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# Incidence of septicaemias and invasive mycoses in children undergoing treatment for solid tumours: a 12-year experience at a single Italian institution

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**Abstract**

We carried out a retrospective study on the infection rate—in episodes per 100 person months at risk (p/m/r)—of septicaemia and invasive mycoses in children with solid tumours treated at a single institution between 1985 and 1996. Among 982 patients, accounting for 8108 p/m/r, 257 infectious episodes were documented, for an infection rate of 3.2. The infection rate for 'intensive' treatment was greater than that for 'less intensive' treatments, 3.7 compared with 0.5, respectively; $P<0.001$. 58% of infectious episodes were associated with neutropenia, 22% were megatherapy-related, and 39% were related to central venous catheter (CVC), while in 13% of the episodes no risk factor was identified. Of the episodes, single organism Gram-positive bacteraemias accounted for 62%, single organism Gram-negative for 23%, multiple organism bacteraemias for 7%, invasive mycoses for 4%, and isolated fungaemias for 4%. The infection rate for Gram-positive organisms decreased significantly over time (−5.9% per year; $P<0.01$), but increased for the Gram-negative organisms (+3.4% per year; $P=0.4$). This study demonstrates that the risk of bacteraemia increases in parallel with the treatment intensity, and that a considerable number of children with solid tumours develop bacteraemia in the absence of an identifiable risk factor. 

*Keywords:* Bacterial infections; Mycoses; Paediatrics; Solid tumour

## 1. Introduction

Infections are an important cause of morbidity and mortality for patients undergoing treatment for cancer [1]. The incidence of infection may vary between institutions because of different prophylactic measures and treatment protocols. Since the risk of infection in cancer patients is multifactorial [2] and is present throughout the entire treatment period, the incidence of severe infectious complications should be evaluated during the entire period of treatment of each patient. Most of the data on this topic derive from studies focused on specific risk factors, e.g. febrile neutropenia [3–5], the use of indwelling central venous catheters (CVC) [6–11], megatherapy with autologous bone marrow or peripheral staminal cells rescue [12,13], oncological surgery [14–16], or antibiotic therapy of febrile neutropenia [17–22]. These data are rarely generated from prospective studies, but usually extrapolated from other studies, e.g. randomised clinical trials of empirical antibiotic therapy for febrile neutropenia. Such studies use only a subset of the population of cancer patients, i.e. only those eligible for the trial, so the overall prevalence estimates do not necessarily represent the entire patient population. Moreover, because of conventional methods of trial reporting, second or third episodes occurring in the same patient are generally missed, leading to an underestimate of the overall infection rates.

Only two studies have reported the epidemiology of infectious complications in children with cancer using data from a single centre during the entire course of

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therapy [23,24]. In one of these, only 24 patients were enrolled [23]. In the other, 217 patients were included, but the rates of infection were based on the total number of febrile episodes and were not adjusted for the length of time at risk for infection [24].

In this paper, we describe the incidence of bloodstream infections and invasive mycoses during the entire treatment course of children with solid tumours except those with brain tumours, admitted during a 12-year period at the Giannina Gaslini Children's Hospital (GGCH) in Genoa, Italy. All episodes are included and all rates are adjusted for the length of time on treatment.

## 2. Patients and methods

### 2.1. Patients

To be eligible for this study, subjects must have been diagnosed at $\leqslant 14$ years of age with a malignant solid tumour, except central nervous system tumours, and to have been admitted for treatment at the division of Pediatric Hematology and Oncology of the GGCH between 1 January 1985 and 31 December 1996. The Italian Association of Pediatric Hematology and Oncology (AIEOP) approved the treatment protocols. The major tumour types were neuroblastoma, non-Hodgkin's lymphoma (NHL), Wilms' tumour, and soft-tissue and bone sarcomas (Table 1). Central nervous system tumours were excluded since most of their treatment was given in the department of neurosurgery where non-homogeneous criteria for reporting infectious complications were used. Patients admitted at the GGCH for counselling only and those with incomplete medical records were also excluded from the study.

For each patient, the medical record was reviewed to identify the underlying disease (tumour type and stage, the date of diagnosis and first admission to GGCH), and the dates of cancer chemotherapy. Duration of therapy was calculated for each subject; initial treatment periods were calculated from the date of diagnosis or from GGCH admission if later, to the first elective end of therapy, the date of last visit to GGCH or to the date of death, whichever occurred first. If a relapse or a second malignant tumour (SMT) occurred after the first end of therapy, another treatment period was calculated using the same criteria starting from the date of relapse or diagnosis of the SMT. When megatherapy with autologous bone marrow or peripheral staminal cells rescue was the last therapeutic procedure, the end of the therapy date was arbitrarily postponed by 3 months.

Table 1
Patients treated for solid tumour or lymphoma at the GGCH between 1985 and 1996

| Type of cancer | Intensive treatment | Less intensive treatment | Total | %[a] |
|---|---|---|---|---|
| Neuroblastoma | 294 | 82 (2)[b] | 376 | 38 |
| Non-Hodgkin's lymphoma | 96 | 30 (2) | 126 | 13 |
| Wilms' tumour | 51 | 75 (9) | 126 | 13 |
| Sarcomas | 148 | 37 | 185 | 19 |
| Rhabdomyosarcoma | 59 | 9 | 68 | 7 |
| Soft-tissue sarcoma | 25 | 9 | 34 | 3 |
| Osteosarcoma | 20 | 2 | 22 | 2 |
| Ewing's sarcoma | 44 | 17 | 61 | 6 |
| Other tumours | 82 | 87 (7) | 169 | 17 |
| Hodgkin's disease | 34 | 39 (4) | 73 | 7 |
| Hepatoblastoma | 19 | 3 | 22 | 2 |
| Teratoma | 7 | 12 (1) | 19 | 2 |
| Retinoblastoma | 1 | 13 (1) | 14 | 1 |
| Germinal tumours | 5 | 8 | 13 | 1 |
| Miscellanea | 16 | 12 (1) | 28 | 3 |
| Total | 671 | 311 (20) | 982 | |
| Number of treatment periods | 691[c] | 311 | 1002 | 100 |
| Estimated number of patients with a CVC device | 688 | 54 | 742 | 74 |
| Number of BMT/PBSCT-procedures[d] | 231 | – | 231 | 23 |
| Number of infectious episodes | 251 | 6 | 257 | 26 |
| Person months at risk (p/m/r) | 6815 | 1293 | 8108 | – |
| Infection rate | 3.7 | 0.5 | 3.2 | – |

CVC, central venous catheter; BMT, bone marrow transplantation; PBSCT, peripheral blood stem cell transplant.

[a] Percentages over the total number of study patients.

[b] Numbers in parentheses refer to patients who shifted to an intensive treatment.

[c] Includes the treatment periods of the patients who shifted to an intensive treatment.

[d] 33 autologous BMT, 198 PBSCT.

Finally, the date and type of all the microbiologically or histologically documented bloodstream infections or invasive mycoses were recorded, so that any single patient may have contributed one or more episodes.

### 2.2. Definitions

#### 2.2.1. Intensity of antineoplastic treatment

Since therapeutic protocols change over time, and schemes considered as aggresive years ago might be considered as not aggresive in our days, each patient's chemotherapy was arbitrarily categorised as 'intensive' or 'less intensive' on the basis of the stage of the disease and the medical history. The 'intensive treatment' category included those with a stage III or IV tumour at diagnosis and those who never achieved remission of the disease. The treatment for patients with a stage I or II tumour at diagnosis who relapsed after the elective discontinuation of therapy, was also included in the 'intensive treatment' category, but only for the period following the relapse. The treatment of all other patients was regarded as 'less intensive'.

#### 2.2.2. Presence of a central venous catheters (CVC)

During the study period, a CVC was routinely used at our institution. However, since GGCH is a tertiary centre for cancer treatment, many patients arrive with cancer already diagnosed and with a CVC inserted. Moreover, data about the presence and type of CVC at the time of first observation were not available for all patients. Therefore, for the purpose of this study all patients treated with an aggressive protocol and those younger than 4 years at diagnosis who received a less-aggressive treatment for a period longer than 6 months were defined as 'patients with a CVC device'. All other patients were considered as those 'without a CVC device'.

#### 2.2.3. Infectious episodes

*Single organism bacteraemia* was defined as the isolation of a single pathogen (bacterial or fungal) from the blood culture. For coagulase-negative staphylococci, corynebacteria other than *Corynebacterium jeikeium*, and other skin contaminants, at least two sets of positive blood cultures were required unless the same pathogen was simultaneously isolated from the blood and another site of infection. *Multi-organism bacteraemia* was defined as the isolation of more than one pathogen from the same blood sample or from two consecutive samples obtained within 24 h. A febrile illness occurring with isolation of fungal organisms in one or more blood cultures, without evidence of visceral involvement, was defined as *fungaemia*. Finally, a clinical illness with microbiological, or pathological and/or radiological documentation of fungal invasion of deep organs was defined as *invasive mycosis*.

An infectious episode was defined as *neutropenia-related* if documented when it coincided with an absolute granulocyte count below $1.0\times10^6$/L/cmm [19]. A *CVC-related infection* was defined according to our previously published criteria [6], and in particular when it occurred in the presence of: (1) fever ($>38$ °C) with chills or rigors after catheter flushing or manipulation; and/or (2) isolation of a possible pathogen from blood drawn through the CVC, but not from simultaneous phlebotomy; (3) isolation of the same pathogen from the CVC tip (after removal) and blood cultures; (4) isolation of the same organism from blood cultures and from purulent material draining from the catheter exit site or the subcutaneous tunnel. In the remaining cases, infection was defined as 'not CVC-related'. Finally, any infectious episode occurring within 3 months after the transplant was defined as *megatherapy-related*.

### 2.3. Standard of care during the study period

During the study period, changes in the management of risk factors occurred. Antibacterial or antifungal prophylaxis was not routinely administered, except that after 1991 patients undergoing megatherapy received penicillin V as anti-streptococcal bacteraemia prophylaxis [12,25]. The combination of a beta-lactam and an aminoglycoside was used as initial empirical antibacterial therapy of febrile neutropenia [26].

Modifications of the initial treatment were performed on the basis of bacterial sensitivity tests or clinical criteria, via addition/substitution of antibacterials or empirical antifungal therapy in persistently febrile, neutropenic patients [26,27]. After 1993, the CVC maintenance procedures performed by parents at home were modified [28]. Finally, during the study period, the hospital buildings underwent extensive interior and exterior construction and renovation works. Outside construction began in 1985 with the erection of new buildings and continued for the entire study period. During the interior renovation of the BMT unit in 1987, patients were separated from the construction site by plastic barriers. Between March and November 1990, during a more extensive renovation project, patients undergoing megatherapy were temporarily moved to an ordinary hospital ward with no air filtration or ventilation system.

Neither granulocyte colony stimulating factor (G-CSF) nor other bone-marrow cells stimulating factors were administered because of their poor efficacy as prophylaxis for severe infections in cancer patients [29,30].

### 2.4. Statistical analysis

For each calendar year, the total number of infectious episodes and the total number of person months at risk (p/m/r) were calculated overall by (a) cancer type, (b) presence of CVC, and (c) intensity of chemotherapy. The number of infectious episodes in a group during a year was regarded as a Poisson variable. All results were

then analysed using Poisson regression with the statistical program, Epicure [31]. All estimates are maximum likelihood estimates. All confidence intervals (CI) were calculated at the 95% level. Statistical tests were two-tailed and the tests were considered significant when $P<0.05$. The incidence rate per 100 months was calculated as 100 times the number of infectious episodes divided by the total p/m/r.

## 3. Results

A total of 1141 patients with solid tumours were evaluated at GGCH during the study period. Of these, 159 (14%) were not eligible for this study: 72 came for only counselling, 36 were older than 15 years at diagnosis, 38 had a CNS neoplasm and 13 had incomplete medical records. Thus, 982 patients (545 males, 437 females) were eligible and evaluable for the study. Their mean age at the time of first observation was 5.3 years (95% confidence interval (CI): 5.1–5.6) and the mean length of treatment was 9.2 months (95% CI: 3.2–60.9).

Table 1 summarises the number of patients by cancer diagnosis and the numbers of patients with a CVC device, megatherapy treatments, documented infectious episodes, and their contribution in p/m/r. A total of 671 subjects were included in the 'intensive' treatment group, while the remaining 311 were defined as receiving 'less intensive' treatment. In 20 cases, their cancer recurred after the first elective discontinuation of therapy. The children were then treated with an intensive protocol. Therefore, a total of 691 'intensive' treatments were administered.

### 3.1. Infectious episodes

246 cases of bloodstream infection and 11 of invasive mycosis were documented during the study period giving a total of 257 infectious episodes in 192 patients. Single agent Gram-positive bacteraemias accounted for 160 episodes (62%); there were 58 (23%) single agent Gram-negative bacteraemias, 19 (7%) multiple organism bacteraemias, and 9 (4%) fungaemias, respectively. The 11 invasive mycoses (4%) were due to yeast in 7 cases and to filamentous fungi in the remaining 4. Details about isolated pathogens are reported in Table 2.

Most infectious episodes (149; 58%), occurred in the presence of neutropenia (140 bloodstream infections and 9 invasive mycoses), but 56 episodes (54 bloodstream infections and 2 invasive mycoses) were defined as megatherapy-related, 47 of them (84%) occurred in the presence of neutropenia. Among the 742 subjects with a CVC device 234 infectious episodes were diagnosed, and 92 (39%; 90 bloodstream infections and 2 invasive mycoses) were defined as CVC-related. Most, (69; 75%) of these infections occurred in the absence of neutropenia. Finally, 33 episodes (13%) occurred in the absence of neutropenia and were neither megatherapy- nor CVC-related. Overall, no epidemic cluster of septicaemia or of invasive mycosis was observed, even during the periods of intensive building renovation.

The outcome of the infectious episodes was favourable in 250 cases (97%). In 7 patients (2 with bloodstream infection and 5 with invasive mycosis), however, the infection persisted despite anti-microbial therapy and the subjects eventually died.

### 3.2. Incidence of infections

The *overall* infection rate for patients treated at GGCH for a solid tumour during the study period was 3.2 (257 episodes observed over 8108 p/m/r) (Table 1). Patients treated with a 'less intensive' protocol had an infection rate of 0.5 (6 episodes over 1293 p/m/r); those treated with an 'intensive' protocol had an infection rate of 3.7 (251 episodes over 6815 p/m/r). This difference was statistically significant ($P<0.001$).

Table 2
Isolated pathogens in 257 microbiologically documented infectious episodes in children with solid tumours treated at GGCH in the period 1985–1996

| Pathogen | Total isolates | Number of isolates |
|---|---|---|
| Gram-positives | 182 | |
| Coagulase negative staphylococci | | 52 |
| *Staphylococcus aureus* | | 59 |
| Viridans streptococci | | 43 |
| *Enterococcus* sp | | 6 |
| *Bacillus* sp | | 5 |
| Other streptococci | | 10 |
| Other Gram-positives | | 7 |
| Gram-negatives | 73 | |
| *Pseudomonas aeruginosa* | | 3 |
| *Stenotrophomonas maltophilia* | | 9 |
| Other *Pseudomonadaceae* | | 3 |
| *Escherichia coli* | | 24 |
| *Klebsiella-Enterobacter-Serratia* (KES) group | | 20 |
| *Citrobacter* sp | | 1 |
| *Acinetobacter* sp | | 5 |
| Other Gram-negatives | | 8 |
| Fungi | 22 | |
| *Candida albicans* | | 7 |
| *Candida*-non *albicans* | | 7 |
| *Hansenula anomala* | | 2 |
| *Trichosporon beigelii* | | 1 |
| *Rhodotorula* sp | | 1 |
| *Fusarium* sp | | 2 |
| *Aspergillus* sp | | 1 |
| Filamentous fungi in bioptic specimen, not growing in culture | | 1 |
| Total | 277[a] | |

sp; species.

[a] 277 isolated pathogens in 257 episodes because of 19 episodes with multiple organism bacteraemia.

In the six episodes that occurred during the 'less intensive' therapy, the underlying disease was a sarcoma in 3 cases and a hepatoblastoma, a neuroblastoma and a Wilms' tumour in the other 3. Gram-negative bacteria were isolated in five episodes, and a Gram-positive in the remaining one. Three episodes were diagnosed in the presence of neutropenia and three were defined as CVC-related. No patient died because of an infectious episode. Because of the low infection rate observed in this group, no further analysis was performed.

A total of 251 infectious episodes were diagnosed among patients receiving 'intensive' treatment; 240 (96%) were bloodstream infections and 11 were invasive mycoses (4%). Single organism Gram-positive bacteraemia was diagnosed in 159 episodes (66%) and a single agent Gram-negative in 53 (22%); 19 episodes (8%) were caused by multiple organisms and 9 (4%) were defined as fungaemias.

The disease-specific infection rates were 4.1 (95% CI: 3.5–4.9) for neuroblastoma, 4.1 (95% CI: 3.0–5.5) for NHL, 3.1 (95% CI: 2.0–5.0) for Wilms' tumour, and 3.4 (95% CI: 2.6–4.6) for sarcomas. From the Poisson regression, the disease-specific infection rates did not differ significantly for these types of cancer ($P=0.543$). The tumour type-specific infection rates decreased significantly over time ($P=0.001$), with an estimate change of −6.3% (95% CI: −2.7 to −9.8) per year. The estimated changes for these underlying diseases were −5.6% for neuroblastoma, −7.5% for NHL, −12.8% for Wilms' tumour, and −5.5% for sarcomas. Except for neuroblastoma (95% CI: −0.9 to −10.1), the rates of change did not differ significantly with the type of underlying cancer ($P=0.800$). The 'other tumours' represented a miscellaneous group of diseases on various treatment protocols. Amongst these patients the infection rate was quite small, 1.9 (95% CI: 1.1–3.4) and increased +4.9% per year ($P=0.564$).

Single organism bacteraemias formed the most common group and multi-organism bacteraemias and fungaemias accounted for only 19 and nine episodes, respectively. The yearly changes in incidence of infections were evaluated only for single-agent Gram-positive and Gram-negative bacteraemias. The annual infection rates were generally higher for Gram-positive organisms than for Gram-negative ($P<0.001$). The estimate for infection rate due to Gram-positives was 2.3 (95% CI: 2.0–2.7), with a significant decreasing trend by year (−5.9% per year, $P=0.009$, 95% CI: −1.5 to −10.1). For Gram-negatives, the maximum likelihood estimate for the infection rate was 0.8 (95% CI: 0.6–1); the trend by year increased but not significantly (+3.4% per year, $P=0.4$, 95% CI: −4.39 to 11.9).

The infection rate for *CVC-related* bloodstream infections among subjects with CVCs was 1.4 (95% CI: 1.1–1.7) ($P<0.001$); and the regression by year was not significant (+3.5% per year, $P=0.219$, 95% CI: −2.5 to 9.9). However, the infection rate for the CVC-unrelated bloodstream infections was 2.4 (95% CI: 2.0–2.8) ($P=0.001$), with a significant regression by year (−9.8% per year, $P=0.001$, 95% CI: −5.5 to −13.9) (goodness of fit test $P=0.003$).

Finally, since there were no available data on the total number and duration of episodes of neutropenia over the 12-year-study period, the infection rate for episodes occurring during neutropenia was not calculated. Only changes in the proportion of infections, in the presence of neutropenia over the 12-year period, were estimated. The differences were not significant ($P=0.264$). However, there was a significant reduction in the proportion of infections during post-megatherapy neutropenia ($P<0.001$) (data not shown).

## 4. Discussion

To the best of our knowledge, this is the first study to estimate the overall incidence of infectious complications in paediatric patients undergoing cancer therapy. We have demonstrated that a significant percentage (13%) of infectious episodes were not associated with neutropenia nor were megatherapy- or CVC-correlated. These data confirm results from a recent multicentre Italian observational study in children with cancer in which nearly 10% of bloodstream infections could not be associated with a major risk factor [32]. Further studies are needed to define additional risk factors—for example, changes of mucosal integrity, hypogammaglobulinaemia, abnormalities of neutrophil function—for these infections.

Another important observation is that the trends of infection rate for Gram-positive and Gram-negative pathogens were different during the study period. Gram-positives were the most frequently isolated pathogens, but there was a significant reduction in the infection rate over time. *Staphylococcus aureus* was mainly isolated in the first years of the study, coagulase negative staphylococci in the later years, and viridans streptococci mainly in patients receiving megatherapy [12,13] as described elsewhere [33,34]. The overall infection rate for Gram-negatives increased over time, although not significantly. Our institution does not encourage prophylactic antibacterial therapy, and does not allow quinolone administration. These 'local' factors may be relevant, but the unexplained increase of Gram-negatives as a cause of bacteraemia in cancer patients has been also reported by Viscoli and colleagues in the multicentre Italian surveillance study [32].

As expected, the intensity of chemotherapy was shown to have an important role in the determination of the risk of infection. Patients receiving 'intensive' antineoplastic chemotherapy experienced an almost 7 times greater incidence of infection then those less 'inten-

sively' treated (3.7 versus 0.5, $P<0.001$). We recognise that our grouping of patients to the aggressive or to the less aggressive treatment category is arbitrary, e.g. patients with localised bone tumours might receive a more aggressive treatment than patients with stage IV Wilms' tumour. However, the impact on the total p/m/r is probably not decisive, e.g. in our series only 19 patients with bone tumour were allocated to the less aggressive treatment group. The underlying cancer type had no clinical relationship to the risk of infection, although some investigators' findings were different [35,36].

We also documented a significant decrease of the overall infection rate over time, the only significant reduction was, however, for patients with neuroblastoma that represented the great majority of our patients (294 out of 691 aggressive treatments), with 132 out of the 231 megatherapies performed (57%). This could be, at least partially, explained by changes in treatment protocols, such as the decision to perform only one megatherapy procedure in the same neuroblastoma patient instead of two, and the introduction in 1991 of an autologous peripheral stem cell transplantation programme in children. Moreover, in the same period changes in supportive care for patients undergoing megatherapy, including the introduction of penicillin V prophylaxis, led to a documented reduction of megatherapy-related bloodstream infections secondary to neutropenia [25].

The overall infection rates for CVC-related infections did not change during the study period. However, between 1989 and 1992, Gram-negatives were the main isolated pathogens in the CVC-related infections [6,37]. During that period, the largest proportion of the isolated strains belonged to the group of bacteria that are usually associated with infusate contamination [38]. We therefore hypothesised that the changes in the proportion of catheter-related Gram-negative infections could be, at least partially, due to inappropriate practices in CVC access performed by non-professional staff [7,8,38]. The guidelines for at-home catheter management were modified in 1993 [28] and the frequency of Gram-negatives CVC-related bacteraemias has been reduced since then. The concomitant reduction in the frequency of non-CVC-related infections, probably due to a reduction in neutropenia and megatherapy-related infections, further emphasises the importance of CVC as a cause of infective episodes in children with cancer [2].

In spite of the retrospective nature of this study, the low incidence of documented invasive mycoses during building renovations seems to suggest that the risk of this complication in children with an intensively treated solid tumour is very low compared with that reported in patients with leukaemia [39,40], probably because of the shorter length of the neutropenic phases in subjects treated for a solid tumour. There were equivalent numbers of infections due to *Candida albicans* and to the *Candida* species. A similar proportion among the *Candida* isolates has recently been described in a multicentre study [41], but the increase in *C*. non-*albicans* fungaemia was reported in the patients with leukaemia and not among those with solid tumours. Because of the low frequency of fungal infections the observations in our series could be due to chance alone.

Unfortunately, data on the total number and duration of episodes of neutropenia were not available, and we could not comment on the role of neutropenia in infectious episodes. In general, however, we observed a decrease in the proportion of episodes occurring in the presence of neutropenia, especially after bone marrow transplantation. This was probably because of a reduction of bacteraemias due to viridans streptococci after the introduction of penicillin V prophylaxis [25] and the utilisation of autologous staminal cells as bone marrow rescue in this patient subgroup [42].

In conclusion, the intensity of chemotherapy in children with solid tumours is clearly related to the risk of infection. Neutropenia, the presence of a CVC, and megatherapy represent well known risk factors, but there are as yet unidentified additional risk factors. Invasive mycoses do not seem to represent a major problem for patients with solid tumours, while septicaemias are frequent and life-threatening.[1]

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[1] Editor's note: On a related theme, please look out for the update article by Sally Kensey on 'The management of infection' to be published next year as part of the Paediatric Update Series 2 'Supportive care, follow-up and late effects'.

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