

The Impact of Antimicrobial Resistance on Oncology Practice

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Disclosures

- Consultant fees from
 - Ansun
 - BMS
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 - F2G
 - Karius
 - Orca
 - Takeda

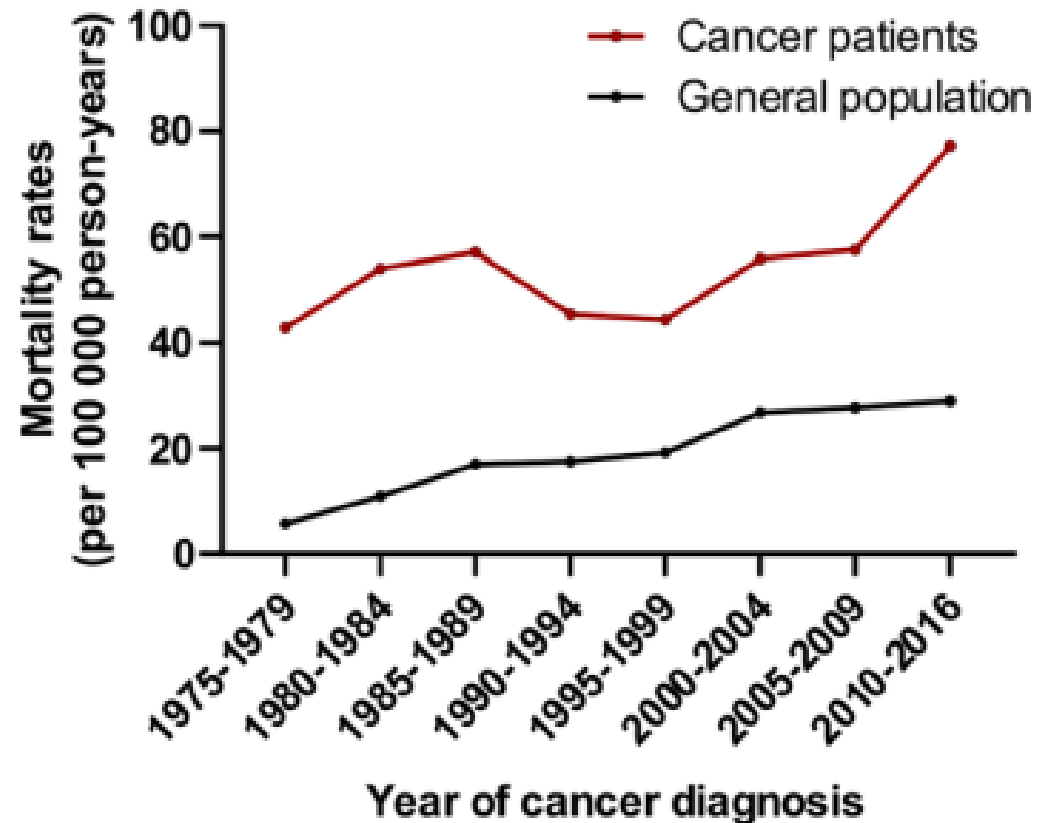
Infection is a major threat to cancer patients

- One of the most common complications
 - 3-fold greater risk of dying from a fatal infection than non-cancer patient
 - second leading cause of death in cancer patients
- Impedes delivery of on-time chemotherapy regimen, compromising oncologic treatment effectiveness
- Associated with higher healthcare costs

Zheng Y, Infect Dis Ther 2021; 10, 871
Zembower TR. Cancer Treat Res 2014;161:43
Del Castillo M, Clin Infect Dis 2016;63:1490

Infections are more deadly in cancer patients

Mortality rates of septicemia



Contributors to the high risk of infection

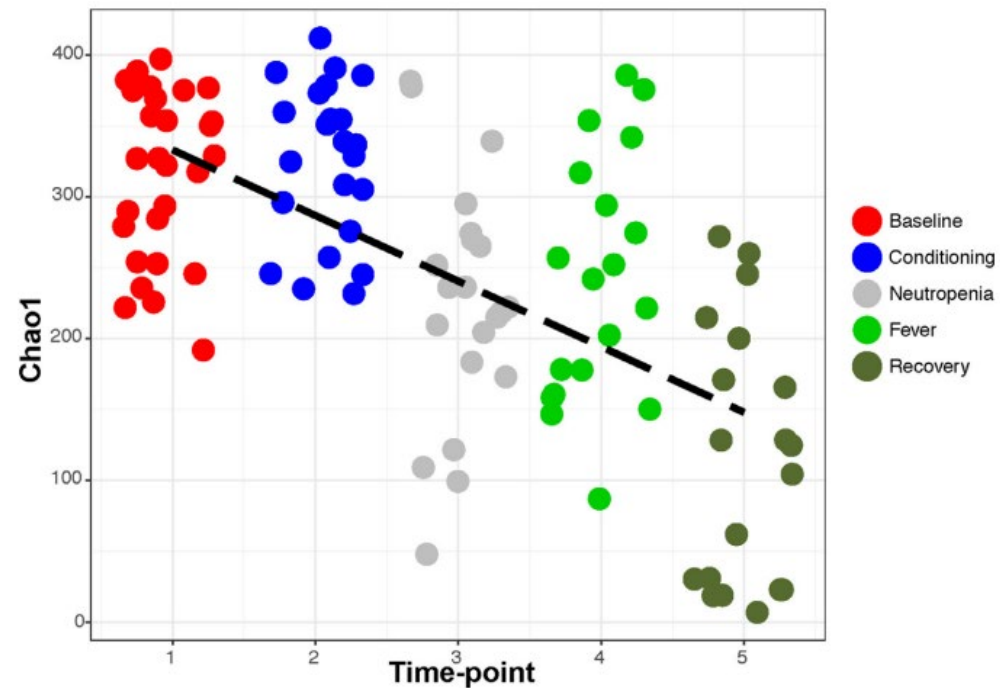
- Cancer is associated with impaired cellular and humoral immunity, impaired myelopoiesis, barrier disruption
- Cancer treatments exacerbate impaired defenses
 - Most chemotherapy regimens are myelosuppressive and cause mucosal injury
 - Bacterial pathogens cause most infections
 - New immunotherapies also pose threats from both bacteria and a wider array of pathogens
- Chemotherapy and antibiotics alter gut microbiome (GM)

FQs = Fluoroquinolones

GM = Gut microbiome

Gut microbiome dyspoiesis increases with chemotherapy and antibiotics

Serial changes in GM before and after chemotherapy



Alpha diversity of the GM

Neutropenic fever: lessons from the past

- Fever occurs frequently during chemotherapy-induced neutropenia
- Infection is clinically documented in 20-30%
 - Mostly bacterial
 - Common sites: GI tract, lung, skin
- Bacteremia documented in 10-25%
- Approximately 80 percent of pathogens arise from the endogenous flora
- Gram negative bacteria are most virulent and guide selection of empiric antibiotics
- Morbidity and mortality is high if antibiotics are delayed
- Prompt empiric broad-spectrum antibiotic therapy should be started within one hour

Freifeld AG, Clin Infect Dis. 2011;52:e56

Wingard JR, Uptodate, https://www.uptodate.com/contents/overview-of-neutropenic-fever-syndromes?search=neutropenic%20fever&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1, accessed 1/28/2024

A Tale of Two Different Groups of Patients

- Solid Tumors
 - Account for 90% of cancers
 - Low intensity chemotherapy, given in repeated cycles (+/- other treatment modalities)
 - Repeated episodes of short-term neutropenia (<7 days)
 - Subcutaneous ports often used
 - Treatment mostly outpatient
 - Frequency of febrile neutropenia highly variable (10-50%), but often <20%
-
- **Antibiotic prophylaxis is NOT recommended**
 - **Myeloid growth factors reduce neutropenic fever and are recommended if risk >20%**
 - **Use of empiric broad-spectrum antibiotics is much less common**

Smith TJ, J Clin Oncol. 2015;33:3199

Freifeld AG, Clin Infect Dis. 2011;52:427

Kuderer, N. M. et al. J Clin Oncol; 2007;25:3158

A Tale of Two Different Groups of Patients

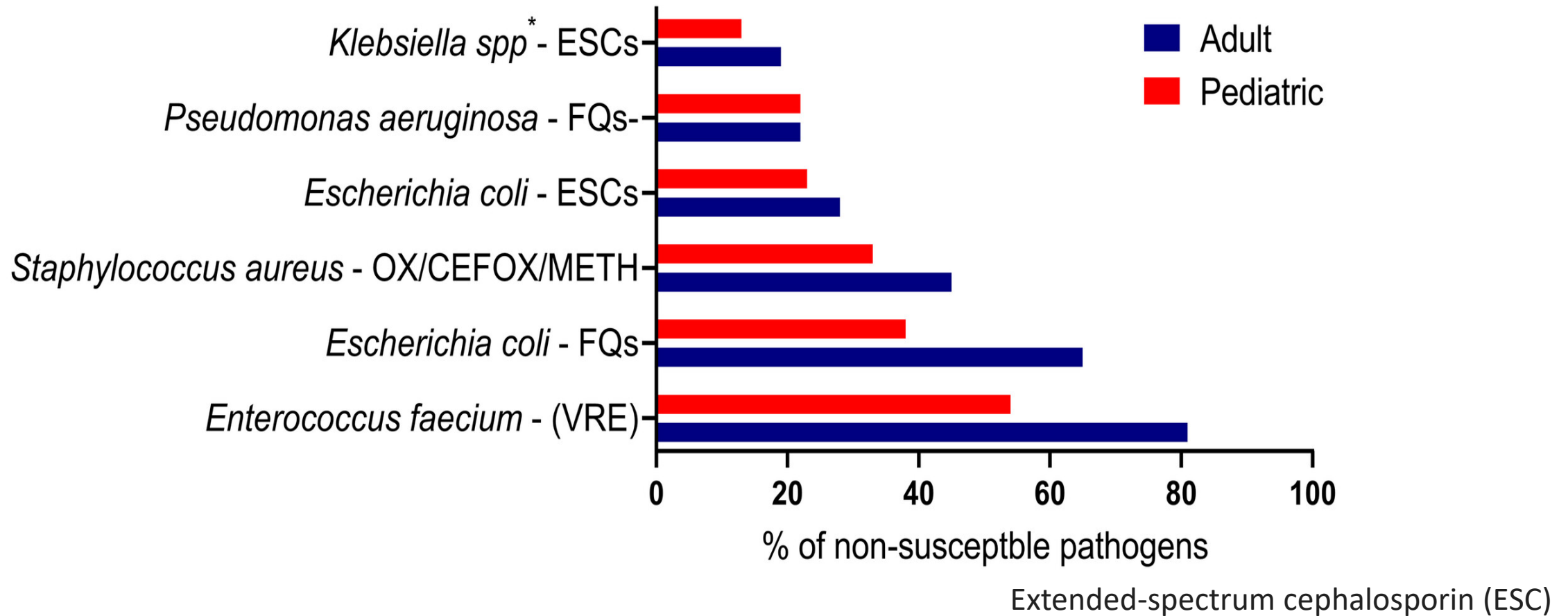
- Hematologic malignancies and stem cell transplant
 - Only about 10% of cancer patients
 - High intensity chemotherapy (+/- other treatment modalities)
 - Long-term, deep neutropenia (>7 days)
 - Indwelling intravenous catheters are frequent
 - Treatment mostly inpatient
 - Mucositis common and often severe
 - Frequency of febrile neutropenia >80%
 - In SCT, bacteremia rates 13-60% with 12-42% mortality
 - Averbuch D, Haematologica. 2013;98:1826:
- **FQ prophylaxis is recommended**
- **Use of empiric broad-spectrum antibiotics is frequent**

Advantages of antibiotic prophylaxis

- Meta-analysis of 109 trials in 13,579 patients
- Mostly hematologic malignancy

Event	Odds Ratio	95% Confidence Interval
Fever	0.80	0.74-0.87
Infection		
Clinical	0.65	0.56-0.76
Microbiologic	0.51	0.42-0.62
Death, all causes	0.66	0.55-0.79
Death, infection-related	0.61	0.48-0.77

The price of success: Antibiotic resistance in cancer patients

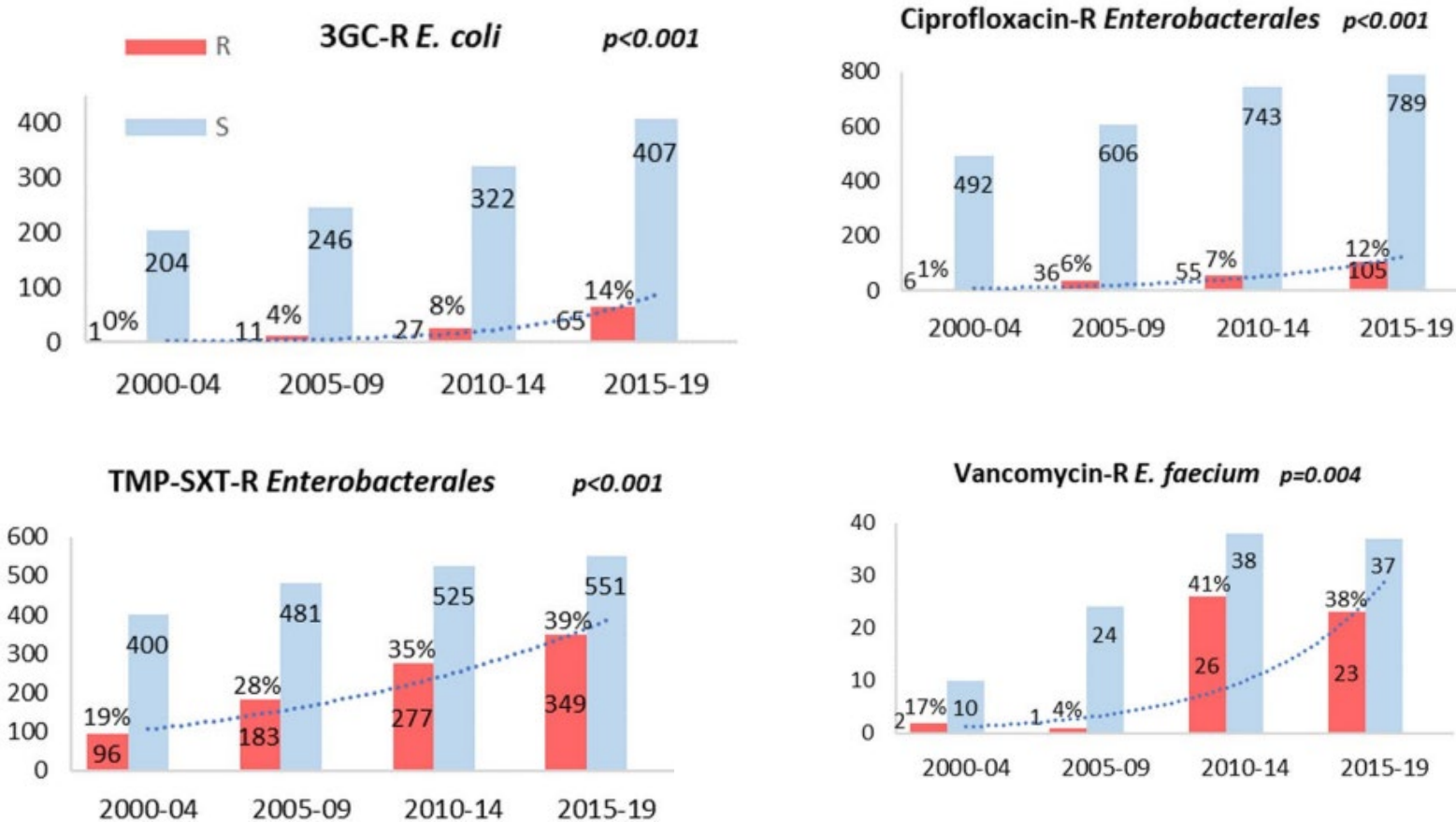


Nanayakkara AK, CA Cancer J Clin. 2021;71:488

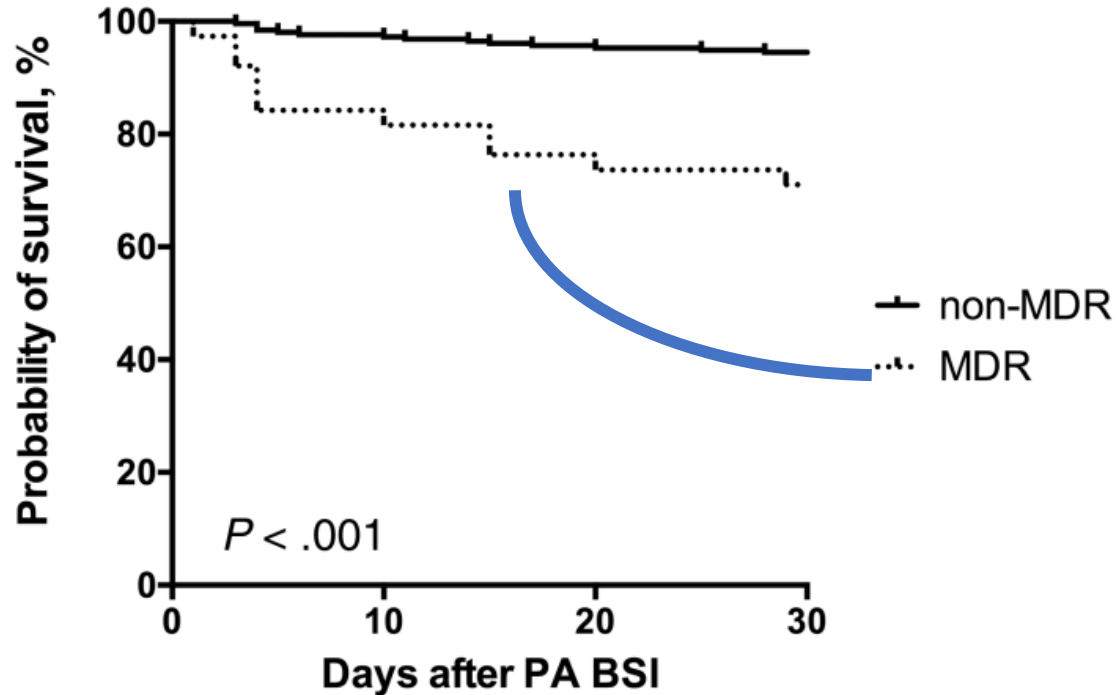
Data obtained from the National Healthcare Safety Network 2015-2017

Antimicrobial resistance is increasing

- 7749 bloodstream infections in 5159 patients with haematologic malignancies in Queensland, Australia over the last 20 years.



Antimicrobial-resistant *P. aeruginosa* BSI is associated with greater mortality



Modeling predicts that if further reduction in antibiotic efficacy against ESKAPE pathogens occurs, there would be:

Percent reduction in antibiotic efficacy	Additional infections (per yr in US)	Additional deaths (per yr in US)
30%	4,000	500
70%	10,000	1,000

Zhao Y, Clin Infect Dis. 2020;71(suppl 4):S386
Bodro M, Support Care Cancer 2014;22:603
Teillant A, Lancet Infect Dis. 2015;15:1429

Promising strategies to control AMR particularly important to oncology practice

- Antibiotic de-escalation can reduce use of empiric broad spectrum antibiotics
 - Aguilar-Guisado M, Lancet Haematol. 2017 Dec;4(12):e573-e583
- Baseline predictors of bacteremia can tailor use of antibiotics
 - Gut microbiome
 - Murthy HS, Biol Blood Marrow Transplant. 2020;26:2001
 - Colonization by fluoroquinolone resistant Enterobacterialis
 - Satlin MJ,. Clin Infect Dis. 2021;73:1257
 - Hakki M, Clin Infect Dis; 68:2045, 2019
- Infusions of engineered myeloid progenitor cells reduce infection
 - Desai PM, J Clin Oncol 2021;39:3261
- Prebiotics to preserve gut microbiota diversity
 - Riwes MM, Nat Med 2023;29:2805

What we also need:

- **New rapid diagnostics & AMR detection assays**
- **Multicenter clinical trials to validate these strategies**

Conclusion

- Infections are common in oncology practice
 - Associated with more serious consequences
 - Empiric broad-spectrum antibiotics are routinely used for neutropenic fever
 - Prophylactic antibiotics are used for high-risk cancer patients
- Antimicrobial resistance:
 - associated with greater risk for death
 - Represents threat to thwart cancer treatment outcomes
 - mostly in high-risk hematologic malignancy patients
 - appears to be increasing, but considerable variability between centers
- New approaches are a high priority