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https://doi.org/10.1016/j.eimc.2017.09.009
0213-005X/



## Blood culture time to positivity in oncology pediatric patients

### *Tiempo de positividad en hemocultivos de pacientes oncológicos pediátricos*

*Dear Editor:*

Bloodstream infections (BSI) are common and severe in patients with oncologic and hematologic diseases, mainly accounting for chemotherapy-induced neutropenia alongside with invasive procedures.[1] In these patients, microorganisms of the saprophytic microbiota are frequently considered clinically significant, as they often colonize intravascular devices (IVD).[2] In our pediatric hospital, we inoculate blood from the IVD[3] only in one blood culture (BC) bottle and we do not usually obtain a peripheral BC, making it more complex to discriminate contamination from infection.[4] We aimed to assess the usefulness of time to blood culture positivity (TTP) to predict significant bacteriemia.

This is an observational prospective study in a cohort of oncology and hematology pediatric patients (<18 years at inclusion) that presented with fever during treatment, in most cases during neutropenia periods, at Hospital Sant Joan de Déu (Barcelona, Spain) from January to December 2016. Blood samples were obtained from IVD, usually a one-lumen tunneled central venous catheter (Port-A-Cath), and inoculated into one pediatric aerobic BacT/Alert PF bottle, to be later processed using BacT/Alert (BioMérieux, Durham, NC, USA) automatic incubation system. As per local protocols, BC were performed at onset of each febrile episode, and consecutively every 24–48 h if fever persisted despite antibiotics.

For isolates belonging to saprophytic microbiota to be considered clinically significant, at least one of the following criteria had to be fulfilled: (a) fever coincided with the use of the IVD; (b) the same strain was isolated in at least 2 consecutive BC; (c) the same strain was isolated from BC and the device exit site; and (d) the same strain was isolated from BC and the device culture after its removal. Clinical and microbiological data were collected and assessed together with the physician in charge of the patient.

During the study period, 1923 BC from pediatric hematology and oncology patients with fever were processed in the microbiology laboratory. Overall, bacterial growth was detected in 151 BC (7.9%, 95%CI: 6.7–9.1%) from 74 patients, of which 86 (4.5%), belonging to 47 episodes of bacteraemia from 37 patients, were considered clinically significant and 65 (3.4%), from 50 patients, were deemed contaminants.

Underlying diseases of patients with a clinically significant positive BC included solid tumors ($n = 39$), acute leukemia ($n = 30$), lymphoma ($n = 1$) and other hematologic diseases ($n = 4$). Primary pathogens included the following (number of isolates/episodes of bacteremia): 17/14 *Enterobacteriaceae*, 11/3 *Staphylococcus aureus*, 4/3 *Pseudomonas aeruginosa*, 2/2 *Streptococcus pneumoniae*, 1/1 *Haemophilus influenzae*, 1/1 *Enterococcus faecium*, 1/1 *Campylobacter jejuni* and 2/1 *Candida parapsilosis*. Microorganisms from the saprophytic microbiota that were considered clinically significant were: 35/14 *Staphylococcus epidermidis*, 5/2 *Staphylococcus hominis*, 3/2 *Micrococcus* spp., 3/2 *Bacillus cereus* and 1/1 *Streptococcus mitis*.

Finally, 42 coagulase-negative staphylococci, 9 *Micrococcus* spp., 2 *Bacillus* spp. and 12 isolates of other species were considered contaminants. Median (IQR) TTP of contaminants (25.2 h [18.0–34.3]) was significantly longer than that of all clinically significant BC (15.1 h [10.3–24.0]; $p < 0.0001$), but not enough to set up a useful TTP cut-off to discriminate both groups.

However, when only the first BC of each episode was considered, the TTP differences (13.2 h [8.9–18.0]) with contaminant BCs increased ($p < 0.0001$); 93.6% of clinically significant isolates (including all those from the saprophytic microbiota) were detected in less than 24 h, *versus* 43.1% of contaminants and 53.8% of significant isolates from non-first BCs ($p < 0.0001$). TTP exceeded 24 h in only 3 first clinically significant BCs (*C. parapsilosis*, *H .influenzae* and *C. jejuni*, which grew after 48, 57 and 91 h, respectively) that are known to usually show a slow growth.[5] Sensitivity, specificity, positive and negative predictive value for a clinically significant first BC to grow within 24 h after inoculation were 0.94, 0.57, 0.61 and 0.93, respectively.

In the oncologic child, the primary focus of bacteraemia is frequently the colonization of IVD,[6] and often the causative agent is part of the saprophytic microbiota. This fact would explain the differences among first and following BC TTP in clinically significant isolates. Despite adequate antibiotic therapy, some microorganisms remain in the inert structure of the IVD, out of reach of antibiotics, and are still detected in subsequent BC. In the latter, lower concentrations of the microorganism in the blood sample would lengthen the BC TTP. *S. epidermidis* was the most frequently isolated microorganism in our study, making it critical to discriminate between true infection and IVD contamination. At present, *S. epidermidis* has been associated with persistent and recurrent bacteriemia, and also with the need for IVD replacement,[1] which has an important impact in the management of patients.

Although there is not a single study that has specifically assessed BC TTP in oncology children, our data are consistent with prior reports in general pediatric[5,7,8] and adult patients,[4,9,10] in which most pathogens grew within the first 24 h of incubation. These data, together with patient clinical status, can be useful for taking management decisions, such as the need for ongoing antibiotic treatments or delays in chemotherapy schedules.

Our study had several limitations. We cannot assure that the time between collection of BC and placement in the incubator system was homogeneous (our protocol suggests less than one hour); therefore, we may have underestimated TTP in some cases. Depending on the age of the patient and other blood tests requested, the amount of blood available for each BC ranged from 1 to 4 ml, which does impact in TTP and also hinders comparisons.[4] Nevertheless, both these facts reflect usual working conditions.

In conclusion, in pediatric oncology patients with IVD presenting with fever, clinically significant isolates almost universally grew within 24 h of first BC inoculation, as did 43% of contaminants. Since in our study, a first BC growth beyond 24 h mostly represented contamination, this 24-h cut-off promises to be a useful tool in the management of fever in this specific and difficult-to-manage population.

## Funding

This study has not received specific funding.

## Conflict of interests

The authors of this study have no conflict of interest in relation to their content.

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https://doi.org/10.1016/j.eimc.2017.09.008
0213-005X/


## Uso de cotrimoxazol en sellado de catéter. A propósito de un caso en una situación difícil

### *The use of co-trimoxazole in catheter lock therapy. A report on a difficult case*

*Sr. Editor:*

En la actualidad, cada vez es más frecuente el empleo de catéteres de larga duración tanto para la administración de agentes terapéuticos (quimioterapia, antibioterapia o derivados sanguíneos o plasmáticos) como para la extracción de muestras sanguíneas[1,2]. Este tipo de dispositivos evita la necesidad de venopunciones repetidas asociadas a molestias para los pacientes y complicaciones derivadas (p. ej., flebitis, etc.). Sin embargo, no es infrecuente que se produzcan infecciones (bacterianas o fúngicas) de los mismos[1]. El manejo de las infecciones asociadas a catéteres es complejo, ya que, por un lado, su retirada disminuye las vías de acceso vascular (muchas veces limitado) y su mantenimiento se asocia al mantenimiento del foco de infección. En algunos casos, puede emplearse una opción alternativa que consiste, además del tratamiento de la bacteriemia por vía sistémica, en la administración de antimicrobianos de forma local, conocida como «sellados»[3]. El empleo de vancomicina (cocos grampositivos) y amikacina (bacilos gramnegativos) está bien establecido[2] y existen datos de la eficacia en el caso de otros antimicrobianos (p. ej., amoxicilina-clavulánico o ciprofloxacino)[2,4]. Sin embargo, hay circunstancias en las que por las características del paciente o el tipo de microorganismo las opciones son más limitadas.

Comunicamos el caso de una mujer de 51 años diagnosticada de miastenia *gravis* (MG) seronegativa a la que se realizó timectomía en febrero del 2003. Posteriormente, precisó varios ingresos hospitalarios por crisis miasténicas, incluso en una ocasión en Medicina Intensiva. Acudió al servicio de Urgencias por presentar fiebre de hasta 40 °C de predominio vespertino acompañada de tiritona desde un mes antes del ingreso. La paciente era portadora de Port-a-Cath® (BARD) desde 2005 para la administración de inmunoglobulinas y no refería otros datos de afectación local, como la existencia de dolor, eritema o exudado purulento en la zona de inserción. En el momento del ingreso, y tras la extracción de hemocultivos de sangre periférica y catéter para estudio mediante métodos cualitativos a través de sistema automatizado, se realizó sellado con vancomicina 4 mg/ml durante 24 h (5 ml) y se inició tratamiento por vía intravenosa de forma empírica, evitando los antimicrobianos contraindicados en pacientes con MG