Antibiotic-resistant Gram-negative Blood Stream Infections in Children With Cancer
A Review of Epidemiology, Risk Factors, and Outcome

Ilana Levene, BM BCh, MRCPCH,⁎ Elio Castagnola, MD, PhD,† and Gabrielle M. Haeusler, MBBS, FRACP‡§¶

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Options are limited to older, frequently toxic and often inferior agents. This review will provide an overview of the epidemiology, risk factors and outcomes of AR Gram-negative blood stream infections (BSI) in children with cancer, with a focus on MDR bacteria. While the definition of MDR is dynamic and varies depending on the type of bacteria, for the purposes of this review, it is defined as acquired nonsusceptibility to at least one agent in 3 or more antibiotic classes.

Key Words: antibiotic resistance, febrile neutropenia, cancer, multidrug resistance

Infection, frequently presenting as fever and neutropenia (FN), is one of the most common and life-threatening complications of the treatment of childhood cancer. With improvements in supportive care, in particular the early administration of broad-spectrum antibiotics, overall mortality is frequently quoted as less than 1%. However, with global increases in antibacterial resistance and paucity of new antibiotics available to combat this threat, the impact of infection on overall survival is likely to change.

The development of antibiotic resistance (AR) in previously susceptible bacteria is complex and multifactorial. The widespread, and often inappropriate, use of antimicrobial drugs favors the emergence and selection of resistant strains, and poor infection prevention and control practices contribute to their spread. Of particular concern are infections caused by multidrug-resistant (MDR) Gram-negative bacteria, as the therapeutic options are limited to older, frequently toxic and often inferior agents. This review will provide an overview of the epidemiology, risk factors and outcomes of AR Gram-negative blood stream infections (BSI) in children with cancer, with a focus on MDR bacteria. While the definition of MDR is dynamic and varies depending on the type of bacteria, for the purposes of this review, it is defined as acquired nonsusceptibility to at least one agent in 3 or more antibiotic classes.

Epidemiology
Approximately half of all BSI in children with cancer are because of Gram-negative bacteria, with Enterobacteriaceae most frequently described. Data on the susceptibility of bacteria causing BSI in this population are commonly single-center reports and therefore highly region specific. In a survey of 37 European hematology–oncology centers (including 15 that treated pediatric patients), the top 3 clinical concerns highlighted were extended-spectrum β-lactamase (ESBL) producing Enterobacteriaceae, fluoroquinolone-resistant Gram-negative bacteria and carbapenem-resistant Pseudomonas aeruginosa.

The survey also found that resistance rates among Gram-negative bacteria were significantly higher in southeast European centers compared with northwest centers.

In India, concerning levels of AR have been reported from 3 large pediatric oncology centers. Of the BSI caused by Gram-negative bacteria, between 24% and 59% were ESBL producing. 10%–27% were carbapenem resistant and as many as 44%, 30% and 15% were MDR, extensively drug–resistant (defined as nonsusceptibility to at least one agent in all but 2 or fewer antimicrobial categories) and pan drug–resistant (defined as nonsusceptibility to all agents in all antimicrobial categories), respectively. Among the 13 Klebsiella pneumoniae BSI in one study, 30% were pan drug–resistant and 70% carbapenem resistant. Community-acquired AR also appears to be an issue for children with cancer in India, with a recent study showing a high prevalence (50%) of MDR bacteria colonizing children with newly diagnosed acute leukemia. A study from Israel, looking specifically at nonfermentative Gram-negative rods, found that 17% of P. aeruginosa and Acinetobacter baumannii BSI were MDR and 17% of Stenotrophomonas maltophilia BSI were resistant to colistin.

In a recent systematic review of BSI with ESBL-producing Enterobacteriaceae in all children, an annual global increase in prevalence of 3.2% was found, with the highest rates detected in Africa, South America and India. Similarly, in the United States, a cohort study of 48 pediatric hospitals identified an increase in the incidence of multiresistant Enterobacteriaceae infection from 2007 to 2015. While these data are not restricted to children with cancer, single-center studies report similar increasing rates of resistance in this population. Notably, a recently published Italian study in children with cancer observed a 3-fold increase in the colonization rate for Carbapenem-resistant Enterobacteriaceae (CRE) and a 4-fold increase of BSI with these bacteria.

Risk Factors
A recent systematic review identified 5 cohort studies exploring risk factors associated with the development of AR Gram-negative BSI in children with cancer. Since this review, one further relevant study has been published. Hospital admission before BSI was identified as an independent risk factor for AR Gram-negative infection, with a 4-fold increase in risk after 48 hours in 2 studies and a 14-fold increase in risk after 14 days in a third which looked specifically at K. pneumoniae BSI. A study evaluating MDR Gram-negative infection in an oncologic pediatric intensive care unit (ICU) also showed that healthcare-associated infection was an independent risk factor for resistance (odds ratio [OR], 18).

Recent administration of empiric or targeted treatment antibiotics is also an

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From the *Children’s Hospital Oxford, Headington, Oxford; Department of Infectious Diseases, Istituto Giannina Gaslini, Italy; †The Paediatric Integrated Cancer Service, Parkville, Victoria, Australia; Department of Infectious Diseases, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; ‡Sir Peter MacCallum Department of Oncology, University of Melbourne, Parkville, Victoria, Australia; and ¶Department of Infection and Immunity, Monash Children’s Hospital, Department of Paediatrics, Monash University, Clayton, Victoria, Australia.
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Address for correspondence: Gabrielle M. Haeusler, MBBS, FRACP, Department of Infectious Diseases, Peter MacCallum Cancer Centre, 365 Grattan Street, Melbourne, Australia, 3000. E-mail: gabrielle.haeusler@petermac.org
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important risk factor for development of AR Gram-negative BSI. However, the evidence for antibiotic prophylaxis as a risk factor for AR is more conflicting. Several nonrandomized studies support the idea that ciprofloxacn prophylaxis (or use of ciprofloxacn by adult hematologic patients in the same hospital) is correlated with increased resistance to ciprofloxacn in colonizing bacteria and bacteremia.20 This does not appear to be the case for trimoxazole prophylaxis, although fewer data are available.  

The impact of immunosuppression on development of AR has been explored in a number of studies. In 2 studies, markers of the depth of immunosuppression were identified as independent risk factors, namely severe neutropenia and chemotherapy likely to cause neutropenia for more than 7 days. Conversely, in another study, duration of neutropenia disappeared as a significant risk factor after multivariate analysis. No studies have specifically explored risk factors for infection with ESBL-producing Gram-negative bacteria or carbapenem-, pan drug- and extensively drug–resistant bacteria in children with cancer. In a pediatric case–control study that included oncology patients, receipt of extended-spectrum cephalosporins within 30 days was significantly associated with an ESBL–producing Enterobacter cloaceae and Klebsiella spp. BSI. Similarly in adults with hematologic malignancies, risk factors for ESBL BSI include recent antibiotic exposure, as well as ICU admission and prolonged hospitalization.

### OUTCOME

The body of research on outcome of AR BSI in children with cancer is hampered by variation in definitions of resistance, the type and definitions of clinical outcomes reported and collation of data on Gram-negative and Gram-positive bacteria. However, despite this heterogeneity, the data suggest that BSI with an AR organism negatively impacts outcome. This is in keeping with studies of adult patients with cancer, as well as data from nonimmunosuppressed populations. A large study investigating the clinical impact of BSI with AR Gram-negative bacteria as compared with antibiotic-sensitive bacteria in children with cancer is available in Table 1.

In an Australian study, AR Gram-negative BSI was significantly associated with prolonged hospital length of stay and ICU length of stay. Those admitted to ICU were also more likely to require invasive ventilation. A large study investigating the impact of the ESKAPE (Enterococcus faecium, methillin-resistant Staphylococcus aureus, K. pneumoniae, A. baumannii, P. aeruginosa, and Enterobacter species) group of pathogens on pediatric oncology patients found that children with ESKAPE

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### TABLE 1. Summary of Publications Exploring Outcome of Antibiotic-resistant Gram-negative Bacteremia in Comparison to Antibiotic-sensitive Bacteremia in Pediatric Oncology Patients

<table>
<thead>
<tr>
<th>Citation</th>
<th>Study Group</th>
<th>Study Type</th>
<th>Key Outcomes</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>Reddy et al</td>
<td>Retrospective single-center cohort (level 2b); India, 2013</td>
<td>No significant difference in mortality between MDR and sensitive group (4/16, 25% vs 0/9, 0%)</td>
<td>MDR defined as resistance to at least one agent in 3 or more antimicrobial categories</td>
<td></td>
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<tr>
<td>Haeusler et al</td>
<td>Retrospective single-center cohort (level 2b); Australia, 2003–2010</td>
<td>Median hospital LOS is longer in AR group (23.5 d vs 14 d, P = 0.0007)</td>
<td>AR defined as resistance to both ticarcillin-clavulanate and gentamicin (empiric FN treatment). Multivariable logistic regression used</td>
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<tr>
<td>Ariffin et al</td>
<td>Prospective single-center cohort (level 2b); Kuala Lumpur, 1996–1997</td>
<td>Mortality rate is higher in AR group (9/16, 56% vs 2/15, 13.3%. OR 6.5; 95% CI, 1.1–38.6, P = 0.02)</td>
<td>AR defined as resistance to cefazidime</td>
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<tr>
<td>Caselli et al</td>
<td>Multicenter retrospective cohort (level 2b); Italy, 2000–2008</td>
<td>Mortality rate is higher in MDR group (14/39, 35.8% vs 11/88, 12.5%. OR 4.3; 95% CI, 1.67–11.07, P = 0.002)</td>
<td>MDR defined as resistance to ≥3 antibiotic classes</td>
<td></td>
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<tr>
<td>Chiu et al</td>
<td>Retrospective single-center cohort (level 2b); Taiwan, 1994–1995</td>
<td>No difference in mortality rate in MDR and susceptible groups (3/10, 30% vs 0/12, P = 0.08)</td>
<td>Part of a larger study of 70 episodes of bacteremia in patients with FN. MDR defined as susceptible only to cefazidime and imipenem</td>
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*Fisher exact test performed by review authors on original data.
†Fever was a single temperature ≥38.3°C or a temperature ≥38°C for 1 hour or twice with minimum interval of 12 hours; neutropenia was an absolute neutrophil count <0.5 × 10⁹/L or <1.0 × 10⁹/L with decline expected in the next 2 days.
‡Fever defined as temperature ≥38°C on 5 occasions over 24 h or a single temperature ≥38.5°C; neutropenia defined as an absolute neutrophil count <0.5 × 10⁹/L, length of stay; MDR, multidrug resistance; OR, odds ratio.

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<tr>
<td>Reddy et al</td>
<td>25 episodes of GN bacteremia; Age not stated; Inc. patients with hematologic and solid malignancies</td>
<td>No significant difference in mortality between MDR and sensitive group (4/16, 25% vs 0/9, 0%)</td>
<td>MDR defined as resistance to at least one agent in 3 or more antimicrobial categories</td>
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<tr>
<td>Haeusler et al</td>
<td>280 episodes of GN bacteremia in 210 patients; Median age 6.5 y (range 0.1–21.7 y); Patients with hematologic and solid malignancies and HSCT</td>
<td>Median hospital LOS is longer in AR group (23.5 d vs 14 d, P = 0.0007)</td>
<td>AR defined as resistance to both ticarcillin-clavulanate and gentamicin (empiric FN treatment). Multivariable logistic regression used</td>
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<tr>
<td>Ariffin et al</td>
<td>31 episodes of Klebsiella pneumonia bacteremia in 29 patients with FN†; Mean age 6.4 y (range 7–13 y); Inc. patients with hematologic and solid malignancies</td>
<td>Mortality rate is higher in AR group (9/16, 56% vs 2/15, 13.3%. OR 6.5; 95% CI, 1.1–38.6, P = 0.02)</td>
<td>AR defined as resistance to cefazidime</td>
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<tr>
<td>Caselli et al</td>
<td>127 first episodes of Pseudomonas aeruginosa bacteremia in 127 patients; Median age 5.5 y (range 14 d to 20.5 y); Inc. patients with hematologic and solid malignancies and HSCT</td>
<td>Mortality rate is higher in MDR group (14/39, 35.8% vs 11/88, 12.5%. OR 4.3; 95% CI, 1.67–11.07, P = 0.002)</td>
<td>MDR defined as resistance to ≥3 antibiotic classes</td>
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<tr>
<td>Chiu et al</td>
<td>22 episodes of Klebsiella pneumonia bacteremia in patients with FN†; Age not stated; Inc. patients with hematologic and solid malignancies</td>
<td>No difference in mortality rate in MDR and susceptible groups (3/10, 30% vs 0/12, P = 0.08)</td>
<td>Part of a larger study of 70 episodes of bacteremia in patients with FN. MDR defined as susceptible only to cefazidime and imipenem</td>
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BSI had prolonged duration of fever and antibiotic treatment as compared with children with BSI with coagulase negative staphylococcal.26 Notably, the rate of MDR among the ESKAPE bacteria was 74% in this study.26

Several studies show a significant increase in infection-related or all-cause mortality in patients with AR BSI.14,16,26,27 Death attributed to sepsis occurred in as many as 50% of children with a ceftazidime-resistant K. pneumoniae in Kuala Lumpur compared with 13% of those with a susceptible isolate (OR, 6.5).26 In an Italian study, an almost 4-fold increase in all-cause mortality was observed in children with multidrug-resistant P. aeruginosa bacteremia.14 In the aforementioned ESKAPE study, all-cause mortality was significantly higher in children with the ESKAPE bacteria as compared with those with coagulase negative staphylococcal (26% versus 4%).26 Studies that have not shown a significant increase in mortality with AR Gram-negative BSI may be explained by insufficient power to detect a difference in this rare outcome.13

The three studies specifically looking at MDR Gram-negative BSI had conflicting results. One found an almost 4-fold increase in mortality in children with MDR P. aeruginosa,14 while 2 others did not show a mortality difference in children with MDR K. pneumoniae25 and MDR Gram-negative bacteria, respectively. The small sample sizes (n = 22 and n = 25) of the latter 2 studies limits any firm conclusions. Regarding BSI with CRE, mortality has been shown to be significantly higher for children with a hematologic/oncologic condition as compared with other patients (OR, 15.7).26 Similarly, in a systematic review of adult neutropenic patients, carbapenem-resistant BSI were associated with a higher mortality (OR, 4.9).24

Recently published data suggest that time to effective administration of antibiotics is an important predictor of outcome in children with FN. Children who receive antibiotics within 60 minutes have been shown to be less likely to develop severe sepsis or require prolonged ICU admission.29 Infection with bacteria resistant to empiric FN antibiotic regimens will result in significant delays to effective antibiotics and provides some explanation for the poor outcome observed. In support of this, one study showed that patients with ceftazidime-resistant K. pneumonia who did not receive appropriate antibiotics within 48 hours of presentation were significantly more likely to have a fatal outcome (OR, 9).16 In adult cancer patients, inappropriate initial antibiotic therapy has been repeatedly shown to be a risk factor for increased mortality.22

PREVENTION AND EMPIRIC TREATMENT

Prevention remains the gold standard approach to manage the increasing threat of AR. In a comprehensive review of the infection control issues in patients with cancer, infection control bundles are recommended as well as integrated multidisciplinary antimicrobial stewardship programs to ensure appropriate antibiotic use.29 Local epidemiology and resistance rates should guide empiric antibiotic selection, and centers are encouraged to adopt dual therapy where resistance to commonly prescribed monotherapy agents (eg, Piperacillin-tazobactam, ceftazidime, cefepime) is high.31

In response to global increase in MDR bacteria and clear association with poor prognosis in adult and pediatric cancer patients, the fourth European Conference in infections in leukemia have proposed an “escalation” and “de-escalation strategy” for empiric FN antibiotics in leukemia and hematopoietic stem cell transplant.32 Patients without risk factors for MDR bacteria continue on a standard “escalation” pathway. Patients with risk factors for MDR start with very broad-spectrum antibiotics or combinations. This is “de-escalated” once microbiology results are known (generally after 72–96 hours of therapy). This strategy attempts to find a balance between avoiding unnecessary overprescribing in patients at low risk of infection with MDR bacteria and delays in administration of appropriate antibiotics in patients at high risk of MDR infections. Coupled with this strategy are recommendations to discontinue antibiotics after 72 hours in patients who are clinically stable, afebrile for 48 hours and with negative microbiology, irrespective of expected duration of neutropenia, provided they remain under close observation.32 However, caution and restraint is required in adopting a de-escalation approach to avoid “scope creep” and inappropriate use of very broad-spectrum antibiotics.

Detailed discussion of the treatment of specific MDR Gram-negative bacteria is beyond the scope of this article. A comprehensive review, albeit adult-focused, of treatment considerations for MDR bacteria, including ESBL-producing Enterobacteriaceae, CRE and MDR P. aeruginosa, A. baumannii and S. maltophilia, in patients with hematologic malignancy can be found elsewhere.22

CONCLUSION

Although the available data on the impact of AR BSI on outcomes in children with cancer have considerable limitations, there is evidence that it is correlated with poorer prognosis. Infection-related and all-cause mortality is significantly higher in children with an AR or MDR bacteria, and factors such as duration of hospitalization and intensity of treatment are also increased. The most robust risk factor for AR and MDR BSI is prior hospitalization for more than 48 hours. Severe neutropenia and previous antibiotic use are associated with AR in several studies. Ciprofloxacin prophylaxis may also be correlated with AR BSI, although data is less robust.

FUTURE

In an era of increasing antimicrobial resistance, further research is required, not only to describe the true impact of resistance on outcomes but also to identify methods of prevention, novel techniques for early detection and optimal treatment strategies. This review supports the need for effective antimicrobial stewardship programs and real-time surveillance of local AR patterns. Innovative approaches such as risk-stratified empiric treatment of FN based on likelihood of AR and escalation/de-escalation strategies warrant further investigation to determine the true impact of this model of care.

REFERENCES


