

SEPSIS KILLS: early intervention saves lives

The increasing incidence of sepsis is well recognised, and is generally attributed to the growing prevalence of chronic conditions in ageing populations.¹⁻³ In New South Wales, the number of patients with a diagnosis of sepsis in the Admitted Patient Data Collection (APDC) has increased, and sepsis was involved in 17.5% of in-hospital deaths in 2009, compared with a mortality of 1.5% for all hospital separations (unpublished data).

The clinical presentation of sepsis may be subtle; fever is not always present.^{4,5} In NSW, failure to recognise and respond to sepsis has been regularly reported. In 2009, 167 incidents were highlighted in a clinical focus report published by the Clinical Excellence Commission (CEC).⁶ A Quality Systems Assessment in 2011, completed by over 1500 respondents across the NSW hospital system, reported that 34% of clinical units did not have guidelines or protocols for managing sepsis.⁷

This article reports on the SEPSIS KILLS program of the CEC, which aims to promote the skills and knowledge needed for recognising and managing patients with sepsis in NSW hospital emergency departments.

Methods

The focus of the program is to RECOGNISE risk factors, signs and symptoms of sepsis; RESUSCITATE with rapid intravenous fluids and antibiotics; and REFER to senior clinicians and teams. Standardised sepsis tools were developed in consultation with NSW emergency physicians, and included adult and paediatric pathways that built on the NSW deteriorating patient system, *Between the Flags* (BTF).⁸ The vital signs assessed in the sepsis pathways were consistent with BTF, and varied marginally from accepted systemic inflammatory response criteria (Box 1).

The SEPSIS KILLS pathways promote bundles of care, with the

Abstract

Objective: To implement a statewide program for the early recognition and treatment of sepsis in New South Wales, Australia.

Setting: Ninety-seven emergency departments in NSW hospitals.

Intervention: A quality improvement program (SEPSIS KILLS) that promoted intervention within 60 minutes of recognition, including taking of blood cultures, measuring serum lactate levels, administration of intravenous antibiotics, and fluid resuscitation.

Main outcome measures: Time to antibiotics and fluid resuscitation; mortality rates and length of stay.

Results: Data for 13 567 patients were entered into the database. The proportion of patients receiving intravenous antibiotics within 60 minutes of triage increased from 29.3% in 2009–2011 to 52.2% in 2013. The percentage for whom a second litre of fluid was started within 60 minutes rose from 10.6% to 27.5% (each $P < 0.001$). The proportion of patients classed as Australasian Triage Scale (ATS) 1 increased from 2.3% in 2009–2011 to 4.2% in 2013, and the proportion classed as ATS 2 rose from 40.7% in 2009–2011 to 60.7% in 2013 ($P < 0.001$). There was a linear decrease in mortality from 19.3% in 2009–2011 to 14.1% in 2013; there was also a significant decline in time in intensive care and total length of stay (each $P < 0.0001$). The mortality rate for patients with severe sepsis (serum lactate ≥ 4 mmol/L or systolic blood pressure [SBP] < 90 mmHg) was 19.7%. The mortality rates for patients with severe sepsis admitted to intensive care and for those admitted to a ward did not change significantly over time. The proportion of patients with uncomplicated sepsis (SBP ≥ 90 mmHg, serum lactate < 4 mmol/L) transferred to a ward increased, and the mortality rate after transfer increased from 3.2% in 2009–2011 to 6.2% in 2013 ($P < 0.05$). The survival benefit was greatest for patients with evidence of haemodynamic instability (SBP < 90 mmHg) but normal lactate levels ($P = 0.03$).

Conclusions: The SEPSIS KILLS program has improved the process of care for patients with sepsis in NSW hospitals. The program has focused attention on sepsis management in the wards.

emphasis on early intervention. The adult bundle includes taking blood cultures, measuring serum lactate levels, administering intravenous antibiotics within an hour of triage and recognition, and administering a fluid bolus of 20 mL/kg, followed by another bolus of 20 mL/kg (if necessary) and inotropic drugs if the patient's condition is not fluid-responsive. If no improvement is observed, senior medical review and admission to intensive care or retrieval to a major centre should be considered (Box 2). The paediatric bundle emphasises the importance of early senior clinical review and decision making. In addition, an empiric antibiotic guideline was developed with advice from expert infectious disease physicians. Emphasis was placed on the first dose of antibiotics, thereby allowing

time for further assessment and diagnosis. Because of wide variations in practice, the guideline also contained details on how antibiotics could be administered most expeditiously.

The program was implemented in 2011 with a top-down, bottom-up approach, with strong leadership from medical and nursing clinical leads, and supported by the local health district Clinical Governance Units. Participation was not mandatory, and no extra resources were provided to participating emergency departments who implemented the program. The CEC team supported clinicians by holding a preliminary launch, monthly CEC–hospital teleconferences, executive reports, newsletters, site visits and workshops. A range of online resources

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1 The SEPSIS KILLS pathway for adult patients in hospital emergency departments, page 1



Sepsis Pathway - Adult - Emergency Department



Use local febrile neutropenia guideline if patient has haematology/oncology diagnosis

RECOGNISE

Does your patient have risk factors, signs or symptoms of infection?

- | | |
|------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|
| <input type="checkbox"/> Immunocompromised | <input type="checkbox"/> Abdomen: pain, peritonism |
| <input type="checkbox"/> Indwelling medical device | <input type="checkbox"/> Lung: cough, shortness of breath |
| <input type="checkbox"/> Recent surgery/invasive procedure | <input type="checkbox"/> Neuro: altered LOC, new onset of confusion, neck stiffness, headache |
| <input type="checkbox"/> History of fever or rigors | <input type="checkbox"/> Skin: wound, cellulitis |
| <input type="checkbox"/> Re-presentation within 48 hours | <input type="checkbox"/> Urine: dysuria, frequency, odour |
| <input type="checkbox"/> Fall not related to mechanism of injury | |

AND

Does your patient have 2 or more yellow criteria?

- | | |
|-------------------------------------------------------------------------|------------------------------------------------------------------------|
| <input type="checkbox"/> Respirations ≤ 10 or ≥ 25 per minute | <input type="checkbox"/> Heart rate ≤ 50 OR ≥ 120 per minute |
| <input type="checkbox"/> SpO ₂ < 95% | <input type="checkbox"/> Altered LOC or new onset of confusion |
| <input type="checkbox"/> Systolic blood pressure ≤ 100 mmHg | <input type="checkbox"/> Temp < 35.5 or > 38.5°C |

YES
Perform venous blood gas if available

Does your patient have any red criteria?

- | | |
|--------------------------------------------------|--------------------------------------------|
| <input type="checkbox"/> SBP < 90mmHg | <input type="checkbox"/> Age > 65 years |
| <input type="checkbox"/> Lactate ≥ 4 mmol/L | <input type="checkbox"/> Immunocompromised |
| <input type="checkbox"/> Base excess < - 5.0 | |

NO

NO

YES

RESPOND & ESCALATE

Sepsis may still be a concern

- Monitor vital signs and fluid balance
- Treat and re-assess
- Consider septic screen

Patient may have SEPSIS

- Obtain senior clinician review within 30 minutes
- Look for other causes of deterioration
- Turn over page for SEPSIS SIX

Patient has SEVERE SEPSIS or SEPTIC SHOCK until proven otherwise

- Obtain IMMEDIATE senior clinician review
- Expedite transfer to resuscitation area or equivalent
- Commence resuscitation as per SEPSIS SIX

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triage category, clinical observations (including systolic blood pressure [SBP] and serum lactate levels), time and date of initial intravenous antibiotic treatment and of commencement of the second litre of intravenous fluid, the presumptive source of sepsis, and the disposition of patients following emergency department treatment. Data were collected either prospectively or by retrospective chart review. The database allowed emergency departments to monitor time to antibiotics and fluids in real time, and to compare this with the corresponding local health district and NSW data.

Ethics approval was obtained from the NSW Sepsis Register, which was developed as a public health and disease register under s98 of the *Public Health Act 2011*. The Sepsis Register is maintained by the CEC.

Data analysis

Analysis of process measures (time to antibiotic, time to intravenous fluid) was based on data from the SEPSIS KILLS database. A total of 13 567 SEPSIS KILLS records were submitted for linkage to the APDC to assess associations between in-hospital mortality and sepsis severity and patient disposition. Patients were classified by emergency department staff according to the Australasian Triage Scale (ATS).⁹ The cases were further classified as being severe or uncomplicated sepsis according to the serum lactate levels and presenting SBP of the patient.

To assess the population-level impact of the SEPSIS KILLS program, we analysed health outcomes (in-hospital mortality, hours in intensive care, length of stay) for paediatric and adult patients separated from NSW hospitals with ICD-10-AM (International Classification of Diseases, 10th revision, Australian modification) discharge diagnosis codes consistent with sepsis¹⁰ recorded in the Admitted Patient, Emergency Department Attendance and Deaths Register. This register was accessed through the NSW Ministry of Health Secure Analytics for Population Health Research and Intelligence (SAPHaRI) system. Linkage was

was provided, including a Sepsis Toolkit (implementation guide) and various education tools.

Emergency departments were encouraged to collect prospective data on paediatric and adult patients

with a provisional diagnosis of sepsis who had received intravenous antibiotics. An online sepsis database (from August 2011) facilitated collection of a minimum dataset for each patient that included their date of birth, triage time and date,

undertaken by the Centre for Health Record Linkage (CHeReL). Only patients admitted to public hospitals with emergency departments were included in the analysis. Trend analysis was performed for the run-in period, August 2009 – December 2011, and for the two following years, 2012 and 2013. Outcomes by sepsis severity could not be analysed at the population level because of the lack of consensus about using ICD-10-AM codes to differentiate between severe and uncomplicated sepsis.

Descriptive and inferential analyses included the calculation of frequencies, odds ratios (ORs) and 95% confidence intervals, and χ^2 tests for trends. Trends over time for process and outcome measures were assessed in regression models. Logistic regression was used to analyse in-hospital deaths, while linear regression models were used for time in intensive care and lengths of stay. Models were adjusted as appropriate for covariates (age, year, triage category and severity of sepsis). Statistical significance was defined as $P < 0.05$.

Results

The SEPSIS KILLS program was implemented as individual emergency departments became ready during 2011. Both retrospective and prospective data were collected by 97 hospitals to 31 December 2013 and entered into the sepsis database. Data were submitted by 13 tertiary, 19 metropolitan and 65 rural hospitals. Because of the low number of paediatric patients, analysis was restricted to data for adult patients.

The provisional sources of sepsis included the lungs (5216 patients, 40.5%), urinary tract (2998, 23.2%), abdomen (1077, 8.4%), skin or soft tissue (975, 7.6%), musculoskeletal system (98, 0.8%), central nervous system (96, 0.7%), vascular device (82, 0.6%), and other systems (973, 7.6%). For 1238 patients (9.6%) the source was unidentified, for 133 (1.0%) no source was recorded.

There were age data in 12 879 records. There was a significant

2 The SEPSIS KILLS pathway for adult patients in hospital emergency departments, page 2

ADULT SEPSIS PATHWAY v2

RESUSCITATE

Does the patient have an Advance Care Directive; are there any treatment limitations?	
Sepsis Six <small>Acknowledgement: The Sepsis Six in this document is an adaptation of the Sepsis Six by Ron Daniels, UK Sepsis Trust.</small>	
1. OXYGEN	Administer oxygen to maintain SpO ₂ > 95%
2. BLOOD CULTURES	Take blood cultures (2 aerobic, 2 anaerobic), FBC, EUC, LFTs, coags, glucose, +/- wound, urine, sputum or other cultures
3. LACTATE	Take blood for formal lactate or VBG
4. IV FLUIDS	Give 20mL/kg 0.9% sodium chloride fluid challenge STAT Aim to achieve MAP of > 65mmHg or SBP > 100mmHg If no response, repeat 20mL/kg 0.9% sodium chloride <i>unless there are signs of pulmonary oedema</i> If no response commence inotropes as per local protocol and in consultation with senior doctor
5. IV ANTIBIOTICS	Prescribe and commence within 60 MINUTES from triage/time of diagnosis <i>or within 30 MINUTES if haematology/oncology patient</i> (refer to local guidelines and seek specialist advice) Do not wait for results of investigations
6. MONITORING	Monitor respiratory rate, SpO ₂ , blood pressure, heart rate, temperature, LOC, fluid balance, urinary output Review antibiotics when blood/specimen results available

RE-ASSESS

SIGNS OF IMPROVEMENT	
<input type="checkbox"/> SpO ₂ > 95%	<input type="checkbox"/> MAP > 65mmHg or SBP > 100mmHg
<input type="checkbox"/> Decreasing tachycardia	<input type="checkbox"/> Decreasing serum lactate level
<input type="checkbox"/> Improving LOC	<input type="checkbox"/> Urine output > 0.5mL/kg/hr
IF IMPROVING TAKE THE FOLLOWING ACTION	
<ul style="list-style-type: none"> Refer to admitting team/ICU Continue monitoring vital signs and fluid balance closely Investigate and treat the source of infection 	

REFER

IF NO IMPROVEMENT THIS PATIENT NEEDS INTENSIVE CARE MANAGEMENT
<ul style="list-style-type: none"> Reassess suitability to continue resuscitation Request review by ICU doctor to occur within 30 minutes If no ICU at your facility, seek advice immediately from the ADULT MEDICAL RETRIEVAL SERVICE 1800 650 004 or local Critical Care Advisory Service <p>Minimum patient monitoring requirements:</p> <ul style="list-style-type: none"> Respiratory rate, SpO₂, blood pressure, heart rate, temperature, LOC Repeat serum lactate every 4 hours Fluid balance, consider measuring urine output via IDC



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reduction in the mean age of patients between 2009 and 2013, from 67.3 years in 2009–2011 to 64.8 years in 2013 ($P < 0.001$ for trend; [Box 3](#)).

Data for the process indicators from the CEC sepsis database are summarised in [Box 3](#). The proportion of

patients who were categorised at triage as ATS 1 (“see immediately”) rose from 2.3% in 2009–2011 to 4.2% in 2013. Those categorised as ATS 2 (“see within 10 minutes”) increased from 40.7% in 2009–2011 to 60.7% in 2013 ($P < 0.001$). There were small reductions in the

3 Characteristics, and process and outcome indicators of sepsis-related hospital separations before and after the launch of the SEPSIS KILLS program

Characteristics	Run-in period	SEPSIS KILLS program in operation		P for trend
	Aug 2009 – Dec 2011	2012	2013	
Number of separations	1585	5396	5905	
Mean age ± SEM, years	67.3 ± 0.5	67.6 ± 0.3	64.8 ± 0.3	< 0.001
Triage category*				< 0.001
1	37 (2.3%)	176 (3.3%)	242 (4.2%)	
2	463 (40.7%)	2765 (51.5%)	3532 (60.7%)	
3	683 (43.2%)	2034 (37.9%)	1767 (30.4%)	
4	207 (13.1%)	378 (7.0%)	267 (4.6%)	
5	10 (0.6%)	16 (0.3%)	12 (0.2%)	
Missing data	5	22	83	
Antibiotic received within 60 min	464 (29.3%)	2165 (40.2%)	3083 (52.2%)	< 0.001
Second litre of intravenous fluid within 60 min	135 of 1272 patients (10.6%)	521 of 3631 patients (14.3%)	991 of 3609 patients (27.5%)	< 0.001

SEM = standard error of the mean. *Percentages exclude patients for whom data was not available (missing data). ♦

proportions of patients classed as ATS 3, 4 or 5.

The proportion of patients who received antibiotics within 60 minutes of triage or recognition increased from 29.3% in 2009–2011 to 52.2% in 2013 (linear trend test, $P < 0.001$). Similarly, the number of patients who started a second litre of intravenous fluid within one hour rose from 10.6% to 27.5% (linear trend test, $P < 0.001$).

The analysis of population-based APDC data, which included all

separations with emergency department involvement from public hospitals in NSW between January 2009 and December 2013, is presented in Box 4. There were 15801 sepsis hospital separations during the run-in period of 2009–2011, with a mortality of 19.3%. This rate declined to 17.2% in 2012 and 14.1% in 2013. There was a significant linear decrease over time ($P < 0.0001$); the OR for death (compared with the run-in period) was 0.87 (95% CI, 0.80–0.94) in 2012, and 0.69 (95% CI, 0.63–0.74) in 2013. Significant linear

declines were also observed for time in intensive care and length of stay (for each trend: $P < 0.0001$).

Linkage of the APDC and sepsis databases showed that the mortality rate for the 1616 patients with severe sepsis (serum lactate ≥ 4 mmol/L or SBP < 90 mmHg) was 19.7%; these patients were significantly more likely to die than patients with uncomplicated sepsis (serum lactate < 4 mmol/L and SBP ≥ 90 mmHg) (OR, 3.7; 95% CI, 3.2–4.4; $P < 0.0001$). The mortality

4 Hospital outcomes prior to and after the launch of the SEPSIS KILLS program, NSW, January 2009 to December 2013

Outcomes	Descriptive statistics	Odds ratio (95% CI)	P for trend
Deaths, numbers (percentage)			< 0.0001
2009–2011	3053/15 801 (19.3%)	1	
2012	979/5683 (17.2%)	0.87 (0.80–0.94)	
2013	870/6167 (14.1%)	0.69 (0.63–0.74)	
Mean time in intensive care (SEM), hours			< 0.0001
2009–2011	32.7 (1.0)		
2012	26.6 (1.4)		
2013	25.8 (1.3)		
Mean length of stay (SEM), days			< 0.0001
2009–2011	13.5 (0.1)		
2012	12.2 (0.2)		
2013	11.5 (0.2)		

SEM = standard error of the mean. Source: Admitted Patient Data Collection, NSW Ministry of Health Secure Analytics for Population Health Research and Intelligence (SAPHaRI). Data extracted on 1 June 2015. ♦

rate for the 893 patients with hyperlactataemia (a lactate level of 4 mmol/L or more; reference interval, 0.5–2.0 mmol/L) was 24.9%, while that for 637 patients presenting with cryptic shock — hyperlactataemia together with normotension (SBP \geq 90 mmHg) — was 21.2%. There was no change in mortality for either group over time. For 734 patients who presented with SBP $<$ 90 mmHg and lactate levels $<$ 4 mmol/L, mortality was 13.5%, which declined significantly across the study period (2009–2011, 16.5%; 2012, 16.0%; 2013, 9.8; $P=0.03$). The overall mortality rate for uncomplicated sepsis patients increased significantly over time: 3.7% (21/567) in 2009–2011, 6.2% (145/2336) in 2012, and 6.7% (145/2164) in 2013 ($P=0.02$).

The mortality rate for the 268 ATS 1 patients was 28.8%. The risk of death for patients over 65 years of age was 3.3 times higher (95% CI, 2.6–4.1) than for patients under 65 years of age ($P=0.001$).

The mortality rate for 543 severe sepsis patients admitted to intensive care did not change significantly over time — 23.4% (2009–2011), 19.5% (2012) and 16.0% (2013) ($P=0.145$) — nor did the proportion of the 1073 patients with severe sepsis who were admitted to the ward and died — 21.4% (2009–2011), 21.5% (2012) and 18.4% (2013) ($P=0.263$). In contrast, the risk of death for 4225 patients with uncomplicated sepsis admitted to the ward increased significantly: 3.2% (15/466) during 2009–2011, 6.0% (115/1914) during 2012, and 6.2% (115/1845) during 2013 ($P=0.047$).

Discussion

SEPSIS KILLS is a quality improvement program that aims to reduce preventable harm to patients with sepsis by recognising the condition early and managing it promptly. It is based on the principle that early recognition and aggressive management with antibiotics and fluids will improve outcomes.^{11–13} It is consistent with the 3-hour

component of the resuscitation bundle outlined in the international guidelines of the Surviving Sepsis Campaign.³

The program was not planned as a before-and-after project, but was independently implemented by individual emergency departments during 2011. More than 80% of NSW emergency departments (175 of 220) used the sepsis pathways, and 97 emergency departments submitted over 13 000 records. The resulting increase in the number of patients for whom antibiotics were initiated within 60 minutes of recognition and the increased likelihood of the second litre of fluids being started in the first hour indicate that the program was successful. Greater urgency is also apparent from the marked increase in the number of patients classified at triage as ATS 2. We cannot, however, explain the significant age difference between the patients seen in 2012 and 2013.

Reviewing the population-based APDC hospitalisations with an ICD-10-AM code for sepsis showed that there was a steady reduction in mortality over time. Contrary to what we expected, the survival benefit in our patients appears to have been greatest for those with evidence of haemodynamic instability (SBP $<$ 90 mmHg) but normal lactate levels.

The mortality rate of 15%–20% for patients admitted to intensive care with severe sepsis (one-third of the overall sample) is consistent with the overall mortality rate in Australian and New Zealand intensive care units.^{14,15} In 2013, the crude mortality rate for the patients admitted to wards was higher than that for the intensive care group. We believe the relatively high proportion of ward patients may be the result of an underappreciation of the potential mortality of sepsis, of the significance of elevated lactate levels, and of the time course of the septic process, as well as of failure to recognise cryptic shock¹⁶ and the obvious and practical problem of intensive care unit bed availability. We did not assess how many had end-of-life treatment limitations in place.

Managing large numbers of patients with sepsis on the wards has been described elsewhere.^{17,18} These patients have not been well studied, although a number of studies have identified deficiencies in care.^{19–21} The significant increase in mortality among patients with uncomplicated sepsis admitted to the ward causes concern that some of our ward patients may have qualified for intensive therapy. An increase in mortality in less severe sepsis has also been documented by other authors.²²

The major challenge was managing the prescribing of antibiotics. Despite general acceptance of expert guidelines for prescribing antibiotics, differences in their prescription and administration were observed. This evidence–practice gap is well recognised,²³ and the empiric antibiotic guideline was developed to promote appropriate antibiotic prescribing practices and optimal outcomes.²⁴ The empiric guideline was consistent with the principles of antimicrobial stewardship, and, while each site was allowed to modify it according to local opinion and antibiotic resistance patterns, changes were infrequent. Particular anxieties were expressed about prescribing and administering gentamicin. The administration component of the guideline was developed to promote the most expeditious method of administration rather than favouring the slow infusion that had become normal practice. Despite the emphasis on the first dose and timely review, antibiotics were often continued long after they should have been reviewed, following consideration of the results of pathology investigations.

Other challenges beyond our control included educating a high turnover workforce in emergency departments, as well as medical engagement, particularly in rural facilities where governance is difficult and there is no doctor on site, or locum medical staff are more common. There were wide variations in the methods of blood culture collection, and a standardised guideline for blood cultures was subsequently added to the Sepsis Toolkit.

Limitations

This work is subject to the limitations of any quality improvement project at multiple sites. The prolonged run-in period was not ideal. Our approach was not to measure compliance with the care bundle, as undertaken elsewhere, but to use time as a measure for promoting behavioural change among emergency department clinicians. Assessing patient outcomes was the major difficulty. The voluntary nature of data collection resulted in its inconsistent submission, and the lack of strict diagnostic criteria for sepsis resulted in patients with conditions from across the inflammatory condition–sepsis spectrum being included in the SEPSIS KILLS database. Resource limitations also meant that some sites implemented the pathways but did not submit data.

Reviewing the outcomes of patients with an ICD-10-AM code for sepsis in the population-based administrative APDC is an accepted approach. This, however, entails the risk of reviewing the outcomes of a different group of patients, a group for whom the final

diagnosis might not be directly related to sepsis or its severity. This is a potential problem when comparing the final diagnosis in the APDC database with the provisional diagnosis in the SEPSIS KILLS data.

Finally, the improved outcomes described in our article may be the result of the SEPSIS KILLS program, but may also be related to other initiatives for improving quality of care.

Implications for clinicians, researchers and policy makers

The observation that patients with severe sepsis are being managed on the wards highlights the need for a shift in the focus of both practice improvement and research from intensive care to ward management. It also raises the problem of sepsis and the deteriorating patient. We informally estimated that around 30% of patients who required a Rapid Response call had sepsis, but this may be an underestimate, with rates possibly as high as 50%–60%.²⁵ Finally, our work confirms the need for continued research into risk

stratification tools for sepsis in the emergency department. In the meantime, all patients with lactate levels of 4 mmol/L or greater require intensive care unit review and admission.

The SEPSIS KILLS program promotes early recognition and management of sepsis during the first few hours in NSW emergency departments. By focusing on the principle of “Recognise, Resuscitate, Refer” it is possible to reduce the time before antibiotics are administered and fluid resuscitation initiated. This program could be applied in other jurisdictions and its integration with antimicrobial stewardship requirements should be considered.

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