Febrile illness in high-risk children: a prospective, international observational study

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Abstract

Purpose

To assess and describe the aetiology and management of febrile illness in children with primary or acquired immunodeficiency at high-risk of serious bacterial infection, as seen in emergency departments in tertiary hospitals.

Methods

Prospective data on demographics, presenting features, investigations, microbiology, management, and outcome of patients within the 'Biomarker Validation in HR patients' database in PERFORM, were analysed. Immunocompromised children (<18 years old) presented to fifteen European hospitals in nine countries, and one Gambian hospital, with fever or suspected infection and clinical indication for blood investigations.

Febrile episodes were assigned clinical phenotypes using the validated PERFORM algorithm. Logistic regression was used to assess effect size of predictive features of proven/presumed bacterial or viral infection.

Results

599 episodes in 482 children were analysed. Only 78 episodes (13.0%) were definite bacterial, 55 definite viral (9.2%), and 190 were unknown bacterial or viral infections (31.7%). Predictive features of proven/presumed bacterial infection were ill appearance (OR 3.1 (95%CI 2.1-4.6)) and HIV (OR 10.4 (95%CI 2.0-54.4)). Ill appearance reduced the odds of having a proven/presumed viral infection (OR 0.5 (95%CI 0.3-0.9)).

82.1% had new empirical antibiotics started on admission (N=492); 94.3% of proven/presumed bacterial, 66.1% of proven/presumed viral, and 93.2% of unknown bacterial or viral infections. Mortality was 1.9% and 87.1% made full recovery.

Conclusions

Aetiology of febrile illness in immunocompromised children is diverse. In one-third of cases no cause for the fever will be identified. Justification for standard intravenous antibiotic treatment for every febrile immunocompromised child is debatable, yet effective. Better clinical decision-making tools and new biomarkers are needed for this population.

What Is Known?

- Immunosuppressed children are at high risk for morbidity and mortality of serious bacterial and viral infection, but often present with fever as only clinical symptom.

- Current diagnostic measures in this group are not specific to rule out bacterial infection, and positivity rates of microbiological cultures are low.

What Is New?

- Febrile illness and infectious complications remain a significant cause of mortality and morbidity in HR children, yet management is effective.

- The aetiology of febrile illness in immunocompromised children is diverse, and development of pathways for early discharge or cessation of intravenous antibiotics is debatable.

- This study illustrates the need for better clinical decision-making tools and biomarkers, to reduce hospital admissions for intravenous antibiotics in this population.

Introduction

Complex comorbidities render a growing number of children who attend the emergency department (ED) at increased risk of infection. This includes children with primary (PID) or acquired immunodeficiencies, but also those who are dependent on total

parenteral nutrition (TPN) with central venous lines. They are at high-risk (HR) for serious bacterial infection (SBI) and life-threatening infectious complications.[1] Some of these children are neutropenic. SBI during febrile neutropenia (FN) is a medical emergency associated with significant morbidity and mortality if left untreated.[1,2] One-third of neutropenic episodes in paediatric patients on cancer treatment or during haematopoietic stem cell transplant (HSCT) is associated with fever.[3]

Differentiating viral, bacterial and inflammatory illness on admission is challenging in HR patients: clinical syndromes are often non-specific and at least 36-48 hours are needed to culture microorganisms.[4,5] Because the risk of having SBI is significant[6,7], immunocompromised patients with febrile illness are virtually always admitted for intravenous antibiotic treatment, awaiting microbiological results, yet only 11.4%-31.3% will have a microbiologically documented infection.[8-11] 41.3-62.3% will have no cause identified.[11-14]

This approach has led to significant reduction in mortality and morbidity[15], but consequently antibiotic overuse, increased risk of antimicrobial resistance, and prolonged hospitalisation. Fever accounts for 60.2% of emergency department (ED) attendance in paediatric cancer[16], and is a significant burden for caregivers[17] and healthcare systems. Commonly used biomarkers, such as C-reactive protein (CRP) and procalcitonin aid the diagnostic process, but are often not sensitive enough to rule out bacterial infection.[18-20] It is suspected a large proportion of HR fever has a viral aetiology, is drug-induced or caused by underlying disease.[2,21,22]

We describe current aetiology and management of fever in immunocompromised children, and assess the risk of bacterial infection in a mixture of immunocompromised patients as seen by paediatricians in tertiary healthcare centre EDs, where they present primarily with fever.

Material And Methods

This prospective, international, multicentre, observational study assessed children recruited to the 'Biomarker Validation in HR patients' cohort within Personalised Risk assessment in Febrile illness to Optimise Real-life Management across the European Union (PERFORM) between 2 June 2016 and 31 December 2019.

Participants

Children, <18 years of age, immunocompromised due to primary or secondary immunodeficiency, were eligible upon presentation to ED, ward or intensive care units (PICUs) admission with: (history of) fever (<72 hours prior to admission, T≥38.0°C) or suspected infection, and clinical indication for blood investigations as per treating clinician's decision. Participants could have multiple episodes, with a two-week minimum between the end and start of consecutive episodes. They were recruited between 2 June 2016 and 31 December 2019.

Participants were recruited from sixteen tertiary centres in ten countries: four each from the United Kingdom (UK) and the Netherlands, and one each from Austria, the Gambia, Germany, Greece, Latvia, Slovenia, Spain, and Switzerland.

Data collection

We collected in-depth clinical data on standardised forms, including clinical symptoms, laboratory results, management, clinical syndromes, 28-day outcome, severity, and mortality. Regular data quality control was performed.

Study Outcomes

All episodes were assigned final phenotypes using the validated algorithm in the PERFORM protocol[23] (Supplementary Information Figure S1), previously described by Nijman et al.[24], and assigned one of eleven phenotypes: definite bacterial, probable bacterial, bacterial syndrome, unknown bacterial/viral, viral syndrome, probable viral, definite viral, trivial, other infection, uncertain infection/inflammation, or inflammatory syndrome. Episodes assigned definite bacterial, probable bacterial or unknown bacterial/viral phenotypes could also have viral or fungal co-infection identified. Phenotypes for all episodes were reviewed by experienced paediatricians before definite assignment.

To evaluate determinants of bacterial and viral infection, we combined definite bacterial, probable bacterial, and bacterial syndrome to a proven/presumed bacterial infection group, and definite viral, probable viral, and viral syndrome to a proven/presumed viral

infection group. The definite bacterial phenotype could only be assigned if the bacterium was isolated from a sterile site.

First, we described our cohort and compared clinical features of proven/presumed bacterial, and proven/presumed viral groups versus the other phenotypes. Neutropenia was defined as absolute neutrophil count (ANC) $<0.5x10^9$/L or $<1.0x10^9$/L but expected $<0.5x10^9$/L within 48 hours, or, if no ANC available, white cell count $<1.0x10^9$/L[25], and lymphopenia defined as lymphocyte count $<1.0x10^9$/L. Second, we described microbiology results and empirical antimicrobial management, utilizing the AWaRe classification[26], categorizing antibiotics in 'access', 'watch' and 'reserve' groups . Last, we described clinical syndromes, severity and outcome.

Statistical analysis

Data was analysed using IBM SPSS Statistics, version 27 [Armonk USA 2020]. For descriptive data, absolute frequencies and percentages were used. Data was not normally distributed; non-parametric tests, medians and interquartile ranges (IQR) were used. Mann-Whitney U tests were used for continuous variables, Pearson's χ^2 or Fisher's exact tests for categorical data. To assess the size effect of significantly associated clinical features for proven/presumed bacterial or viral infections, odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using univariate binary logistic regression. Subsequently multivariate binary logistic regression was performed on variables with significant ORs after univariate binary logistic regression. P-values <0.05 were considered significant.

Ethics approval and consent to participate

Ethical approval was obtained for all countries via respective national ethics committees, for the UK: IRAS 209035, REC 16/LO/1684. Informed consent was obtained from all participants or their legal guardians, assent where appropriate.

Results

599 episodes in 482 children were analysed. 84 children had multiple febrile episodes, with a maximum of six episodes in one child. 343 episodes were in males (57.3%), and median age at admission was 7.7 years (IQR 4.1-12.8 years). 8 patients were from the Gambia (1.3%)

Final phenotype diagnoses

174 episodes (29.0%) were proven/presumed bacterial, of which 78 definite bacterial (13.0%). 127 episodes were proven/presumed viral (21.2%), of which 55 were definite viral (9.2%). 190 episodes (31.7%) were unknown bacterial or viral infections (Figure 1).

Demographics

Table 1 gives a demographic overview, with detailed data on underlying conditions in Supplementary Information Table S1). Most common underlying conditions were malignancies in 354 episodes (59.2%), followed by non-malignant haematological disease in 79 (13.2%), and inflammatory disease and PID with 47 episodes (7.8%) each. Of the Gambian patients, 7 had sickle cell disease, and 1 HIV, as underlying condition.

In univariate binary logistic regression the following clinical features at admission were associated with proven/presumed bacterial infections versus all other phenotypes: ill appearance (OR 3.3 (95%CI 2.2-4.7)), tachypnoea (OR 1.8 (95%CI 1.1-2.9)), tachycardia (OR 1.6 (95%CI 1.1-2.4)), requiring a lifesaving intervention (OR 2.5 (95%CI 1.4-4.4)), solid organ transplant recipients (OR 4.7 (95%CI 2.1-9.9)), HIV (OR 7.6 (95%CI 1.5-37.8)), inflammatory disease (OR 0.4 (95%CI 0.2-0.9)), and tacrolimus use (OR 3.4 (95%CI 1.6-6.9)). Neutropenia at admission, or any immunosuppressant use at admission were not associated. After multivariate binary logistic regression, HIV (OR 10.4(95%CI 2.0-54.4)) and ill appearance (OR 3.1 (95%CI 2.1-4.6)) were the two covariates remaining significant.

Ill appearance reduced the odds of having a proven/presumed viral infection (OR 0.6 (95%CI 0.3-0.9)), and other underlying conditions increased the odds (OR 3.5 (95%CI 1.4-8.9)) in univariate binary logistic regression. Both covariates remained significant after multivariate binary logistic regression (ill appearance (OR 0.5 (95%CI 0.3-0.9), other underlying conditions (OR 3.9 (95%CI 1.5-10.0)).

Microbiology

Blood cultures were obtained in 563 episodes (94.0%), with a positive yield of 15.1% (N=85). Urine cultures were performed in 165 episodes (27.5%), with a yield of 13.9% (N=23). Polymerase chain reactions, primarily utilised for the detection of viral pathogens, were performed in 258 episodes (43.1%), with a yield of 46.9% (N=121) for any tested pathogen. Rapid antigen testing (N=86, 14.4%), serology (N=61, 10.2%), and tuberculosis testing (N=14, 2.3%), were less frequently performed, with yields of 15.1%, 39.3%, and 7.1%, respectively.

An overview of identified causative pathogens is given in Figure 2. In the definite bacterial group, with positive cultures from sterile sites, 118 bacterial isolates were cultured, of which 67 gram-negative (56.7%), and 49 gram-positive (41.5%). Two patients (1.8%) had mycobacterial pathogens identified. Common pathogens in our cohort were *Escherichia coli* (N=25), *Pseudomonas aeruginosa (N=15)*, and *Staphylococcus aureus* (N=10). Coagulase negative staphylococci were the most common gram-positive pathogen, in 14 episodes.

For viral pathogens, respiratory syncytial virus (N=14), Influenza A (N=12), and adenovirus (N=10) were detected most frequently. In 5 patients, a fungal pathogen was deemed causative. Co-infection was documented in 31 episodes, of which 29 were viral, and 2 fungal.

Empirical antimicrobial treatment

In 492 episodes (82.1%) new empirical antibiotics were started on admission (group by antibiotic class in Table 2, more detailed in Supplementary Information Table S2). 164 proven/presumed bacterial, 84 proven/presumed viral, and 177 unknown bacterial or viral episodes had new antibiotics started on admission.270 episodes had been treated with non-prophylactic antibiotics within 7 days prior to admission (45.1%). Most given empirical antibiotics were piperacillin-tazobactam (N=197, 40.0%), and teicoplanin (N=115, 23.4%). 440 episodes were started on ‘watch’ antibiotics (73.5%) empirically, and one was started on linezolid, a ‘reserve’ antibiotic, to use only as a last resort drug, according to the World Health Organization AWaRe classification[26].

Median duration of antibiotic treatment was 7 days (IQR 4-10 days). The proven/presumed bacterial group was treated significantly longer (median 10 days (IQR 7-14 days), p<0.001) and the proven/presumed viral group significantly shorter (median 5 days (IQR 3-8 days), p=0.001). The unknown bacterial or viral group was treated for median of 5 days (IQR 3-8 days).

Clinical syndromes

Common foci for febrile illness were upper respiratory tract infections (N=93, 15.5%), and sepsis syndromes (10.4%), who had no specific localised focus for fever, but did have a positive blood culture. 144 episodes were classed as undifferentiated fever, and 42 episodes had febrile neutropenia only, meaning 31.1% of febrile episodes in children at high-risk for SBI had no source for the fever identified (Figure 3, detailed in Supplementary Information Table S3). 81 episodes (13.5%) had non-infectious causes of fever.

Severity and outcome

Mortality within the febrile illness episode was 1.9% (11 children). Four had a malignancy, three PID, two solid organ transplant, one sickle cell disease, and one was on prolonged steroids following ischaemic brain injury. Three children died due to viral infection: one had disseminated adenoviraemia, one congenital cytomegalovirus reactivation, and one influenza A whilst developing multi-organ failure due to chemotoxicity from HSCT medication. Two died of sepsis: one *Streptococcus pneumoniae,* one *Candida albicans.* Two children had clinical lower respiratory tract infections but no pathogen isolated. One child died of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome and one of gastrointestinal infection already in palliative care. Two children died of non-infectious cancer-related complications.

In 522 episodes (87.1%), patients made full recovery at 28-day follow up, with no significant difference between proven/presumed bacterial or proven/presumed viral groups. Median length of in-patient stay (LOS) was 5 days (IQR 2-13 days), with longer admissions in the proven/presumed bacterial group (median 7 days (IQR 4-25 days, p<0.001)), and shorter admissions in the proven/presumed viral group (median 2 days (IQR 1-6 days), p<0.001) compared to other phenotypes. PICU admissions were required for 54 episodes (9.0%), which was associated with a proven/presumed bacterial infection (p=0.005). Median admission duration to PICU was 6 days (IQR 2-15). A proven/presumed viral infection was associated with a shorter PICU admission duration (p=0.007)

versus other phenotypes. In 17 episodes (2.8%) inotropic support was required, of which 12 had proven/presumed bacterial infections. 69 episodes required supplemental oxygen (11.5%), 24 (4.0%) non-invasive ventilation, and 27 (4.5%) invasive ventilation. Inotropic support, non-invasive ventilation, and invasive ventilation were associated with proven/presumed bacterial infection when compared to other phenotypes ($p<0.001$, $p=0.001$, and $p=0.008$, respectively).

Discussion

Our study provides insights into current aetiology and management of febrile illness in immunocompromised children at HR for SBI. In one-third of febrile episodes, no focus for the fever was identified, regardless of advances in laboratory and microbiological investigations. This is lower than previously reported in children with FN[3]. Our 13.0% rate of definite bacterial infection was comparable to 11.4%-37.0% reported in recent literature.[8,9,27,28]

Objective clinical features and laboratory investigations at admission did not discriminate well between bacterial or viral infection in our cohort, and neutropenia at admission in our cohort did not significantly change the risk of having a proven/presumed bacterial or viral infection.

Looking at any immunosuppressant use, we did not observe significant associations. Ill appearance was associated with proven/presumed bacterial infection and is known to be risk factor for bacterial infection[29,30]. Ill appearance also reduced the risk of having a proven/presumed viral infection. HIV increased the odds of having a proven/presumed bacterial infection, however we acknowledge the number of patients with HIV was low and these results may be skewed by inclusion bias.

We observed considerable variability in empirical antibiotic use across sites, with 29 empirical antibiotics used. This can be partially explained by protocol differences, some centres preferring different glycopeptides, and some children requiring specific antibiotic cover, e.g. for *Burkholderia* in chronic granulomatous disease. A significant proportion of patients, mainly oncology or HSCT patients, was empirically treated with piperacillin-tazobactam with or without teicoplanin, in accordance with guidance on treatment of suspected FN sepsis.[31,32]

There are grounds to assume a significant proportion of HR children are overtreated with intravenous antibiotics, and, similar to the general paediatric population, have self-limiting febrile illness[2,21,22]. However, infections remain the main cause of morbidity and mortality in the HR population.[6,18] Withholding or early discontinuation of antibiotics remains controversial. We do not have sufficient evidence to effectively alter current practice[5,31,33]. Immunocompromised children remain frequently hospitalised for intravenous antibiotic treatment, which has a negative impact on patient and family quality of life.[17]

We acknowledge that the small proportion of Gambian patients represent different epidemiology and aetiology, and that these patients have less access to biologicals, and specialised diagnostic tests compared to the other sites in this cohort, a known issue in LMIC.

Currently there is no validated risk stratification tool for this population.[34] In adults, there is a well-used risk stratification for high-risk patients, allowing for short course, oral, and outpatient parenteral antibiotics that reduced both hospital admission and broad-spectrum antibiotic use.[35] It is not yet proven helpful in children.[36]

For patients with T cell deficiencies, seen in certain PID and HSCT patients, viral infections are just as significant as bacterial infections requiring antiviral or immunoglobulin treatment.[37,38] Both SBI and 'serious viral infection' cause significant morbidity and mortality, as demonstrated by the fatal cases in our cohort.

In our cohort mortality was low at 1.9%, but 9% PICU admission rate demonstrates significant morbidity.

The high percentage of children with no definitive diagnosis demonstrates the need for better diagnostic tests to optimise early, effective and targeted treatment.

Strengths and limitations

Study strengths lie in the international and multicentre approach, allowing us to evaluate management across Europe and the Gambia. We collected in-depth patient data, with 28-day follow-up, and included a wide range of immunocompromised children

reflecting the clinical spectrum at university hospital EDs. Study limitations lie in the nature of recruitment: episodes in this cohort are biased by referrals and inclusion rates of participating centres across different countries. Therefore, it cannot be judged as a general epidemiological perspective or estimate for proportional incidence rates, nor is management generalizable to other LMIC as the availability of LMIC data in our cohort was low.

Conclusions

Febrile illness and infectious complications remain a significant cause of morbidity and mortality in immunocompromised children. Current management is effective and mortality low, but a significant proportion of children requires PICU care.

Swift and accurate diagnosis of febrile illness in this population remains challenging. Justifying broad-spectrum intravenous antibiotic treatment of fever for every high-risk patient is costly in terms of drugs, burden of antibiotic resistance, hospitalization and costs to families and overburdened healthcare systems. Identifying low-risk febrile patients could reduce hospital admission in this patient population. Future research should focus on development of new rapid clinical decision-making tools and biomarkers targeting immunocompromised paediatric population.

Abbreviations

ANC: absolute neutrophil count

CI: confidence interval

CRP: C-reactive protein

ED: emergency department

FN: febrile neutropenia

HIV: human immunodeficiency virus

HR: high-risk

HSCT: haematopoietic stem cell transplant

IQR: interquartile range

LMIC: low- and middle-income country

LOS: length of in-patient stay

PERFORM: Personalised Risk assessment in Febrile illness to Optimise Real-life Management across the European Union

OR: odds ratio

PICU: paediatric intensive care unit

PID: primary immunodeficiency

SBI: serious bacterial infection

UK: United Kingdom

Declarations

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Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Author contributions

Fabian J.S. van der Velden was the main author of this manuscript and performed the analyses on the data supervised by Emma Lim and Marieke Emonts. Gabriella de Vries and Alexander Martin were involved in the preparation of the final clinical database and involved in patient recruitment

Emma Lim, Ulrich von Both, Laura Kolberg, Enitan D. Carrol, Aakash Khanijau, Jethro A. Herberg, Taco W. Kuijpers, Federico Martinón-Torres, Irene Rivero-Calle, Clementien L. Vermont, Nienke N. Hagedoorn, Marko Pokorn, Andrew J. Pollard, Luregn J. Schlapbach, Maria Tsolia, Irini Elefhteriou, Shunmay Yeung, Dace Zavadska, Colin Fink, Marie Voice, Werner Zenz, Benno Kohlmaier, Philipp K.A. Agyeman, Effua Usuf, Fatou Secka, Ronald de Groot, Michael Levin, Michiel van der Flier, and Marieke Emonts were all responsible for the conduct of the PERFORM study and patient recruitment for their respective sites. Tisham De was responsible for the digital clinical database system and its maintenance.

Rachel Galassini and Jethro Herberg were responsible for the ethics surrounding this study and the wider PERFORM study.

All authors have read and provided valuable input during the writing of this manuscript.

All authors agree to submission of this manuscript.

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Ethics approval

Ethical approval was obtained for all countries via respective national ethics committees, for the UK: IRAS 209035, REC 16/LO/1684.

Consent to participate

Informed consent was obtained from all participants or their legal guardians, assent where appropriate.

Consent to publish

N/A

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Tables

Table 1: Cohort demographics at admission. GCS: Glasgow Coma Scale; HIV: human immunodeficiency virus; HSCT: haematopoietic stem cell transplant. *age-adjusted vital parameters as per APLS 2017 (>95th centile or <5th centile) Data is presented as N= episodes (%) or median (IQR). P-values were calculated using χ^2, Fisher's exact or Mann-Whitney U tests, as appropriate.

	All (N=599)	Proven/presumed bacterial (N=174)	Proven/presumed bacterial vs all other phenotypes (p-value)	Proven/presumed viral (N=127)	Proven/presumed viral vs all other phenotypes (p-value)	Missing values (N=599)
Male	343 (57.3%)	101 (58.0%)	0.80	70 (55.1%)	0.58	-
Age (years)	7.7 (4.1-12.8)	7.9 (3.5-12.9)	0.91	7.2 (4.4-12.2)	0.61	-
HSCT patient	69 (11.5%)	15 (8.6%)	0.16	19 (15.0%)	0.17	-
Underlying condition						
Malignancy	354 (59.2%)	98 (56.4%)	0.38	69 (54.3%)	0.22	-
Haematological disease	79 (13.2%)	21 (12.1%)	0.60	19 (15.0%)	0.51	-
Inflammatory syndromes	47 (7.8%)	7 (4.0%)	0.03	9 (7.1%)	0.72	-
Primary immunodeficiency	47 (7.8%)	10 (5.7%)	0.22	14 (11.0%)	0.13	-
Solid organ transplant	30 (5.0%)	19 (10.9%)	<0.001	4 (3.1%)	0.28	-
HIV	8 (1.3%)	6 (3.4%)	0.004	0	0.21	-
Nephrotic syndrome	6 (1.0%)	3 (1.7%)	0.36	1 (0.8%)	1.00	-
Cystic fibrosis	5 (0.8%)	2 (1.2%)	0.63	1 (0.8%)	1.00	-
Short bowel syndrome	4 (0.7%)	2 (1.2%)	0.58	1 (0.8%)	1.00	-
Other conditions	19 (3.2%)	6 (3.4%)	0.81	9 (7.1%)	0.01	-
Clinical features						
Ill appearance	176 (29.4%)	83 (47.7%)	<0.001	26 (20.5%)	0.01	-
Lifesaving intervention required	54 (9.0%)	26 (14.9%)	0.001	8 (6.3%)	0.23	-
Diarrhoea	45 (7.5%)	14 (8.0%)	0.75	10 (7.9%)	0.86	-
Increased work of breathing	36 (6.0%)	11 (6.3%)	0.84	10 (7.9%)	0.32	-
Vomiting	28 (4.7%)	12 (6.9%)	0.10	6 (4.7%)	0.98	-
Non-blanching rash	15 (2.5%)	6 (3.4%)	0.39	2 (1.6%)	0.75	-
Clinical dehydration	15 (2.5%)	6 (3.4%)	0.39	4 (3.1%)	0.54	-
Seizures	8 (1.3%)	4 (2.3%)	0.24	0	0.21	-
Meningism	3 (0.5%)	1 (0.6%)	0.87	1 (0.8%)	0.51	-
Vital parameters, age adjusted*						
Tachypnoea	79	32 (18.4%)	0.02	15 (11.8%)	0.61	151

	(13.2%)					
Bradypnoea	9 (1.5%)	5 (2.9%)	0.13	1 (0.8%)	0.69	151
Low saturation (<94% in air)	39 (6.5%)	11 (6.3%)	0.91	8 (6.3%)	0.91	123
Tachycardia	189 (31.6%)	69 (39.7%)	0.01	35 (37.6%)	0.28	63
Bradycardia	3 (0.5%)	1 (0.6%)	1.00	0	1.00	63
Hypotension	48 (8.0%)	14 (8.0%)	0.99	11 (8.7%)	0.76	190
Hypertension	179 (29.9%)	56 (32.2%)	0.43	36 (28.3%)	0.67	190
Prolonged capillary refill time (>2 seconds)	16 (2.7%)	8 (5.5%)	0.11	2 (1.6%)	0.54	142
Decreased consciousness (AVPU <A, GCS <= 13)	5 (0.8%)	2 (1.1%)	0.63	0	0.59	-
Fever (documented/history => 38.0°C)	528 (88.1%)	155 (89.1%)	0.65	115 (90.6%)	0.35	-
Blood investigations						
Neutropenia	212 (35.4%)	61 (35.1%)	0.87	33 (26.0%)	0.01	3
Lymphopenia	265 (44.2%)	75 (51.7%)	0.63	63 (49.6%)	0.65	103
Procalcitonin (ng/mL)	0.53 (0.19-1.91)	4.4 (0.54-17.25)	0.02	0.25 (1.00-4.66)	0.48	571
Immunomodulating drug use						
Biologicals	34 (5.7%)	6 (3.4%)	0.13	5 (3.9%)	0.34	-
Ciclosporin	35 (5.8%)	10 (5.7%)	0.95	9 (7.1%)	0.50	-
Colchicine	1 (0.2%)	0	1.00	1 (0.8%)	0.21	-
Immunoglobulin	39 (6.5%)	9 (5.2%)	0.4	10 (7.9%)	0.48	-
Methotrexate	118 (19.7%)	31 (17.8%)	0.46	32 (25.2%)	0.08	-
Steroids	112 (20.4%)	41 (23.6%)	0.21	21 (16.5%)	0.23	-
Tacrolimus	32 (5.3%)	18 (10.3%)	<0.001	5 (3.9%)	0.43	-
Other immunomodulating drug	262 (43.7%)	78 (44.8%)	0.73	65 (51.2%)	0.06	-

Table 2: Empirical antimicrobials started on admission by episodes (N=599), antibiotics are grouped by class. The total number of antimicrobials exceeds the number of episodes as ≥1 antimicrobial could be started for a single episode.

Antimicrobial group	N= 599	%
Penicillins	257	42.9
Glycopeptides	138	23.0
Aminoglycosides	109	18.2
3rd generation cephalosporins	106	17.7
4th generation cephalosporins	71	11.9
Carbapenems	41	6.8
Macrolides	29	4.8
Imidazoles	19	3.2
2nd generation cephalosporins	15	2.5
Fluroquinolones	15	2.5
Other antibiotics	12	2.0
Lincosamides	10	1.7
DHFR inhibitors	9	1.5
1st generation cephalosporins	3	0.5
Amphenicols	2	0.3
Oxazolidinones	1	0.2
Antivirals	37	6.2
Antifungals	23	3.8
No antimicrobials	77	12.9

Figures

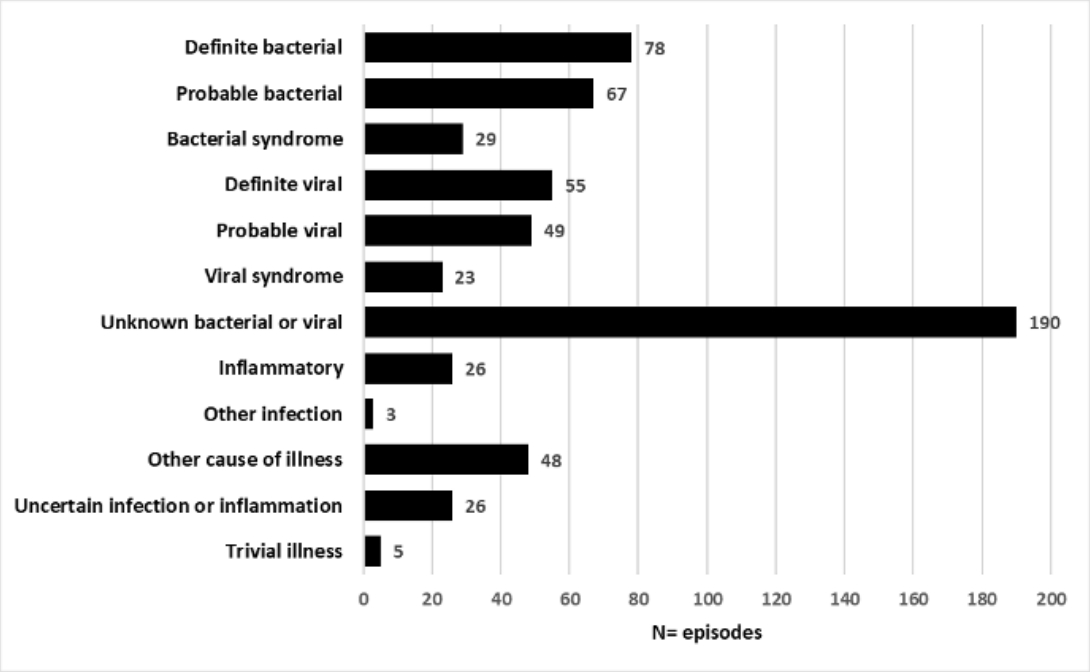

Figure 1

Final phenotypes assigned by episode as per PERFORM protocol (N=599 episodes)

Figure 2

Causative pathogens isolated or detected by episode, in 5 episodes ≥1 causative bacteria were isolated, and in 10 episodes ≥1 virus was detected. A) bacteria: other gram-negative: *Burkholderia cepacia complex, Citrobacter freundii, Delftia acidovorans, Fusobacterium nucleatum, Haemophilus influenzae (unspecified), Serratia marcescens,* all once isolated. Other gram-positive: Corynebacterium spp., Kytococcus schroeteri, Lactobacillus rhamnosus,

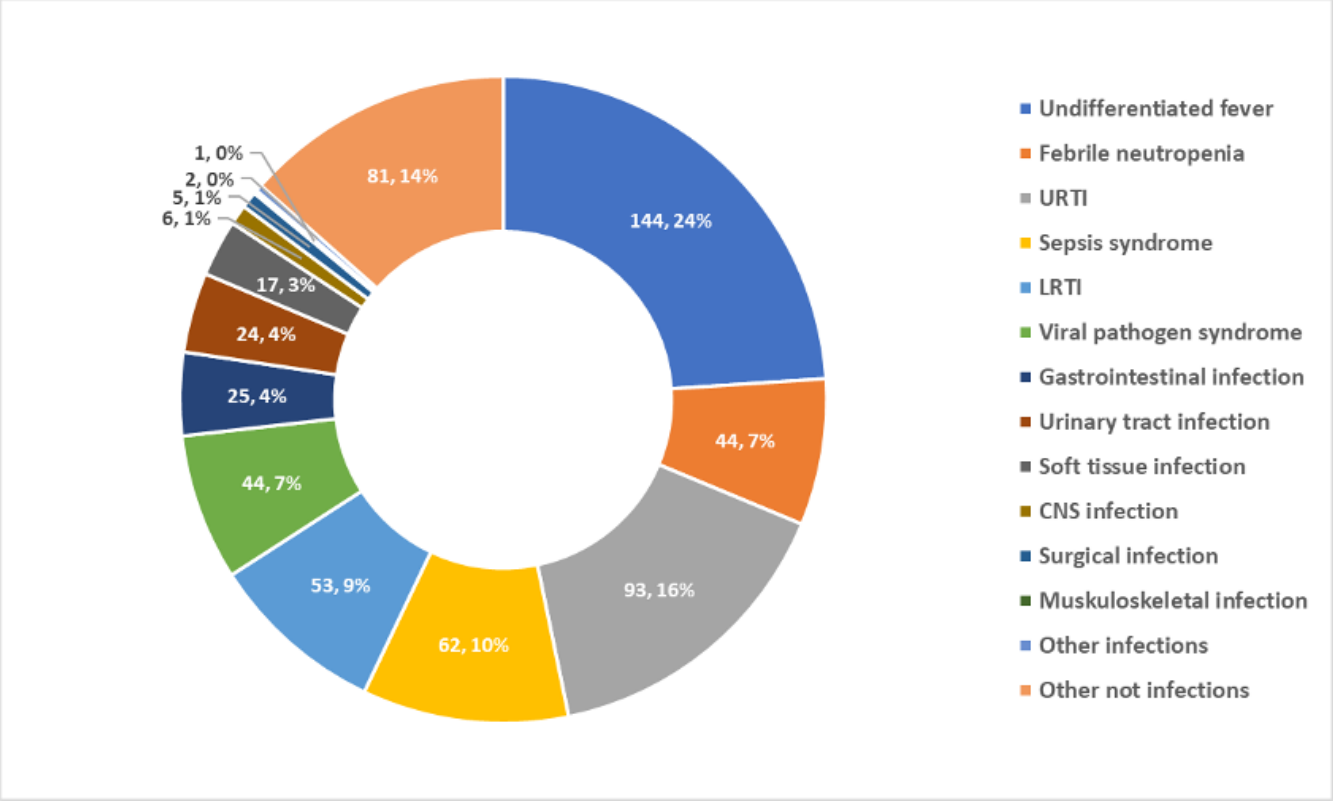

Figure 3

Clinical syndromes by group and by episodes (N=599).

Supplementary Files

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