Antimicrobial Stewardship in Immunosuppressed Patients

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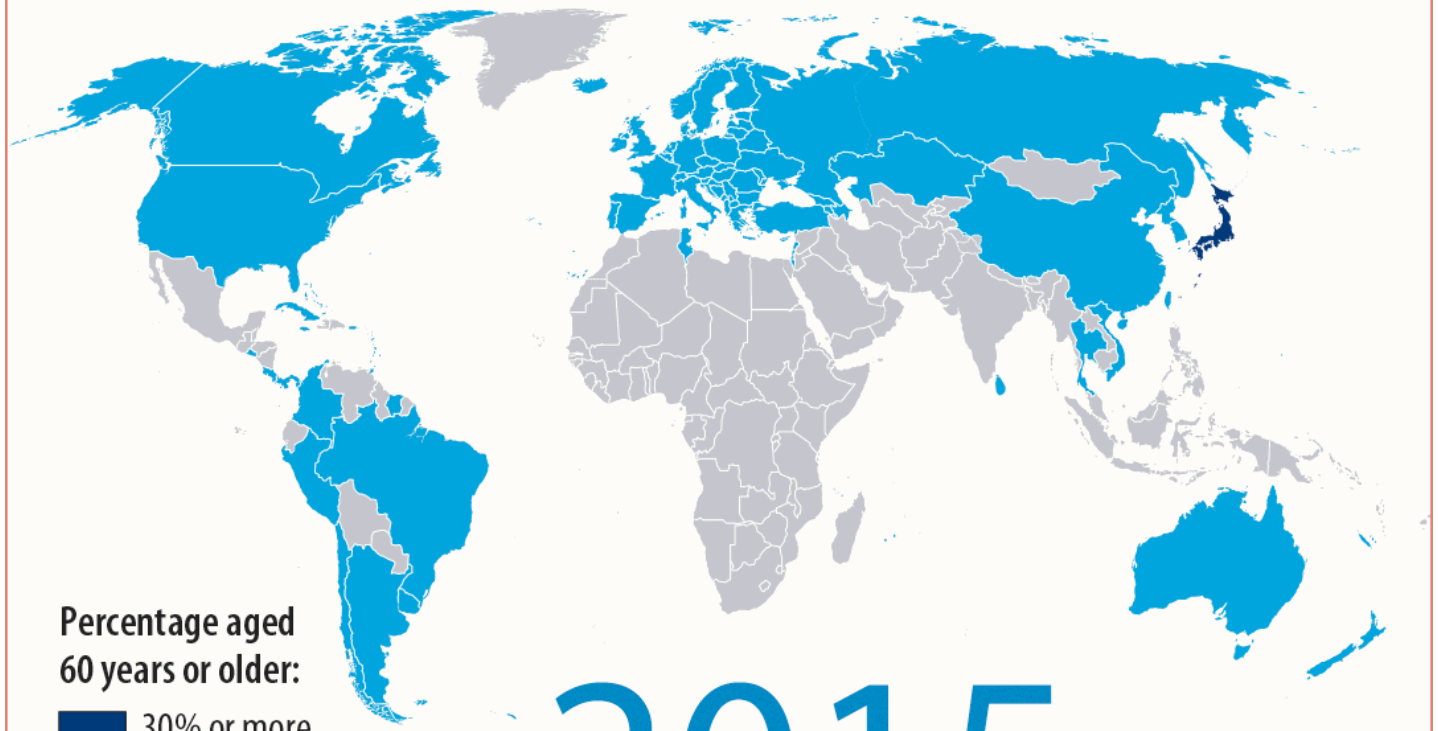
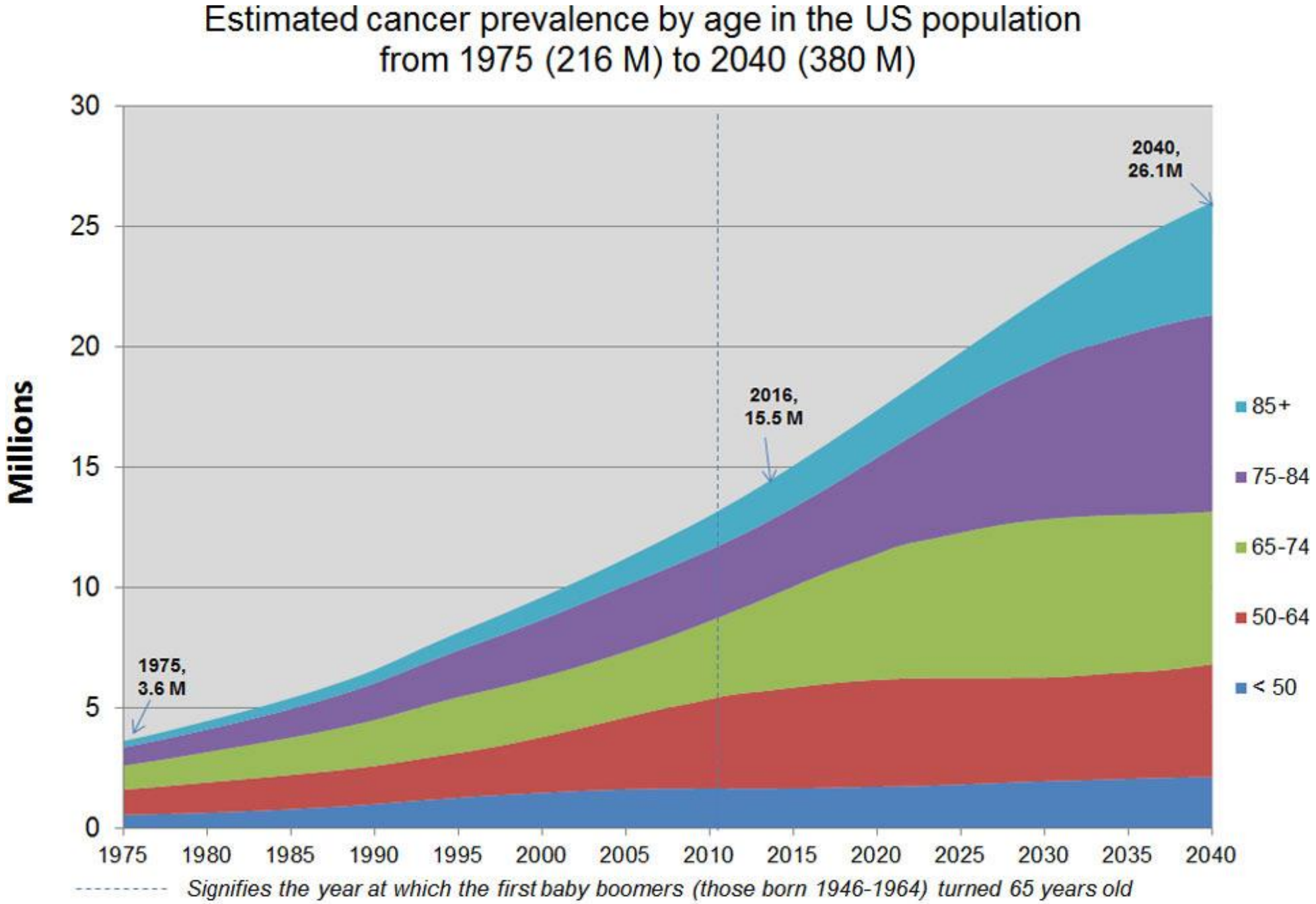
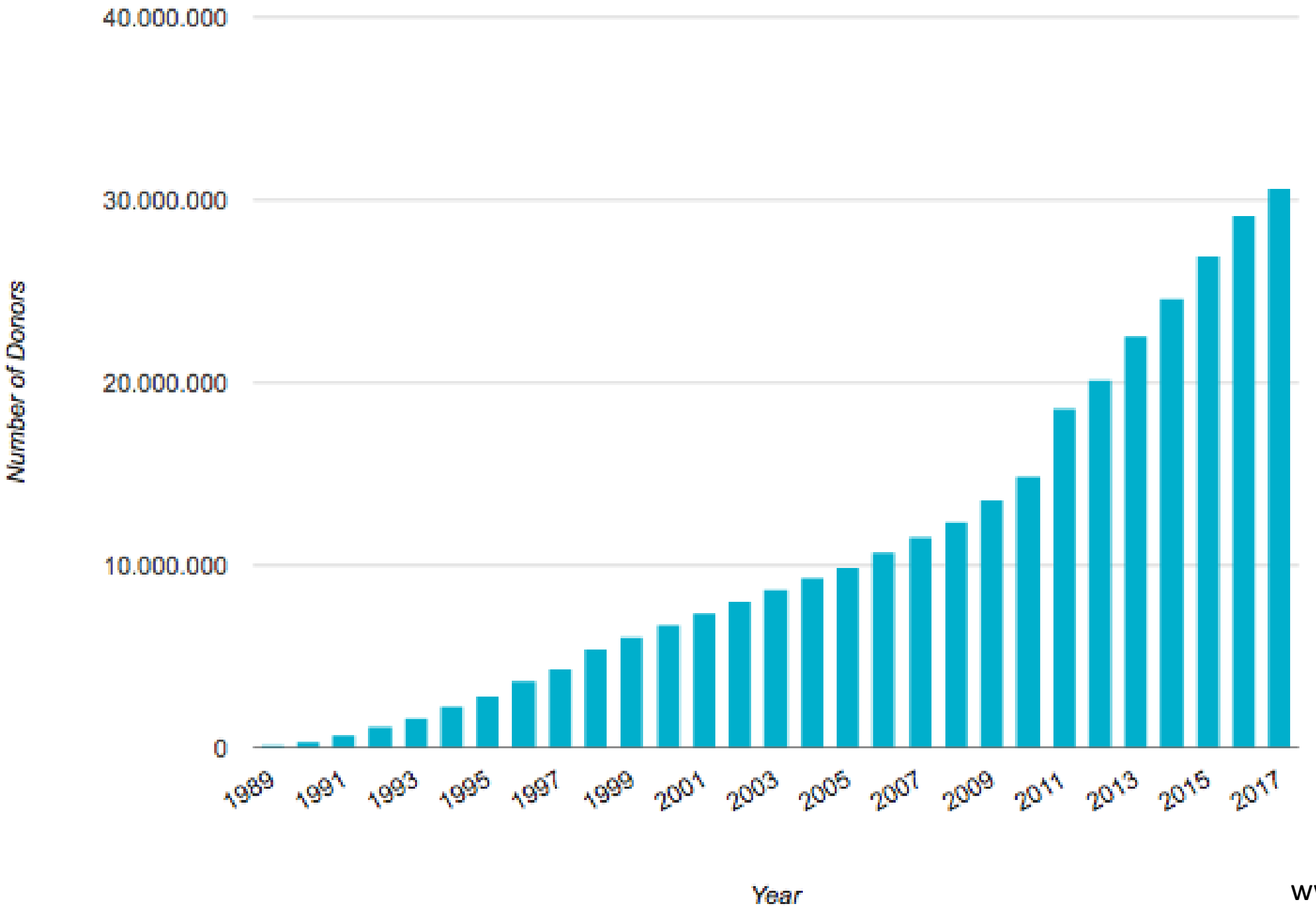
- Background/History
- Challenges/Barriers In AMS
- AMS Programmes
  - 1. Multidisciplinary approach
  - 2. Guidelines, protocols
  - 3. Feed-back
  - 4. Rapid diagnostic tests
  - 5. Infection control
- Conclusion

Populations are getting older



World Health Organization

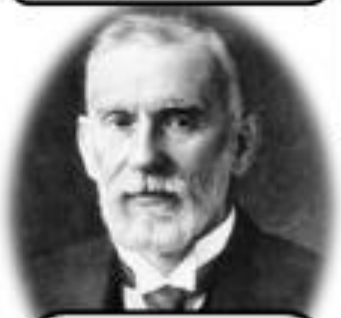

Estimated cancer prevalence by age in the US population
from 1975 (216 M) to 2040 (380 M)
Millions
30
25
20
15
10
5
0
1975
1980
1985
1990
1995
2000
2005
2010
2015
2020
2025
2030
2035
2040
1975, 3.6 M
2016, 15.5 M
2040, 26.1M
85+
75-84
65-74
50-64
< 50
Signifies the year at which the first baby boomers (those born 1946-1964) turned 65 years old


40.000.000
30.000.000
20.000.000
10.000.000
0
Number of Donors
1989
1991
1993
1995
1997
1999
2001
2003
2005
2007
2009
2011
2013
2015
2017
Year

Timeline history of chemotherapy development

Alexander Fleming 1928- Penicillin

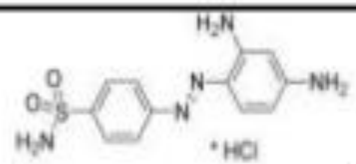
1908- Discovery of Arsphenamine



Paul Ehrilich
Father of Chemotherapy

Gerhard Domagk 1939- Sulfonamidochrysoidine (Prontosil)

1900- *Paul Ehrilich* Chemotherapy Animal model developed



1932- Prontosil- First sulfonamide- Bayer's Laboratory

1959- Antitumor antibiotics

1958- Methotrexate

1957- 5-Fluorouracil

1951- Thiopurines

1948- Anitfolates

1944- Waksman *et al.*, discovered streptomycin.

1943- Nitrogen mustard in lymphomas

1963- Vinca alkaloids

1962- nalidixic acid

1963 to 1970- Treatment for Hodgkin's disease

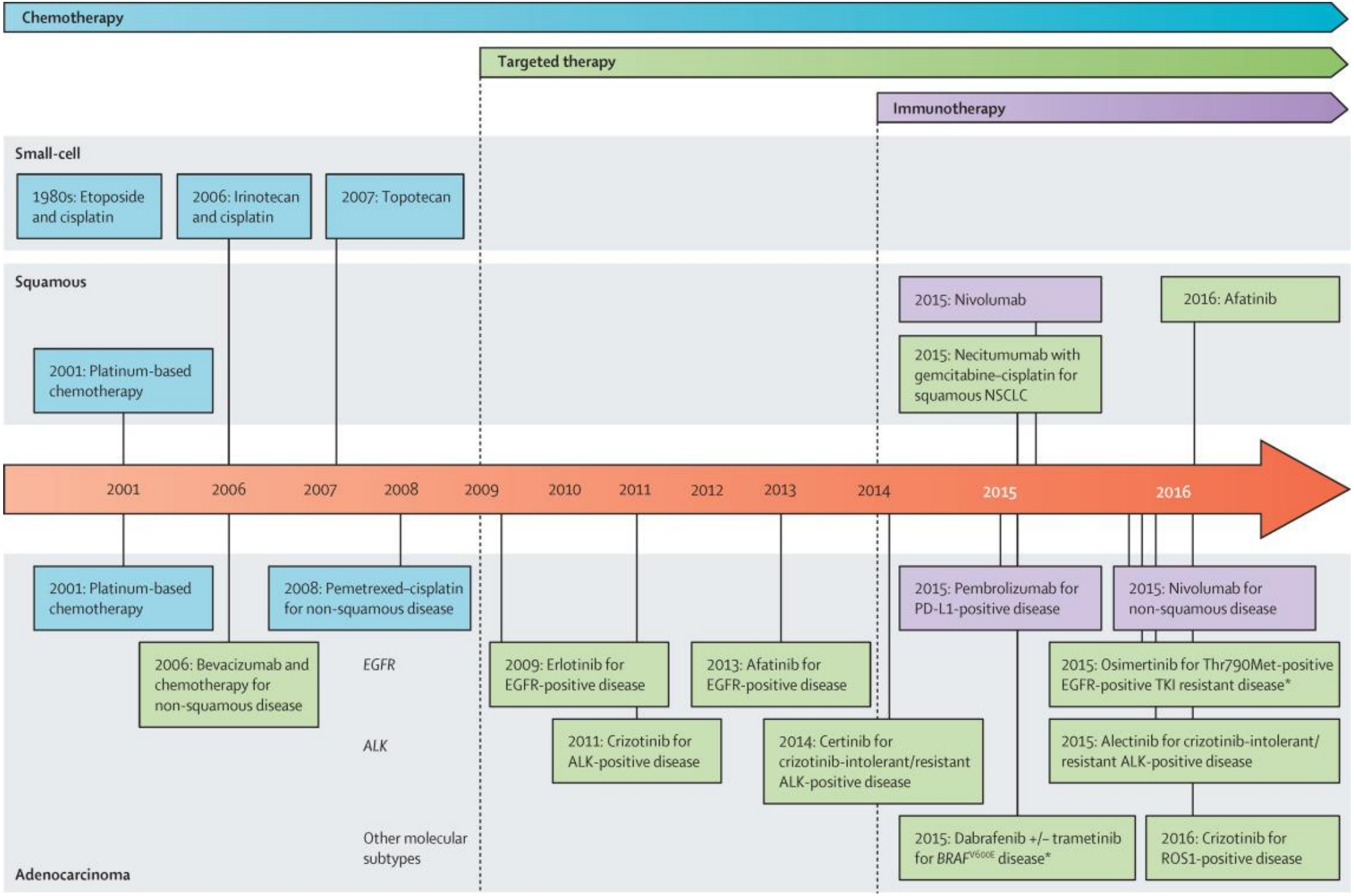
2007- Target specific screens

2005- Tyrosine kinase inhibitors

1997- Monoclonal antibody approved for the treatment of tumor.

1996- Imatinib

1900 1920 1940 1960 1980 2015


Chemotherapy
Targeted therapy
Immunotherapy
Small-cell
1980s: Etoposide and cisplatin
2006: Irinotecan and cisplatin
2007: Topotecan
Squamous
2001: Platinum-based chemotherapy
2015: Nivolumab
2016: Afatinib
2015: Necitumumab with gemcitabine–cisplatin for squamous NSCLC
2001
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2001: Platinum-based chemotherapy
2008: Pemetrexed–cisplatin for non-squamous disease
2006: Bevacizumab and chemotherapy for non-squamous disease
EGFR
2009: Erlotinib for EGFR-positive disease
2013: Afatinib for EGFR-positive disease
2015: Pembrolizumab for PD-L1-positive disease
2015: Nivolumab for non-squamous disease
2015: Osimertinib for Thr790Met-positive EGFR-positive TKI resistant disease*
ALK
2011: Crizotinib for ALK-positive disease
2014: Certinib for crizotinib-intolerant/resistant ALK-positive disease
2015: Alectinib for crizotinib-intolerant/resistant ALK-positive disease
Other molecular subtypes
2015: Dabrafenib +/– trametinib for BRAF V600E disease*
2016: Crizotinib for ROS1-positive disease
Adenocarcinoma

Population is getting older

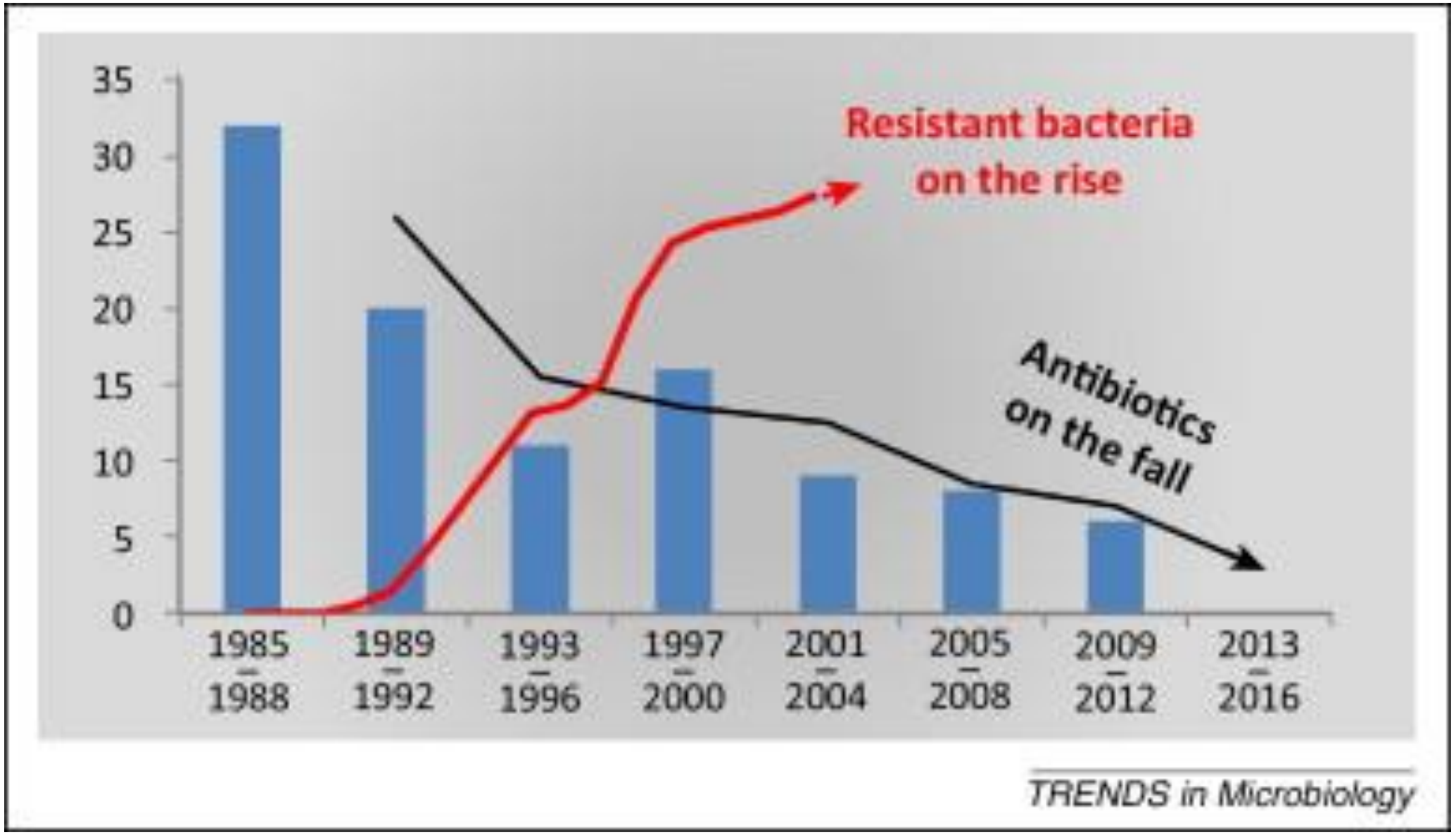
Malignancies are increasing

New chemotherapy and immunomodulator drugs are increasing

Transplantations are increasing

Immunosuppressed Patients are increasing all over the world

New Antimicrobials- Antimicrobial resistance



Schaberle, Hack. Trends Microbiol. 2014; 22(4): 165-7

Clinical Infectious Diseases

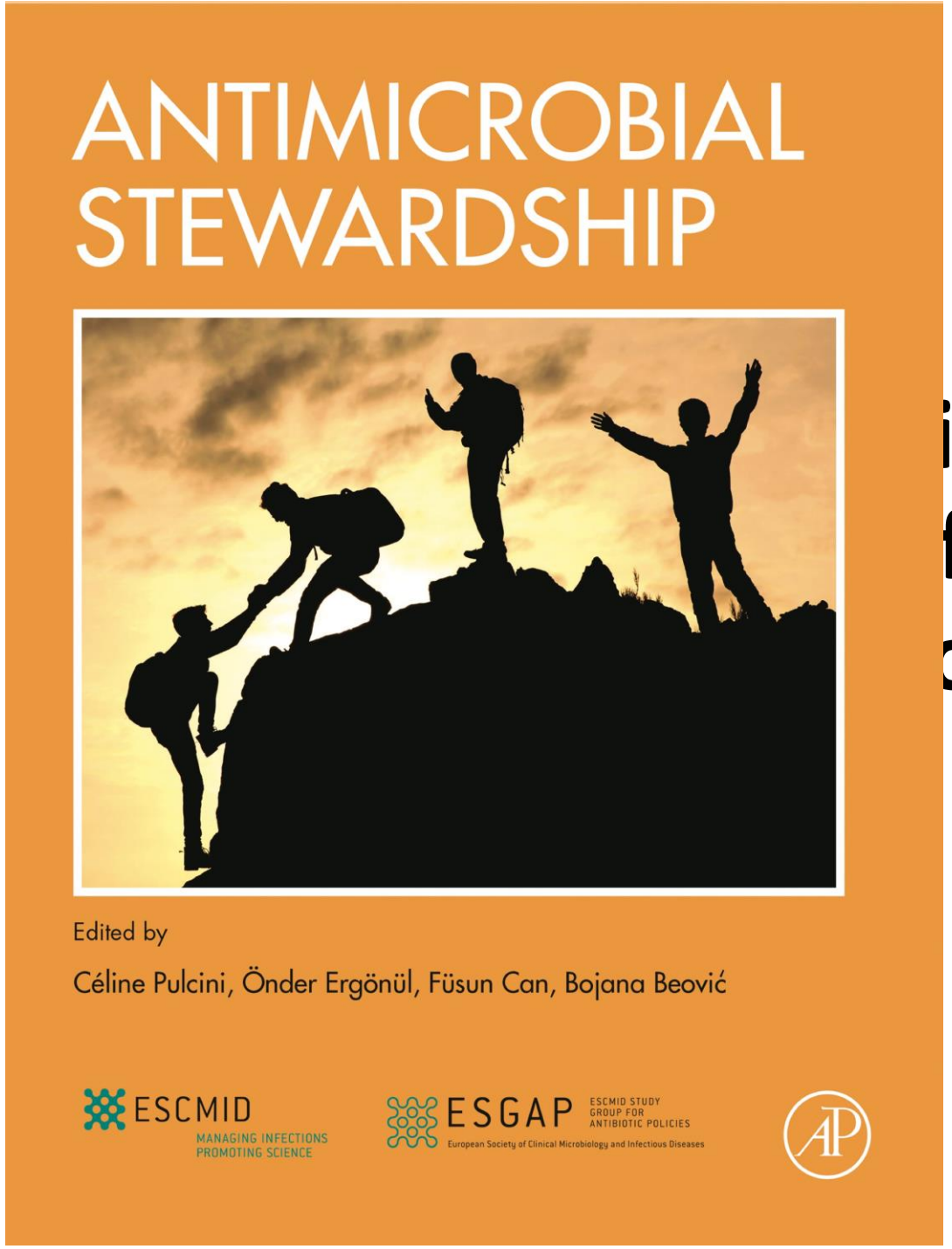
IDSA GUIDELINE

Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America

Tamar F. Barlam,[1,a] Sara E. Cosgrove,[2,a] Lilian M. Abbo,[3] Conan MacDougall,[4] Audrey N. Schuetz,[5] Edward J. Septimus,[6] Arjun Srinivasan,[7] Timothy H. Dellit,[8] Yngve T. Falck-Ytter,[9] Neil O. Fishman,[10] Cindy W. Hamilton,[11] Timothy C. Jenkins,[12] Pamela A. Lipsett,[13] Preeti N. Malani,[14] Larissa S. May,[15] Gregory J. Moran,[16] Melinda M. Neuhauser,[17] Jason G. Newland,[18] Christopher A. Ohl,[19] Matthew H. Samore,[20] Susan K. Seo,[21] and Kavita K. Trivedi[22]

[1]Section of Infectious Diseases, Boston University School of Medicine, Boston, Massachusetts; [2]Division of Infectious Diseases, Johns Hopkins University School of Medicine, Baltimore, Maryland; [3]Division of Infectious Diseases, University of Miami Miller School of Medicine, Miami, Florida; [4]Department of Clinical Pharmacy, School of Pharmacy, University of California, San Francisco; [5]Department of Medicine, Weill Cornell Medical Center/New York–Presbyterian Hospital, New York, New York; [6]Department of Internal Medicine, Texas A&M Health Science Center College of Medicine, Houston; [7]Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia; [8]Division of Allergy and Infectious Diseases, University of Washington School of Medicine, Seattle; [9]Department of Medicine, Case Western Reserve University and Veterans Affairs Medical Center, Cleveland, Ohio; [10]Department of Medicine, University of Pennsylvania Health System, Philadelphia; [11]Hamilton House, Virginia Beach, Virginia; [12]Division of Infectious Diseases, Denver Health, Denver, Colorado; [13]Department of Anesthesiology and Critical Care

Barlam TF, et al. Clin Infect Dis. 2016;62(10):e51-77



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focus
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Chapter 17

Antimicrobial Stewardship in Hematology Patients

Murat Akova
Hacettepe University School of Medicine, Ankara, Turkey

INTRODUCTION

Among the several risk factors predisposing to infections in hematology patients, the most important one is neutropenia [1]. Patients with acute myeloid leukemia (AML) and those undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT) are at the highest risk of developing profound and persistent (lasting >10 days) neutropenia, which may abate inflammatory signs and symptoms of infections. Thus, fever may be the only sign of severe infection. Overall, only up to 50% of patients with febrile neutropenia will have a microbiologically and/or clinically documented infection. Febrile neutropenia is a medical emergency and would require the initiation of immediate empirical antimicrobial therapy targeting the most frequent infecting pathogens. The choice of empirical antibacterials should depend on the local epidemiology [1–3]. Although this empirical approach will be preventing early mortality, it may cause an ecological impact that leads to selection of highly resistant bacteria and pathogens like *Clostridium difficile* [4,5]. A rational antimicrobial stewardship (AMS) strategy in patients with febrile neutropenia should include prompt initiation of appropriate empirical antibacterials, which should be adapted upon results of cultures when available. The strategy should also address prophylactic antimicrobial use, duration of empirical and targeted antibiotic therapies, appropriate pharmacokinetics/pharmacodynamics (PK/PD) applications, and infection control measures in selected groups of hematology patients. Above all, close cooperation between primary physician(s) in charge (i.e., hemato-/oncologist) and the infectious diseases (ID) specialists, the clinical microbiologists, and the clinical pharmacists is strongly advised [6].

Antimicrobial Stewardship. http://dx.doi.org/10.1016/B978-0-12-810477-4.00017-9

Challenging issues?
Barriers?

1. Physician perceptions and attitudes: “My patient is sicker than yours”

2. Wide range of possible infectious etiologies with diagnostic uncertainty

3. Difficulty in making an early diagnosis

4. Urgency for empiric effective antimicrobial theraphy

Abbo LM, et al. Infect Dis Clin North Am. 2014;28(2):263-79

1. Physician perceptions and attitudes: “My patient is sicker than yours”

2. Wide range of possible infectious etiologies with diagnostic uncertainty

3. Dif

4. Urg

21 years old patient
AML, HSCT
Profound neutropenia for 2 months
Car R *P. aeruginosa* BSI
Invazive pulmonary aspergillosis
Geotrichum clavatum BSI
E. faecium BSI

Abbo LM, et al. Infect Dis Clin North Am. 2014;28(2):263-79

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3. Difficulty in making an early diagnosis

4. Urgency for empiric effective antimicrobial theraphy

Abbo LM, et al. Infect Dis Clin North Am. 2014;28(2):263-79

5. Significant drug toxicities and potent drug interactions

20 years old, f, AML, HSCT

Colistin (7) + amikacin + ciprofloxacin

Chorea athetosis, tremor

35 years old, m, Lymphoma

Colistin + meropenem

14th day: Acute kidney failure

6. An microbial resistance

7. Diffi ith controlling the sou
such as ocytopenia

8. ssed state increases the risk
fo h and uncommon infections

9. Prolonged exposure to prophylactic antimicrobials

Abbo LM, et al. Infect Dis Clin North Am. 2014;28(2):263-79

5. Significant drug toxicities and potent drug interactions

6. Antimicrobial resistance

7. Difficulty with controlling the source of infection due to issues, such as thrombocytopenia

8. Prolonged duration of immunosuppressed state increases the risk for uncommon presentations of common and uncommon infections

9. Prolonged exposure to prophylactic antimicrobials

Abbo LM, et al. Infect Dis Clin North Am. 2014;28(2):263-79

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Abbo LM, et al. Infect Dis Clin North Am. 2014;28(2):263-79

20 years old, f, AML, HSCT

Profound neutropenia for 2 months

Car R *P. aeruginosa* BSI

Invazive pulmonary aspergillosis

Geotrichum clavatum BSI

E. faecium BSI

74 years old, m, MDS

DM, chronic kidney injury

Profound neutropenia

Prolonged fever

Geotrichum capitata BSI

8. Prolonged duration of immunosuppressed state increases the risk for uncommon presentations of common and uncommon infections

9. Prolonged exposure to prophylactic antimicrobials

Abbo LM, et al. Infect Dis Clin North Am. 2014;28(2):263-79

5. Significant drug toxicities and potent drug interactions

6. Antimicrobial resistance

7 urce of infection due to issues,
s

8 uppressed state increases the risk
for common and uncommon infections

45 years old, f, AML

Posaconazole prophylaxis

Micafungin for Candidiasis

IPA: L. Amphoterisin B

9. Prolonged exposure to prophylactic antimicrobials

Abbo LM, et al. Infect Dis Clin North Am. 2014;28(2):263-79

IMPLEMENTATION OF ANTIMICROBIAL STEWARDSHIP STRATEGIES FOR IMMUNOCOMPROMISED HOSTS

WHAT ARE THE GENERAL RECOMMENDATIONS?

1. Multidisciplinary approach

2. Guidelines, protocols

3. Feed-back

4. Rapid diagnostic tests

5. Infection control

Abbo LM, et al. Infect Dis Clin North Am. 2014;28(2):263-79

Multidisciplinary Approach

REVIEW

CURRENT OPINION

The impact of infectious diseases consultation on oncology practice

Bruno P. Granwehr[a] *and Dimitrios P. Kontoyiannis*[b]

Granwehr BP. Curr Opin Oncol. 2013;25(4):353-9

- Infectious diseases consultation results in improved outcomes in inpatient and outpatient settings.

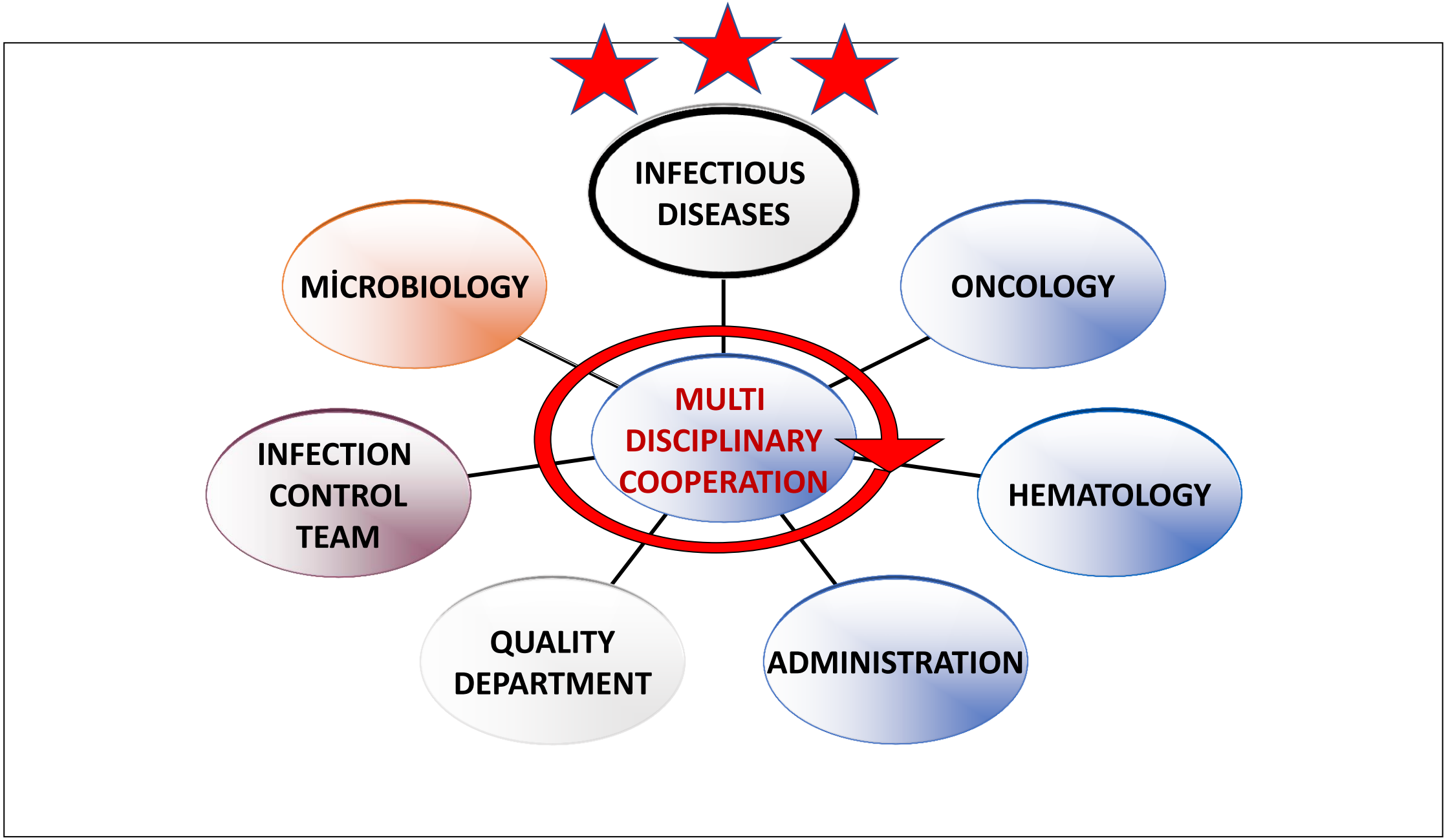
- Mortality of *S. aureus* bacteremia and candidemia is reduced with infectious diseases consultation.

- Adherence with infectious diseases recommendations is associated with improved outcomes.

- Routine infectious diseases consultation for outpatient parenteral antibiotic therapy is associated with more appropriate utilization of antibiotics, including discontinuation.

- Telephone, curbside, or other informal consultation is inferior to bedside consultation, resulting in increased mortality.

Granwehr BP. Curr Opin Oncol. 2013;25(4):353-9


INFECTIOUS DISEASES
MİCROBIOLOGY
ONCOLOGY
MULTI DISCIPLINARY COOPERATION
INFECTION CONTROL TEAM
HEMATOLOGY
QUALITY DEPARTMENT
ADMINISTRATION

1. Multidisciplinary approach

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Abbo LM, et al. Infect Dis Clin North Am. 2014;28(2):263-79

Alghoritms, Protocols and Guidelines

Table 1. Principles of antimicrobial stewardship for hematology patients.

– The initiation of empirical antibiotic treatment should be prompted by fever and clinical signs, and not by C-reactive protein or other biomarkers, as studies of these have shown inconsistent results;[10] antibiotics should not be initiated on the basis of colonization by resistant organisms.

– Empirical antibiotic treatment should never be started or changed before taking at least two blood cultures, along with relevant specimens from the clin-

IDSA GUIDELINES

Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America

Alison G. Freifeld,[1] Eric J. Bow,[9] Kent A. Sepkowitz,[2] Michael J. Boeckh,[4] James I. Ito,[5] Craig A. Mullen,[3] Issam I. Raad,[6] Kenneth V. Rolston,[6] Jo-Anne H. Young,[7] and John R. Wingard[8]

[1]Department of Medicine, University of Nebraska Medical Center, Omaha, Nebraska; [2]Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York; [3]Department of Pediatrics, University of Rochester Medical Center, Rochester, New York; [4]Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research, Seattle, Washington; [5]Division of Infectious Diseases, City of Hope National Medical Center, Duarte, California; [6]Department of Infectious Diseases, Infection Control and Employee Health, The University of Texas M.D. Anderson Cancer Center, Houston, Texas; [7]Department of Medicine, University of Minnesota, Minneapolis, Minnesota; [8]Division of Hematology/Oncology, University of Florida, Gainesville, Florida; and [9]Departments of Medical Microbiology and Internal Medicine, the University of Manitoba, and Infection Control Services, Cancer Care Manitoba, Winnipeg, Manitoba, Canada

Gyssens IC. ECIL-4. Haematologica. 2013;98(12):1821-5.

IDSA Guideline. Clin Infect Dis. 2011;52(4):e56-93.

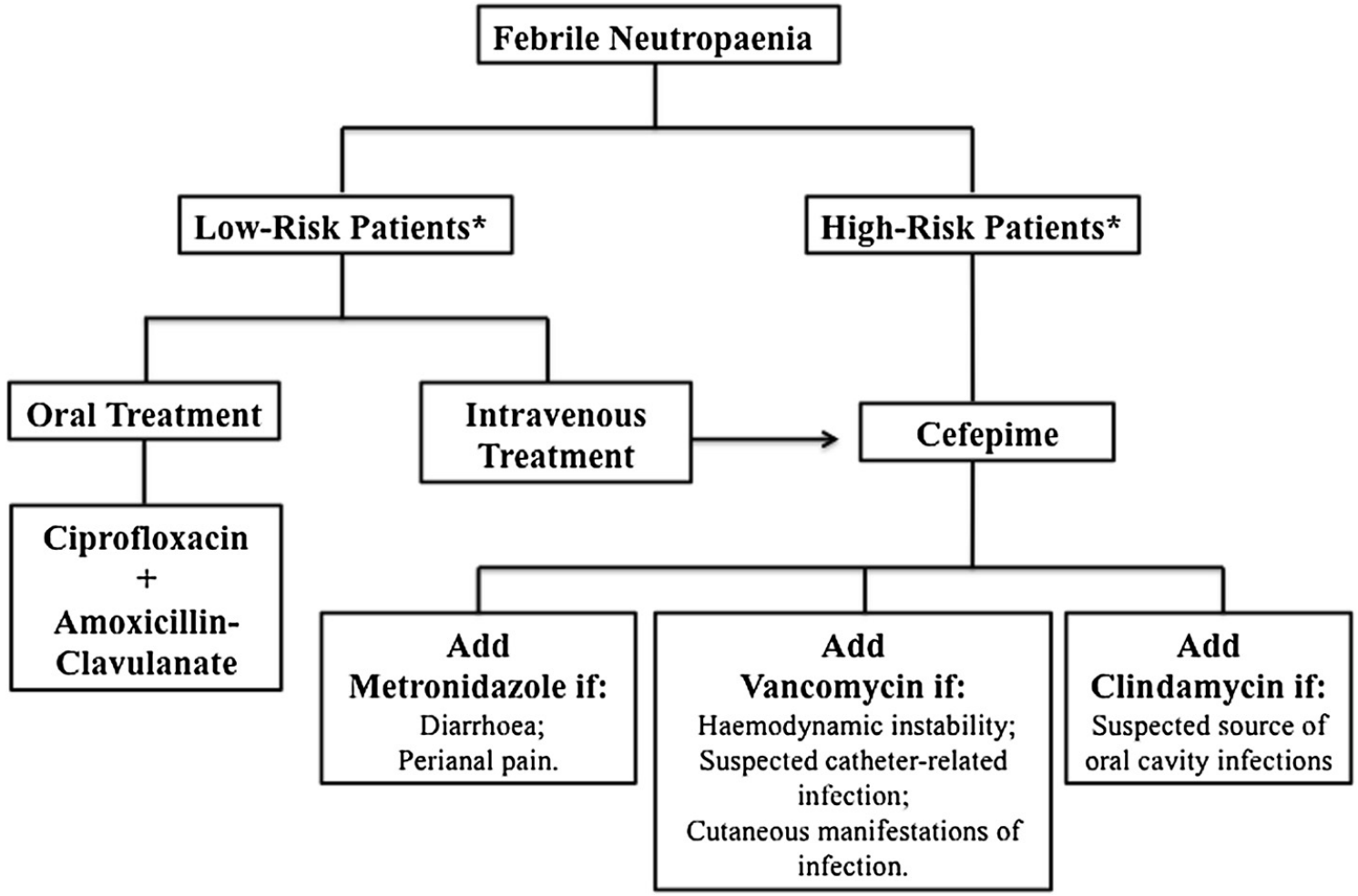

Figure 1 Initial antimicrobial selection for the in-patient treatment of FN according to the ASP of the Hospital de Clínicas de Porto Alegre. *High-risk patients = MASCC score < 21 points; Low-risk patients = MASCC score ≥ 21 points. Low-risk patients were treated with intravenous antibiotics if they had one or more of the following: presence of clinical comorbidities, FN after high-dose chemotherapy, expectation of duration of neutropenia > 7 days, documented infection, clinical instability (e.g. hypotension, acute respiratory failure, acute renal failure) and gastrointestinal intolerance (e.g. severe mucositis, vomiting). ASP, antimicrobial stewardship program; FN, febrile neutropaenia; MASCC, Multinational Association for Supportive Care in Cancer.

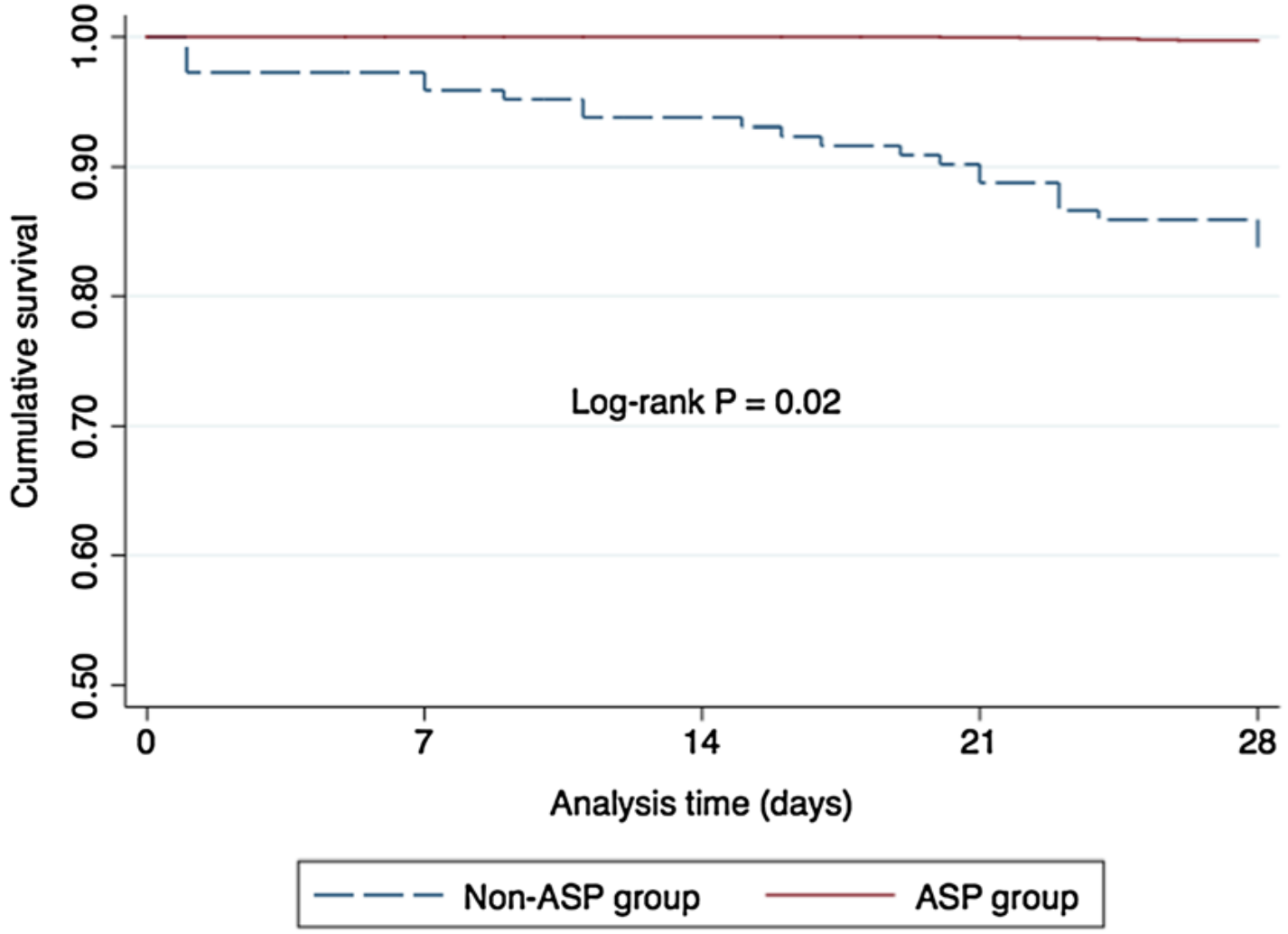

Figure 2 Kaplan–Meier curves of 28-day mortality according adherence to ASP after propensity score weighting.

Rosa RG, et al. BMC Infect Dis. 2014 May;14:286.

1. Multidisciplinary approach

2. Guidelines, protocols

3. Feed-back

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Abbo LM, et al. Infect Dis Clin North Am. 2014;28(2):263-79

Feed-back

- Local antimicrobial resistance rates
- Healthcare associated infections of hospital
- Feed back of infection control measures
  - Hand hygiene compliance
  - Isolation precautions adherence rates
- Reporting inappropriate antibiotic use

Eur J Clin Microbiol Infect Dis (2012) 31:583–590
DOI 10.1007/s10096-011-1351-6

ARTICLE

Prospective audit and feedback on antibiotic prescription in an adult hematology-oncology unit in Singapore

C.-L. Yeo · D. S.-G. Chan · A. Earnest · T.-S. Wu · S.-F. Yeoh · R. Lim · R. Jureen · D. Fisher · L.-Y. Hsu

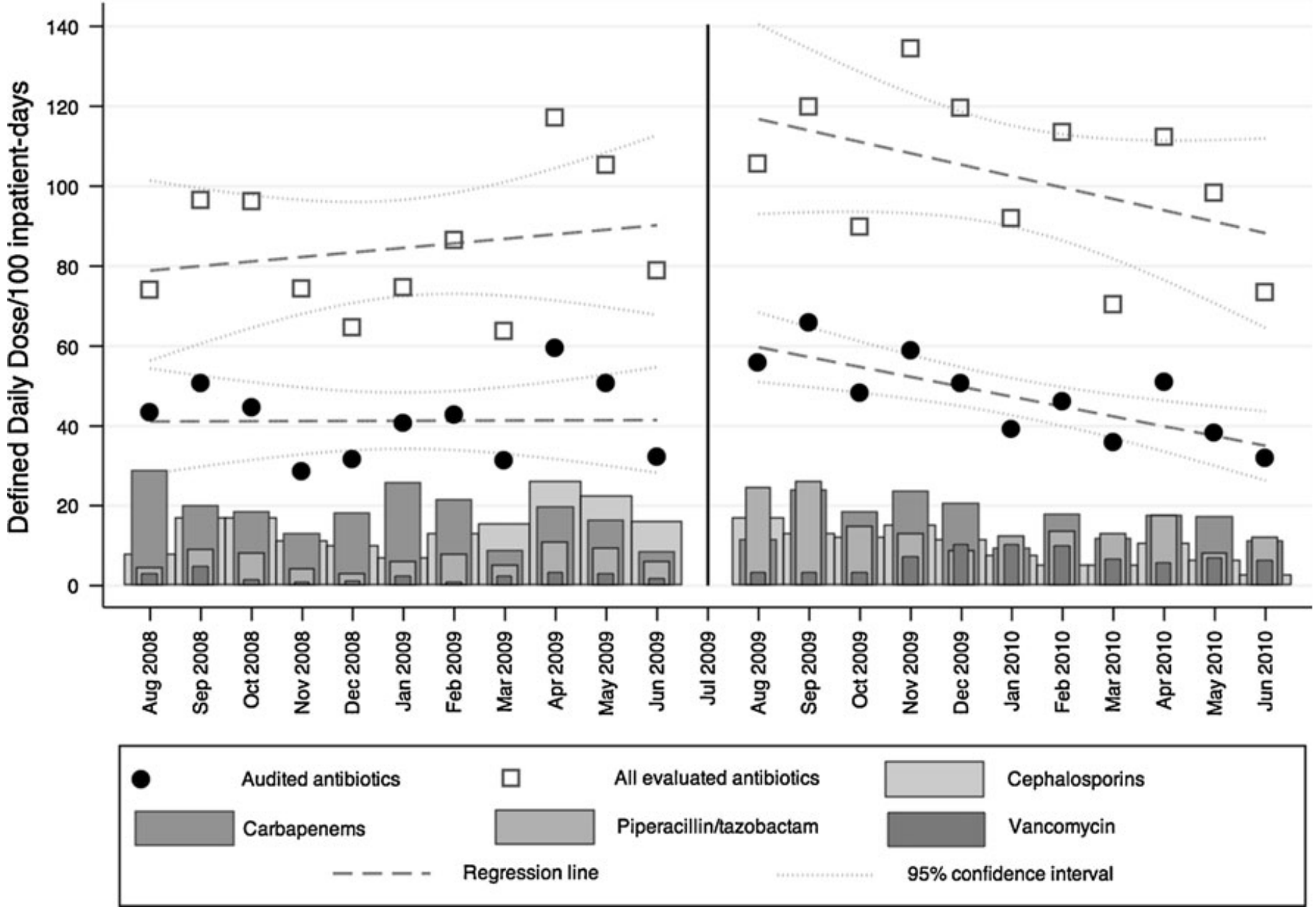

Fig. 2 Antibiotic prescription trends for National University Cancer Institute, Singapore (NCIS) inpatients pre-intervention and post-antimicrobial stewardship program (ASP) implementation

1. Multidisciplinary approach

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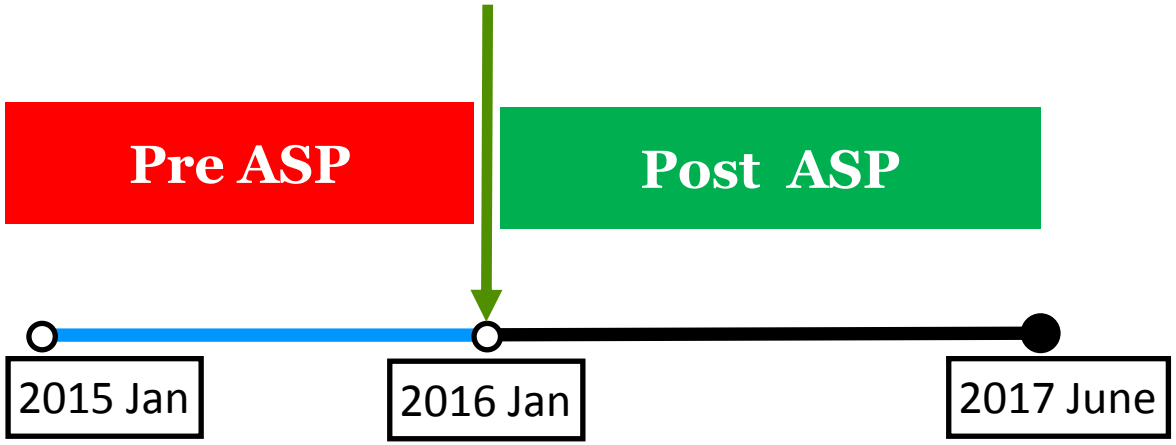
Rapid Diagnostic Tests

- PCR based tests
  - Respiratory system panel test
  - Gastrointestinal pathogen test
  - Blood PCR test for bacteremia
  - Rapid antibiotic resistance test
- Point-of-care tests

Antimicrobial Stewardship Programme



Clinical Pathway for Febrile Neutropenia

Cases

Fever (A single tympanic temperature measurement of ≥ 38.3°C or a temperature of 38 °C sustained over a 1 hour period) and neutropenia (absolute neutrophil count (ANC) of < 1,000 cells/mm^3 or an ANC that is expected to decrease to < 500 cells / mm^3 during the next 48 h)

On admission

- Don't enter in to the patient's room without mask.
- The **MASCC** (Multinational Association for Supportive Care in Cancer) Score should be calculated and noted by the primary physician of the patient.
- Basic diagnostic tests: Complete blood count, CRP, procalcitonin, serum levels of liver enzymes, bilirubin and blood urea nitrogen, creatinine), blood culture (At least two sets) and if present from each lumen of the central venous catheter and chest X-ray.

First Step

Appropriate empiric antibiotic therapy have to be initiated according to the patient's **MASCC** score

- **Low Risk** (MASCC≥21); If the patients is able to tolerate; **oral Ciprofloxacin + Amoxicillin-clavulanate**, if not, the patients are hospitalized and **IV ciprofloxacin + Ampicilline-sulbactam treatment is started.**
- **High Risk** (MASCC<21); IV **Piperacillin-tazobactam** or **Carbapenem** or **Ceftazidime** or **Cefepime.**

Second Step

- The initial empiric therapy could be changeg according to clinical condition and microbiological data.
- **Vancomycin** is not a standard part of empiric antibiotic therapy for fever and neutropenia. (These agents should be considered for special clinical indications, including suspected catheter – related infection, skin or soft tissue infection, pneumonia or hemodynamic instability).
- Add **metronidazole** for abdominal symptoms and signs or suspect of C.difficile infection
- Empiric antifungal coverage should be considered in high-risk patients who have persistent fever after 4–7 days of a broad-spectrum antibacterial regimen and with no identified fever source.

Third Step

- Initial antibiotic therapy can be prolonged if there is suspect of infection.
- In the absence of fever and no detection of microorganism, the antimicrobials should be discontinued after four days.

- Examine and re-image (CT-MR) for new or worsening sites of infection.
- Culture, biopsy, drain sites of worsening infection should assess.
- Antibiotic spectrum and dose should be re-evaluated.

- Observe 4-24 hours in clinic to ensure that empiric antibiotics are tolerated and patient remains stable prior to discharge for outpatient therapy.

	Total n=95 (%)	Pre-ASP n=50	Post-ASP n=45	p
Mean age (sd; min-max)	57 (15; 21-82)	57 (17; 18-82)	56 (15; 21-84)	0.781
Number of FN attacks per patient (min-max)	1.6 (1-5)	1.63 (1-5)	1.57 (1-4)	0.725
Duration of neutropenia per FN attack	4.2	4.9	3.5	0.1
Diagnosis				
Leukemia	35 (37)	22 (44)	13 (29)	0.127
Lymphoma	26 (27)	12 (24)	14 (31)	0.437
Multiple Myeloma	6 (6)	3 (6)	3 (6)	0.893
Solid tumors	4 (4)	2 (4)	2 (4)	0.914
MASCC < 21 (high risk)	81 (85)	45 (90)	36 (80)	0.352
Fatality	20 (21)	15 (30)	5 (11)	0.024

	Pre-ASP Appropriateness/FN attack (%)	Post-ASP Appropriateness/FN attack (%)	p
Appropriateness of antimicrobials			
Appropriate empirical use (first step)	60/78 (77)	52/71 (73)	0.603
Appropriate adding or changing antimicrobial (second step)	19/36 (53)	35/43 (81)	0.006
Appropriate continuation or de-escalation or discontinuation (third step)	32/60 (53)	60/71 (85)	<0.001

	FN attacks n=152	Pre-ASP n=81 (%)	Post-ASP n=71 (%)	p
Gram positive bacteria	26	19(23)	7(10)	0.020
Staphylococcus spp	24	18(22)	6(8)	0.020
Methicillin resistance	15	12 (67)	3 (50)	0.025
Enterococcus faecium	2	1 (1)	1(1)	0.925
Gram negative bacteria	50	35(43)	15(20)	0.003
E. coli	19	12(15)	7(10)	0.357
K. pneumoniae	16	11(14)	5(7)	0.190
P. aeruginosa	10	8(10)	2(3)	0.080
Acinetobacter	3	2(2)	1(1)	0.639
Salmonella	1	1(1)	0(0)	0.348
K. oxytoca	1	1(1)	0(0)	0.348
Carbapenem resistance	12	11 (31)	1 (7)	0.005
Fungal agents				
Candida	26	16(20)	10(14)	0.354
Total	102	70(86)	32(45)	0.003

- After implementation of ASP, case fatality rate among the patients with FN decreased.
- Appropriate antimicrobial use increased and overall antimicrobial consumption was reduced.
- Bacterial infections and Candida infections decreased.

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Abbo LM, et al. Infect Dis Clin North Am. 2014;28(2):263-79

Infection Control

Review

Infection control issues in patients with haematological malignancies in the era of multidrug-resistant bacteria

Markus Ruhnke, Renate Arnold, Petra Gastmeier

Drug-resistant Gram-negative and Gram-positive bacteria are now increasingly identified as a cause of infections in immunocompromised hosts. Bacteria identified include the multidrug-resistant (MDR) and even pandrug-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, as well as carbapenem-resistant Enterobacteriaceae spp. The threat from MDR pathogens has been well-documented in the past decade with warnings about the consequences of inappropriate use of antimicrobial drugs. Resistant bacteria can substantially complicate the treatment of infections in critically ill patients and can have a substantial effect on mortality. Inappropriate antimicrobial treatment can affect morbidity, mortality, and overall health-care costs. Evidence-based data for prevention and control of MDR pathogen infections in haematology are scarce. Although not yet established a bundle of infection control and prevention measures with an anti-infective stewardship programme is an important strategy in infection control, diagnosis, and antibiotic selection with optimum regimens to ensure a successful outcome for patients.

Lancet Oncol 2014; 15: e606–19

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Ruhnke M, et al. Lancet Oncol. 2014;15(13):e606-19.

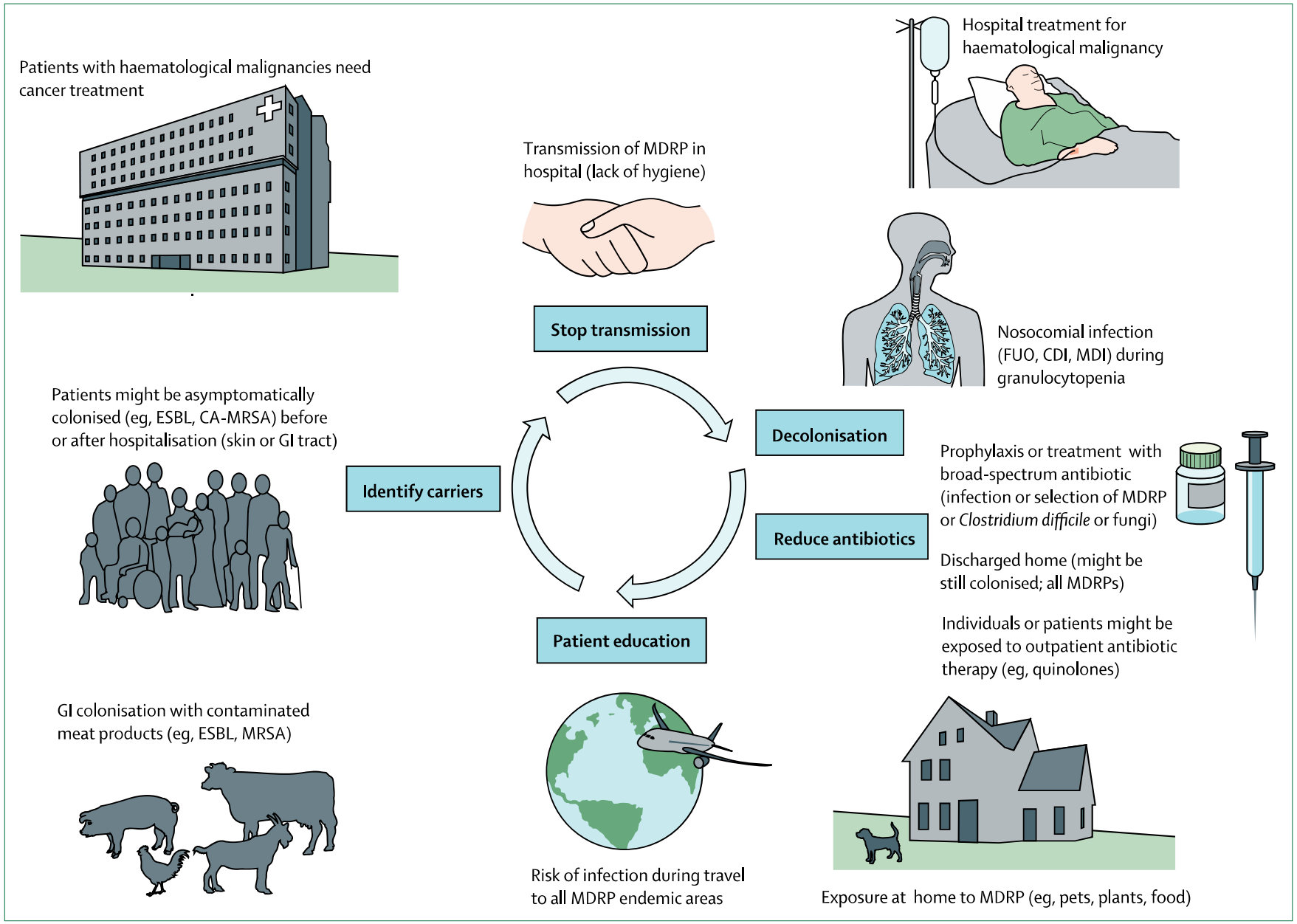

Figure 1: **Settings contributing to transmission of MDR pathogens in patients with haematological malignancies, and infection control interventions**
MDRP=multidrug-resistant pathogen. ESBL=extended-spectrum β-lactamase. CA-MRSA=community-acquired meticillin-resistant *Staphylococcus aureus*. GI=gastro-intestinal. FUO=fever of unknown origin. CDI=clinically defined infection. MDI=microbiologically documented infection.

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In Conclusion

A very special and critical population.

Early diagnosis, early microbiological analysis, early treatment is life saving

Multi-disciplinary approach and collaboration

Protocols, algoritms, adherence to guideline and feedback increase appropriate antimicrobial use.