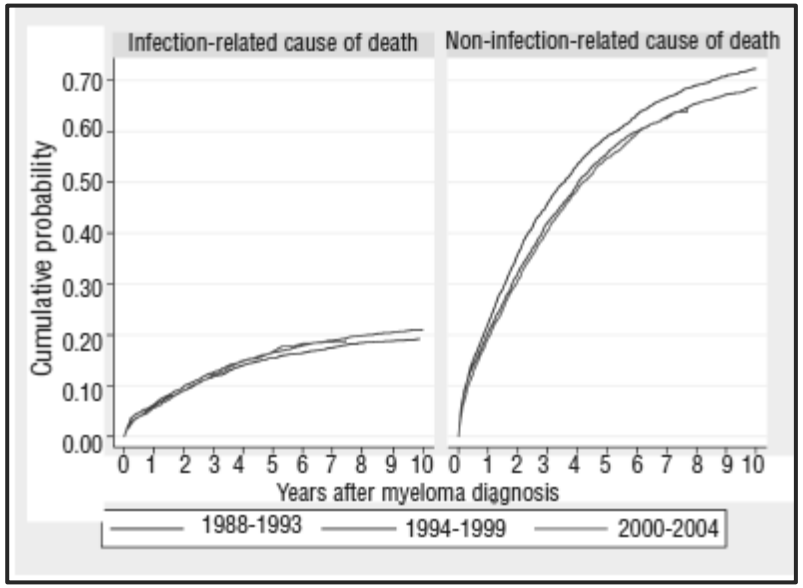
Characteristics of Infection Episodes	Overall No. Infections = 345 (%)
Categories of infection	
Microbiologically defined-bacterial	45 (13.0)
Microbiologically defined-fungal	5 (1.5)
Microbiologically defined-viral	50 (14.5)
Clinically defined	200 (58.0)
Fever of unknown focus	45 (13.0)
Sites of infection	
Respiratory tract	196 (56.8)
Urinary tract	17 (4.9)
Gastrointestinal tract	38 (11.0)
Skin and soft tissue	29 (8.4)
Blood	17 (4.9)
Multiple	3 (0.9)
Unknown	45 (13.0)
Treatment within 30 days of infection episode	
IMiD-based	43 (12.5)
PI-based	71 (20.6)
mAb-based	22 (6.4)
IMiD + PI combination	110 (31.9)
mAb combination with IMiD, PI	99 (28.7)

Infection-related early **mortality** in patients with MM



- 3,107 newly diagnosed MM patients from UK MRC MM trials between 1980 and 2002
- death rated within 2 months: **10%**
- **45%** of deaths attributable to infection
- renal failure as predisposing factor

Augustson et al. J Clin Oncol 2005;23:9219



- Swedish population based study
- n = 9,253 diagnosed between 1988 and 2004
- death rate within 2 months: **10%**
- **22%** of deaths attributable to infection
- 3y death risk of infection: 12% (vs 2% in controls)

Blimark et al. Haematologica 2015;100:107

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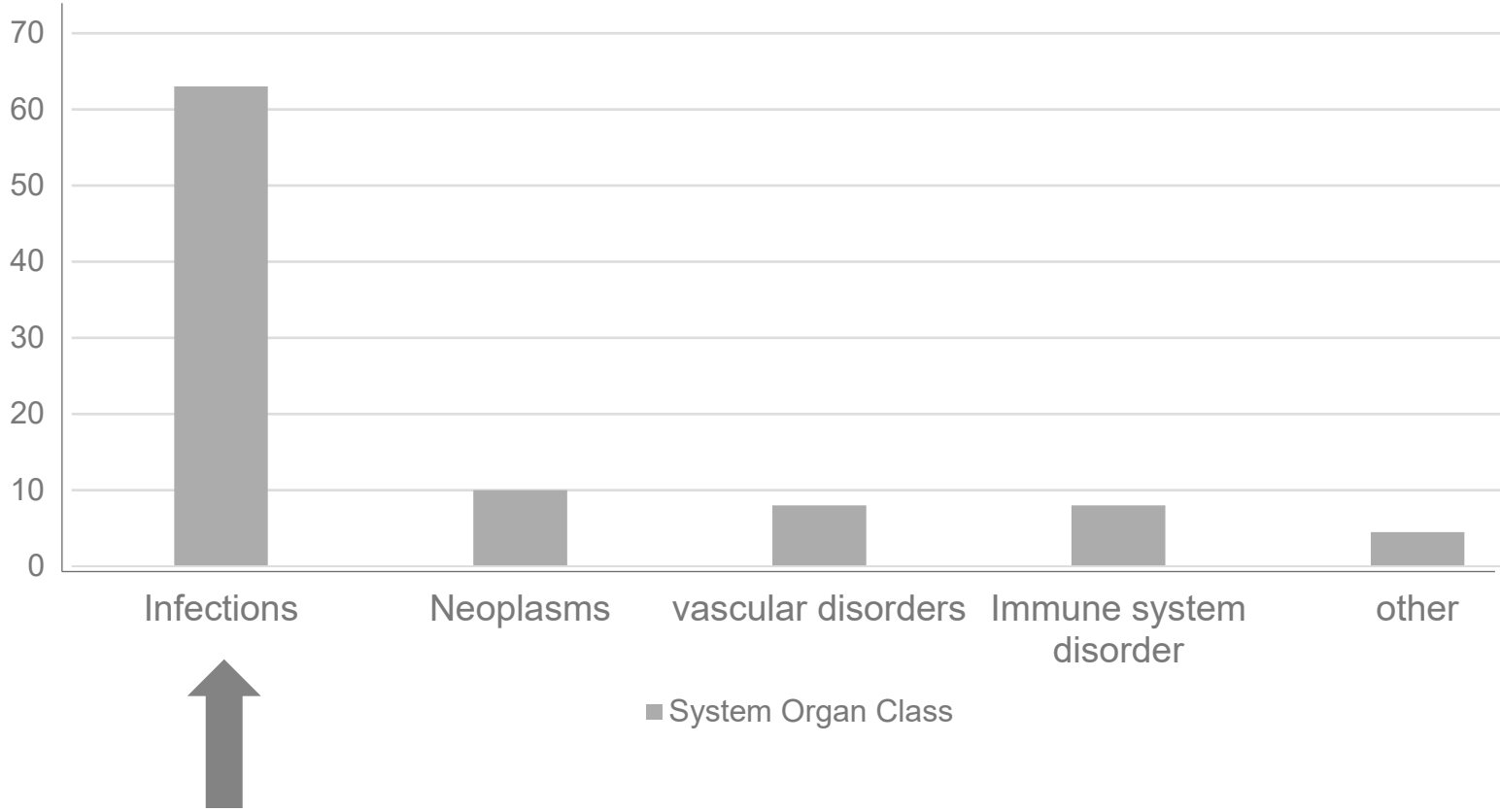
Therapy-related causes of death in MM

transplant-eligible patients

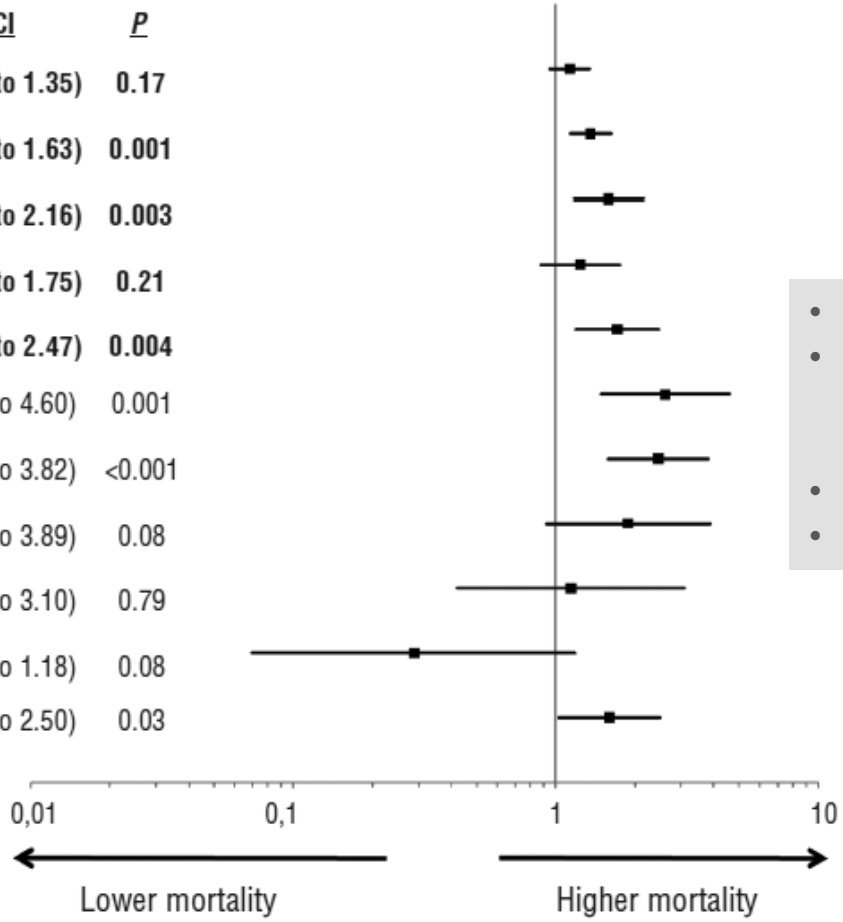


- n = 818 MM patients
- treated between 1992 -2013
- Upfront treated with ASCT
- Causes of death classified according to MedDRA terminology (System Organ Class)

Therapy-related causes of death in MM

non transplant-eligible patients

	HR 95% CI	*P*
Male	**1.13 (0.95 to 1.35)**	**0.17**
Age ≥ 75 years	**1.36 (1.14 to 1.63)**	**0.001**
Serum creatinine ≥ 2 mg/dL	**1.59 (1.18 to 2.16)**	**0.003**
Grade 3 to 4 hematologic AEs*	**1.24 (0.88 to 1.75)**	**0.21**
Grade 3 to 4 non-hematologic AEs*	**1.72 (1.19 to 2.47)**	**0.004**
Cardiac AEs*	2.61 (1.49 to 4.60)	0.001
Infective AEs*	2.46 (1.58 to 3.82)	<0.001
Gastrointestinal AEs*	1.89 (0.92 to 3.89)	0.08
Venous thrombosis AEs*	1.14 (0.42 to 3.10)	0.79
Peripheral neuropathy AEs*	0.29 (0.07 to 1.18)	0.08
Drug discontinuation due to AEs*	1.61 (1.03 to 2.50)	0.03



- n = 1435 MM patients
- Patients enrolled in 4 EU trials with bortezomib and/or thalidomide
- Median follow-up of 33 mo
- Median overall survival: 50 mo

Bringhen et al. Haematologica 2013;98:980

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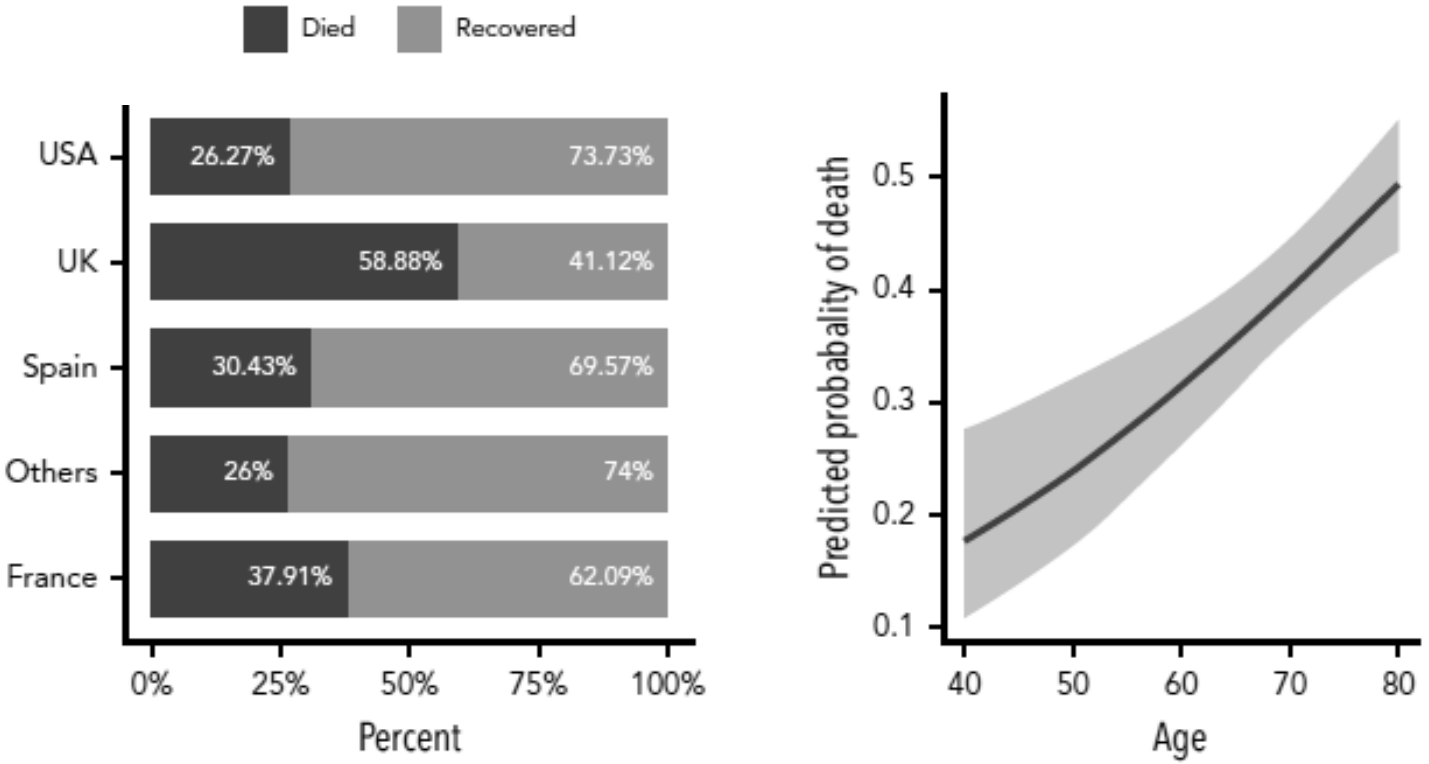
COVID-19: a serious threat for MM patients



N = 650

Infection risk with dara-based combinations in newly diagnosed MM patients

	Dara-Rd[1]	Rd
N	364	365
Grade ≥ 3 neutropenia	**50%**	35%
Grade ≥ 3 Infections	**32%**	23%
Pneumonia	**14%**	8%

	Dara-VTd[1]	VTd
N	536	538
Grade ≥ 3 neutropenia	**28%**	15%
Grade ≥ 3 Infections	**22%**	20%
Pneumonia	**4%**	2%

	Dara-VMP[2]	VMP
N	346	354
Grade ≥ 3 neutropenia	**40%**	39%
Grade ≥ 3 Infections	**23%**	15%
Pneumonia	**11%**	4%

	Dara-VRd[4]	VRd
N	99	102
Grade ≥ 3 neutropenia	**41%**	22%
Grade ≥ 3 Infections	**23%**	22%
Pneumonia	**9%**	11%

1. Facon et al. N Engl J Med 2019;380:2104
2. Mateos et al. N Engl J Med 2018;378:518
3. Moreau et al. Lancet 2019;394:29
4. Voorhees et al. Blood 2020;136:936

Infection risk with anti-CD38 based combinations in relapsed MM patients

	Dara-Kd[1]	Kd
N	308	153
Grade ≥ 3 neutropenia	**10%**	6%
Grade ≥ 3 lymphopenia	7%	7%
Grade ≥ 3 infections*	**27%***	15%*
Pneumonia	**13%**	9%

	Isa-Kd[2]	Kd
N	177	122
Grade ≥ 3 neutropenia	**19%**	7%
Grade ≥ 3 lymphopenia	NR	NR
Grade ≥ 3 infections*	**32%***	24%*
Pneumonia	**21%**	14%

	Dara-Pd[3]	Pd
N	149	150
Grade ≥ 3 neutropenia	**68%**	51%
Grade ≥ 3 lymphopenia	12%	3%
Grade ≥ 3 infections	**24%**	20%
Pneumonia	**11%**	6%

	Isa-Pd[4]	Pd
N	152	149
Grade ≥ 3 neutropenia	**85%**	70%
Grade ≥ 3 lymphopenia	NR	NR
Grade ≥ 3 infections	NR	NR
Pneumonia	**16%**	14%

NR: Not Reported

* respiratory infections

1. Dimopoulos et al. Lancet 2020;396:186
2. Moreau et al. Lancet 2021;397:2361
3. Dimopoulos et al. Lancet Oncol 2021;22:801
4. Attal et al. Lancet 2019;394:2096

Infection risk with T-cell redirecting therapies

Cilta-cel	N = 97	
	Any grade	Grade ≥ 3
neutropenia	96%	**95%**
lymphopenia	53%	50%
Infection	58%	**20%**
hypogammaglobulinemia	NR	NR

Berdeja et al. Lancet 2021: Epub june 24

Ide-cel	N = 128	
	Any grade	Grade ≥ 3
neutropenia	91%	**89%**
lymphopenia	27%	27%
Infection	69%	**22%**
hypogammaglobulinemia	21%	< 1%

Munshi et al. New Engl J Med 2021;348:705

	Teclistamab[1] (RP2D, N = 40)	Elranatamab[2] (N = 30)	Talquetamab[3] (RP2D, N = 30)
grade ≥ 3 neutropenia	40%	53%	60%
grade ≥ 3 lymphopenia	NR	83%	30%
grade ≥ 3 infection	23%	NR	3%

NR: not reported
RP2D: Recommended Phase 2 Dosing

1. Krishan et al. ASCO 2021, abstract 8007
2. Bahlis et al. ASCO 2021, abstract 8006
3. Berdeja et al. ACO 2021, abstract 8008

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Management of neutropenic fever

Patient with neutropenic fever (≥ 38.3°C and ANC < 500/µl)
initial management

Low-risk
- MASCC score ≥ 21
- anticipated neutropenia < 7 days
- no hemodynamic instability

Outpatient management
- blood cultures
- symptom-directed work-up
- IV antibiotics (first dose)
- observe in clinic for ≥ 4 h
- early follow-up in clinic

FQ prophylaxis ?

NO

Oral antibiotic options
- ciprofloxacin plus amoxicillin-clavulanate
- moxifloxacin

YES

Outpatient IV antibiotic
- cefepime

High-risk
- MASCC score < 21
- anticipated neutropenia ≥ 7 days
- stem cell transplantation

Inpatient management
- blood cultures
- symptom-directed work-up
- daily assessment (clinical and laboratory)

Empiric IV antibiotic options
- cefepime
- piperacillin+tazobactam (if anaerobic coverage needed)
- meropenem (if history of ESBL)

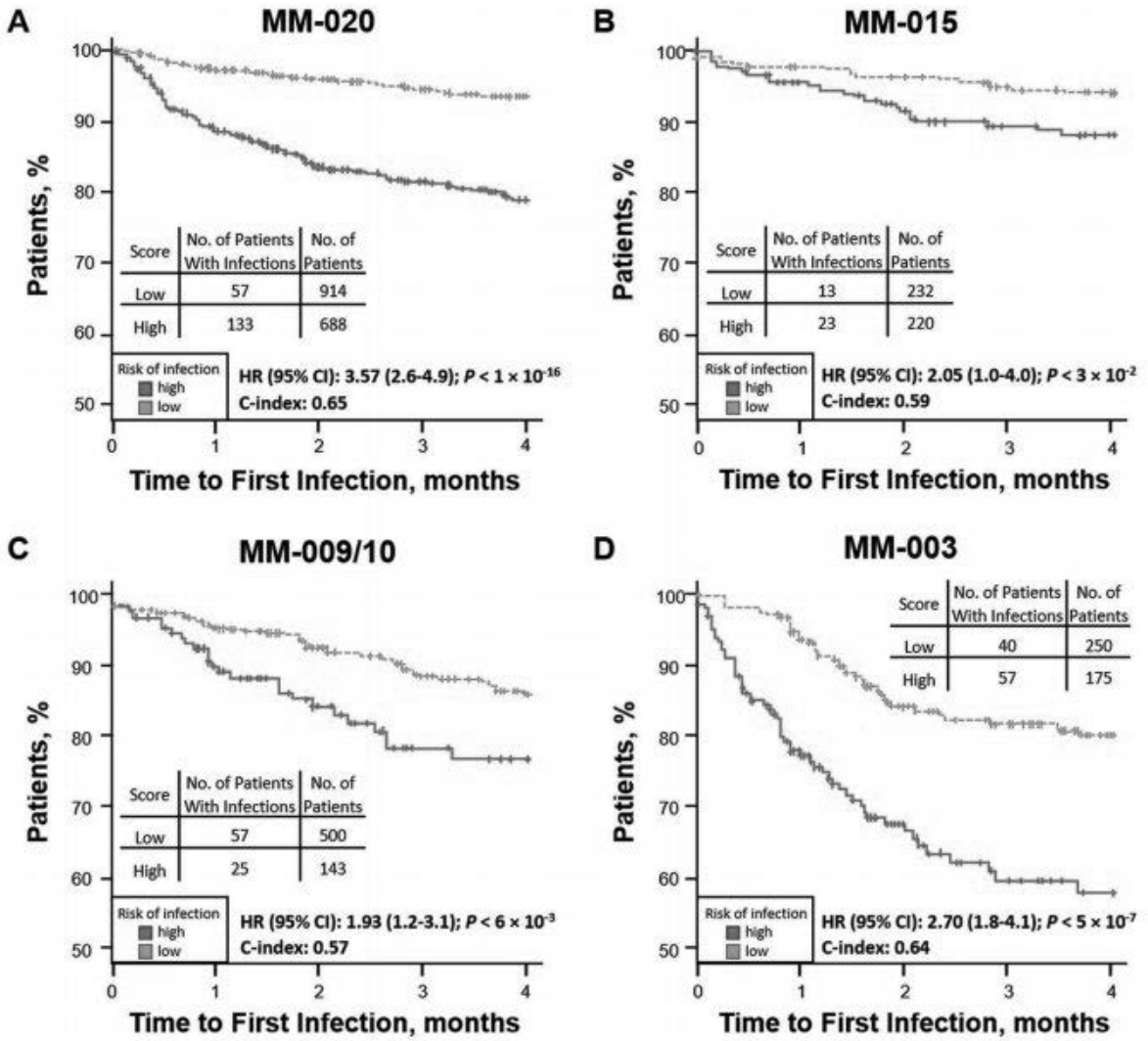
MASCC: Multinational Association for Supportive Care in Cancer
ESBL: extended-spectrum β-lactamase
FQ: fluoroquinolone

adapted from Zimmer et al. J Oncol Pract 2019;15:19

HOW TO PREVENT INFECTIONS

- Awarenes
- Risk assessment
- Prophylactic/pre-emptive treatment
- Vaccination

Risk stratification predictive model for infection in MM



Parameter	Category
ECOG	≥ 2
LDH	≥ 200 U/l
Hemoglobin	≤ 11 g/dl
Serum β2 microglobulin	≥ 6 mg/l

High-risk patiënts had 24% risk of an early severe infection vs 7% in low-risk patients

Risk stratification for infection risk in MM
newly diagnosed elderly and daratumumab-based

- Pooled analysis from Alcyone and Maia data
- Identification of predictive markers for grade ≥ 3 infections during first 6 mo

Parameter	Category	points
Age (y)	≥ 75	4
LDH	High	6
Albumin (g/l)	≤ 35	6
Elevated AST	Abnormal	7

- Patients with ≥ 2 risk factors were at increased risk (29.3% vs 15.7%) for infection during treatment with daratumumab

Predictive factors for Covid-19 outcome in MM patients

Variable	P	OR (95% CI)
Age	**0,006**	1,04 (1,01 - 1,08)
ISS3	0,899	1,05 (0,49 - 2,22)
High-risk disease	**0,013**	2,35 (1,20 - 4,66)
Renal disease	**0,014**	2,71 (1,23 - 6,08)
Active or progressive disease	**0,063**	1,91 (0,96 – 3,81)
Comorbidities	0,711	0,88 (0,44 – 1,75)
Prior anti-CD38	0,558	0,77 (0,31 – 1,85)
Active anti-CD38	0,262	1,68 (0,68 – 4,21)
Active IMiD	0,769	1,10 (0,59 – 2,07)

N = 650; 36% diagnosed in 2019 or 2020; 54% received first-line treatment
Results shown for multivariate analysis

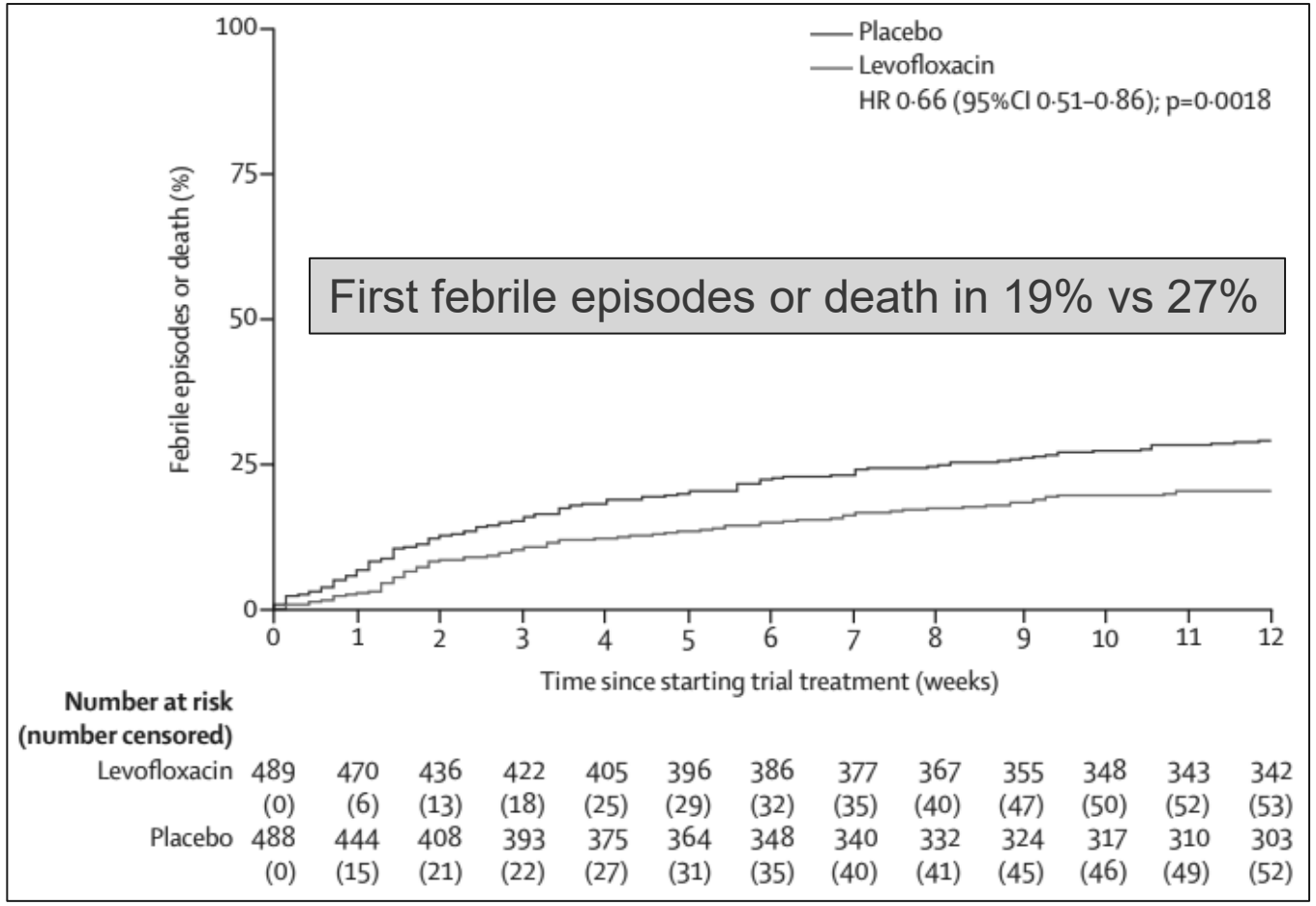
General strategies for infection prevention in MM*

Prophylaxis	agent
antibiotics	fluoroquinolone, (TMP-SMX)
antiviral	VZV prophylaxis • when: post ASCT and during treatment with PI and MoAbs • how: aciclovir, valaciclovir, famciclovir, penciclovir
antifungal	PCJ: • when: in case of severe lymphopenia (CD4 < 200/µl) • how: TMP-SMX/pentamidine Candida • when: high-dose steroids, prolonged neutropenia, broad-spectrum AB • how: azole
G-CSF	Severe neutropenia or moderate neutropenia + risk factors
polyclonal immunoglobulins	secondary prevention of severe bacterial infections

* without vaccination
PCJ:Pneumocystis jerovecii
TMP-SMX: trimethoprim-sulfamethoxazole

adapted from Delforge and Ludwig, Blood 2017; 129:2359

Antibiotic prophylaxis for newly diagnosed MM patients



- n = 977 newly diagnosed patients
- Randomized between 500 mg of oral levofloxacin and placebo for 12 weeks
- Treatment initiated within 2 weeks of start anti-myeloma therapy

Drayson et al. Lancet Oncol 2019;20:1760

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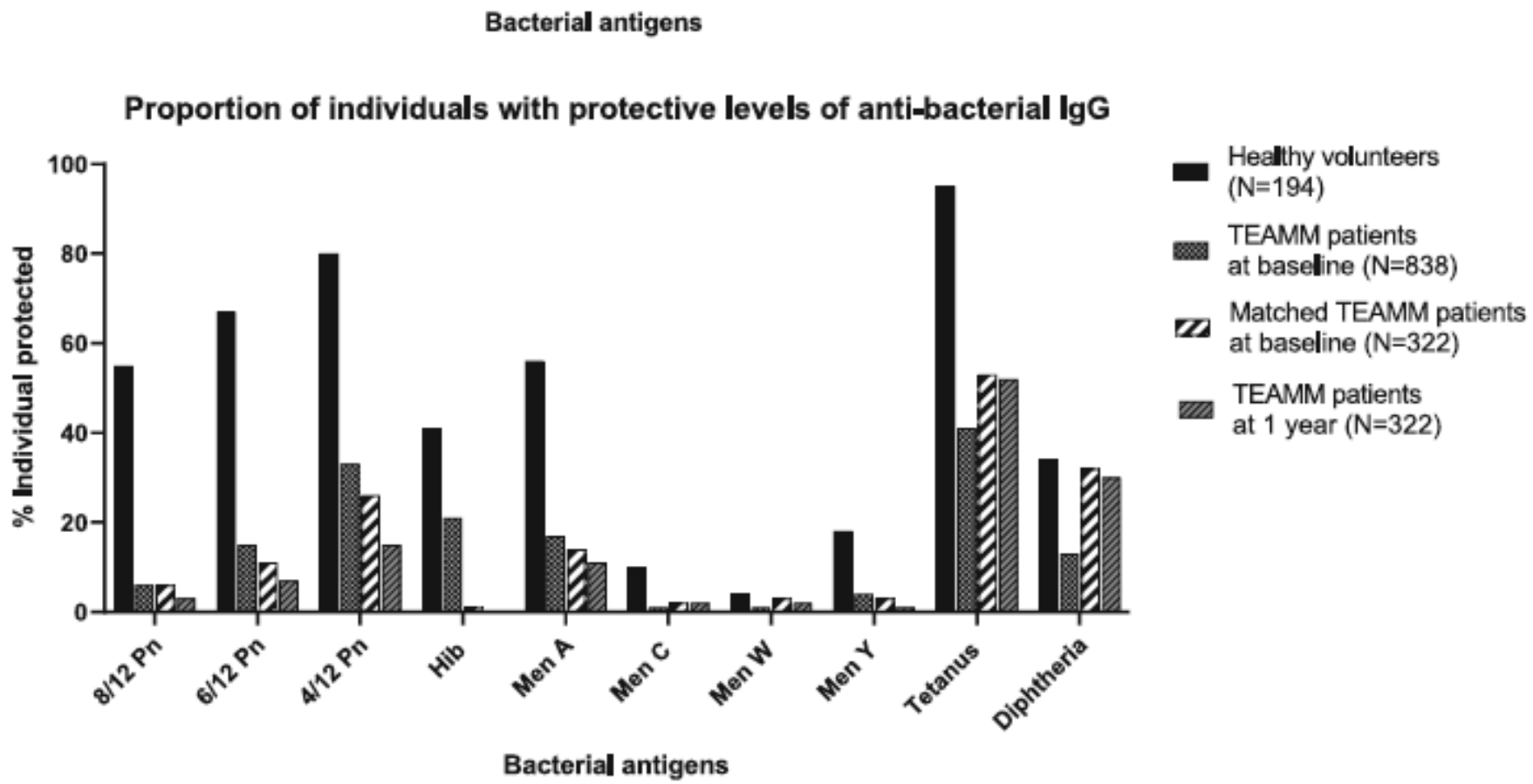
MM patients have low titers of protective antibodies



Chicca et al.Blood Cancer J 2020;10:114

General strategies for infection prevention in MM*

Prophylaxis	agent
antiviral	VZV prophylaxis • when: post ASCT and during treatment with PI and MoAbs • how: aciclovir, valaciclovir, famciclovir, penciclovir Hepatitis B & C: according to viral serology (and PCR)
antifungal	PCJ: • when: in case of severe lymphopenia (CD4 < 200/µl) • how: TMP-SMX/pentamidine Candida • when: high-dose steroids, prolonged neutropenia, antibiotics • how: azole
G-CSF	Severe neutropenia or moderate neutropenia + risk factors
polyclonal immunoglobulins	secondary prevention of severe bacterial infections

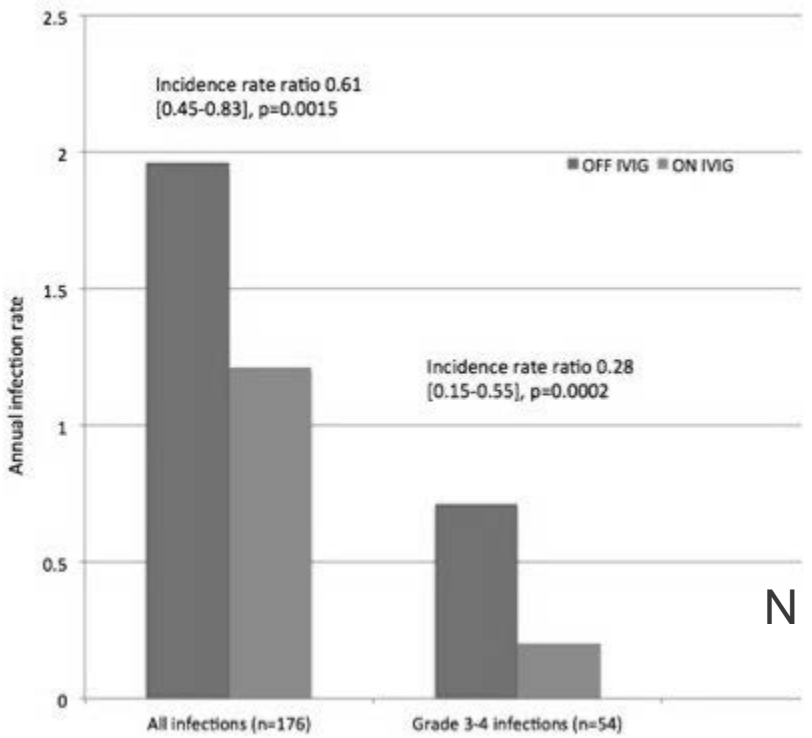
* without vaccination
PCJ:Pneumocystis jerovecii, G-CSF: granulocyte-Colony Stimulating Factor
TMP-SMX: trimethoprim-sulfamethoxazole

adapted from Delforge and Ludwig, Blood 2017; 129:2359

Prophylactic use of intravenous immunoglobulins in MM patients

- Limited number of recent studies available
- hypogammaglobulinemia increases with disease duration and new treatments
- IVIg are expensive with limited availability
- according to guidelines IVIg can be recommended for:
  - patients with severe **and symptomatic** hypogammaglobulinemia
  - 0,4- 0,5 g/kg every 3-4 weeks

Infections in patients on daratumumab with or without IVIg substituion



N = 43

Raanani et al. Leukemia & Lymphoma 2009;50:764-772
EMA guidelines 15 dec 2016

Lancman et al. ASH 2020; poster 1404

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Conclusions

- remember that infections are the most important cause of non-disease related mortality in multiple myeloma
- bacterial and viral infections are frequent and mostly affect the respiratory tract
- infections primarily occur in the first months after diagnosis and after multiple relapses when the immune system is more exhausted
- combined treatment modalities and prolonged treatment require continuous vigilance for infection
- anti-viral and antibiotic prophylaxis is key for infection prevention and should be based on guidelines and patient-related risk factors
- prompt initiation of anti-infectious treatment is required to reduce infection-related mortality