

Evidence review: prevention and management of neutropenic sepsis in cancer patients

Reference and country	Study type and period	Number of patients	Prevalence	Patient characteristics	Tests used in initial assessment	Timing of test	Reference standard	Outcomes	Source of funding	Additional comments
Ammann 2003. Switzerland	Retrospective observational study. Consecutive sample.  1993-2001.	285 FN episodes in 111 children.	Severe bacterial infection: 106/285 (37%).	Paediatric cancer patients (<18 years) with neutropenia (ANC <500/mm <sup>3</sup> or <1000/mm <sup>3</sup> and falling) and fever (≥39.0°C or ≥38.5°C for ≥2 hours) after non-myeloablative chemotherapy.  Median age at the first FN episode was 6.3 years. Proportion with haematological cancers was not reported.	Haemoglobin level: thresholds > 71 g/L and >100 g/L  ANC: thresholds >0.11 X 10 <sup>9</sup> /L and >0.5 X 10 <sup>9</sup> /L  AMC: thresholds >0.11 X 10 <sup>9</sup> /L and >0.5 X 10 <sup>9</sup> /L  Phagocyte count: thresholds >0.11 X 10 <sup>9</sup> /L and >0.5 X 10 <sup>9</sup> /L  Thrombocyte count: thresholds >11 X 10 <sup>9</sup> /L	Study does not report when tests were done, although the aim was to find predictive factors for use within the first 2 hours of fulfilment of the febrile neutropenia criteria.	Severe (significant) bacterial infection: defined as bacteraemia, positive urine culture, pneumonia, clinically unequivocal diagnosis of infection, serum CRP >150 mg/L or unexpected death from infection.	<i>Diagnostic accuracy for severe bacterial infection:</i>  See D2 evidence tables  <i>Influence on management</i>  Not reported  <i>Time to diagnosis</i>  Not reported	Not reported	Serum CRP incorporated into reference standard.

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					<p>and <math>&gt;150 \times 10^9/L</math></p> <p>Serum CRP: thresholds <math>&gt;5 \text{ mg/l}</math> and <math>&gt; 50 \text{ mg/l}</math> (<math>5 \text{ mg/l}</math> defined as normal)</p> <p>Serum creatinine: thresholds <math>&gt;75 \text{ mg/L}</math>,</p> <p>and other tests</p>					
Asturias 2010. Guatemala	Prospective observational study. Consecutive sample. 2008	96 episodes of FN in 88 patients.	Bacteraemia: 11/96 episodes	Children ( $<18$ years) with fever ( $\geq 38.5^\circ\text{C}$ or $\geq 38.0^\circ\text{C}$ for a least 1hour) and neutropenia ( $\text{ANC} \leq 1.0 \times 10^9/L$ ), hospitalised at a single institution during 2008.	<p>Serum CRP: threshold <math>\geq 96 \text{ mg/L}</math></p> <p>Platelet count: <math>\leq 50 \times 10^9/L</math></p>	At admission	Bacteraemia: 2 blood cultures positive for any pathogen except coagulase-negative staphylococci.	<p><i>Diagnostic accuracy, see topic D2 evidence tables</i></p> <p><i>Influence on management</i></p> <p>Not reported</p>	Unidad Nacional de Oncología y Pediatría, Guatemala	

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				<p>74/96 (77%) episodes were in patients with haematological malignancies. Mean age was 6.5 years.</p> <p>Those hospitalised for less than 48 hours, those who had received antibiotics before admission and those receiving bone marrow transplants were excluded</p>				<p><i>Time to diagnosis</i></p> <p>Not reported</p>		
Avabratha 2009. India	Prospective observational study, consecutive sample.  Study period not reported.	50 FN episode in 33 children	Microbiologically documented infection: 9/50  Clinically documented infection:	Children (<16 years) with malignancy and chemotherapy related fever ( $\geq 38.3^{\circ}\text{C}$ or $\geq 38.0^{\circ}\text{C}$ for at least 1 hour) and neutropenia ( $\text{ANC} < 0.5 \times 10^9/\text{l}$ or predicted to fall to this) admitted to a	Clinical examination, tests for haemoglobin, CBC, peripheral smear, blood culture and CRP	At admission – before antibiotics started.	Microbiologically documented infection: clinical and/or radiological evidence of infection and culture positivity.	<p><i>Diagnostic accuracy, see topic D2 evidence tables</i></p> <p><i>Influence on management</i></p> <p>Not reported</p>	None	

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			19/50	single hospital.  Mean age 6.9 years. At least 73% of patients had haematological malignancy.	estimation.		Clinically documented infection: identifiable site of infection without a positive culture.	Time to diagnosis  Not reported														
Badiei (2011). Iran	Case series, unclear whether prospective  2008 to 2009.	120 FN episodes in 68 patients	Life threatening infection: 35/120.	Children younger than 18 years referred for fever ( $\geq 38.5^{\circ}\text{C}$ or $\geq 38.0^{\circ}\text{C}$ for at least 1 hour) and neutropenia ( $\text{ANC} < 0.5 \times 10^9/\text{l}$ ) admitted to a single hospital.	Temperature, mucositis, WBC, ANC, haemoglobin level, platelet count, chest X-ray	At the time of admission with neutropenia and fever.	Life threatening infection: positive culture from blood, CSF, urine or catheter), sepsis, septic shock or death from infection.	<table border="1"> <thead> <tr> <th></th> <th colspan="2">Life threatening infection</th> </tr> <tr> <th></th> <th>+</th> <th>-</th> </tr> </thead> <tbody> <tr> <td>Chest X-ray +*</td> <td>8</td> <td>2</td> </tr> <tr> <td>Chest X-ray -</td> <td>27</td> <td>83</td> </tr> </tbody> </table> <p>*lobar or interstitial infiltration</p>		Life threatening infection			+	-	Chest X-ray +*	8	2	Chest X-ray -	27	83	Not reported	
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								Sn 23%, Sp 98%													
Blot (1998). France	Retrospective case series. 1994-1996.	64 patients	Catheter related sepsis: 28/64	Patients with suspected catheter related infection in whom <i>both</i> central and peripheral cultures were positive for the same microorganism.	DPT- differential time to positivity between simultaneous central and peripheral blood cultures.	Not reported	<i>Catheter related sepsis</i> (CRS) was defined as no detectable focus of infection except the catheter plus one of the following:  1) Local signs of infection at the CVC insertion site.  2) Disappearance of CVC	<table border="1"> <thead> <tr> <th rowspan="2"></th> <th colspan="2"><i>Catheter related sepsis*</i></th> </tr> <tr> <th>+</th> <th>-</th> </tr> </thead> <tbody> <tr> <td>DPT &gt; 2hrs</td> <td>27</td> <td>11</td> </tr> <tr> <td>DPT ≤ 2hrs</td> <td>1</td> <td>25</td> </tr> </tbody> </table> <p>Sn 96%, Sp 69%</p>		<i>Catheter related sepsis*</i>		+	-	DPT > 2hrs	27	11	DPT ≤ 2hrs	1	25	Not reported	
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							infection signs and normal temperature within 24hours of catheter removal and antibiotics  3) Positive catheter culture, with isolation of the same microorganism in the blood stream	*22 cases where diagnosis was not established were added to the CRS-column.  <i>Influence on management</i>  Not reported  <i>Time to diagnosis</i>  Not reported														
Chayakulkeere e. 2003  Thailand.	Retrospective case series.  Consecutive sample.  1999 -2000.	267 episodes (220 patients).	38/267, clinically documented infection,  90/267  microbiologically documented infection	Adult or adolescent patients (>12 years) with febrile (>38°C) neutropenic (<0.5X10 <sup>9</sup> /L) episodes admitted to a single hospital.  158/220 (72%) had haematological malignancy. Mean	Duration of neutropenia, temperature, blood pressure, pulse rate, respiratory rate. Lab tests including white blood cell counts, BUN,	Not reported	Favourable outcome: fever resolved in 5 days of starting treatment and without complications           Unfavourable outcome:	<table border="1"> <tr> <td></td> <td colspan="2"><i>Unfavourable outcome</i></td> </tr> <tr> <td></td> <td>+</td> <td>-</td> </tr> <tr> <td>CXR +</td> <td>115</td> <td>90</td> </tr> <tr> <td>CSR-</td> <td>44</td> <td>18</td> </tr> </table>		<i>Unfavourable outcome</i>			+	-	CXR +	115	90	CSR-	44	18	Thailand Research fund.	Very high rate of abnormal chest X-rays (endemic tuberculosis?)
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			159/267 high risk or unfavourable outcome  205/267 had abnormal chest X-ray	age was 44.7 years.	creatinine, electrolytes. Chest X-ray (CXR). Blood cultures.		Death, serious complications, modification of initial therapy, relapse of resolved fever or fever longer than 5 days.  Reference standard was clinical follow up reported in medical records.	<p>Sn 72%, Sp 17%</p> <table border="1"> <tr> <td></td> <td colspan="2"><i>Unfavourable outcome</i></td> </tr> <tr> <td></td> <td>+</td> <td>-</td> </tr> <tr> <td>Bicarbonate &lt; 24 mmol/L</td> <td>82</td> <td>51</td> </tr> <tr> <td>Bicarbonate ≥ 24 mmol/L</td> <td>77</td> <td>57</td> </tr> </table> <p>Sn 52%, Sp 53%</p> <p><i>Influence on management</i></p> <p>Not reported</p> <p><i>Time to diagnosis</i></p>		<i>Unfavourable outcome</i>			+	-	Bicarbonate < 24 mmol/L	82	51	Bicarbonate ≥ 24 mmol/L	77	57		
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Diepold 2008. Germany	Prospective observational study. Unclear whether consecutive or random sample.	123 FN episodes in 69 patients.	Documented infection: 85/113 (10 were excluded from analysis)	Children and young adults (<20 years) with cancer or haematological disorders with fever (>38.5°C or >38.0°C from more than 1 hour ) and neutropenia (ANC <0.5X10 <sup>9</sup> /L) admitted to a single hospital.  64/69 patients had cancer. 55% of patients had haematological cancer. Median age	CRP, IL-6, and IL-8. Blood and urine cultures, cultures from suspected lesions.	Within 24 hours of the start of fever	Documented infection: bacteraemia (positive blood culture) or febrile episode of five days or more (these patients were presumed to have either a serious infection or signs of clinical sepsis - without microbiologically documented infection).	<table border="1"> <thead> <tr> <th rowspan="2"></th> <th colspan="2"><i>Doc. infection</i></th> </tr> <tr> <th>+</th> <th>-</th> </tr> </thead> <tbody> <tr> <td>CRP &gt; 10 mg/l</td> <td>71</td> <td>11</td> </tr> <tr> <td>CRP ≤ 90 mg/l</td> <td>14</td> <td>17</td> </tr> </tbody> </table> <p>Sn 83%, Sp 59%</p> <p><i>Influence on management</i></p> <p>Not reported</p>		<i>Doc. infection</i>		+	-	CRP > 10 mg/l	71	11	CRP ≤ 90 mg/l	14	17	None	
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				was 7.67 years.				<p><i>Time to diagnosis</i></p> <p>Not reported</p>																	
El-Magraby 2007. Egypt	Prospective observational study. Unclear whether consecutive or random sample. 2004 to 2005	85 FN episodes in 76 children.	Documented infection in 59/85 FN episodes.  Bacteraemia: 20/85 episodes	Children with haematological cancer fever (>38.5°C or >38.0°C on 2 occasions during 6 hours) and neutropenia (ANC < 0.5X10 <sup>9</sup> /L), who received chemotherapy at a single institution .  Mean age was 7.8 years for those with fever of unknown origin and 6.8 years for those with documented	CRP, threshold 90 mg/l (normal value defined as <6mg/l)	Tests were done within the first 24 hours of admission.	Documented infection: positive blood cultures and/or documented clinical sepsis and/or local infection.	<table border="1"> <thead> <tr> <th rowspan="2"></th> <th colspan="2"><i>Doc. infection</i></th> </tr> <tr> <th>+</th> <th>-</th> </tr> </thead> <tbody> <tr> <td>CRP &gt; 90 mg/l</td> <td>41</td> <td>7</td> </tr> <tr> <td>CRP ≤ 90 mg/l</td> <td>18</td> <td>19</td> </tr> </tbody> </table> <p>Sn 70%, Sp 73%</p> <table border="1"> <thead> <tr> <th></th> <th><i>Bacteraemia</i></th> </tr> </thead> <tbody> <tr> <td></td> <td></td> </tr> </tbody> </table>		<i>Doc. infection</i>		+	-	CRP > 90 mg/l	41	7	CRP ≤ 90 mg/l	18	19		<i>Bacteraemia</i>			Not reported	
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				infection. All had haematological malignancy.				<table border="1"> <tr> <td></td> <td>+</td> <td>-</td> </tr> <tr> <td>CRP &gt; ? mg/l</td> <td>20</td> <td>56</td> </tr> <tr> <td>CRP ≤ ? mg/l</td> <td>0</td> <td>9</td> </tr> </table> <p>Sn 100%, Sp 14% (unclear what the cutoff value was)</p> <p><i>Influence on management</i></p> <p>Not reported</p> <p><i>Time to diagnosis</i></p> <p>Not reported</p>		+	-	CRP > ? mg/l	20	56	CRP ≤ ? mg/l	0	9		
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Erten 2004. Turkey	Observational study (unclear whether prospective or whether consecutive/random sample).  2001-2002	45 episodes in 36 patients.	9/45 had bacteraemia. 15/45 episodes were classed as severe	Adult patients (>16 years) with haematological cancer, fever (> 38.3°C or > 38°C for at least an hour) and neutropenia (<0.5 X10 <sup>9</sup> /L or predicted to fall to this value).  All had haematological cancer, median age was 48 years..	CRP: threshold 6 mg/L  Procalcitonin: threshold 0.5 ng/mL	Blood samples were obtained on the first day of fever (after admission?)	Severe sepsis: defined as fever of more than 7 days, or with shock, or complex infection.  Reference standard was clinical follow up.	<i>Diagnostic accuracy</i>  See outcomes for topic D2  <i>Influence on management</i>  Not reported  <i>Time to diagnosis</i>  Not reported	Istanbul University Research Foundation	

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Ha 2010. Korea	Retrospective observational study. Consecutive sample.  1995 - 2007.	993 FN episodes in 802 patients.	Bacteraemia: 101/993 episodes (10%).	Adult patients (>18 years) after anticancer chemotherapy with neutropenia (ANC <500/mm <sup>3</sup> or <1000/mm <sup>3</sup> and expected to be <500/mm <sup>3</sup> within 48 hours), fever (≥38.3°C or ≥38.0°C for ≥1 hour) at low risk of complications (MASCC ≥ 21). Patients presented to the emergency department of a single institution.  Mean age was 50 years. 27% of episodes were in patients with haematological cancers.	ANC: threshold <50/mm <sup>3</sup>  CRP: threshold ≥ 10 mg/Dl, plus others.	Not reported when tests were done (presumably on admission to the ED).	Bacteraemia: defined as the isolation of bacterial pathogens from blood cultures alongside signs and symptoms of infection (excluding single positive cultures for coagulase-negative staphylococci).	<i>Diagnostic accuracy</i>  See outcomes for topic D2  <i>Influence on management</i>  Not reported  <i>Time to diagnosis</i>  Not reported		

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Hatzistilianou. 2005. Italy.	Observational study (unclear whether prospective or consecutive/random sample).	94 FN episodes in 20 children.	Microbial infection: 62/96	Children with acute lymphoblastic leukaemia, with fever (>38.5°C or >38°C over 6 hours) and neutropenia (ANC <0.5X10 <sup>9</sup> /l)  All had haemological malignancy. Mean age was 5.8 years	CRP, threshold 5 mg/ml	On admission with FN.	Documented infection: defined as microbiologically documented infection or clinically documented infection.	<p><i>Diagnostic accuracy</i></p> <p>See outcomes for topic D2</p> <p><i>Influence on management</i></p> <p>Not reported</p> <p><i>Time to diagnosis</i></p> <p>Not reported</p>	Altana Pharma Canada												
Heney 1992 UK	Case series (consecutive sample, unclear whether prospective)	47 febrile episode in 33 patients	Bacteraemia: 16/47	Children being treated for solid or haematological malignancies with fever (>38.5°C or >38.0°C on 2 occasions during 24 hours).  Mean age 7 years (range 0.5 to 15 years)	CRP  IL-6, blood cultures, additional cultures if indicated.	Done on admission for fever and neutropenia.	Bacteraemia: blood culture – but criteria for bacteraemia were not reported in detail.	<table border="1"> <thead> <tr> <th rowspan="2"></th> <th colspan="2">Bacteraemia</th> </tr> <tr> <th>+</th> <th>-</th> </tr> </thead> <tbody> <tr> <td>CRP &gt; 40 mg/l</td> <td>9</td> <td>15</td> </tr> <tr> <td>CRP ≤ 40 mg/l</td> <td>7</td> <td>16</td> </tr> </tbody> </table> <p>Sn 56%, Sp 58%</p>		Bacteraemia		+	-	CRP > 40 mg/l	9	15	CRP ≤ 40 mg/l	7	16	Candle-lighters trust.	
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				66% haematological cancer.				<p><i>Influence on management</i></p> <p>Not reported</p> <p><i>Time to diagnosis</i></p> <p>Not reported</p>		
Hitoglou-Hatzi 2005. Greece	Prospective observational sample. Unclear whether consecutive or random sample.	120 children	29 with fever (>38.5°C or >38.0°C for at least 6 hours) and microbial infection, 38 with fever but without microbial infection and 53 without fever or microbial infection (not included in this analysis).	Children (<15 years) with acute lymphoblastic leukaemia and neutropenia (ANC <0.5X10 <sup>9</sup> /l or absolute leucocyte count of <1.0X10 <sup>9</sup> /l).			Documented infection: microbiologically documented infection was defined as positive cultures of blood, urine, faeces and throat swabs. Clinically documented infection was defined as fever in connection with	<p><i>Diagnostic accuracy</i></p> <p>See outcomes for topic D2</p> <p><i>Influence on management</i></p> <p>Not reported</p> <p><i>Time to diagnosis</i></p> <p>Not reported</p>		

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							unambiguous signs of localised infection.			
Karan 2002. Turkey	Observational study (unclear whether prospective or consecutive sample).	26 FN episodes in 26 patients.	Severe sepsis: 14/26	Adult patients (>16 years) with haematological cancer and chemotherapy related fever (>38.5°C or >38.0°C on two occasions within 24 hours) and neutropenia (ANC <1.0X10 <sup>9</sup> /l).  All had haematological cancer. Mean age was 40 years.	CRP, thresholds reported as 100, 250 and 500 mg/l	Serum tests were done on the first day of fever, the first day of neutropenia+ fever and when fever resolved.	Severe sepsis: defined as FN episode longer than 7 days, progress to septic shock or death.	<p><i>Diagnostic accuracy</i></p> <p>See outcomes for topic D2</p> <p><i>Influence on management</i></p> <p>Not reported</p> <p><i>Time to diagnosis</i></p> <p>Not reported</p>	Istanbul University Research Foundation	

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Katz 1992 USA	Prospective case series  Nov 1989 – June 1990	122 episodes  74 patients	Documented infection:  52/122  Bacteraemia:  7/122	Children with malignant disease admitted to hospital because of fever in the presence of neutropenia  82/122 episodes were in patients with haematological malignancies and 40/122 in patients with solid tumours. Mean age was 6.3 years (range 2 months to 17 years).	Complete blood count  Peripheral blood culture  Central venous catheter culture  Urinalysis  Urine culture  Chest radiograph  CRP	8-24 hours after onset of fever	Physical examination, complete blood count, peripheral blood culture, CVC blood culture, urinalysis, urine culture, chest radiograph  Bacteraemia: defined as positive blood culture and toxic	<table border="1"> <tr> <td></td> <td colspan="2"><i>Doc. inf.</i></td> </tr> <tr> <td></td> <td>+</td> <td>-</td> </tr> <tr> <td>CRP &gt; 20 mg/l</td> <td>37</td> <td>43</td> </tr> <tr> <td>CRP ≤ 20 mg/L</td> <td>15</td> <td>20</td> </tr> </table> <p>Sn 71%, Sp 32%</p> <table border="1"> <tr> <td></td> <td colspan="2"><i>Doc. inf.</i></td> </tr> <tr> <td></td> <td>+</td> <td>-</td> </tr> <tr> <td>CRP &gt; 50</td> <td>24</td> <td>16</td> </tr> </table>		<i>Doc. inf.</i>			+	-	CRP > 20 mg/l	37	43	CRP ≤ 20 mg/L	15	20		<i>Doc. inf.</i>			+	-	CRP > 50	24	16	National Institute of Health  The Children's Cancer Fund of Dallas  Weekend to Wipe Out Cancer	
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							appearance at presentation - with or without cardiovascular instability.	<table border="1"> <tr> <td>mg/l</td> <td></td> <td></td> </tr> <tr> <td>CRP ≤ 50 mg/L</td> <td>28</td> <td>47</td> </tr> </table> <p>Sn 46%, Sp 75%</p>	mg/l			CRP ≤ 50 mg/L	28	47								
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								<table border="1"> <tr> <td>mg/L</td> <td></td> <td></td> </tr> </table> <p>Sn 100%, Sp 32%</p> <table border="1"> <tr> <td></td> <td colspan="2"><i>Bacteraemia</i></td> </tr> <tr> <td></td> <td>+</td> <td>-</td> </tr> <tr> <td>CRP &gt; 50 mg/l</td> <td>5</td> <td>38</td> </tr> <tr> <td>CRP ≤ 50 mg/L</td> <td>2</td> <td>77</td> </tr> </table> <p>Sn 71%, Sp 67%</p> <table border="1"> <tr> <td></td> <td colspan="2"><i>Bacteraemia</i></td> </tr> <tr> <td></td> <td>+</td> <td>-</td> </tr> <tr> <td>CRP &gt; 100 mg/l</td> <td>5</td> <td>33</td> </tr> <tr> <td>CRP ≤ 100 mg/L</td> <td>2</td> <td>82</td> </tr> </table> <p>Sn 71%, Sp 94%</p>	mg/L				<i>Bacteraemia</i>			+	-	CRP > 50 mg/l	5	38	CRP ≤ 50 mg/L	2	77		<i>Bacteraemia</i>			+	-	CRP > 100 mg/l	5	33	CRP ≤ 100 mg/L	2	82		
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								<p><i>Influence on management</i></p> <p>Not reported</p> <p><i>Time to diagnosis</i></p> <p>Not reported</p>		
Kitanovski 2006. Slovenia	Prospective observational study. Unclear whether consecutive sample.	68 FN episodes in 32 children	32/68 episodes were clinically documented infection, 36/68 were fever of unknown origin	Children (<19 years) with malignancy, fever (not defined), neutropenia (ANC < 0.5 10 <sup>9</sup> /l, or expected to fall to this value within 24 hours)  Median age 7.6 years. 50/68 had haematological malignancy	Complete blood counts and CRP were measured daily.		Clinically documented infection: bacteraemia, clinical sepsis (septic episode with negative blood cultures) or local infection (fever with clinically or microbiologically documented local infection).	<p><i>Diagnostic accuracy</i></p> <p>See outcomes for topic D2</p> <p><i>Influence on management</i></p> <p>Not reported</p> <p><i>Time to diagnosis</i></p> <p>Not reported</p>	Ministry of Education, Solvenia	

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Klastersky. 2000.	Prospective study. Consecutive or random sample (depending on centre). Multinational. 1994-1997	756 FN episodes in 756 patients (derivation set).	111/756	Adult patients (> 16 years) with malignancy treated with chemotherapy and neutropenia (ANC >500/mm <sup>3</sup> ) and fever (>38.0°C).  Median age was 52 years.  331/756 (44%) patients had haematological cancer	haemoglobin level: threshold < 8 g/dL  Absolute neutrophil count: threshold < 0.1 X 10 <sup>9</sup> / L  Platelet count: threshold 5000 / µL  Creatinine: threshold ≥ 2 mg/dL	Tests were done at fever onset	Adverse events: defined as fever resolution for five consecutive days with occurrence of a serious medical complication including death.	Any abnormality on chest X-ray:  <table border="1"> <thead> <tr> <th></th> <th colspan="2">Adverse event</th> </tr> <tr> <th></th> <th>+</th> <th>-</th> </tr> </thead> <tbody> <tr> <th>CXR +</th> <td>37</td> <td>97</td> </tr> <tr> <th>CXR -</th> <td>74</td> <td>548</td> </tr> </tbody> </table> <p>Sn 33%, Sp 85%</p> <p>Abnormality on chest X-ray suggestive of infection:</p> <table border="1"> <thead> <tr> <th></th> <th>Adverse event</th> </tr> </thead> <tbody> <tr> <td></td> <td></td> </tr> </tbody> </table>		Adverse event			+	-	CXR +	37	97	CXR -	74	548		Adverse event				
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					Bilirubin: threshold $\geq 2$ mg/dL  Albumin level: threshold $< 2.5$ g/dL,  Chest X-ray (CXR), and others			<table border="1"> <tr> <td></td> <td></td> <td></td> </tr> <tr> <td></td> <td>+</td> <td>-</td> </tr> <tr> <td>CXR infection +</td> <td>27</td> <td>53</td> </tr> <tr> <td>CXR infection -</td> <td>84</td> <td>592</td> </tr> </table> <p>Sn 24%, Sp 92%</p> <p><i>Influence on management</i></p> <p>Not reported. The study proposed a risk index score (MASCC) – but the individual influence of chest X-ray results on clinical decisions is not reported.</p> <p><i>Time to diagnosis</i></p> <p>Not reported</p>					+	-	CXR infection +	27	53	CXR infection -	84	592		
	+	-																				
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Lodahl 2011. Denmark	Prospective case series. 2000-2001	230 episodes in 85 patients	Bacteraemia. 61/230	Children < 16 years treated with chemotherapy or haematological disease, with fever.  Fever was >38.5°C once or >38.0° twice within 4 – 6 hours.	Clinical evaluation.PC T and routine blood samples drawn from CVC. Blood cultures were done before start of antibiotics	On admission with fever.	Cause of fever was classified by the treating physician using results of tests (including bacterial cultures) and the total clinical course of the episode.	<table border="1"> <thead> <tr> <th></th> <th colspan="2"><i>Bacteraemia</i></th> </tr> <tr> <th></th> <th>+</th> <th>-</th> </tr> </thead> <tbody> <tr> <td>CRP &gt; 336 nmol/l</td> <td>24</td> <td>71</td> </tr> <tr> <td>CRP ≤ 336 nmol/l</td> <td>3.7</td> <td>98</td> </tr> </tbody> </table> <p>Sn 39%, Sp 58%</p> <table border="1"> <thead> <tr> <th></th> <th colspan="2"><i>Bacteraemia</i></th> </tr> <tr> <th></th> <th>+</th> <th>-</th> </tr> </thead> <tbody> <tr> <td>CRP &gt; 537 nmol/l</td> <td>13</td> <td>41</td> </tr> <tr> <td>CRP ≤ 537 nmol/l</td> <td>48</td> <td>128</td> </tr> </tbody> </table> <p>Sn 21%, Sp 76%</p>		<i>Bacteraemia</i>			+	-	CRP > 336 nmol/l	24	71	CRP ≤ 336 nmol/l	3.7	98		<i>Bacteraemia</i>			+	-	CRP > 537 nmol/l	13	41	CRP ≤ 537 nmol/l	48	128	Danish MRC and Brahms Diagnostic a who supplied PCT LUMI test.	CRP was part of standard care and could have been incorporated into the reference standard.
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Manian 1995. USA	Prospective observational study. Consecutive sample. 1990 -1993.	82 FN episodes in 40 patients.	Significant infection: 23/82.  Documented or presumed bacterial or fungal infections with negative blood cultures 32/82.	Adult patients (>18 years) neutropenia (ANC <1.0x10 <sup>9</sup> /L or expected to fall to this) suspected infection seen at a single oncology unit.  35/40 (88%) had haematological malignancy. Median age was 52 years	CRP: thresholds 40, 80, 100, 150 and 200 mg/L	CRP was measured 1 day after diagnosis of febrile neutropenia, and then on every day until discharge.	Significant documented infection: documented bacterial or fungal infections with positive cultures	<i>Diagnostic accuracy</i>  See outcomes for topic D2  <i>Influence on management</i>  Not reported  <i>Time to diagnosis</i>  Not reported	Beckman Instruments (CRP kits).	



Evidence review: prevention and management of neutropenic sepsis in cancer patients

Reference and country	Study type and period	Number of patients	Prevalence	Patient characteristics	Tests used in initial assessment	Timing of test	Reference standard	Outcomes	Source of funding	Additional comments
Martinez-Albarran. 2009. Mexico	Prospective observational study. Consecutive sample. 2006-2007	54 FN episodes in 54 children	18/54 had documented infection	Children (<18 years) with cancer, fever (>38.5°C for at least an hour) and neutropenia (ANC < 0.5 X10 <sup>9</sup> /L) treated between 2006 and 2007.  Mean age was 6.1 years in those without documented infection and 7.6 years in those with documented infection. 32/53 (59%) had haematological	CRP, threshold 9.06 mg/dL (data driven threshold)	Tests were done as soon as the diagnosis of febrile neutropenia was made (before initiation of antibiotics),	Severe infection: positive blood or urine culture, clinical signs of sepsis or onset of fever <7 days from the end of last chemotherapy.	<p><i>Diagnostic accuracy</i></p> <p>See outcomes for topic D2</p> <p><i>Influence on management</i></p> <p>Not reported</p> <p><i>Time to diagnosis</i></p> <p>Not reported</p>	Not reported.	

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Massaro 2007	Prospective case series  Aug 2004 – Sept 2006	52 episodes  52 patients	Severe infection: 26/52	Adult patients hospitalised with severe neutropenia (neutrophil count of less than 500/mm <sup>3</sup> or less than 1000/mm <sup>3</sup> and expected to decline to 500/mm <sup>3</sup> ) and fever.	PCT  CRP	At fever onset	Patients diagnosed with severe infection (fever + positive blood culture for bacteria or fungi) or clinical signs of sepsis or proven fungal infection on the basis of clinical data including physical signs, haematology and chemistry parameters,	<table border="1"> <thead> <tr> <th></th> <th colspan="2">Severe inf.</th> </tr> <tr> <th></th> <th>+</th> <th>-</th> </tr> </thead> <tbody> <tr> <td>CRP &gt; 21 mg/l</td> <td>23</td> <td>25</td> </tr> <tr> <td>CRP ≤ 21 mg/L</td> <td>3</td> <td>1</td> </tr> </tbody> </table> <p>Sn 88%, Sp 4%</p> <table border="1"> <thead> <tr> <th></th> <th colspan="2">Severe inf.</th> </tr> <tr> <th></th> <th>+</th> <th>-</th> </tr> </thead> <tbody> <tr> <td>CRP &gt; 40</td> <td>18</td> <td>24</td> </tr> </tbody> </table>		Severe inf.			+	-	CRP > 21 mg/l	23	25	CRP ≤ 21 mg/L	3	1		Severe inf.			+	-	CRP > 40	18	24	Not reported	
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							results of blood, urine and tissue secretion cultures, radiographs and CT scans of the thorax, paranasal sinuses and abdomen, when necessary.	<table border="1"> <tr> <td>mg/l</td> <td></td> <td></td> </tr> <tr> <td>CRP ≤ 40 mg/L</td> <td>8</td> <td>2</td> </tr> </table> Sn 69%, Sp 7%	mg/l			CRP ≤ 40 mg/L	8	2							
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	<i>Severe inf.</i>																				
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Mato 2010 USA	Prospective case control study. Unclear whether consecutive or random sample.	230 patients and 184 controls matched on length of hospital stay.	Septic shock: 46/230	Adult patients (>18 years) with haematological malignancy who developed fever (>38°C) and neutropenia (ANC < 1.0 X 10 <sup>9</sup> / L) while admitted to hospital for chemotherapy or an acute medical condition.  Mean age was 54 years for cases and	Serum lactate: threshold ≥ 2 mmol/L	Tests were done at the onset of febrile neutropenia.	Septic shock: defined as the presence of refractory hypotension with a documented or suspected infection within 48 hours of the start of febrile neutropenia.	<table border="1"> <thead> <tr> <th rowspan="2"></th> <th colspan="2">Septic shock</th> </tr> <tr> <th>+</th> <th>-</th> </tr> </thead> <tbody> <tr> <td>Lactate ≥ 2 mmol/L</td> <td>12</td> <td>6</td> </tr> <tr> <td>Lactate &lt; 2 mmol/L</td> <td>34</td> <td>178</td> </tr> </tbody> </table> Sn 26%, Sp 97%  <i>Influence on management</i>		Septic shock		+	-	Lactate ≥ 2 mmol/L	12	6	Lactate < 2 mmol/L	34	178	Not reported	
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				51 years for controls.				Not reported  <i>Time to diagnosis</i>  Not reported																					
Moon 2009  South Korea	Retrospective case series.  2004-2007	192 episodes  168 patients	Complicated neutropenic fever: 28/192	Adult patients (>18 years) with malignancy presenting to the emergency department with neutropenia (ANC <500/mm <sup>3</sup> ) and fever (≥38.3°C or ≥38.0°C for ≥1 hours). Blood pressure > 90 mm Hg at presentation.  Median age was 53 years. 59/168 ( 31%) had haematological cancers.	WBC, platelets, monocytes, neutrophils, lymphocytes, total protein, albumin, BUN, creatinine, CRP, urine nitrates,  Pulmonary infiltration on chest X-ray	Unclear, likely tests were done on presentation to the emergency department	Complicated neutropenic fever classified as not resolving within 5 days of starting treatment, death or serious medical complications	<table border="1"> <thead> <tr> <th rowspan="2"></th> <th colspan="2"><i>Complicated fever.</i></th> </tr> <tr> <th>+</th> <th>-</th> </tr> </thead> <tbody> <tr> <td>CRP &gt; 100 mg/l</td> <td>26</td> <td>52</td> </tr> <tr> <td>CRP ≤ 100 mg/L</td> <td>12</td> <td>102</td> </tr> </tbody> </table> <p>Sn 68%, Sp 66%</p> <table border="1"> <thead> <tr> <th rowspan="2"></th> <th colspan="2"><i>Complicated fever.</i></th> </tr> <tr> <th>+</th> <th>-</th> </tr> </thead> <tbody> <tr> <td></td> <td></td> <td></td> </tr> </tbody> </table>		<i>Complicated fever.</i>		+	-	CRP > 100 mg/l	26	52	CRP ≤ 100 mg/L	12	102		<i>Complicated fever.</i>		+	-				Not reported	
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								<p><i>Influence on management</i></p> <p>Not reported.</p> <p><i>Time to diagnosis</i></p> <p>Not reported</p>														
Oude Nijuis (2003). Netherlands	Prospective case series. 1999-2002	109 episodes of FN in 89 patients.	<i>Bacterial pneumonia:</i> 2/109 episodes.	<p>Median age 45 years (range 18 to 77)</p> <p>26% had haematological malignancy.</p> <p>Fever was &gt;38.5°C once or &gt;38.0°C for 6 hours.</p> <p>Neutropenia was granulocytes &lt; 0.5X10<sup>9</sup>/L or leucocytes &lt; 1X10<sup>9</sup>/L.</p>	Chest X-ray, sinus X-ray, physical examination, lab tests and bacterial cultures.	Done at presentation with FN.	Not reported	<table border="1"> <thead> <tr> <th></th> <th colspan="2"><i>Bacterial pneumonia</i></th> </tr> <tr> <th></th> <th>+</th> <th>-</th> </tr> </thead> <tbody> <tr> <td>Chest x-ray +</td> <td>2</td> <td>34</td> </tr> <tr> <td>Chest x-ray -</td> <td>0</td> <td>73</td> </tr> </tbody> </table> <p><i>Influence on management</i></p> <p>No changes in antibiotic therapy due to chest x-ray</p>		<i>Bacterial pneumonia</i>			+	-	Chest x-ray +	2	34	Chest x-ray -	0	73	University Hospital, Groningen	Total number of patients with bacterial pneumonia unclear
	<i>Bacterial pneumonia</i>																					
	+	-																				
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				All were hospitalised and treated with broad spectrum IV antibiotics.				results.													
Oude Nijhuis, 2003.  Netherlands	Prospective case series.  1998-2000	66 episodes in 57 patients	Bacteraemia:	<p>Patients with fever, neutropenia and cancer.</p> <p>Neutropenia was granulocytes &lt;math&gt;0.5 \times 10^9/L&lt;/math&gt; or leucocytes &lt;math&gt;&lt; 1 \times 10^9/L&lt;/math&gt;</p> <p>Fever was &gt;38.5°C once or &gt;38.0°C for 6 hours.</p> <p>Median age was 22</p>	Not reported	Done at presentation with FN – before antibiotics were started.	<p>Bacteraemia: presumably blood cultures but not specified in detail.</p> <table border="1"> <thead> <tr> <th></th> <th colspan="2"><i>Bacteraemia</i></th> </tr> <tr> <th></th> <th>+</th> <th>-</th> </tr> </thead> <tbody> <tr> <td>CRP &gt; 100 mg/L</td> <td>11</td> <td>12</td> </tr> <tr> <td>CRP ≤ 100 mg/L</td> <td>7</td> <td>36</td> </tr> </tbody> </table> <p>Sn 61%, Sp 60%</p> <p><i>Influence on management</i></p> <p>Not reported</p>		<i>Bacteraemia</i>			+	-	CRP > 100 mg/L	11	12	CRP ≤ 100 mg/L	7	36	University Hospital, Groningen	
	<i>Bacteraemia</i>																				
	+	-																			
CRP > 100 mg/L	11	12																			
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Evidence review: prevention and management of neutropenic sepsis in cancer patients

Reference and country	Study type and period	Number of patients	Prevalence	Patient characteristics	Tests used in initial assessment	Timing of test	Reference standard	Outcomes	Source of funding	Additional comments											
				years (range 1 to 76).  82% had haematological malignancy				Time to diagnosis  Not reported													
Park 2010.  Korea	Retrospective case series	259 FN episode in 137 patients.	Serious complication: 70/259	Patients with haematological cancer and chemotherapy related febrile neutropenia.	Chest radiography, CBC, BUN, creatinine, AST, ALT. Bilirubin, albumin, bicarbonate, ESR, CRP, PT and complete urinalysis.	Just prior to the initiation of chemotherapy and on the fifth day of chemotherapy.	Serious complications: defined as hypotension (systolic blood pressure <90 mmHg), respiratory failure, altered mental status, congestive heart failure, uncontrolled arrhythmia, hepatic or renal failure requiring treatment, blood	<table border="1"> <thead> <tr> <th rowspan="2"></th> <th colspan="2">Serious complication</th> </tr> <tr> <th>+</th> <th>-</th> </tr> </thead> <tbody> <tr> <td>Bicarbonate &lt; 21 mmol/L</td> <td>31</td> <td>25</td> </tr> <tr> <td>Bicarbonate ≥ 21 mmol/L</td> <td>39</td> <td>15 4</td> </tr> </tbody> </table> <p>Sn 44%, Sp 86%</p>		Serious complication		+	-	Bicarbonate < 21 mmol/L	31	25	Bicarbonate ≥ 21 mmol/L	39	15 4	Not reported	
	Serious complication																				
	+	-																			
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Evidence review: prevention and management of neutropenic sepsis in cancer patients

Reference and country	Study type and period	Number of patients	Prevalence	Patient characteristics	Tests used in initial assessment	Timing of test	Reference standard	Outcomes	Source of funding	Additional comments											
							transfusion due to bleeding, ICU admission or death.	<table border="1"> <thead> <tr> <th rowspan="2"></th> <th colspan="2"><i>Serious complication</i></th> </tr> <tr> <th>+</th> <th>-</th> </tr> </thead> <tbody> <tr> <td>CRP ≥ 20 mg/L</td> <td>52</td> <td>51</td> </tr> <tr> <td>CRP &lt; 20 mg/L</td> <td>18</td> <td>128</td> </tr> </tbody> </table> <p>Sn 74%, Sp 72%</p> <p>The authors included both CRP ≥ 20 mg/L and bicarbonate &lt; 21 mmolo/L in their final risk stratification model</p> <p><i>Influence on management</i></p> <p>Not reported</p>		<i>Serious complication</i>		+	-	CRP ≥ 20 mg/L	52	51	CRP < 20 mg/L	18	128		
	<i>Serious complication</i>																				
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Evidence review: prevention and management of neutropenic sepsis in cancer patients

Reference and country	Study type and period	Number of patients	Prevalence	Patient characteristics	Tests used in initial assessment	Timing of test	Reference standard	Outcomes	Source of funding	Additional comments											
								<p><i>Time to diagnosis</i></p> <p>Not reported</p>													
Persson, 2004. Sweden	Prospective observational study. Consecutive sample.  Study period not reported	94 FN episodes in 60 patients.	Bacteraemia: 29/94	<p>Adults (≥17 years) with haematological cancer, fever (&gt;38.5°C or &gt;38°C in 2 readings over 4 hours) and neutropenia (ANC&lt;0.5X10<sup>9</sup>/l) admitted to a single haematology ward.</p> <p>All had haematological cancer.</p> <p>Median age ranged from 53 years to 56 years depending on</p>	Samples for bacteriological cultures (blood, urine and nasopharyngeal tract) CRP, PCT and IL-6, IL-8	At time of blood culture following onset of fever	The cause of febrile episodes was determined using clinical and microbiological findings.	<table border="1"> <thead> <tr> <th rowspan="2"></th> <th colspan="2"><i>Bacteraemia(non coag-neg staph.)</i></th> </tr> <tr> <th>+</th> <th>-</th> </tr> </thead> <tbody> <tr> <td>CRP &gt; 94 mg/l</td> <td>9</td> <td>18</td> </tr> <tr> <td>CRP ≤ 94 mg/L</td> <td>12</td> <td>55</td> </tr> </tbody> </table> <p><i>Sn 42%, Sp 75%</i></p> <p><i>Influence on management</i></p> <p>Not reported</p>		<i>Bacteraemia(non coag-neg staph.)</i>		+	-	CRP > 94 mg/l	9	18	CRP ≤ 94 mg/L	12	55	Swedish Cancer Society, Orebo UnOiversity Hospital Research Foundation	
	<i>Bacteraemia(non coag-neg staph.)</i>																				
	+	-																			
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Evidence review: prevention and management of neutropenic sepsis in cancer patients

Reference and country	Study type and period	Number of patients	Prevalence	Patient characteristics	Tests used in initial assessment	Timing of test	Reference standard	Outcomes	Source of funding	Additional comments												
				the study group (CNS-bacteraemia, non-CNS bacteraemia, documented infection)				Time to diagnosis Not reported														
Phillips (2011)	Systematic review and meta-analysis,	4 studies with 278 patients and 478 FN episodes	<i>Pneumonia</i> Overall 22/478 (5%)	Children of young people (18 years or less) receiving treatment for cancer or leukaemia presenting with febrile neutropenia.	Respiratory distress signs and symptoms	At presentation	Radiographically diagnosed pneumonia – (pneumonia evident on chest X-ray)	<table border="1"> <thead> <tr> <th></th> <th colspan="2"><i>Radiographically diagnosed pneumonia</i></th> </tr> <tr> <th>Resp. signs/symptoms</th> <th>+</th> <th>-</th> </tr> </thead> <tbody> <tr> <th>+</th> <td>17</td> <td>111</td> </tr> <tr> <th>-</th> <td>5</td> <td>332</td> </tr> </tbody> </table> <p>Univariate meta analysis of sensitivity and specificity: Sensitivity 77% (95% C.I. 56%</p>		<i>Radiographically diagnosed pneumonia</i>		Resp. signs/symptoms	+	-	+	17	111	-	5	332	MRC	Methodological quality of the 4 included studies was variable, specifically:  ¼ had definite or unclear partial verification,  2/4 had definite or unclear differential verification, ¼ unclear blinding in
	<i>Radiographically diagnosed pneumonia</i>																					
Resp. signs/symptoms	+	-																				
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Evidence review: prevention and management of neutropenic sepsis in cancer patients

Reference and country	Study type and period	Number of patients	Prevalence	Patient characteristics	Tests used in initial assessment	Timing of test	Reference standard	Outcomes	Source of funding	Additional comments
								<p>to 90%)</p> <p>Specificity 69% (95% C.I. 57% to 78%).</p> <p>Assuming a prevalence of pneumonia of 5%, clinical examination has a negative predictive value of 98% (95 C.I. 96% to 99%). The probability of pneumonia in someone with negative clinical examination was estimated at 1.9%.</p>		outcome assessment

Evidence review: prevention and management of neutropenic sepsis in cancer patients

Reference and country	Study type and period	Number of patients	Prevalence	Patient characteristics	Tests used in initial assessment	Timing of test	Reference standard	Outcomes	Source of funding	Additional comments									
Renoult (2004). Canada	Retrospective case series. 2001-2002	170 episodes of FN (157 with admission chest X-ray) in 88 patients.	<i>Bacterial pneumonia:</i> 8/157 episodes.	Mean age 6.9 years, range (1.1 to 19.7).  52% had haematologic malignancy.  All outpatients at presentation.  Fever was >38.5°C once or >38.0°C one 2 or more occasions within 12 hours.  Neutropenia was $ANC < 0.5 \times 10^9/L$  All were hospitalised and treated with broad spectrum IV antibiotics.	Peripheral blood culture in those with central line, bacterial cultures of urine, throat, stool, central catheter exit site, chest x-ray (at the discretion of the admitting physician).	Done at the onset of febrile neutropenia (on admission)	The diagnosis recorded by the clinician in the discharge summary.	<p><i>Bacterial pneumonia</i></p> <table border="1"> <tr> <td>Chest x-ray</td> <td>+</td> <td>-</td> </tr> <tr> <td>X-ray +</td> <td>8</td> <td>12</td> </tr> <tr> <td>X-ray -</td> <td>0</td> <td>137</td> </tr> </table> <p>Sn = 100%</p> <p>Sp = 92%</p> <p><i>Influence on management</i></p> <p>No changes in antibiotic therapy due to abnormal chest x-ray results.</p> <p><i>Time to diagnosis</i></p> <p>Not reported</p>	Chest x-ray	+	-	X-ray +	8	12	X-ray -	0	137	Not reported	
Chest x-ray	+	-																	
X-ray +	8	12																	
X-ray -	0	137																	

Evidence review: prevention and management of neutropenic sepsis in cancer patients

Reference and country	Study type and period	Number of patients	Prevalence	Patient characteristics	Tests used in initial assessment	Timing of test	Reference standard	Outcomes	Source of funding	Additional comments
Rikonen 1993 Finland.	Observational study, prospective. Unclear whether it was a consecutive or random sample.  1989-1990	91 FN episodes in 46 children.	Bacteraemia in 17/91 FN episodes.	Children (1 to 16 years) with fever (>39°C or >38°C on two occasions within 4 hours) and neutropenia (ANC < 0.2 X 10 <sup>9</sup> /L) caused by anti-cancer treatment.  57% had haematological cancers.	CRP: thresholds 20 and 50 mg/l (normal value 18 mg/l), other tests were done.	Tests were done on admission (and on days 1,2 and 3 of antimicrobial therapy).	Documented infection: clinical and laboratory methods described in sufficient detail  Bacteraemia: at least one positive peripheral blood culture or two positive cultures if Staphylococcus epidermidis was isolated.	<i>Diagnostic accuracy</i>  See outcomes for topic D2  <i>Influence on management</i>  Not reported  <i>Time to diagnosis</i>  Not reported	Foundation for Paediatric Research, Helsinki	



Evidence review: prevention and management of neutropenic sepsis in cancer patients

Reference and country	Study type and period	Number of patients	Prevalence	Patient characteristics	Tests used in initial assessment	Timing of test	Reference standard	Outcomes	Source of funding	Additional comments
Rondinelli. 2006. Brazil	Retrospective observational study. Consecutive sample. 2000-2003.	283 FN episodes in 283 patients.	93/283 had severe infection.	Children (< 18 years) with cancer, fever (>38°C or >37.8°C on 3 occasions within 24 hours) and neutropenia (<0.5 X 10 <sup>9</sup> /l or < 1 X 10 <sup>9</sup> /l and falling) admitted to a single hospital. Mean age was 5.2 years. 48.5% had haematological cancers.	Granulocyte count: threshold 0.5 X 10 <sup>9</sup> /L Monocyte count: threshold 0.5 X 10 <sup>9</sup> /L Leucocytes: threshold 0.5 X 10 <sup>9</sup> /L Platelets: threshold 20000 units Haemoglobin level: threshold 7 g/dL	Not reported when tests were done.	Severe infection: defined as the presence of sepsis and/or shock and/or bacteraemia / fungaemia and/or death from infection	<p><i>Diagnostic accuracy</i></p> <p>See outcomes for topic D2</p> <p><i>Influence on management</i></p> <p>Not reported</p> <p><i>Time to diagnosis</i></p> <p>Not reported</p>	Not reported.	

Evidence review: prevention and management of neutropenic sepsis in cancer patients

Reference and country	Study type and period	Number of patients	Prevalence	Patient characteristics	Tests used in initial assessment	Timing of test	Reference standard	Outcomes	Source of funding	Additional comments
Santolaya 1994. Chile	Observational study, consecutive sample. 1991-1992	85 FN episodes in 75 children.	Documented bacterial infection: 24/85 episodes  Clinically documented infection in 31/85  In 30/85 there was either viral infection or no infection.	Children admitted for treatment of malignancy at a single hospital.  Children with fever (>38°C on 2 occasions within 24 hours) and neutropenia (ANC < 0.5 X10 <sup>9</sup> /l) were included in the study.  85% of the children had haematological malignancy.	CRP, threshold 40 mg/l (10 mg/l was considered normal).	Tests were first done before the first dose of antibiotic was administered	Documented bacterial infection: one blood culture positive for a well recognized pathogen, or two blood cultures positive for an opportunistic pathogen, or positive cultures from a clinically relevant focus (urine or skin).  Clinically documented infection: a severe clinical course or findings indicative of bacterial	<i>Diagnostic accuracy</i>  See outcomes for topic D2  <i>Influence on management</i>  Not reported  <i>Time to diagnosis</i>  Not reported		

Evidence review: prevention and management of neutropenic sepsis in cancer patients

Reference and country	Study type and period	Number of patients	Prevalence	Patient characteristics	Tests used in initial assessment	Timing of test	Reference standard	Outcomes	Source of funding	Additional comments
							infection, in the absence of positive cultures.			
Santolaya 2001. Chile	Prospective observational study. Consecutive sample. 1996-1997	447 FN episodes in 257 children	178/447 (40%) episodes had invasive bacterial infection	Paediatric cancer patients ( $\leq 18$ years) receiving cancer chemotherapy with neutropenia (ANC $\leq 500/\text{mm}^3$ ) and fever ( $\geq 38.5^\circ\text{C}$ or $\geq 38.0^\circ\text{C}$ for $\geq 2$ hours)  68% had haematological malignancy. Median age was 7 years.	ANC, AMC, CRP, platelets, temperature, blood pressure, haemoglobin.	Tests were done on admission with fever and neutropenia.	Invasive bacterial infection: defined as bacteraemia, a positive bacterial culture from an otherwise sterile site, clinical laboratory findings strongly suggestive of a sepsis syndrome or focal organ involvement in	<i>Diagnostic accuracy</i>  See outcomes for topic D2  <i>Influence on management</i>  Not reported  <i>Time to diagnosis</i>  Not reported		

Evidence review: prevention and management of neutropenic sepsis in cancer patients

Reference and country	Study type and period	Number of patients	Prevalence	Patient characteristics	Tests used in initial assessment	Timing of test	Reference standard	Outcomes	Source of funding	Additional comments
							a child with haemodynamic instability and intense malaise.			
Scheienmann (2010). Canada	Retrospective case series 2002-2007	318 FN episodes in 224 patients	Bacteraemia: 228/318  Likely contaminant: 90/318	Children with central venous catheters receiving chemotherapy or after stem-cell transplant, who had central and peripheral cultures on the same day, where at least one was positive for a microorganism.  Median age 8.5 years (range 0.03 to 19.5 years).  68% haematological	Central and peripheral blood cultures	Before antibiotics were started	Bacteraemia: positive blood cultures with common contaminants were classified as bacteraemia if multiple cultures were positive for the same organism or if sepsis was present	28 case of bacteraemia were identified only in peripheral culture, 85 were identified only in central culture. 90 cases were considered as likely due to contaminants (not bacteraemia),	Canadian Institute of Health	Study excludes bacteraemia missed on both central and peripheral cultures (may have overestimate d sensitivity)

	<i>Bacteraemia</i>	
Periph. culture	+	-
+	143	N.R.
-	85	N.R.

Evidence review: prevention and management of neutropenic sepsis in cancer patients

Reference and country	Study type and period	Number of patients	Prevalence	Patient characteristics	Tests used in initial assessment	Timing of test	Reference standard	Outcomes	Source of funding	Additional comments												
				<p>cancers.</p> <p>Fever was <math>\geq 38.3^{\circ}\text{C}</math> once or <math>\geq 38.0^{\circ}\text{C}</math> one 2 or more occasions within 12 hours.</p> <p>Neutropenia was <math>\text{ANC} &lt; 0.5 \times 10^9/\text{L}</math></p>				<p>Sn 63%</p> <table border="1" data-bbox="1496 523 1749 887"> <thead> <tr> <th></th> <th colspan="2"><i>Bacteraemia</i></th> </tr> <tr> <th>Central culture</th> <th>+</th> <th>-</th> </tr> </thead> <tbody> <tr> <th>+</th> <td>200</td> <td>N.R.</td> </tr> <tr> <th>-</th> <td>28</td> <td>N.R.</td> </tr> </tbody> </table> <p>Sn 88%</p> <p><i>Influence on management</i></p> <p>Healthcare professionals were surveyed about their attitudes to obtaining peripheral blood cultures. The main reason given for not obtaining peripheral blood cultures was</p>		<i>Bacteraemia</i>		Central culture	+	-	+	200	N.R.	-	28	N.R.		
	<i>Bacteraemia</i>																					
Central culture	+	-																				
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Reference and country	Study type and period	Number of patients	Prevalence	Patient characteristics	Tests used in initial assessment	Timing of test	Reference standard	Outcomes	Source of funding	Additional comments											
								that they do not provide any additional information and that phlebotomy is associated with a risk of complications  <i>Time to diagnosis</i>  Not reported													
Secmeer, 2007.  Turkey.	Prospective observational study. Unclear whether consecutive  2004 - 2005	60 FN episodes in 49 patients.	Documented infection: 25/60	Children (<19 years) with chemotherapy related fever ( $\geq 38.3^{\circ}\text{C}$ or $> 38^{\circ}\text{C}$ for at least one hour) and neutropenia (not defined) admitted to a single hospital.  47% had haematological malignancy. 31/49 patients had documented infection.	PCT, CRP, ESR, blood cultures	On admission, and at the 8 <sup>th</sup> , 24 <sup>th</sup> and 48 <sup>th</sup> hour after admission.	Documented infection: microbiologically or clinically documented infection.  Bacteraemia: at least one positive culture for bacteraemia (or 2 in the case of coagulase-negative staphylococcus	<table border="1"> <thead> <tr> <th rowspan="2"></th> <th colspan="2"><i>Doc. Infect.</i></th> </tr> <tr> <th>+</th> <th>-</th> </tr> </thead> <tbody> <tr> <td>CRP &gt; 50 mg/l</td> <td>14</td> <td>19</td> </tr> <tr> <td>CRP ≤ 50 mg/L</td> <td>11</td> <td>16</td> </tr> </tbody> </table> <p>Sn 58%, Sp 48%</p> <p><i>Influence on management</i>  Not reported.</p>		<i>Doc. Infect.</i>		+	-	CRP > 50 mg/l	14	19	CRP ≤ 50 mg/L	11	16	Not reported	
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Evidence review: prevention and management of neutropenic sepsis in cancer patients

Reference and country	Study type and period	Number of patients	Prevalence	Patient characteristics	Tests used in initial assessment	Timing of test	Reference standard	Outcomes	Source of funding	Additional comments																			
				Median age was 7.7 years in those without documented infection and 7.2 in those with documented infection.			).	<p><i>Time to diagnosis</i></p> <p>Not reported</p>																					
Wilbur, 2000.	Patients were enrolled on one of 2 randomised trials. 1982-1987.	394 FN episodes in 292 patients	Early death (within first 5 days of FN episode)  32/394	Adult patients with cancer, fever (>38.3°C or >38.0°C on 2 occasions) and neutropenia (ANC <1.0X10 <sup>9</sup> /L), Mean age was 59 years 65% had haematological malignancy.	BUN, blood pressure, mental status, ANC, Albumin, Creatinine, Platelets, chest X-ray, glucose, height. Weight, temperature, ambulation, total protein, LDG, potassium, pulse rate,	Most chest X-rays were done on the day antibiotics were started but some were done up to 48 hours later.	Death within the first five days of antibiotic treatment.	<p>Chest X-ray showing probable infection:</p> <table border="1"> <thead> <tr> <th rowspan="2"></th> <th colspan="2"><i>Early death.</i></th> </tr> <tr> <th>+</th> <th>-</th> </tr> </thead> <tbody> <tr> <td>CXR infection +</td> <td>12</td> <td>53</td> </tr> <tr> <td>CXR infection -</td> <td>17</td> <td>267</td> </tr> </tbody> </table> <p>Sn 41%, Sp 83%</p> <table border="1"> <thead> <tr> <th rowspan="2"></th> <th colspan="2"><i>Early death.</i></th> </tr> <tr> <th>+</th> <th>-</th> </tr> </thead> <tbody> <tr> <td></td> <td></td> <td></td> </tr> </tbody> </table>		<i>Early death.</i>		+	-	CXR infection +	12	53	CXR infection -	17	267		<i>Early death.</i>		+	-				Supported in part by grants from Eli Lilly and Glaxo Inc.	
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					cholesterol			<table border="1"> <tr> <td>Glucose &gt; 170 mg/dL</td> <td>14</td> <td>51</td> </tr> <tr> <td>Glucose &lt; 170 mg/dL</td> <td>16</td> <td>294</td> </tr> </table> <p>Sn 46%, Sp 85%.</p> <p><i>Influence on management</i></p> <p>Not reported.</p> <p><i>Time to diagnosis</i></p> <p>Not reported</p>	Glucose > 170 mg/dL	14	51	Glucose < 170 mg/dL	16	294		
Glucose > 170 mg/dL	14	51														
Glucose < 170 mg/dL	16	294														
Yonemori, 2009. Japan	Retrospective case series. 1997 to 1999	106 FN episodes in 47 patients.	28/106 episodes had clinically documented infection.	Adult (> 16 years) haematological cancer patients with neutropenia (< 1.0X10 <sup>9</sup> /l) who went on to develop fever (>38.0°C) and were admitted to hospital.	Not reported	Around the start of the febrile episode.	Documented infection: documented bacterial or fungal infection, with positive blood cultures; or documented or	<p><i>Diagnostic accuracy</i></p> <p>See outcomes for topic D2</p> <p><i>Influence on management</i></p> <p>Not reported</p>								



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Reference and country	Study type and period	Number of patients	Prevalence	Patient characteristics	Tests used in initial assessment	Timing of test	Reference standard	Outcomes	Source of funding	Additional comments
				Median age was 56 years. All had haematological cancer.			presumed bacterial or fungal infections based on clinical or radiological findings with negative blood cultures	<p><i>Time to diagnosis</i></p> <p>Not reported</p>		