Original article

Infants 21–90 days presenting with a possible serious bacterial infection – are evaluation algorithms from high income countries applicable in the South African public health sector?

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ABSTRACT

Background: Young infants with a possible serious bacterial infection (SBI) are a very common presentation to emergency centres (ECs). It is often difficult to distinguish clinically between self-limiting viral infections and an SBI. Available evaluation algorithms to assist clinicians are mostly from high-income countries. Data to inform clinical practice in low- and middle-income countries are lacking.

Objectives: To determine the period prevalence of SBI and invasive bacterial infection (IBI) and describe current practice in the assessment and management of young infants aged 21–90 days presenting with a possible SBI to a Paediatric Emergency centre (PEC) in Cape Town, South Africa.

Methods: A retrospective cross-sectional review of infants 21–90 days old presenting to the Tygerberg Hospital PED between 1 January 2016 and 31 May 2016.

Results: A total of 248 infants 21–90 days were included in the study. Sixty-two patients (25%, 95% CI 20–30) had an SBI and 13 (5.2%, 95% CI 3–8) had an IBI. One hundred and sixty-five infants had a possible SBI based on WHO IMCI criteria. The sensitivity of the WHO IMCI criteria in detecting SBI was 82.3% (95% CI 70.5–90.8) and the specificity 38.7% (95% CI 31.7–46.1). More than half (51.2%) of the infants received antibiotics within the 48 h prior to presentation, of which 33.5% included intramuscular injection of Ceftriaxone. Only 20 (8.0%) patients in this age group were discharged home after initial evaluation. A significant relationship was noted between fever and the risk of SBI (p-value 0.010) and IBI (p-value 0.009). There also appeared to be a significant relationship between nutritional status and IBI (p-value 0.013).

Conclusion: Period prevalence of SBI and IBI was higher compared to that published in the literature. Validated evaluation algorithms to stratify risk of SBI are needed to assist clinicians in diagnosing and managing infants appropriately in low- and middle-income settings.

African relevance

• Young infants with a possible serious bacterial infection (SBI) are a very common presentation to emergency centres
• Available evaluation algorithms to assist clinicians are mostly from high-income countries.
• Validated evaluation algorithms to stratify risk of SBI are needed to assist clinicians in diagnosing and managing infants appropriately in low- and middle-income settings.

Introduction

In young infants it can be difficult to distinguish clinically between viral infections and a serious bacterial infection [1]. Whilst the more common viral infections are often self-limiting, the delayed diagnosis and management of an SBI can have serious consequences [2,3]. This creates a clinical dilemma for medical practitioners who must weigh the risk of missing an SBI against the potential risk, harm and cost implications of investigating and managing a febrile infant who does not have an SBI.

Evaluation algorithms have been developed to evaluate young infants with possible SBI, with a view to stratifying risk and avoiding
unnecessary investigations and treatment. Earlier algorithms, such as the Boston [4], Rochester [5], Philadelphia [6] and Milwaukee [7] criteria, were all published prior to the availability and widespread use of the Haemophilus influenzae type B (Hib) and pneumococcal vaccines [8]. More recent algorithms, such as the ‘Step by Step’ approach [9] or that of Kupperman et al. [10] have shown good sensitivity and negative predictive value in modern European and North American contexts respectively, but rely on procalcitonin (PCT), a test which is not routinely available in the state sector in SA. These algorithms may not be appropriate for the South African context, given health system resource limitations, high prevalence of malnutrition and HIV infection, and the use of WHO Integrated Management of Childhood Illness (IMCI) guidelines [11,12] and patients’ social circumstances.

The incidence of SBIs in febrile infants younger than 3 months is reportedly between 9% and 14% [13,14]. Data are lacking on the estimated incidence in SA. There is currently no standardised evaluation algorithm in the South African Standard Treatment Guidelines and Essential Drugs List for managing young infants <90 days with a possible serious bacterial infection. A recently released Western Cape provincial draft protocol [15] guides the initial investigation and management of infants <90 days of age presenting with a possible SBI to a hospital and incorporates the National Institute for Health and Care Excellence (NICE) traffic light system of clinical risk factors in infants younger than three months (see Appendices 1–3). We sought to determine the period prevalence of SBI and IBI and describe current practice in the assessment and management of young infants aged 21–90 days presenting with a possible SBI to a PEC in a lower middle-income country. Secondary objectives were to describe factors associated with increased risk of SBI/IBI and determine the sensitivity and specificity of the WHO IMCI criteria for possible SBI in the young infant.

Methods

Tygerberg Hospital (TBH) is a large central hospital and provides secondary and tertiary paediatric specialist services for half of the Cape Town metropole. The PEC sees about 15,000 children per annum, of which about a third are admitted. Patients are referred predominantly from primary health care facilities (including private general practitioners) and district hospitals. About 30% of patients are un-referred.

A retrospective cross-sectional review was done. The study population included all infants aged 21–90 days old presenting to the PEC between 1 January and 31 May 2016. The rationale for including infants in this age range was to compare the period prevalence of SBI and IBI between infants aged 21–27 days (neonatal period) to those aged 28–90 days of age. Clinicom®, a Western Cape provincial government patient administration system application, was used to identify infants in this age group and ECM, a Western Cape electronic content management system, was used to access clinical records. Children in whom clinical notes were incomplete were excluded.

Basic demographic information was recorded. Clinical records were reviewed looking specifically at the initial triage and clinical evaluation. On history HIV exposure and status, antibiotic administration in past 48 h, immunization status, birth gestation and weight-for-age were documented. Clinical notes were incomplete were excluded.

Performance of WHO IMCI criteria for possible SBI in young infants

Of 248 infants, 165 (66.5%) met the WHO IMCI criteria for possible SBI (Fig. 1 and Table 3). Some infants fulfilled more than one inclusion criterion. The most common reason for possible SBI according to IMCI criteria was fast breathing (56%), followed by severe chest-indrawing (36%). Of the 165 patients identified as having a possible SBI by the WHO IMCI criteria, 51 (30.9%) had a confirmed SBI. Eleven patients with SBI, including two with IBI, did not fulfil any of the WHO IMCI criteria. The performance of the WHO IMCI criteria in detecting SBI compared to two other clinical triage tools for febrile infants is depicted in Table 4.

Current management practices

The majority (127/248, 51.2%) of infants received antibiotics within the 48 h prior to presentation to the PEC. This included intramuscular, intravenous and oral antibiotics. Intramuscular injection of Ceftriaxone according to IMCI guidelines was administered to 33.5% of infants prior to presentation. The special investigations performed are demonstrated in Fig. 2. Thirty-three (13.3%) patients had a “full septic work-up” (WCC, CRP,
血培养、胸部X光、尿液分析和腰椎穿刺。33个接受完整脓毒症工作流程的患者中，13人（39.4%）最终没有脓毒症。在33个体温（≥38°C）的患者中，只有6人（18.2%）接受了“完整脓毒症工作流程”。

21名患者有阳性细菌培养（血液、尿液或脑脊液），排除了可疑污染。6名（28.6%）的21名患者在使用IMCI皮下注射头孢曲松前采集的样本中仍有阳性培养结果。

在首次就诊时使用的经验性抗生素组合中最常使用的是静脉滴注氨苄青霉素和庆大霉素（36.2%），口服阿莫西林（14.5%）和静脉滴注氨苄青霉素和头孢他啶（14.1%）。没有脓毒症的婴儿中有96人（51.9%）接受了静脉滴注抗生素。

最终诊断和结局

呼吸道合胞病毒（RSV）是最常见的诊断。唯一死亡的患者以呼吸暂停入院，并被诊断为侵袭性细菌感染（酿脓链球菌）。

讨论

婴儿期的脓毒症和菌血症的时期患病率为25.4%和5.2%。文献中估计，21–90天的婴儿中，脓毒症的患病率为9%–14%[13,14]。在最近的多中心研究中，脓毒症的患病率在有发热的婴儿中为4%[9]。我们研究中脓毒症（39.4%）和菌血症（18.2%）的患病率明显高于文献中报道的数值[9,13,14]。

可能的解释包括：首先，我们没有常规进行呼吸道合胞病毒的检测，因此肺炎可能被临床误诊为细菌性。其次，我们纳入了所有符合脓毒症和菌血症标准的婴儿，而不仅仅是发热的婴儿。第三，相当比例的婴儿是 HIV 暴露、早产、体重低于同龄正常水平或部分免疫化，因此构成了一个高风险人群。TBH 作为转诊中心，这可能会导致一些选择偏倚，因此该发现的普适性应考虑在内。

发热与脓毒症和菌血症的患病率增加关联。有显著的相关性（p-value 0.013）。考虑到这一点，我们建议在修订的本地南非西开普省指南中将体重过轻纳入风险因素。

近20%的婴儿在我们的研究中暴露于 HIV。与 Slogrove et al. [16] 相比，HIV 暴露的婴儿没有显著增加脓毒症和菌血症的风险，但人数稀少。根据当前的省指南的建议，HIV 暴露的婴儿应被评估为 SBI 和 IBI。在我们的研究中，CRP > 80 的91.7%的患者有脓毒症。一个菌血症的患者 CRP < 5。CRP > 80 的预测价值在我们研究中可能在年龄组较高。

Box 1
WHO IMCI criteria for possible SBI in the young infant.

Not being able to feed since birth or stopped feeding well (confirmed by observations)
Convulsions
Fast breathing (60 breaths per minute or more)
Severe chest in-drawing
Fever (38 °C or greater)
Low body temperature (less than 35.5 °C)
Movement only when stimulated or no movement at all

Table 1
Epidemiologic and clinical characteristics on history of all infants 21–90 days.

| Age       | N = 248 |
|-----------|---------|
| Mean age in days (standard deviation) | 52 (18.9) |
| 21–27 days, n (%) | 23 (9.3) |
| 28–90 days, n (%) | 225 (90.7) |

| Sex, n (%) | |
|-----------|----------|
| Male      | 147 (59.3) |
| Female    | 101 (40.7) |

| Gestation, n (%) | |
|------------------|----------|
| Term (<27 weeks) | 63 (25.4) |
| Preterm (≥27 weeks) | 46 (18.5) |
| Unknown          | 28 (11.3) |

| Immunizations, n (%) | |
|----------------------|----------|
| Up to date           | 174 (70.2) |
| Not up to date       | 46 (18.5) |
| Unknown              | 28 (11.3) |

| HIV status, n (%) | |
|-------------------|----------|
| HIV test not done | 152 (61.3) |
| Confirmed negative| 91 (36.7) |
| Confirmed positive | 5 (2) |

| Nutrition, n (%) | |
|------------------|----------|
| Normal           | 162 (65.3) |
| Underweight for age (below –2 Z score) | 48 (19.4) |
| Severely underweight for age (below –3 Z score) | 38 (15.3) |
population, compared to that described by Dyer et al. in children [17]. There appeared to be a significant relationship between leukopenia and leucocytosis in predicting SBI (p-value 0.001) and IBI (p-value 0.002) in infants 21–90 days. The literature is conflicting with regards to the predictive value of WCC in SBI and IBI. Bonso et al. showed in two separate studies that the WCC is an inaccurate screen for bacteraemia in febrile young infants [18] and that it cannot be used to predict which febrile infants will need a lumbar puncture [19]. However, Olaciregui et al. [20] evaluated CRP, PCT and WCC and found all three to have intrinsic predictive value for SBI in febrile infants <90 days. They also found that the diagnostic value of PCT is greater than CRP for IBI and for fever of short duration [20]. A recent study [21] also showed better diagnostic accuracy from PCT assay than CRP measurement for detecting IBI [21].

Urine dipsticks were performed in only 36% of patients, despite urinary tract infections being a common cause of SBI in vaccinated infants [5]. A recent study (2016) also showed better diagnostic accuracy from PCT assay than CRP measurement for detecting IBI [21].

Most authors agree that a febrile neonate should be admitted and that the full battery of screening tests including lumbar puncture should

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**Table 1**

Features on history, clinical examination and special investigations associated with SBI/IBI.

|                | SBI (%) | No SBI (%) | p-Value | IBI (%) | No IBI (%) | p-Value |
|----------------|---------|------------|---------|---------|------------|---------|
| Age 21–27 days | 9 (7.7) | 15 (9.1)   | 0.687   | 3 (23)  | 20 (8.5)   | 0.065   |
| 28–90 days     | 16 (9.3) | 109 (9.9)  | (76.9)  | 91.5    |
| Sex Male       | 113 (54.8) | 60.8 (61.5)| 0.208   | 8 (139) | 0.441      |
| Female         | 73 (54.8) | 8 (61.5)   | (76.9)  | 91.5    |
| Gestation Term (<37 weeks) | 131 (73.3) | 10 (76.9) | 0.479   | 16 (10) | 0.048      |
| Preterm        | 47 (26.7) | 3 (26.4)   | (23.1)  | 26.7    |
| HIV exposure   | Unexposed | 151 (73.8) | 0.074   | 9 (187) | 0.312      |
| Exposed        | 32 (16)  | 3 (15.4)   | (26.8)  |        |
| Immunization status Immunizations not up to date | 33 (23.6) | 20 (20.0) | 0.282   | 4 (42)  | 0.193      |
| Immunizations up to date | 132 (76.4) | 80.0 (69.2) | 0.074   | 16 (33) | 0.048      |
| Clinical appearance | Appears well | 53 (19.4) | 2 (14.9) | 0.079   | 6 (26.8) | 0.196    |
|                | 133 (80.6) | 1172 (73.2) | 0.079   | 6 (26.8) | 0.196      |
| Nutrition Normal (above –2 Z score) | 122 (64.5) | 65.6 (65.5) | 0.976   | 8 (154) | 0.013      |
| Low weight for age (on or below –2 Z score) | 36 (19.4) | 19.4 (19.6) | 2 (46)  | 0.074   | 0.013      |
| Very low weight for age (on or below –3 Z score) | 28 (16.1) | 15.0 (11.5) | 3 (5)   | 0.074   | 0.013      |
| Temperature Normal (≥38 °C) | 125 (79.0) | 81.7 (82.6) | 0.010   | 7 (194) | 0.009      |
| Fever (<38 °C) | 20 (12.0) | 10.8 (11.5) | 3 (46.2) | 0.010   | 0.009      |
| Hypothermia (<35.5 °C) | 0 (0.0) | 0 (0.0) | 14 (6.0) | 0.010   | 0.009      |
| C-reactive protein CRP 0 to 5 | 75 (34.5) | 61.0 (55.6) | 0.001   | 1 (94)  | 0.001      |
| CRP 6 to 20 | 26 (13.0) | 26.0 (18.3) | 0.001   | 1 (94)  | 0.001      |
| CRP 21 to 80 | 21 (12.0) | 21.1 (22.5) | 0.001   | 1 (94)  | 0.001      |
| CRP 81 to 200 | 21 (12.0) | 21.1 (22.5) | 0.001   | 1 (94)  | 0.001      |
| CRP >200 | 0 (0.0) | 0 (0.0) | 14 (6.0) | 0.001   | 0.001      |
| White cell count Normal WCC | 96 (31.9) | 96.0 (76.2) | 0.001   | 5 (122) | 0.002      |
| Leukopenia | 26 (8.6) | 8 (3.1) | 0.253   | 8 (88.9) | 0.234      |
| Leucocytosis | 26 (8.6) | 3.1 (3.2) | 0.253   | 8 (88.9) | 0.234      |
| Neutrophil count | 26 (8.6) | 3.1 (3.2) | 0.253   | 8 (88.9) | 0.234      |

*See Appendix 4 for cut-off values.

**Table 2 (continued)**

|                | SBI (%) | No SBI (%) | p-Value | IBI (%) | No IBI (%) | p-Value |
|----------------|---------|------------|---------|---------|------------|---------|
| Normal neutrophil count | 29 (63.0) | 55 (59.8) | 0.253   | 8 (88.9) | 0.234      |
| Neutropenia (<2.00 × 109/L) | 6 (13.0) | 22 (23.9) | 0.253   | 8 (88.9) | 0.234      |
| Neutrophilia (>8.00 × 109/L) | 11 (23.9) | 15 (16.3) | 1 (11.1) | 1 (19.4) | 0.234      |

**Table 3**

Number of infants presenting with WHO IMCI inclusion criteria.

| Criterion                                      | n (%)        |
|------------------------------------------------|--------------|
| Not being able to feed since birth or stopped feeding well (Confirmed by observations) | 23 (13.9%)   |
| Convulsions or apnoea                          | 18 (10.9%)   |
| Fast breathing (60 breaths per minute or more) | 92 (55.8%)   |
| Severe chest-in-drawing                       | 59 (35.7%)   |
| Fever (≥38 °C or greater)                     | 33 (20%)     |
| Low body temperature (less than 35.5 °C)      | 14 (8.5%)    |
| Movement only when stimulated or no movement at all | 5 (3%)     |

**Fig. 1** Performance of WHO IMCI criteria as screening tool.
be performed [22]. However, Schwartz et al. found that infants 21 to 28 days old presenting with a fever without a clinical source, had a similar prevalence of bacterial infections compared with older patients and a lower rate than infants ≤21 days old [23]. In our sample the rate of SBI and IBI did not differ significantly between the 21–27 day and the 28–90 days age groups. It is interesting to note however that half of the SBI’s (3/6) in the 21–27-day age group were IBI’s.

Most patients were admitted (92%), and more than half of patients who did not have an SBI received initial IV antibiotics. It appeared as if clinicians were cautious to send infants in this age group home. Practical constraints such as delayed availability of laboratory results and patient lack of transport are likely to influence current practice, as out-patient management is often not feasible in our setting. IMCI criteria had a higher negative predictive (NPV) value compared to the NICE and SIS tools. IMCI is designed to be used at primary care level in low-resource settings where diagnostic supports such as radiology and laboratory services are minimal and drugs and equipment are often limited [12]. Based on our findings, IMCI seems to be performing acceptably compared to NICE, with similar NPV and negative likelihood ratio. The low positive predictive value means that several children will potentially be referred and receive antibiotics unnecessarily. In the African context, the ‘costs’ of unnecessary use of

The WHO IMCI tool was less sensitive than the NICE guideline for identifying infants with an SBI (sensitivity of 82.3% vs 93.3%). However, IMCI, in our study, had a higher negative predictive (NPV) value compared to the NICE and SIS tools. IMCI is designed to be used at primary care level in low-resource settings where diagnostic supports such as radiology and laboratory services are minimal and drugs and equipment are often limited [12]. Based on our findings, IMCI seems to be performing acceptably compared to NICE, with similar NPV and negative likelihood ratio. The low positive predictive value means that several children will potentially be referred and receive antibiotics unnecessarily. In the African context, the ‘costs’ of unnecessary use of

### Table 4

|                      | Infants classified as high risk, n/total (%) | Prevalence of SBI among high risk infants n/total (%) | Sensitivity (95% CI) | Specificity (95% CI) | PPV (95% CI) | NPV (95% CI) | Positive likelihood ratio (95% CI) | Negative likelihood ratio (95% CI) |
|----------------------|---------------------------------------------|----------------------------------------------------|----------------------|----------------------|--------------|--------------|------------------------------------|----------------------------------|
| NICE [25]            | 932/1057 (88.2)                             | 304/932 (32.6)                                      | 93.3 (90.0–95.7)     | 14.1 (11.7–16.8)     | 32.6 (31.7–33.5) | 82.4 (75.1–87.9) | 1.09 (1.0–1.1)                   | 0.48 (0.3–0.7)                   |
| SIS [25]             | 768/1057 (78.7)                             | 258/768 (33.6)                                      | 79.1 (74.3–83.4)     | 30.2 (26.9–33.7)     | 33.6 (32.0–35.3) | 76.5 (71.9–80.5) | 1.13 (1.1–1.2)                   | 0.7 (0.5–0.9)                    |
| WHO IMCI             | 165/248 (66.5)                              | 51/165 (30.9)                                       | 82.3 (70.5–90.8)     | 38.7 (31.7–46.1)     | 30.9 (27.6–34.5) | 86.75 (78.8–92.0) | 1.34 (1.1–1.6)                   | 0.46 (0.3–0.8)                   |

**Fig. 2.** Special investigations performed on all infants 21–90 days.

Intramuscular injection of Ceftriaxone according to IMCI guidelines was administered to 33.5% of infants prior to presentation. However, of the 21 patients who had positive cultures, six (28.6%) received IMCI guided intramuscular Ceftriaxone injection. It is, therefore, important to still do all relevant cultures even if the patient received Ceftriaxone prior to presentation.

A recent analysis of emergency centre prediction tools in evaluation of febrile young infants (<3 months) at risk of serious infections (SI) was done in Singapore [25]. Their definition of serious infections also included serious viral infections like viral meningitis and encephalitis. They compared the effectiveness of the National Institute for Health and Care Excellence (NICE) guideline and the Severity Index Score (SIS). The NICE guideline outperformed the SIS. Table 4 compares the NICE and SIS criteria from the Singapore study [25] with the WHO IMCI criteria from our study. It is important to note that we did not include serious viral infections in our case definition and our numbers were smaller.

The WHO IMCI tool was less sensitive than the NICE guideline for identifying infants with an SBI (sensitivity of 82.3% vs 93.3%). However, IMCI, in our study, had a higher negative predictive (NPV) value compared to the NICE and SIS tools. IMCI is designed to be used at primary care level in low-resource settings where diagnostic supports such as radiology and laboratory services are minimal and drugs and equipment are often limited [12]. Based on our findings, IMCI seems to be performing acceptably compared to NICE, with similar NPV and negative likelihood ratio. The low positive predictive value means that several children will potentially be referred and receive antibiotics unnecessarily. In the African context, the ‘costs’ of unnecessary use of
health resources needs to be balanced with the risk of missing serious infection, preventing death or need for intensive care, and other considerations such as antibiotic stewardship.

The retrospective nature of the study could have influenced data collection. TBH as tertiary referral centre may have resulted in possible selection bias of sicker infants. Axillary temperature, rather than rectal, was measured during triage, which could have resulted in under-reporting of fever on presentation. Not all patients presenting with a suspected lower respiratory tract infection had viral testing done due to cost implications. This would have enabled greater confidence in differentiating between viral and bacterial pneumonia [2]. The study was conducted during summer and autumn and not over a one-year period and seasonal variation in disease epidemiology might have skewed the results. The clinical team making the final diagnosis, often included junior doctors which may have resulted in an over-diagnosis of bacterial pneumonia.

Conclusion

The period prevalence of SBI and IBI in our study is significantly higher than that quoted in the literature, and application of international algorithms may be imprudent. IMCI performed reasonably well considering such as antibiotic stewardship. Health resources needs to be balanced with the risk of missing serious infection – an appraisal of the Rochester Criteria and implications for management. Febrile Infant Collaborative Study Group. Pediatrics 1994;94(3):390–6.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1177/0161310200900202.
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