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Supportive care utilization and treatment toxicity in children with Down syndrome and acute lymphoid leukaemia at free-standing paediatric hospitals in the United States

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Summary

Although inferior outcomes of children with Down syndrome (DS) and acute lymphoid leukaemia (ALL) are established, national supportive care patterns for these patients are unknown. A validated retrospective cohort of paediatric patients diagnosed with ALL from 1999 to 2011 was assembled from the US Pediatric Health Information System (PHIS) database to examine organ toxicity, sepsis, and resource utilization in children with and without DS. Among 10699 ALL patients, 298 had DS-ALL (2.8%). In a multivariate model, DS was associated with increased risk of cardiovascular (odds ratio [OR] 2.0, 95% confidence interval [CI] 1.6–2.7), respiratory (OR 2.1, 95% CI: 1.6–2.9), neurologic (OR 3.4, 95% CI 1.9–6.2), and hepatic (OR 1.4, 95% CI 1.0 – 1.9) dysfunction and sepsis (OR 1.8, 95% CI: 1.4 – 2.4). Children with DS-ALL used significantly more respiratory support, insulin, and anti-infectives, including broad-spectrum Gram-positive agents, quinolones, and azoles. They used significantly fewer analgesics and antiemetics compared to non-DS-ALL children. Ultimately, this study confirms the increased risk of infectious and end-organ toxicity in children with DS-ALL and quantifies important differences in resource utilization between children with DS and non-DS ALL. These findings highlight the importance of investigating the impact of these care variations and developing specific supportive care guidelines for this population.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table SI. ICD-9 definitions for congenital cardiac abnormalities.

Keywords

acute lymphoid leukaemia; Down syndrome; paediatric leukaemia; supportive care; chemotherapy toxicity

Children with Down syndrome (DS) have a 10- to 50-fold increased risk of developing acute lymphoblastic leukaemia (ALL) compared to the general population (Hasle, 2001). Unfortunately, in addition to an increased risk of ALL, children with DS are more likely to experience sepsis (Garrison *et al*, 2005). Children with DS-ALL are also more likely to experience treatment-related toxicities, such as organ dysfunction (Chessells *et al*, 2001; de la Fuente *et al*, 2005; Garrison *et al*, 2005; Maloney *et al*, 2006; Rabin *et al*, 2012; O'Connor *et al*, 2014), which have the potential to translate into treatment-related mortality (TRM) (Buitenkamp *et al*, 2014; Patrick *et al*, 2014). In fact, a recent international multicentre study found increased infection rates among DS patients were associated with increased TRM (7% vs. 2%) during all courses of therapy (Buitenkamp *et al*, 2014).

In 2006, in response to concerns of treatment-related toxicities and TRM, the Children's Oncology Group (COG) modified therapeutic protocols to intensify supportive care in children with DS-ALL on clinical trials (de la Fuente *et al*, 2005; Maloney *et al*, 2006). COG protocol amendments for trials AALL0331, a study for standard risk B precursor ALL, and AALL0232, a study for high risk B precursor ALL, included DS-specific recommendations for prophylactic antibiotics, hospitalization for febrile neutropenia, leucovorin after intrathecal methotrexate, maintenance of immunoglobulin levels greater than 5 g/l, and initiation of stress-dose steroids and/or filgrastim in severely ill patients with DS-ALL. Current COG ALL trials, AALL0932, a study for standard risk B precursor ALL, and AALL1131, a study for high risk B precursor ALL, also require leucovorin following intrathecal methotrexate, response-based therapy intensification during induction in high-risk patients, and elimination of a second delayed intensification to decrease further TRM in children with DS-ALL.

While it is clear that children with DS-ALL sustain a substantial number of treatment-related toxicities and that recommendations are in place to reduce these outcomes, data comparing the use of resources in patients with DS and non-DS ALL are lacking. Directly comparing the rates of toxicities and supportive care resource utilization patterns between DS-ALL and non-DS-ALL can provide insights regarding the degree of increased risks of toxicity for DS patients and variation in the requirements of resources needed to manage both populations during the chemotherapy treatment period. Further, assessment of specific resource utilization patterns before and after 2006 can provide insight into the uptake and impact of recommendations made in 2006 to improve supportive care. Such data would allow for further refinement of supportive care recommendations for children with DS-ALL with the ultimate goal of improving outcomes of this vulnerable population.

In order to compare toxicity rates and resource utilization between DS-ALL and non-DS-ALL patients, we utilized a previously established and validated cohort of paediatric patients receiving treatment for ALL at one of 43 children's hospitals contributing data to the US Pediatric Health Information System (PHIS) database (Fisher *et al*, 2014; Miller *et al*, 2015).

We predicted that organ dysfunction and sepsis would be significantly increased in patients with DS-ALL compared to those with non-DS-ALL and that the presence of congenital cardiac abnormalities would increase the risk of these outcomes within DS patients. Additionally, we hypothesized that DS-ALL patients would have increased exposure to resources aimed at managing toxicities (e.g. oxygen supplementation, opiate use) or aimed at preventing toxicities (e.g. fluoroquinolone and azole use). Furthermore, we predicted that there would be a decrease in inpatient mortality after 2006, in correlation with recommendations aimed to improve supportive care.

Methods

Study design and data source

A retrospective cohort study design was used. Data were obtained from PHIS, an administrative database containing inpatient billing data from 43 not-for-profit, tertiary children's hospitals affiliated with the Child Health Corporation of America (Overland Park, KS). Contributing hospitals are located in 17 major metropolitan areas and account for 85% of admissions to US freestanding children's hospitals. PHIS data are composed of inpatient information including patient demographics, dates of service, discharge disposition and International Classification of Diseases, Ninth Revision (ICD-9) diagnosis and procedure codes (up to 41 per admission). Additionally, the database contains daily billing data for specific resources, including medications, imaging, and other clinical services. PHIS data quality is overseen by the Children's Hospital Association, Truven Health Analytics (data processing partner, Ann Arbor, MI), and the participating hospitals. Data for each admission are de-identified at submission and subject to numerous audits for entry validity (e.g., identifiable ICD-9 diagnosis codes) and reasonable patient information (e.g., birth weight).

Study cohort

Patients with newly diagnosed ALL between 1 January 1999 and 31 December 2011 were identified from a previously defined and validated paediatric cohort (Fisher *et al*, 2014). These analyses included all available inpatient data. Patients were followed from index cohort admission until 3 years follow-up, death, or stem cell transplant, whichever occurred first.

Primary exposure

An individual was considered positive for the primary exposure, Down syndrome (DS), if the DS ICD-9 code (758.0) was present in greater than 70% of admissions from index cohort admission over a 3-year follow-up period. All other patients were considered non-DS-ALL patients.

Outcomes

The outcomes of interest included the presence of organ dysfunction and resource utilization over the 3-year period. Specific organ system dysfunction (cardiac, hepatic, neurologic, renal and respiratory) was defined by using a composite of ICD-9 diagnosis codes, ICD-9 procedure codes, and resource utilization billing codes as previously described (Maude *et al*, 2014). Sepsis was defined using a combination of previously described ICD-9 diagnosis

codes (Watson *et al*, 2003; Weiss *et al*, 2012; Maude *et al*, 2014). Each organ dysfunction and sepsis was dichotomized as present or absent within the 3-year follow-up period for the primary analysis, and also dichotomized as present or absent within each admission for the sub-analysis. The frequency of inpatient resource utilization was determined for each patient based on daily billing data for the following resources: complete blood counts, blood cultures, antimicrobial agents, blood products, opioid analgesics, antihypertensive medications, vasopressors, diuretics, antiemetics, supplemental oxygen, mechanical ventilation, extracorporeal membrane oxygenation, radiology imaging, parenteral nutrition, nasogastric tube placement, insulin, and dialysis. Each resource variable was dichotomized (exposure or no exposure) for each inpatient day, summarized as the total number of exposure days over the follow-up period for each patient and indexed to number of inpatient days during that patient's follow-up period. This methodology has been previously used to assess resource utilization with similar datasets (Kavcic *et al*, 2013).

Covariates

Demographic data and insurance status were defined at the time of the index admission. Age was categorized into the following groups: <1 year, 1 to <5 years, ≥5 years to <10 years, ≥10 years to <15 years and ≥15 years. Other demographic variables included gender and race, dichotomized into white or non-white (black, Asian/Pacific islander, native American, other and unknown). Insurance status was categorized into private, public (Medicaid, Medicare, other government and Title V), and other (self-pay and other). Congenital cardiac abnormalities were defined by presence of ICD-9 code in the index admission and were adapted from previously described categorizations of complex cardiac conditions (Table SI) (Feudtner *et al*, 2001). Year of index admission was dichotomized to 1999–2005 and in or after 2006 given changes in supportive care guidelines that were introduced during this period (de la Fuente *et al*, 2005; Maloney *et al*, 2006).

Statistical analyses

Descriptive statistics were used to summarize patient demographics. Chi-square tests were used for bivariate comparison of the distribution of each demographic variable among the patients with and without DS. The rates of organ dysfunction and sepsis were described and compared using chi-square tests for patients with and without DS. Multivariate logistic regressions were performed to evaluate the association of DS with organ dysfunction and sepsis while adjusting for demographics, presence or absence of congenital cardiac abnormalities and year of index admission. For the resource utilization analysis, resource utilization days per 1000 inpatient days were reported. Poisson regressions were used to compare the rates of resource utilization between patients with and without DS with resource days as the outcome and inpatient days as the offset. To adjust for potential over dispersion in Poisson regressions, the Pearson scale adjustment was applied.

Sub-analysis was performed to evaluate the change of 3-year mortality after 2006, in DS and non-DS patients separately. Another sub-analysis was performed to evaluate the association of sepsis and organ dysfunction in the DS patients only, using all admissions in the 3-year follow-up period. In this sub-analysis, separate logistic regressions were constructed for each organ dysfunction, with sepsis as a predictor and adjusting for patient covariates.

Because a patient could contribute multiple admissions in this sub-analysis, the generalized estimating equation was applied to control for potential correlation of within-patient admissions.

Human subjects protection

In accordance with the Common Rule (45 CFR 46.102(f)) and the policies of The Children's Hospital of Philadelphia Institutional Review Board, this study, using a de-identified dataset, was not considered human subjects research.

Results

Between 1 January 1999 and 31 December 2011, 10699 patients with ALL were identified. Patients with DS-ALL ($n = 298$) compromised 2.8% of the cohort, which is consistent with published data (Bassal *et al*, 2005; Patrick *et al*, 2014). Table I compares the baseline demographics of patients with DS and non-DS ALL. Patients with DS were similar to patients without DS with respect to age, with a very small percentage of patients with DS-ALL presenting less than 1 year of age, as expected (Chessells *et al*, 2001; Arico *et al*, 2008). A higher percentage of DS-ALL patients were female, white, had public insurance, had congenital cardiac defects, and were admitted in or after 2006. Patients with DS-ALL were hospitalized for an average number of 55.0 d while patients with non-DS-ALL were hospitalized on average for 43.9 d ($P < 0.0001$) over the 3-year observation period.

In order to determine whether children with DS were more likely to experience sepsis and organ dysfunction, a multivariate analysis adjusted for congenital cardiac defects, year of initial admission and demographics was performed (Table II). DS patients had a significantly increased risk of each organ dysfunction and for sepsis. Within the overall population, congenital cardiac defect was significantly associated with cardiovascular dysfunction (odds ratio [OR] 1.6, 95% confidence interval [CI] 1.2–2.1) and respiratory dysfunction (OR 1.5, 95% CI 1.1–2.1). Within the DS population, the association between congenital cardiac defect and cardiovascular dysfunction (1.6, 95% CI 0.9–2.9, $P = 0.09$) and respiratory dysfunction (1.6, 95% CI 0.8–3.0, $P = 0.18$) trended toward significance.

Admission in or after 2006 was associated with decreased risk of cardiovascular dysfunction and sepsis for all patients. Specifically among DS patients, the inpatient mortality rate for children diagnosed in or after 2006, was decreased compared to those diagnosed prior to 2006, and this decrease approached significance (7.1% to 2.7%, $P = 0.063$). Children with non-DS-ALL had a smaller but statistically significant decline in mortality rate between the two time periods (4.6% to 2.0%, $P < 0.0001$). In the sub-analyses of association of sepsis and organ dysfunction using all admissions in the 3-year period for DS patients only, the presence of sepsis in an admission was associated with an increased risk of cardiovascular dysfunction (OR 1.34, 95% CI: 1.2–1.5) and respiratory dysfunction (OR 1.3, 95% CI: 1.2–1.4).

Table III compares summary resource utilization data for patients with and without DS. In adjusted analyses, patients with DS had significant increases in 7 of the 36 resource metrics measured. There was increased usage of multiple antimicrobial agents, including broad

gram-positive antibiotic coverage, fluoroquinolones, amphotericin products and azoles. Patients with DS also had a significantly increased usage of supplemental oxygen, ventilation, chest x-rays and insulin. Patients with DS also had a significantly decreased utilization of antiemetics and pain medications, including opioid and non-opioid analgesics and patient-controlled analgesics. Finally, children with DS-ALL had a significantly decreased usage of imaging studies including abdominal ultrasounds and chest computerized tomography scans in adjusted analyses.

Discussion

Previous reports of DS-ALL patients enrolled on cooperative group trials revealed an increased risk for treatment-related toxicity (Robison *et al*, 1984; Kalwinsky *et al*, 1990; Levitt *et al*, 1990; Ragab *et al*, 1991; Dordelmann *et al*, 1998; Chessells *et al*, 2001; Bassal *et al*, 2005; Buitenkamp *et al*, 2014; Patrick *et al*, 2014). We confirmed the increased risk for sepsis and end-organ toxicity in children with DS-ALL using a cohort of paediatric ALL patients assembled from an administrative data source. Futhermore, our findings are generalizable, as our cohort was inclusive of DS-ALL patients both enrolled and not enrolled on clinical trials at paediatric hospitals across the United States. More importantly, the PHIS database afforded the opportunity to compare resources utilized between DS and non-DS patients. Consistent with this increased risk of toxicity, children with DS-ALL had significantly increased usage of associated antimicrobial and respiratory supportive care resources. Unexpectedly, children with DS-ALL had decreased analgesic and antiemetic use despite higher acuity of illness. These findings highlight the importance of supportive care management plans that target DS patients and provide a mechanism to identify specific areas to target for improvement and the possibility to monitor for changes in resource utilization over time.

Our study quantifies the increased risk for organ toxicity and sepsis among DS-ALL patients as 1.5–3 times the risk for non-DS patients, consistent with prior clinical trials, as summarized in Table IV (Robison *et al*, 1984; Kalwinsky *et al*, 1990; Levitt *et al*, 1990; Ragab *et al*, 1991; Dordelmann *et al*, 1998; Chessells *et al*, 2001; Bassal *et al*, 2005; de la Fuente *et al*, 2005; Maloney *et al*, 2006, 2010; Arico *et al*, 2008; Buitenkamp *et al*, 2014; Patrick *et al*, 2014). Additionally, we were able to quantify that within the ALL population, congenital cardiac defect was associated with an approximate 1.5-fold risk of cardiovascular dysfunction and respiratory dysfunction. In the DS-ALL population, this effect was mirrored; however the association trended toward significance, probably secondary to the smaller sample size. The observed increase in organ toxicities may explain previously described prolonged hospitalizations of children with DS-ALL (Bassal *et al*, 2005; Rabin *et al*, 2012).

This study is the first attempt to quantify supportive care resources administered to patients with DS-ALL compared to non-DS ALL patients. We hypothesize that the observed increased utilization of certain resources among the DS patients is secondary to the increased frequency of toxicities. For instance the increased usage of supplemental oxygen, ventilation and chest x-rays in children with DS-ALL supports the finding of increased respiratory toxicity in these patients. Alternatively, it is possible that some of the observed

increase in resource utilization is secondary to implementation of preventative supportive care measures. For instance, the observed increase in quinolone utilization suggests that the recommendations of certain experts for ciprofloxacin prophylaxis during periods of intense therapy are being implemented at a national level (Izraeli *et al*, 2014). While there are no consensus recommendations for antifungal prophylaxis for children with DS-ALL, it is plausible that the identified increased azole use is reflective of increased implementation of antifungal prophylaxis at a national level (Izraeli *et al*, 2014). The addition of laboratory and imaging data to the PHIS database will facilitate future research to determine whether the uptake of prophylactic supportive care resources, such as antibacterial or antifungal prophylaxis, are the source of observed improvements in clinical outcomes, such as bacteremia or invasive fungal infection (Narus *et al*, 2011).

The decreased utilization of analgesics and antiemetics in children with DS-ALL was unexpected. A previous small, single-centre study found no increased use of opiate analgesia or parenteral nutrition in patients with DS-ALL (Shah *et al*, 2009). Studies of post-operative pain management of children with DS suggest either an increased or similar need of post-operative pain analgesia as compared to non-DS patients (Gakhal *et al*, 1998; Valkenburg *et al*, 2012; Van Driest *et al*, 2013). Recent studies quantitatively comparing pain thresholds in children with and without DS have demonstrated that children with DS experience pain at the same frequency as children without DS, with delays in acute pain expression and magnified pain response (McGuire & Defrin, 2015; Valkenburg *et al*, 2015). Given that research reports equivalent pain frequency in children with DS, our finding of decreased analgesia use among DS-ALL patients may signify important deficiencies in current clinical care of these patients. Ensuring adequate assessment and treatment of pain and antiemetic needs of children with DS-ALL is clinically imperative. This result also highlights the strength of nationally representative pharmacy billing data to detect clinically important deficits in current supportive care practices.

We did observe a trend towards decreased mortality in DS-ALL and a significantly decreased mortality in non-DS ALL patients after 2006. Previous studies have demonstrated decreased TRM in patients with standard risk, but not high risk, DS-ALL after implementation of DS-specific supportive care guidelines (Maloney *et al*, 2011). Although our findings did not reach statistical significance, inpatient mortality decreased from 7.1% to 2.7% for children with DS-ALL and from 4.6% to 2.0% for children without DS. The size of this mortality differences suggests that it may be clinically significant and the small population size of children with DS-ALL limited its statistical significance. While this decrease in mortality is temporally associated with the implementation of the 2006 supportive care guidelines, additional advances in ALL care may also contribute to this improvement in mortality. Additional research is warranted to determine the degree of mortality benefit attributable to a consistent application of increased supportive care in children with DS-ALL.

The presented findings need to be interpreted in the context of several limitations. First, Down syndrome was defined by an ICD-9 diagnosis code with previously described moderate sensitivity and positive predictive value (Jensen *et al*, 2013). By defining Down syndrome status as greater than 70% of admissions with a DS ICD-9 code, this study

attempted to increase the positive predictive value of this measure. While this revised definition was not independently validated, the similarity in demographic characteristics to published DS cohorts provides validity to this definition (Dordelmann *et al*, 1998; Chessells *et al*, 2001; Arico *et al*, 2008; Maloney *et al*, 2010; Buitenkamp *et al*, 2014; Patrick *et al*, 2014). Secondly, organ dysfunction and sepsis were defined by ICD-9 diagnosis and procedure codes as well as resource utilization rather than laboratory data or clinician documentation; however, previously validated ICD-9 codes were used to the extent possible. It is expected that misclassification of these outcomes would be non-differential across DS and non-DS patients and thus have a small impact on relative differences in outcomes between children with DS and non-DS-ALL (Fisher *et al*, 2013; Maude *et al*, 2014). Our estimated risk of sepsis may be lower than other reported estimates of infectious complications given that our definition did not include all possible infections. Additionally, this study did not analyse directly mucositis and hyperglycaemia as these associated ICD-9 codes had not been previously validated; however, the significantly increased use of insulin in DS patients provides confirmation of the increased risk of hyperglycaemia. This study did not examine outpatient data, limiting the generalizability of the results to the inpatient setting only. Finally, the lack of microbiology, laboratory and radiology results limits the specific inferences that we can make about the specific infections or aetiologies that drive the observed resource utilization patterns, such as whether antibiotics were administered prophylactically or therapeutically.

In summary, children with DS-ALL have an increased risk for sepsis and organ dysfunction and an associated increase in the utilization of a number of resources related to management or prevention of these toxicities. Simultaneously, they had decreased analgesic and antiemetic exposure despite increased toxicities. This suggests a deficiency in provision of pain and nausea management. While the decreasing trend in mortality is encouraging, additional focus on improving the provision of supportive care for children with DS-ALL is imperative. Research assessing the comparative effectiveness of currently employed supportive care measures, such as quinolone and antifungal prophylaxis, is necessary to better quantify their benefits relative to potential risks such as monetary costs or induction of resistance. Evaluation of the impact of specific supportive care measures on clinical outcomes is necessary to determine how to best allocate resources to improve overall outcomes in children with DS-ALL.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

All authors contributed to the research design. Dr. Salazar and Dr. Li performed the analysis. All authors contributed to the interpretation of the data. Dr. Salazar wrote the paper. All authors critically revised the paper and approved of the final draft.

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Table I

Demographics of paediatric patients with acute lymphoid leukaemia with and without Down syndrome.

	All patients (*N* = 10699)	**Patients with Down syndrome (*N* = 298)**	**Patients without Down syndrome (*N* = 10401)**	***P value*** [*]
Age, *n* (%)				
<1 year	291 (3)	1 (0.3)	290 (3)	
≥1 year and <5 years	4823 (45)	142 (48)	4681 (45)	0.07
≥5 years and <10 years	2744 (26)	76 (26)	2668 (26)	
≥10 years and <15 years	1757 (16)	43 (14)	1714 (16)	
≥15 years	1084 (10)	36 (12)	1048 (10)	
Gender, *n* (%)				
Male	6001 (56)	142 (48)	5859 (56)	0.003
Female	4698 (44)	156 (52)	4542 (44)	
Race, *n* (%)				
White	8095 (76)	246 (83)	7849 (75)	0.005
Non-White [†]	2604 (24)	51 (17)	2552 (25)	
Insurance at first admission, *n* (%)				
Private	4286 (40)	100 (34)	4186 (40)	0.002
Public [‡]	4135 (39)	144 (48)	3991 (38)	
Other [§]	2278 (21)	51 (18)	2224 (21)	
Congenital Cardiac Abnormalities, *n* (%)				
Yes	277 (3)	78 (26)	199 (2)	<0.0001
No	10422 (97)	220 (74)	10202 (98)	
Year of Admission, *n* (%)				
1999–2005	4643 (43)	112 (38)	4521 (44)	0.04
2006–2011	6056 (57)	186 (62)	5870 (56)	

[*] P value is from chi-square tests.

[†] Non-white includes Black, Asian/Pacific Islander, American Indian, Other and Unknown.

[‡] Public includes Medicaid, Medicare, other government and Title V.

[§] Other includes Self-pay, Other and Unknown.

Table II

Multivariate analyses of percentage organ dysfunction by Down syndrome status[†].

Organ dysfunction	Number of DS patients (*n* = 298)	Number of Non-DS patients (*n* = 10401)	Adjusted OR of Organ dysfunction by DS[†]
Cardiovascular Dysfunction, *n* (%)	98 (33)	1960 (19)	2.0 (95% CI: 1.6–2.7) [*]
Respiratory Dysfunction, *n* (%)	69 (23)	1273 (12)	2.1 (95% CI: 1.6–2.9) [*]
Sepsis, *n* (%)	86 (29)	1907 (18)	1.8 (95% CI: 1.4–2.4) [*]
Neurologic Dysfunction, *n* (%)	16 (5)	157 (2)	3.4 (95% CI: 1.9–6.2) [*]
Hepatic Dysfunction, *n* (%)	64 (21)	1648 (16)	1.4 (95% CI: 1.0–1.9) [*]

DS, Down syndrome; OR, odds ratio; 95% CI, 95% confidence interval.

[*] $P < 0.05$.

[†] Adjusted for age, race, insurance status, year of admission, congenital cardiac defects.

Table III

Resource utilization rate (days of resource exposure per 1000 hospital days) in patients with and without DS.

Resources measured	Rate for DS (*n* = 298)	Rate for Non-DS (*n* = 10401)	IRR (95% CI)	Adjusted IRR[†] (95% CI)
Complete blood count	753.6	717.8	**1.0 (1.0–1.1)** [*]	1.0 (1.0–1.1)
Blood culture	32.8	34.5	1.0 (0.8–1.2)	0.9 (0.7–1.1)
Antibiotics				
Total (of the 5 subclasses)	857.2	813.5	**1.1 (1.0–1.1)** [*]	1.0 (1.0–1.1)
Broad Gram–positive coverage[‡]	194.5	170.8	**1.1 (1.0–1.2)** [*]	**1.1 (1.0–1.2)** [*]
Beta lactam anti-*Pseudomonas* coverage[§]	424	426.5	1.0 (0.9–1.1)	1.0 (0.9–1.0)
Carbapenems with anti-*Pseudomonas* activity[¶]	69.3	68.2	1.0 (0.8–1.2)	1.0 (0.9–1.2)
Quinolones	31.4	19.6	**1.6 (1.2–2.1)** [*]	**1.5 (1.2–2.0)** [*]
Aminoglycosides	115.2	116.7	1.0 (0.9–1.1)	1.0 (0.8–1.1)
Antifungals				
Total (of the 3 subclasses)	331.9	276.2	**1.2 (1.1–1.3)** [*]	**1.2 (1.1–1.3)** [*]
Amphotericins	43.2	56.1	**0.8 (0.6–1.0)** [*]	**0.8 (0.6–1.0)** [*]
Echinocandins	41.6	30.1	**1.4 (1.0–1.8)** [*]	**1.0 (0.7–1.3)**
Azoles	247.1	190.0	**1.3 (1.2–1.5)** [*]	**1.3 (1.2–1.5)** [*]
Antivirals	131.8	116.6	1.1 (1.0–1.3)	1.1 (0.9–1.3)
Blood products				
Packed red blood cells	78.8	93.9	**0.8 (0.8–0.9)** [*]	**0.8 (0.7–0.9)** [*]
Platelets	94.9	101.5	0.9 (0.8–1.0)	0.9 (0.8–1.0)
Fresh frozen plasma	9.8	7.3	1.3 (1.0–1.8)	1.3 (0.9–1.7)
Cryoprecipitate	2.1	2.3	0.9 (0.5–1.8)	1.0 (0.5–1.9)
Analgesics				
Non-opioid	202.2	248.0	**0.8 (0.8–0.9)** [*]	**0.8 (0.7–0.9)** [*]
Opioid (all routes) [**]	213.5	243.0	**0.9 (0.8–1.0)** [*]	**0.8 (0.8–0.9)** [*]
Patient-controlled analgesics	14.3	25.3	**0.6 (0.4–0.9)** [*]	**0.6 (0.4–0.9)** [*]
Anti-emetics	244.3	375.1	**0.7 (0.6–0.7)** [*]	**0.7 (0.6–0.7)** [*]
Parenteral nutrition	78.9	90.2	0.9 (0.7–1.1)	0.9 (0.7–1.1)
Anti-hypertensives	85.5	96.9	0.9 (0.7–1.1)	0.8 (0.6–1.1)
Diuretics	75.3	66.6	1.1 (1.1–1.3)	1.1 (0.9–1.3)
Vasopressors				
Dopamine	10	7.7	1.3 (0.9–1.9)	1.2 (0.8–1.7)
Other	20.5	18.5	1.1 (0.9–1.4)	1.1 (0.9–1.4)
Supplemental oxygen	97.6	40.2	**2.4 (2.1–2.8)** [*]	**1.3 (1.2–1.5)** [*]
Ventilation	43.5	22.5	**1.9 (1.5–2.5)** [*]	**2.0 (1.5–2.7)** [*]
ECMO	0.7	0.4	1.8 (0.3–12.7)	2.0 (0.2–17.8)
Dialysis	6.2	4.3	1.4 (0.8–2.7)	1.1 (0.6–2.1)

Resources measured	Rate for DS (n = 298)	Rate for Non-DS (n = 10401)	IRR (95% CI)	Adjusted IRR[†] (95% CI)
Radiology imaging				
Chest x-ray	137.4	96.8	**1.4 (1.3–1.5)** [*]	**1.4 (1.2–1.5)** [*]
Abdominal ultrasound	5	7.4	**0.7 (0.5–0.9)** [*]	**0.6 (0.5–0.8)** [*]
Head CT	6.2	7.7	0.8 (0.6–1.0)	0.8 (0.6–1.1)
Chest CT	6.9	9.8	**0.7 (0.6–0.9)** [*]	**0.7 (0.5–0.8)** [*]
Head MRI	3.7	4.4	0.8 (0.6—1.1)	0.8 (0.6–1.0)
Insulin	37.8	14.9	**2.5 (1.9–3.2)** [*]	**1.3 (1.1–1.5)** [*]

DS, Down syndrome; ECMO, extracorporeal membrane oxygenation; CT, computerized tomography; MRI, magnetic resonance imaging; IRR, incidence rate ratio; 95% CI, 95% confidence interval.

[*] $P > 0.05$.

[†] Adjusted for age, race, insurance status, year of admission and congenital cardiac defects.

[‡] Includes vancomycin, linezolid, daptomycin, quinopristin/dalfopristin.

[§] Includes ceftazidime, cefepime, piperacillin/tazobactam, ticarcillin/clavulanate.

[¶] Includes imipenem and meropenem.

[**] Includes norepinephrine, epinephrine and dobutamine.

Table IV

Toxicities reported on previous clinical trials in children with DS-ALL.

Study name	Patient cohort	Cardiac toxicity	Respiratory toxicity	Sepsis	Liver toxicity	Neuro toxicity
Patrick *et al* (2014)	86 DS-ALL on UKALL 2003	–	–	34 infections. 3 fungal infections	Described	2 seizures
Buitenkamp *et al* (2014)	653 DS-ALL on multiple trials	–	Pulmonary infection described	38 infectious deaths	–	–
Maloney *et al* (2006)	20 DS-ALL on AALL0232, 26 DS-ALL on AALL0331	Described	–	Described	–	–
de la Fuente *et al* (2005)	37 DS-ALL on UK MRC ALL 97	1 cardiac death.	–	8 infectious deaths	–	–
Bassal *et al* (2005)	59 DS-ALL on CCG-1952	–	–	Described	–	–
Chessells *et al* (2001)	55 DS-ALL on UK MRC ALL X or XI	–	–	4 infectious deaths	–	–
Dordelmann *et al* (1998)	61 DS-ALL on BFM 81, 83, 86 and 90	2 cardiac toxicities	Pulmonary infection described	Described	–	–
Ragab *et al* (1991)	33 DS-ALL on POG trials	–	–	14 Grade 3/4 toxicities	3 Grade 3/4 toxicities	–
Kalwinsky *et al* (1990)	28 DS-ALL on SJCRH trials	1 cardiac death	33% bronchitis 26% pneumonia	29% sepsis in induction	–	4% seizures
Levitt *et al* (1990)	63 DS-ALL on multiple trials	2 cardiac deaths	–	16 infectious deaths	–	1 case of status epilepticus
Robison *et al* (1984)	95 DS-ALL on CCSG trials	1 cardiac death	7 pneumonia deaths	6 bacterial sepsis deaths	–	1 death due to CNS haemorrhage

DS, Down syndrome; ALL, acute lymphoblastic leukaemia; CNS, central nervous system; UK MRC, United Kingdom Medical Research Council; CCG, Children's Cancer Group; BFM, Berlin-Frankfurt-Munster Group; POG, Pediatric Oncology Group; SJCRH, St. Jude's Childrens' Research Hospital; CCSG, Childrens Cancer Study Group.

–Indicates not reported in manuscript.