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Commentary

Clinical decision rules for infectious risk stratification of children with febrile neutropenia: Are we looking for the Yeti?

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Febrile neutropenia (FN) is one of the most frequent complications of antineoplastic chemotherapy in children, with different incidences in acute leukaemia or solid tumours. In the early 60′ of the last century the introduction of empirical antibacterial therapy reduced the high mortality associated with this condition, that nowadays is about 4% when antibiotic resistant pathogens are not involved [1]. Currently one of the most important goal in the management of FN is the identification of episodes with different risk of severe infections and/or complications, with the aim to personalize cure management: different antibiotic selections, possible early intensive care admission or early hospital discharge and/or full home-care approach. With this purposes, Haeusler et al. [2] compared the performance of 9 different clinical decision rules (CDR) using prospectively collected data during 858 episodes of FN in children with cancer by adopting a pragmatic, "real life" approach that for example included also repeated episodes of FN occurring in the same patient. Eight of these nine CRDs were reproducible, with similar sensitivity or specificity, but none of them was able to accurately differentiate high from low risk episodes. Interestingly, the performance of CDRs improved when the same parameters were re-evaluated on day 2, when the analysis included additional outcomes that become available, thus confirming the difficulties of getting "a priori" predictive indicators. Authors conclude that in the everyday clinical practice CDRs with highest sensitivity and negative-predictive value could be used for a home-based treatment of FN, while those with lower sensitivity could be used to select patients suitable for short in-hospital evaluation (12–48 h) before home discharge. If we further elaborate on this and apply the recommendations of the GRADE group for evaluation of diagnostic tests [3], we observe that the likelihood ratio of the results [a measure of how much the results of the test change the pre-test probability of a disease to be present (positive) or absent (negative)] is very low both for the entire population (low or high risk of infections/complications) and for the detection of patients with microbiologically documented infections or "likely bacterial infection". This confirms that none of the CDRs applied as a diagnostic test will significantly improve the possibility to correctly identify the risk of infection/complication of a given episode of FN [4]. Moreover, if extrapolating from the data reported in the study [2], we calculate the informedness of the test (a tool that by encompassing both sensitivity and specificity [(sensitivity+specificity)−1] [5] measures the probability of taking an "informed" clinical decision) we observe a value <0.60 for all CRDs that defines them as not so "informative"- at best (Table 1).

The most recent Guideline for the management of FN in cancer children [6] recommends to adopt a validated risk stratification strategy to classify episodes of FN and to incorporate it in routine clinical management. However, the above findings do not stand in favour of the currently available CRDs as a robust predictive tool when used outside the Groups and the contexts that have generated them [7–10]. Possible explanations for this are geographical differences (e.g. reflecting differences in chemotherapy protocols) and the lack or the non-uniformity of clinical parameters included in the CDRs. However within this framework, the study from the Australian colleagues [2] is important, since it suggests that CDRs derived by one Centre can be used in other Centres, provided that some cautions are adopted, as the authors warned: "appropriate safe guards together with a structured home-based program incorporating clear recommendations for readmission, and with rigorous evaluation" [2].

A popular way of describing something very important and useful, but practically impossible to find is: "It is like the Yeti: everyone talks about him but nobody has ever seen him". We think that in the truck for searching a CDR capable to correctly identify the risk of infection in febrile neutropenic children and that could be applicable everywhere, we have "not seen the Yeti yet", but we have clues suggesting the direction to finally find him.

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Table 1
Performance of the prediction rules. Sensitivity, specificity, predictive values and likelihood ratio are the mean values reported in the study we are commenting on, as well as the "name" of the rules (1st Author or Group that published it) [2]; informedness has been calculated [5] from these data.

Rule	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Likelihood Ratio	Informedness
Predicting Microbiologically Documented Infection						
d-PICNICC	0.915	0.212	0.29	0.877	1.2	0.13
Pv-PICNICC	0.872	0.208	0.367	0.755	1.1	0.08
Predicting adverse outocme						
d-SPOG-AE	0.918	0.515	0.433	0.939	1.9	0.43
Pv-SPOG-AE	0.722	0.446	0.437	0.73	1.3	0.17
d-Hakim	0.745	0.764	0.35	0.946	3.2	0.51
Pv-Hakim	0.417	0.856	0.382	0.873	2.9	0.27
d-Alexander	0.909	0.646	0.408	0.964	2.6	0.56
Pv-Alexande	0.637	0.44	0.387	0.686	1.1	0.08
d-Klaassen	0.837	0.415	0.253	0.916	1.4	0.25
Pv-Klaassen	0.852	0.259	0.177	0.903	1.2	0.11
Predicting bacteraemia						
d-SPOG bacteraemia	1	0.152	0.182	1	1.2	0.15
Pv-SPOG bacteraemia	0.946	0.171	0.145	0.955	1.1	0.12
d-Amman	0.953	0.365	0.037	0.96	1.5	0.32
Pv-Amman	0.955	0.179	0.147	0.964	1.2	0.13
d-Baorto	0.947	0.157	0.178	0.939	1.1	0.10
Pv-Baorto	0.937	0.189	0.146	0.953	1.2	0.13
d-Rackoff	0.417	0.879	0.476	0.851	3.5	0.30
Pv-Rackoff [1]	0.351	0.929	0.234	0.896	2.1	0.28
Pv-Rackpoff[2]	0.91	0.264	0.155	0.952	1.2	0.17
Diagnosis of "likely bacterial infection"						
PICNICC	0.909	0.208	0.266	0.884	1.2	0.12
SPOG-AE	0.758	0.479	0.304	0.868	1.5	0.24
Hakim	0.293	0.838	0.352	0.798	1.8	0.13
Alexander	0.697	0.446	0.274	0.831	1.3	0.14
Klaassen	0.874	0.276	0.266	0.879	1.2	0.15
SPOG-bacteraemia	0.909	0.176	0.249	0.866	1.1	0.09
Amman	0.929	0.189	0.256	0.899	1.2	0.12
Baorto	0.899	0.194	0.251	0.865	1.1	0.09
Rackoff[1]	0.273	0.829	0.323	0.792	1.6	0.10
Rackoff[2]	0.874	0.276	0.266	0.979	1.2	0.15

d=derivation study.
Pv=prospective evaluation study.
[1] intermediate and low risk combined into a single low-risk group.
[2] intermediate and high-risk combined into a single high-risk group.

Declaration of competing interest

None.

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