Empiric Antibiotic Treatment Reduces Mortality in Severe Sepsis and Septic Shock From the First Hour: Results From a Guideline-Based Performance Improvement Program

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背景

- 休克病人治療：aggressive resuscitation bundles, adequate source control, appropriate antibiotic therapy, and organ support
- 抗生素延遲給予->Risk factor for mortality
- 治療protocols :對於severe sepsis and septic shock的病人，快速給予適當的抗生素為一關鍵性處置
- Surviving Sepsis Campaign (SSC) Guidelines：需儘快給予廣效性抗生素->一般病房病人：1小時；ER病人：3小時

研究目的

分析severe sepsis and septic shock的病人抗生素給予的時機以及死亡率之間的關係來找出empiric antibiotic的最佳使用時機

方法

- Retrospective analysis
- 分析200501~201002歐洲、美國、南美165個ICU共28150位sepsis病人在抗生素給予以及在院死亡率的關係
- Eligible subjects:
  A.疑似感染入住ICU　B.≥2 SIRS criteria　C.≥1 organ dysfunction
- Time of presentation:
  - ED病人：The time of triage
  - 入住ICU病人：chart review-診斷severe sepsis的時間
- Time to first Abx administration：
  - Time of presentation~ first Abx administration

結果

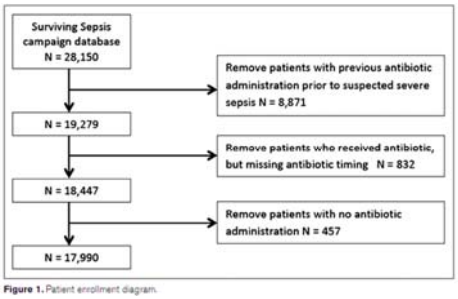

Figure 1. Patient enrollment diagram.

結果

TABLE 1. Patient Characteristics by Timing in Hours to the First Antibiotic

Patient Characteristic, *n* (%)	Antibiotic Timing (Hr)							
	0.0–1.0	1.0–2.0	2.0–3.0	3.0–4.0	4.0–5.0	5.0–6.0	> 6.0	*p**
n	4,728	4,595	3,020	1,734	1,037	640	2,239	
Hospital mortality	1,512 (32.0)	1,292 (28.1)	863 (28.6)	517 (29.8)	337 (32.5)	234 (36.6)	885 (39.6)	< 0.001
Severity sepsis score, median (IQR)	58 (42–73)	50 (36–66)	49 (35–64)	49 (35–66)	51 (37–68)	53 (38–69)	57 (40–71)	< 0.001
Nosocomial infection	812 (17.2)	357 (7.8)	229 (7.6)	173 (10.0)	128 (12.3)	89 (13.9)	403 (18.0)	< 0.001
Septic shock	3,289 (69.6)	2,880 (62.7)	1,847 (61.2)	1,047 (60.4)	684 (66.0)	441 (68.9)	1,370 (61.3)	< 0.001
Hospital LOS, median days (IQR)	13 (6.4–25)	10 (5.6–19)	10.0 (5.6–19)	11 (5.9–20)	12 (6.3–23)	12 (6.3–22)	14 (7.3–29)	< 0.001
ICU LOS, median days (IQR)	5.1 (2.4–11)	4.1 (2.1–8.9)	4.2 (2.1–8.8)	4.3 (2.0–9.5)	4.9 (2.4–11)	4.6 (2.1–10)	6.7 (2.8–15)	< 0.001
LOS prior to ICU, median days (IQR)	0.1 (0.0–0.8)	0.1 (0.0–0.3)	0.1 (0.0–0.3)	0.1 (0.0–0.4)	0.2 (0.0–0.5)	0.2 (0.0–0.7)	0.2 (0.0–1.4)	< 0.001
Location where sepsis identified								
ED	3,028 (64.0)	3,716 (80.9)	2,424 (80.3)	1,322 (76.2)	727 (70.1)	417 (65.2)	1,294 (57.9)	< 0.001
ED mortality	797 (26.3)	935 (25.2)	629 (26.0)	352 (26.6)	209 (28.8)	132 (31.7)	404 (31.2)	< 0.001
Ward	1,198 (25.3)	680 (14.8)	469 (15.5)	326 (18.8)	244 (23.5)	177 (27.7)	689 (30.8)	< 0.001
Ward mortality	481 (40.2)	274 (40.3)	195 (41.6)	131 (40.8)	94 (38.5)	83 (46.9)	332 (48.2)	< 0.001
ICU	502 (10.6)	199 (4.3)	127 (4.2)	86 (5.0)	66 (6.4)	46 (7.2)	253 (11.3)	< 0.001
ICU mortality	234 (46.6)	83 (41.7)	39 (30.7)	34 (39.5)	34 (51.5)	19 (41.3)	149 (58.9)	< 0.001

結果

Site of infection							
Pneumonia	2,388 (50.5)	2,308 (50.2)	1,398 (46.3)	729 (42.0)	430 (41.5)	252 (39.4)	982 (43.9)	<0.001
Urinary tract infection	1,076 (22.8)	1,392 (29.0)	950 (31.5)	518 (29.9)	273 (26.3)	164 (25.6)	444 (19.9)	<0.001
Abdominal	914 (19.3)	738 (16.1)	545 (18.1)	387 (22.3)	225 (21.7)	146 (22.8)	550 (24.6)	<0.001
Meningitis	101 (2.1)	57 (1.2)	39 (1.3)	23 (1.3)	16 (1.5)	5 (0.8)	36 (1.6)	0.002
Skin	294 (6.2)	294 (6.4)	212 (7.0)	119 (6.9)	66 (6.4)	35 (5.5)	113 (5.1)	0.040
Bone	46 (1.0)	57 (1.2)	48 (1.6)	28 (1.6)	7 (0.7)	9 (1.4)	37 (1.7)	0.075
Wound	206 (4.4)	242 (5.3)	124 (4.1)	78 (4.5)	50 (4.8)	20 (3.1)	95 (4.3)	0.080
Catheter	169 (3.6)	157 (3.4)	106 (3.5)	75 (4.3)	37 (3.6)	29 (4.5)	88 (3.9)	0.596
Endocarditis	46 (1.0)	42 (0.9)	33 (1.1)	15 (0.9)	14 (1.4)	11 (1.7)	26 (1.2)	0.548
Device	54 (1.1)	51 (1.1)	43 (1.4)	24 (1.4)	16 (1.5)	9 (1.4)	22 (1.0)	0.704
Other infection	260 (9.7)	528 (11.5)	399 (13.2)	216 (12.5)	145 (14.0)	95 (14.8)	337 (15.7)	<0.001
Baseline acute organ dysfunction							
Cardiovascular	4,221 (89.3)	4,123 (89.7)	2,689 (89.0)	1,510 (87.1)	888 (85.6)	541 (84.5)	1,800 (80.5)	<0.001
Pulmonary	1,456 (30.8)	1,120 (24.4)	610 (20.2)	383 (22.1)	240 (23.1)	145 (22.7)	681 (30.5)	<0.001
Renal	1,824 (38.6)	1,717 (37.4)	1,139 (37.7)	644 (37.1)	415 (40.0)	238 (37.2)	890 (39.8)	0.002
Hepatic	393 (8.3)	415 (9.0)	285 (9.4)	170 (9.8)	107 (10.3)	74 (11.6)	280 (12.5)	<0.001
Hematologic	1,171 (24.8)	904 (19.7)	706 (23.4)	405 (23.4)	251 (24.2)	175 (27.3)	595 (26.6)	<0.001

結果

TABLE 1. (*Continued*). Patient Characteristics by Timing in Hours to the First Antibiotic

Patient Characteristic, *n* (%)	Antibiotic Timing (Hr)							
	0.0–1.0	1.0–2.0	2.0–3.0	3.0–4.0	4.0–5.0	5.0–6.0	> 6.0	*p*[a]
Number of acute organ dysfunction								
1	1,898 (40.1)	2,078 (45.2)	1,363 (45.1)	777 (44.8)	458 (44.2)	275 (43.0)	942 (42.1)	
2	1,653 (35.0)	1,587 (34.5)	1,060 (35.1)	608 (35.1)	358 (34.5)	227 (35.5)	732 (32.7)	
3	847 (17.9)	681 (14.8)	436 (14.4)	268 (15.5)	154 (14.9)	99 (15.5)	387 (17.3)	<0.001
4	265 (5.6)	207 (4.5)	131 (4.3)	68 (3.9)	51 (4.9)	31 (4.8)	134 (6.0)	
5	65 (1.4)	42 (0.9)	30 (1.0)	13 (0.8)	16 (1.5)	8 (1.3)	41 (1.8)	
Cardiovascular								
No cardiovascular dysfunction	376 (7.9)	379 (8.3)	265 (8.8)	168 (9.7)	115 (11.1)	57 (8.9)	349 (15.6)	
Cardiovascular dysfunction/no hypertension	803 (17.0)	1,004 (21.8)	659 (21.8)	402 (23.2)	174 (16.8)	116 (18.1)	403 (18.0)	
Total shock	3,549 (75.1)	3,212 (69.9)	2,096 (69.4)	1,164 (67.2)	748 (72.1)	467 (73.0)	1,484 (66.4)	<0.001
Lactate > 4	260 (5.5)	332 (7.2)	249 (8.3)	117 (6.8)	64 (6.2)	26 (4.1)	114 (5.1)	
Vasopressors only	2,273 (48.1)	1,938 (42.2)	1,309 (43.3)	769 (44.4)	522 (50.3)	346 (54.1)	1,126 (50.4)	
Lactate > 4 and vasopressors	1,016 (21.5)	942 (20.5)	538 (17.8)	278 (16.0)	162 (15.6)	95 (14.8)	244 (10.9)	

IQR = interquartile range, LOS = length of stay, ED = emergency department.
[a]*p* value based on Pearson chi-square test for categorical variables and Wilcox rank-sum test for continuous variables.

結果

TABLE 2. Adjusted Hospital Mortality Odds Ratio and Probability of Mortality for Time to Antibiotics Based on a Generalized Estimating Equation Population Averaged Logistic Regression Model

Time to Antibiotics (Hr)	OR[a]	95% CI	*p*	Probability of Mortality (%)[b]	95% CI
0–1[c]	1.00			24.6	23.2–26.0
1–2	1.07	0.97–1.18	0.165	25.9	24.5–27.2
2–3	1.14	1.02–1.26	0.021	27.0	25.3–28.7
3–4	1.19	1.04–1.35	0.009	27.9	25.6–30.1
4–5	1.24	1.06–1.45	0.006	28.8	25.9–31.7
5–6	1.47	1.22–1.76	<0.001	32.3	28.5–36.2
>6	1.52	1.36–1.70	<0.001	33.1	30.9–35.3

OR = odds ratio.
[a]Hospital mortality odds ratio referent group is 0–1 hr for the time to antibiotics and is adjusted by the sepsis severity score (SSS), ICU admission source (ED, ward, vs ICU), and geographic region (Europe, United States, and South America).
[b]Probability of hospital mortality is estimated using the generalized estimating equation population averaged logistic regression model and is based on the subject having the following characteristics: from the United States, admission source is the ED, and the SSS is 52 (median of all observations).
[c]Antibiotics administered in the first hour are the referent group and thus the odds ratio by definition is 1.00 while the 95% CI and the *p* value are not generated by the regression model.

討論

- 延遲給予Abx-> increased in-hospital mortality
- 每延遲一小時給予Abx與死亡的風險呈線性增加(from 1st-6th hour after patient identification)
- Sepsis 病人的Survival benefit和Abx給予相關
- Limitations：
  1. Retrospective study-potential for residual confounding
  2. 只評估給予時間，沒有評估Abx的approapriateness，inappropriate or inadequate Abx會影響結果
  3. 沒有評估延遲給予Abx的原因

結論

- 此篇結果強調在院早期identification and treatment of septic patient的重要
- Sepsis->time-dependent condition, 需視為緊急狀況並即時反應！

12 questions to help you make sense of cohort study

How to use this appraisal tool

Three broad issues need to be considered when appraising a cohort study:

- **Are the results of the study valid?** **(Section A)**
- **What are the results?** **(Section B)**
- **Will the results help locally?** **(Section C)**

The 12 questions on the following pages are designed to help you think about these issues systematically. The first two questions are screening questions and can be answered quickly. If the answer to both is "yes", it is worth proceeding with the remaining questions.

There is some degree of overlap between the questions, you are asked to record a "yes", "no" or "can't tell" to most of the questions. A number of prompts are given after each question. These are designed to remind you why the question is important. Record your reasons for your answers in the spaces provided.

(A) Are the results of the study valid?

Screening Questions

1. Did the study address a clearly focused issue? ☑ Yes ☐ Can't tell ☐ No

HINT: A question can be 'focused' in terms of
- The population studied
- The risk factors studied
- The outcomes considered
- Is it clear whether the study tried to detect a beneficial or harmful effect?

抗生素給予時間以及在院死亡率的關係

2. Was the cohort recruited in an acceptable way? ☑ Yes ☐ Can't tell ☐ No

HINT: Look for selection bias which might compromise the generalisibility of the findings:
- Was the cohort representative of a defined population?
- Was there something special about the cohort?
- Was everybody included who should have been included?

1. 200501~201002歐洲、美國、南美165個ICU共28150位sepsis 病人
2. Can't tell
3. Eligible subjects: A.疑似感染入住ICU B.≥2 SIRS criteria C.≥1 organ dysfunction

Is it worth continuing?

3. Was the exposure accurately measured to minimise bias? ☐ Yes ☑ Can't tell ☐ No

HINT: Look for measurement or classification bias:
- Did they use subjective or objective measurements?
- Do the measurements truly reflect what you want them to (have they been validated)?
- Were all the subjects classified into exposure groups using the same procedure

1. Yes, Abx administration
2. can't tell
3. no，Abx種類，劑量不知

4. Was the outcome accurately measured to minimise bias? ☑ Yes ☐ Can't tell ☐ No

HINT: Look for measurement or classification bias:
- Did they use subjective or objective measurements?
- Do the measures truly reflect what you want them to (have they been validated)?
- Has a reliable system been established for detecting all the cases (for measuring disease occurrence)?
- Were the measurement methods similar in the different groups?
- Were the subjects and/or the outcome assessor blinded to exposure (does this matter)?

1. Yes, Mortality
2. Can't tell
3. Yes
4. Yes
5. No, but it doesn't matter

5. (a) Have the authors identified all important confounding factors? ☐ Yes ☐ Can't tell ☑ No

List the ones you think might be important, that the author missed.

Retrospective study-Underlying disease

(b) Have they taken account of the confounding factors in the design and/or analysis? ☐ Yes ☑ Can't tell ☐ No

List:

HINT: Look for restriction in design, and techniques e.g. modelling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors

6. (a) Was the follow up of subjects complete enough? ☑ Yes ☐ Can't tell ☐ No

(b) Was the follow up of subjects long enough? ☐ Yes ☑ Can't tell ☐ No

HINT: Consider
- The good or bad effects should have had long enough to reveal themselves
- The persons that are lost to follow-up may have different outcomes than those available for assessment
- In an open or dynamic cohort, was there anything special about the outcome of the people leaving, or the exposure of the people entering the cohort?

(B) What are the results?

7. What are the results of this study?

HINT: Consider

- What are the bottom line results?
- Have they reported the rate or the proportion between the exposed/unexposed, the ratio/the rate difference?
- How strong is the association between exposure and outcome (RR,)?
- What is the absolute risk reduction (ARR)?

1.延遲給予抗生素會增加in-hospital morality
每延遲一小時給予Abx與死亡的風險呈線性增加

2. Yes

3.

Tx	mortality Rate	RR	ARR
0~1	32		
1~2	28.1	0.878125	-3.9
2~3	28.6	0.89375	-3.4
3~4	29.8	0.93125	-2.2
4~5	32.5	1.015625	0.5
5~6	36.6	1.14375	4.6
>6	39.6	1.2375	7.6

8. How precise are the results?

HINT: Look for the range of the confidence intervals, if given.

9. Do you believe the results?

☐ Yes ☑ Can't tell ☐ No

HINT: Consider

- Big effect is hard to ignore!
- Can it be due to bias, chance or confounding?
- Are the design and methods of this study sufficiently flawed to make the results unreliable?
- Bradford Hills criteria (e.g. time sequence, dose-response gradient, biological plausibility, consistency)

(C) Will the results help locally?

10. Can the results be applied to the local population?

☑ Yes ☐ Can't tell ☐ No

HINT: Consider whether

- A cohort study was the appropriate method to answer this question
- The subjects covered in this study could be sufficiently different from your population to cause concern
- Your local setting is likely to differ much from that of the study
- You can quantify the local benefits and harms

11. Do the results of this study fit with other available evidence?

☑ Yes ☐ Can't tell ☐ No

12. What are the implications of this study for practice?

HINT: Consider

- One observational study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making
- For certain questions observational studies provide the only evidence
- Recommendations from observational studies are always stronger when supported by other evidence