Definizione di Antimicrobial Stewardship

Pierluigi Viale  Clinica di Malattie Infettive  Policlinico S. Orsola – Malpighi
KPC-producing *K. pneumoniae* of Clonal Complex 11

The first reported cases of KPC-Kp
ST258

early 2011
ST258, ST512

late 2012
ST512
ST258
THE EQUATION OF THE INFECTIOUS RISK

\[ \text{BACTERIAL LOAD} \times \text{VIRULENCE} + \text{DRUG RESISTANCE} = \text{INFECTIOUS RISK} \]

\[ \text{HOST IMMUNITY} \]

\[ \text{DEATHS} \]
\[ \text{COSTS} \]
\[ \text{SUPERBUGS} \]
Infection control measures for Gram neg colonized patients

*Courtesy E. Tacconelli & N. Petrosillo - ESCMID/SHEA guidelines*

Multifaceted approaches

- Hand hygiene
- Physical separation of patients
- Education
- Detection/surveillance
- Environmental cleaning
- Cohort patients’ and staff
- Antimicrobial stewardship
INFECTIOUS RISK  CONTROL – A THREE PHASES ACTION

PREVENTION OF INFECTIONS

MANAGEMENT OF INFECTIONS

PREVENTION OF RESISTANCES
La Gestione del rischio infettivo in Emilia-Romagna
il nuovo assetto organizzativo

DELIBERAZIONE DELLA GIUNTA REGIONALE 25 MARZO 2013, N. 318
Linee di indirizzo alle Aziende per la gestione del rischio infettivo: infezioni correlate all’assistenza e uso responsabile di antibiotici

Comitato Infezioni Ospedaliere

Nucleo Strategico

Nucleo Operativo per il controllo delle ICA

Nucleo Operativo per l’uso responsabile di antibiotici
Antimicrobial Stewardship: DEFINITIONS

An activity that optimizes antimicrobial management and includes selection, dosing, route and duration of antimicrobial therapy.

A marriage of infection control (Epidemiologist), and antimicrobial management (Infectious Diseases specialist) finalized to share the principles of the optimized treatment between the bench to bed side point of view and the hospital-wide vision.
THE HISTORICAL PERIODS of ANTIMICROBIAL STEWARDSHIP

The MIDDLE AGE
COMPELLSORY PROGRAMS

The REINASSANCE
SEMI-COMPELLSORY PROGRAMS (post prescription reviews)

The NEXT FUTURE
SHARED NEW PARADIGMS for MANAGEMENT
PROBLEM-DRIVEN PROTOCOLS and PROGRAMS
There are 2 core strategies, both proactive, that provide the foundation for an antimicrobial stewardship program. These strategies are not mutually exclusive.

A. **Prospective audit with intervention and feedback.** Prospective audit of antimicrobial use with direct interaction and feedback to the prescriber, performed by either an infectious diseases physician or a clinical pharmacist with infectious diseases training, can result in reduced inappropriate use of antimicrobials (A-I).

B. **Formulary restriction and preauthorization.** Formulary restriction and preauthorization requirements can lead to immediate and significant reductions in antimicrobial use and cost (A-II) and may be beneficial as part of a multifaceted response to a nosocomial outbreak of infection (B-II). The use of preauthorization requirements as a means of controlling antimicrobial resistance is less clear, because a long-term beneficial impact on resistance has not been established, and in some circumstances, use may simply shift to an alternative agent with resulting increased resistance (B-II).
A marriage of infection control (Epidemiologist) and antimicrobial management (Infectious Diseases specialist) finalized to share the principles of the optimized treatment between the bench to bed side point of view and the hospital-wide vision.

THE GOAL IS THE APPROPRIATENESS of the prescriptions not only the costs saving.

The REINASSANCE
The MULTIFACETED concept of APPROPRIATENESS

- RIGHT INDICATION (epidemiologically, microbiologically and PK/PD driven)
- RIGHT DAILY DOSE
- RIGHT MODALITY OF ADMINISTRATION
- RIGHT PRESCRIBER
- SHARED CRITERIA FOR DE-ESCALATION / INTERRUPTION
- IMPROVEMENT OF MICROBIOLOGICAL WORK UP

Transforming the hospital formulary in a true clinical instrument!
From the formulary to a shared management guidelines
How to lay out a stewardship program?

- Hospital wide
- Drug directed
- Setting directed
- Disease directed
Antimicrobial stewardship programs—The devil is in the details

_Cunha CB et al, Virulence 2013; 4:2, 147-149_

Antimicrobial stewardship is a developing field, and every program must be tailored to its respective institution and each article has a distinctive focus and perspective.
Global impact of an educational antimicrobial stewardship programme on prescribing practice in a tertiary hospital centre.  

*Cisneros JM et al, Clin Microbiol Infect 2013 Feb 27*

Methodology of active intervention

The main activity of the program consists of a training program directed towards all antibiotic prescribers in the centre based on counselling interviews, carried out by a group of clinical experts who were selected by the PRIOAM operations team, and included 7 ID specialists, 6 critical-care specialists and 4 paediatricians.

PRIOAM advisors were selected from local leaders in the management of patients with infectious diseases in each area. Each advisor conducted counselling interviews in his/her area of responsibility.

The number of counselling interviews scheduled for each clinical department was proportional to its antimicrobial consumption: < 50 DDDs -> one per week, 50 to 100 DDD -> two per week > 100 DDD -> 3 per week.
Global impact of an educational antimicrobial stewardship programme on prescribing practice in a tertiary hospital centre.  

Cisneros JM et al, Clin Microbiol Infect 2013 Feb 27

The advisor reviewed the antimicrobial treatment with the prescriber, examined the patient’s clinical data and discussed the main aspects of the prescribed treatment and diagnosis of the infectious syndrome using a specific questionnaire. Prescriptions were considered as ‘appropriate’ when all items of the questionnaire had been accomplished correctly. If one or more of them were incorrectly performed, the prescription was evaluated as ‘inappropriate’.

To guarantee homogeneity, the PRIOAM team also coordinated monthly training meetings with these advisors, which also served to monitor the progress of the programme.
A total of 1206 CIs were performed during the first year of the programme. Interviews lasted approximately, 10 min, the equivalent of 201 working hours for the 1206 CIs.

The most frequently performed assessments were for empirical prescriptions (52.2%, n = 630), followed by targeted treatments (25.4%, n = 306) and surgical prophylaxis (22.4%, n = 270).
Global impact of an educational antimicrobial stewardship programme on prescribing practice in a tertiary hospital centre.  

*Cisneros JM et al, Clin Microbiol Infect 2013 Feb 27*

**rates of inappropriate antimicrobial use**
Global impact of an educational antimicrobial stewardship programme on prescribing practice in a tertiary hospital centre.  

Cisneros JM et al, Clin Microbiol Infect 2013 Feb 27

Evolution of the consumption by class of antibiotics
A marriage of infection control (Epidemiologist) and antimicrobial management (Infectious Diseases specialist) finalized to share the principles of the optimized treatment between the bench to bed side point of view and the hospital-wide vision.

RUN FOR THE APPROPRIATENESS
The S. Orsola-Malpighi Stewardship program

Checking the quality instead of the quantity
The S. Orsola-Malpighi Teaching Hospital
2012

Beds number: 1,425 DO + 155 DH/DS

N. of discharged pts = 71,303
- Day Hospital: 20,5%
- Medical DRG: 62,2%
- Surgical DRG: 37,8%
- % complicated DRG: 42,7%

Surgical activity
- N. of interventions: 32,771
- General Surgery: 21.7%
- Cardio Surgery: 5.2%
- Specialized Surgery: 73.1%

<table>
<thead>
<tr>
<th>Transplant Activity</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIVER</td>
<td>71</td>
<td>78</td>
<td>65</td>
<td>77</td>
</tr>
<tr>
<td>KIDNEY</td>
<td>63</td>
<td>66</td>
<td>60</td>
<td>84</td>
</tr>
<tr>
<td>HEART</td>
<td>27</td>
<td>23</td>
<td>28</td>
<td>19</td>
</tr>
<tr>
<td>LUNG</td>
<td>3</td>
<td>1</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>BOWEL</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>MULTI</td>
<td>2</td>
<td>6</td>
<td>7</td>
<td>3</td>
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<tr>
<td>OVERALL</td>
<td>167</td>
<td>177</td>
<td>168</td>
<td>186</td>
</tr>
<tr>
<td>HSTC</td>
<td>167</td>
<td>167</td>
<td>177</td>
<td>169</td>
</tr>
<tr>
<td>OVERALL</td>
<td>334</td>
<td>344</td>
<td>335</td>
<td>355</td>
</tr>
</tbody>
</table>
S. Orsola-Maplighi Teaching Hospital - the ID consultant team

Four Seniors + 3 Fellows
Daily Consultation in TX Center / Cardio Surgery / ICUs / Hospitalwide on demand

Consultations per year

Stewardship program
"Run for the appropriateness"
The change

- Formulary restrictions
- Preauthorization requirements
- Retrospective Audits
- Diffusion of international and local guidelines

Run for the appropriateness

- Shared definitions of appropriateness
- No pre-defined restrictions but ...
- "Real time" evaluation of any prescription by the ID consultant team
Run for the appropriateness

Prescription

on duty pharmacist

ID team

registration

Distribution
Coverage for 48 h

NO
Shift Stop

YES
5-7 days of therapy
“Run for the appropriateness” project

Appropriateness trend – first prescriptions by others than ID

<table>
<thead>
<tr>
<th></th>
<th>baseline</th>
<th>100 d after</th>
<th>150 d after</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>38.9</td>
<td>41.6</td>
<td>66.2</td>
</tr>
</tbody>
</table>
Consumi (DDD/100ggdd) e costi: 10m 2013 vs 2012

<table>
<thead>
<tr>
<th>Gruppo terapeutico</th>
<th>Farmaco</th>
<th>DDD</th>
<th>VAR% DDD</th>
<th>VAR COSTI</th>
<th>VAR% costi</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DAPTOMICINA</td>
<td>0,88</td>
<td>50,2%</td>
<td>60.990</td>
<td>47,9%</td>
</tr>
<tr>
<td></td>
<td>LINEZOLID</td>
<td>0,65</td>
<td>32,7%</td>
<td>59.792</td>
<td>29,8%</td>
</tr>
<tr>
<td></td>
<td>MEROPENEM</td>
<td>1,80</td>
<td>-38,7%</td>
<td>-61.836</td>
<td>-40,9%</td>
</tr>
<tr>
<td></td>
<td>TIGECICLINA</td>
<td>0,42</td>
<td>-44,3%</td>
<td>-124.155</td>
<td>-45,5%</td>
</tr>
<tr>
<td></td>
<td><strong>ANTIBATTERICI PER USO SISTEMICO</strong></td>
<td>3,74</td>
<td><strong>-21,4%</strong></td>
<td><strong>-65.209</strong></td>
<td><strong>-8,7%</strong></td>
</tr>
<tr>
<td></td>
<td>AMFOTERICINA</td>
<td>1,20</td>
<td>-8,1%</td>
<td>-45.660</td>
<td>-10,1%</td>
</tr>
<tr>
<td></td>
<td>CASPOFUNGIN</td>
<td>0,25</td>
<td>8,7%</td>
<td>21.180</td>
<td>6,2%</td>
</tr>
<tr>
<td></td>
<td>VORICONAZOLO</td>
<td>0,24</td>
<td>5,0%</td>
<td>2.036</td>
<td>1,9%</td>
</tr>
<tr>
<td></td>
<td><strong>ANTIMICOTICI PER USO SISTEMICO</strong></td>
<td>1,68</td>
<td><strong>-4,3%</strong></td>
<td><strong>-22.444</strong></td>
<td><strong>-2,5%</strong></td>
</tr>
<tr>
<td></td>
<td>Totale farmaci sorvegliati</td>
<td>5,42</td>
<td><strong>-16,7%</strong></td>
<td><strong>-87.653</strong></td>
<td><strong>-5,3%</strong></td>
</tr>
</tbody>
</table>

ALMA MATER STUDIORUM - UNIVERSITÀ DI BOLOGNA
"Run for the appropriateness" project

Appropriateness trend – first prescriptions by others than ID

<table>
<thead>
<tr>
<th>%</th>
<th>baseline</th>
<th>100 d after</th>
<th>150 d after</th>
</tr>
</thead>
<tbody>
<tr>
<td>38.9</td>
<td></td>
<td>41.6</td>
<td>66.2</td>
</tr>
</tbody>
</table>

Hematology Unit fired
NEW PARADIGMS OF MANAGEMENT FOR SPECIFIC PROBLEMS

- SESPIS TEAM
  observational phase ongoing / interventional phase planned from March 2014
- PNEUMONIA TASK FORCE
  ongoing
  - BUNDLE FOR THE MANAGEMENT OF CANDIDEMIA
    observational phase ongoing
  - BD GLUCAN DRIVEN DE-ESCALATION OF EMPIRICAL ANTIFUNGAL TX
    under submission to Ethical Committee
  - AMBIHOW PROTOCOL
    enrollment ongoing
  - SCORE /CTPA DRIVEN ANTIMOLDS Tx FOR POSSIBLE INFECTIONS
    multidisciplinary discussion ongoing
  - CORRECT PCT USE
    ongoing (40% reduction of requests)
S. Orsola-Malpighi Teaching Hospital

SEPSIS TEAM
Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department

Table 6. In-hospital mortality: Time from triage to appropriate antibiotics

<table>
<thead>
<tr>
<th>Cutoffs</th>
<th>Number</th>
<th>Mortality, %</th>
<th>Difference, %</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>p</th>
<th>Probability of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1 hr</td>
<td>41</td>
<td>19.5</td>
<td>13.7</td>
<td>0.30</td>
<td>0.11–0.83</td>
<td>.02</td>
<td>.13 vs .29</td>
</tr>
<tr>
<td>&gt;1 hr</td>
<td>220</td>
<td>33.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2 hrs</td>
<td>124</td>
<td>28.2</td>
<td>5.4</td>
<td>0.54</td>
<td>0.29–1.03</td>
<td>.06</td>
<td>.22 vs .31</td>
</tr>
<tr>
<td>&gt;2 hrs</td>
<td>137</td>
<td>33.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤3 hrs</td>
<td>172</td>
<td>27.9</td>
<td>9.2</td>
<td>0.53</td>
<td>0.27–1.01</td>
<td>.05</td>
<td>.23 vs .34</td>
</tr>
<tr>
<td>&gt;3 hrs</td>
<td>89</td>
<td>37.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤4 hrs</td>
<td>200</td>
<td>28.5</td>
<td>10.8</td>
<td>0.62</td>
<td>0.31–1.24</td>
<td>.18</td>
<td>.25 vs .34</td>
</tr>
<tr>
<td>&gt;4 hrs</td>
<td>61</td>
<td>39.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5 hrs</td>
<td>218</td>
<td>30.7</td>
<td>1.8</td>
<td>0.82</td>
<td>0.37–1.79</td>
<td>.62</td>
<td>.27 vs .29</td>
</tr>
<tr>
<td>&gt;5 hrs</td>
<td>43</td>
<td>32.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The epidemiology of adults with severe sepsis and septic shock in Scottish emergency departments.


Table 1  Presumed source of infection

<table>
<thead>
<tr>
<th>Source of infection</th>
<th>(n=)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory tract</td>
<td>411</td>
<td>64.5</td>
</tr>
<tr>
<td>Acute abdominal infection</td>
<td>55</td>
<td>8.6</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>51</td>
<td>8.0</td>
</tr>
<tr>
<td>Skin/soft tissue</td>
<td>21</td>
<td>3.3</td>
</tr>
<tr>
<td>Other</td>
<td>12</td>
<td>1.9</td>
</tr>
<tr>
<td>Unknown source</td>
<td>87</td>
<td>13.7</td>
</tr>
<tr>
<td>Total</td>
<td>637</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Full dataset collected for 3,890 (74%) cases

Full dataset not collected for 1,395 (26%) cases

626 patients with 637 presentations developed signs of ‘severe sepsis’ prior to leaving ED
The epidemiology of adults with severe sepsis and septic shock in Scottish emergency departments.


Sepsis resuscitation bundle compliance

MORTALITY 28.3%

- Lactate measurement: 55%
- Blood culture taken: 29%
- ATB within 3 h: 66%
- Fluid resuscitation when SBP < 90 mmHg: 48%
SEPSIS TEAM for patients admitted to ED with a diagnosis > severe sepsis

**STUDY ARM**

ED EVALUATION

Severe sepsis/septic shock diagnosis

RESUSCITATORY BUNDLE

+ ID EVALUATION (within 20')

DIAGNOSTIC and
THERAPEUTIC MANAGEMENT

**CONTROL ARM**

ED EVALUATION

Severe sepsis/septic shock diagnosis

RESUSCITATORY BUNDLE

+ DIAGNOSTIC and
THERAPEUTIC MANAGEMENT
SEPSIS TEAM for patients admitted to ED with a diagnosis of severe sepsis

observational phase: The first 100 cases

Sepsis resuscitation bundle compliance

MORTALITY 28.3%
MORTALITY 31.3%
S. Orsola-Malpighi Teaching Hospital

PENUMONIA TASK FORCE

An Infectivologist / Pneumologist connection finalized to ...
  Standardize antimicrobial approach
  Guarantee an Early Respiratory Support
  Avoid unnecessary days of therapy
  Reduce Length of Hospital Stay
What Are the Potential Cost Savings Associated with Decreased Length of Stay with CAP?

A cost savings for each day of reduction in length of stay between $2,273 and $2,373 in 2009 USD

Economic benefit of a 1-day reduction in hospital stay for CAP


Prospective, randomized trial. Enrolled patients (401 adults who required hospitalization for CAP) were randomly assigned to follow a 3-step critical pathway including early mobilization and use of objective criteria for switching to oral antibiotic therapy and for deciding on hospital discharge or usual care. Primary End Point: LOS.

The 3-steps of the critical pathway were (1) early mobilization of patients; (2) use of objective criteria for switching to oral antibiotic therapy; and (3) use of predefined criteria for deciding on hospital discharge.

**Early mobilization** was defined as movement out of bed with a change from the horizontal to the upright position for at least 20 minutes during the first 24 hours of hospitalization, with progressive movement each subsequent day during hospitalization, as described elsewhere. **Criteria for switching** were ability to maintain oral intake; stable vital signs (considered as temperature 37.8°C, respiratory rate <24 breaths/min, systolic blood pressure > 90 mm Hg without vasopressor support for at least 8 hours); and absence of exacerbated major comorbidities (ie, heart failure, COPD) and/or septic metastases. **Predefined criteria for hospital discharge** were meeting criteria for switching to oral antibiotic, baseline mental status, and adequate oxygenation on room air (PaO2 60 mm Hg or pulse oximetry >90%).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>3-Step Critical Pathway Group (n = 200)</th>
<th>Usual Care Group (n = 201)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>132 (66.0)</td>
<td>129 (64.2)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>71.5 (14.0)</td>
<td>69.7 (15.1)</td>
</tr>
<tr>
<td>Age group, y, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-49</td>
<td>19 (9.5)</td>
<td>20 (10.0)</td>
</tr>
<tr>
<td>50-69</td>
<td>43 (21.5)</td>
<td>63 (31.3)</td>
</tr>
<tr>
<td>70-97</td>
<td>138 (69.0)</td>
<td>118 (58.7)</td>
</tr>
<tr>
<td>Alcohol consumption &gt; 80 g/d, No. (%) a</td>
<td>28 (14.8)</td>
<td>40 (20.6)</td>
</tr>
<tr>
<td>Tobacco smoking, No. (%) b</td>
<td>38 (20.0)</td>
<td>48 (24.6)</td>
</tr>
<tr>
<td>Influenza vaccine c</td>
<td>113 (62.4)</td>
<td>102 (55.4)</td>
</tr>
<tr>
<td>Pneumococcal vaccine, 5 y d</td>
<td>36 (20.6)</td>
<td>48 (27.1)</td>
</tr>
<tr>
<td>Comorbid conditions, No. (%)</td>
<td>166 (83.0)</td>
<td>169 (84.1)</td>
</tr>
<tr>
<td>Oxygen saturation with room air, mean (SD), % e</td>
<td>90.6 (6.1)</td>
<td>90.8 (5.4)</td>
</tr>
<tr>
<td>Multilobar pneumonia, No. (%)</td>
<td>50 (25.0)</td>
<td>46 (22.9)</td>
</tr>
<tr>
<td>Severity risk class, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I, II, III</td>
<td>77 (38.5)</td>
<td>76 (37.8)</td>
</tr>
<tr>
<td>IV</td>
<td>88 (44.0)</td>
<td>92 (45.8)</td>
</tr>
<tr>
<td>V</td>
<td>35 (17.5)</td>
<td>33 (16.4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Event</th>
<th>3-Step Critical Pathway Group (n = 200)</th>
<th>Usual Care Group (n = 201)</th>
<th>Difference (95% CI)(^a)</th>
<th>P Value(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary end point: LOS, median (IQR), d</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>3.9 (2.79 to 5.75)</td>
<td>6.0 (4.75 to 8.83)</td>
<td>-2.1 (-2.7 to -1.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>IDIBELL—Hospital Universitari de Bellvitge</td>
<td>4.0 (2.83 to 5.75)</td>
<td>6.0 (4.62 to 8.88)</td>
<td>-2.0 (-2.7 to -1.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SCIAS—Hospital de Barcelona</td>
<td>3.7 (2.71 to 5.67)</td>
<td>6.3 (4.87 to 8.71)</td>
<td>-2.6 (-3.2 to -1.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Secondary end points</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of intravenous antibiotic therapy, median (IQR), d</td>
<td>2.0 (2.0 to 3.0)</td>
<td>4.0 (2.0 to 6.0)</td>
<td>-2.0 (-2.0 to -1.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Adverse drug reactions, No. (%)</td>
<td>9 (4.5)</td>
<td>32 (15.9)</td>
<td>-11.4 (-17.2 to -5.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Phlebitis</td>
<td>8 (4.0)</td>
<td>21 (10.4)</td>
<td>-6.4 (-11.5 to -1.4)</td>
<td>.02</td>
</tr>
<tr>
<td>Skin eruption</td>
<td>0</td>
<td>2 (1.0)</td>
<td>-1.0 (-2.4 to 0.4)</td>
<td>.50</td>
</tr>
<tr>
<td>Vomiting/diarrhea</td>
<td>0</td>
<td>4 (2.0)</td>
<td>-2.0 (-3.9 to -0.1)</td>
<td>.12</td>
</tr>
<tr>
<td>Allergy</td>
<td>1 (0.5)</td>
<td>1 (0.5)</td>
<td>0 (-1.4 to 1.4)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Transaminitis</td>
<td>0</td>
<td>3 (1.5)</td>
<td>-1.5 (-3.2 to 0.2)</td>
<td>.25</td>
</tr>
<tr>
<td><strong>Medical complications, No. (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Empyema</td>
<td>3 (1.5)</td>
<td>6 (3.0)</td>
<td>-1.5 (-4.4 to 1.4)</td>
<td>.50</td>
</tr>
<tr>
<td>Cardiac complication(^c)</td>
<td>8 (4.0)</td>
<td>16 (8.0)</td>
<td>-4.0 (-8.6 to 0.7)</td>
<td>.14</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>15 (7.5)</td>
<td>8 (4.0)</td>
<td>3.5 (-1.0 to 8.1)</td>
<td>.14</td>
</tr>
<tr>
<td>Acute confusion</td>
<td>7 (3.5)</td>
<td>8 (4.0)</td>
<td>-0.5 (-4.2 to 3.2)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Renal failure</td>
<td>7 (3.5)</td>
<td>8 (4.0)</td>
<td>-0.5 (-4.2 to 3.2)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Nosocomial infection</td>
<td>2 (1.0)</td>
<td>3 (1.5)</td>
<td>-0.5 (-2.7 to 1.7)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Severe hyperglycemia</td>
<td>3 (1.5)</td>
<td>9 (4.5)</td>
<td>-3.0 (-6.3 to 0.3)</td>
<td>.14</td>
</tr>
<tr>
<td>Shock</td>
<td>2 (1.0)</td>
<td>3 (1.5)</td>
<td>-0.5 (-2.7 to 1.7)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td><strong>Subsequent hospital admission (&lt;30 d), No. (%)(^d)</strong></td>
<td>18 (9.1)</td>
<td>15 (7.5)</td>
<td>1.6 (-3.8 to 7.1)</td>
<td>.59</td>
</tr>
<tr>
<td><strong>Overall case-fatality rate (&lt;30 d), No. (%)</strong></td>
<td>4 (2.0)</td>
<td>2 (1.0)</td>
<td>1.0 (-1.4 to 3.4)</td>
<td>.45</td>
</tr>
</tbody>
</table>