CHAPTER 7

General discussion
Chapter 2 was set the scene for this thesis, but as well forms the linking pin between much of the work done here. Notably, Chapter 2 will now be discussed after most of the other chapters are considered. A review of the economic evaluations of studies concerning preoperative prophylactic antibiotics, administered either locally or systemically (Chapter 3), shows that they are considered to be (cost-)effective interventions for surgical site infection (SSI) prevention.\(^1\) In the review, the SSI rates ranged from 0 to 71%, with costs amounting to US$ 480–22,130 depending on the type of surgery. Twenty-four types of bacteria were identified as causative agents of SSIs. Gram-negative bacteria were the dominant causes of SSIs, especially in general surgery, neurosurgery, cardiothoracic surgery, and obstetric cesarean sections. The independent potentially contributing variables identified for deep SSI (dSSI) risk in major surgery, notably older patient age and neoplasm comorbidity, need to be monitored intensively, and prophylactic antibiotics should, in fact, be considered prior to initial incision.

The impacts of dSSIs were also investigated in Chapter 4 in an academic hospital in Groningen, in the Netherlands. These impacts were reflected in readmission rates, extended LoS and additional costs. Patients with SSIs in our study had a high readmission rate compared with non-SSI patients. Also, dSSIs were found to contribute to prolonged LoS and high costs.\(^2\) The explanation is that dSSI cases were readmitted for revision surgery because of wound infections at the surgery sites and due to other post-surgical complications such as bleeding, dehydration, renal failure, embolism, cardiovascular events, and ileus.\(^3,4\) Notably, dSSI patients were readmitted at least once for revision surgery or wound debridement.\(^5,6\) As a strategy to reduce readmission rates, post-surgical readmission could be replaced with home visits, or outpatient care within a 30-day medical follow-up after surgical discharge, possibly alleviating the costs.\(^7\) The timing of unanticipated readmissions after surgical discharge, which is mainly contingent on the emergence of crises relating to serious complications or existing comorbidities, requires further investigation.\(^4\)

In addition, we found that dSSI patients aged 65 years or above were at a significantly higher risk of readmission. The LoS for hospitalization and post-surgery readmission of elderly patients with SSIs was three times greater than that for non-SSI patients. The mean cost incurred by older patients was found to be double the cost incurred by non-SSI patients.\(^8\)

The additional cost incurred for SSI cases is plausibly reflected in prolonged hospitalization and readmissions.\(^9–12\) The cost, LoS and readmission rates of SSI cases were higher than those of non-SSI cases in all types of surgery. Clean surgeries associated with the head and neck, thorax, extremities, and spine were performed most frequently at this hospital, followed by contaminated and dirty surgeries in which the abdominal region was commonly the targeted site. We discovered that having SSI and being aged \(\geq 65\) were the two independent factors predicting extended LoS. Elderly, neoplasm and cardiovascular diseases were also predictive at a higher risk of SSI, whereas patients taking prophylactic antibiotics were at a lower risk of SSI. The cost of a day’s hospital stay and rehospitalization, especially in the short-term, is virtually fixed, however.\(^13\) Moreover, the costs due to antimicrobial resistance, included as an indication of the secondary cost of advanced medication to overcome resistance rates, are eventually expected to become variable.
As we revealed in Chapter 5, hospitalized community-acquired pneumonia (CAP) in Indonesia is caused not only by Gram-positive bacteria (GBP) but also frequently by Gram-negative bacteria (GNB). The pathogens generally remained sensitive to third-generation cephalosporins, which are also recommended in the Indonesian national guideline. We identified *A. baumannii* as an uncommon causative agent for CAP with high antimicrobial resistance. Our results are in line with other regional studies, in which GNB has been determined to be the dominant class of pathogens causing CAP in Indonesia and other countries within Asia. Multidrug-resistant (MDR) *Acinetobacter* species are problematic, especially in immunocompromised hosts. In our study, around 60% of *Acinetobacter* species were highly resistant to ciprofloxacin, similar to the results of the Walter Reed Army Medical Center (WRAMC) study. In addition, we found that *E. coli*, *K. pneumoniae*, and *Enterobacter* spp had poor sensitivity to penicillins. The CAP etiology reported in Semarang, the sixth biggest city in Indonesia, showed that *K. pneumonia* was most commonly identified among the bacteria causing hospitalized CAP.

In view of the elevated mortality rates, the timing of culture collection, and unspecified results from clinical and radiological methods for determining bacterial infections, the established international guidelines of the British Thoracic Society (BTS), American Thoracic Society (ATS), and National Institute for Health and Care Excellence (NICE) concur that empirical treatment of CAP with antibiotics is urgently needed. In our study, microbiological culturing of sputum and blood provided clinically relevant information on the identity of pathogens and their susceptibility to antimicrobials. We found that *S. pneumoniae* was the most common pathogen among hospitalized CAP cases, comparable to findings in thirteen other Asian countries. Mixed presence of pathogens reflects an important consideration, since they may lead to delayed response or even a lack of clinical improvement. In line with the systematic review of studies in Asia, our findings revealed the mixed occurrence of infections often by *S. pneumoniae* and *M. tuberculosis* or *H. influenzae*. The characteristics of the pathogens causing hospitalized CAP should, therefore, be considered when the healthcare stakeholders provide Indonesian national guidelines on the use of empirical antibiotics.

Empirical treatment confirmed by microbiological cultures and antimicrobial susceptibility testing referred to as culture-based treatment (CBT), has advantages in terms of both cost and life expectancy (LE) for hospitalized CAP patients. A pharmacoeconomics evaluation showed that CBT was dominant (Chapter 6), not exceeding the GDP threshold in terms of cost-effectiveness (three times GDP) and even producing cost savings. This method can therefore reasonably be implemented for adults in general hospitals in Indonesia. Without culture analysis, fully empirical treatments (ET) are more expensive and result in lost life-years, particularly in geriatric patients and high-severity classes of patients.

There is convincing evidence of a positive correlation between pneumonia and SSI and sepsis. In this thesis, the economic burden for focal infections associated with sepsis for surviving and deceased patients in Indonesia was addressed in Chapter 2. Sepsis was mostly induced by lower-respiratory tract infections (LRTIs), including CAP. In addition to the findings of sepsis burden in Indonesia which conveyed in Chapter 2, multivariate and survival analyses of the mortality outcome were performed.
Recommendations

Desired impacts of the proper use of prophylactic antibiotics in SSI prevention are both clinical and economic: shorter lengths of stay, lower resistance and related better cure rates, and ultimately a reduction in cost. There was some evidence of a positive relationship between infection rates and LoS, reflecting that inpatients are at high risk of nosocomial infection by antibiotic- and multi-resistant microorganisms. The microbial etiology of SSIs and antibiotic resistance are often omitted from reports on the mid- and long-term clinical and economic impact of antibiotic use but should get proper attention. Therefore, the use of prophylactic antibiotics, especially for SSIs, should take into account the diagnostic-based antibiotic treatments using local epidemiological data on pathogens from microbiological evaluations including patterns of antimicrobial susceptibility.

Clinical outcome measurements provide some evidence that systemic prophylactic antibiotics have a significant impact on minimizing the incidence of SSIs and medical costs in high-risk patients, especially those undergoing major surgical procedures. Preoperative measures and protocols for prophylactic antibiotics include adherence to their proper use in terms of selection, optimal dosing and timing. To achieve high efficacy, a current strategy is a prophylactic combination added locally to the standard prophylaxis, especially in deep surgical sites, using intra-wound antibiotics, for instance. The use of a local or intra-wound antibiotic as add-on treatment is predicted to be more effective since the site-target concentration of antibiotics with local treatment is higher than that without local antibiotics. However, a cost-effectiveness analysis of the effect of add-on local wound prophylactic antibiotics on SSI outcomes is needed, particularly in developing countries. Prophylactic antibiotics should be administered within 60 minutes (except for vancomycin prophylaxis), as this is the optimal time to achieve clinically-effective SSI prevention. Moreover, it is essential to monitor postoperative measures, focusing on the prolonged use of prophylactic antibiotics and the timing of drain removal. Prolonged prophylactic use later than 24 hours post-surgery did not show any benefit in terms of cost and SSI prevention.

The clinical outcome not only depends on the prophylactic antibiotics given prior to surgical procedures but also on whether the intervention is limited to preventing tissue damage, which has the effect of accelerating wound healing. Other influential issues that should be considered regarding the adequacy, quality, and cost of managing surgical patients include surgical techniques, the availability of skilled surgeons, the types of disease, and the for-profit or not-profit nature of the healthcare services involved.

Empirical antibiotic utilization for hospitalized CAP patients should be continued with a diagnostic-based antibiotic treatment supported by microbiological information from CBT. Culture analysis is part of good-practice diagnostic stewardship to support antimicrobial identification and infection prevention programs. CBT should be part of such integrated management, based on a theragnostic approach, involving multi-disciplines and a personalized treatment approach. The CBT can play a critical role at this point to gain the improvement of treatment prescriptions and clinical outcomes and cost reduction. In a resource-limited setting such as Indonesia, gram-staining and sputum culture procedures are very useful for inpatient treatment plans and ICU patients, guiding CAP diagnosis and antimicrobial selection. The organisms in the microbiological
culture are more likely to accurately represent respiratory tract pathogens in CAP patients. The implementation of blood and sputum culture analysis should be considered in patients with moderate and severe CAP with a poor clinical prognosis, who are very susceptible to bacteremia. The targeted population for CBT should include elderly patients.

Multivariate analyses revealed that mortality resulting from sepsis was significantly correlated with patients aged ≥ 60 years, with gastrointestinal-tract infections (GTIs), LRTIs, neuromuscular infections (NMs), multi-focal infections, having SSIs, neoplasms, DM, cardiovascular disease, renal disease, and ICU admission (Table 7.1). Overall, the survival rate of these patients was 39.3%. The rate was lowest for sepsis patients with having SSIs (18.1%), followed by those with LRTIs (37.8%), three or more focal infections (38.1%), two focal infections (39.7%), NMs (41.6%), GTIs (42.5%), and UTIs (56.1%). Figure 7.1 shows the Kaplan-Meier analysis revealing a significant difference in 30-day survival rates among sepsis patients with site infections (log-rank test, p < 0.001). In addition, low albumin levels, elevated levels of leukocytes, and prolonged prothrombin time were clinically considered as independent predictors of mortality among adult patients with sepsis (Annex to Chapter 7).

**Table 7.1.** Predictor factors for 30-day mortality among patients with sepsis.

<table>
<thead>
<tr>
<th>Covariate</th>
<th>N(%)</th>
<th>aOR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>6,609(47.0)</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7,467(53.0)</td>
<td>0.975</td>
<td>0.903–1.052</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;60 years</td>
<td>12,429(88.4)</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>≥60 years</td>
<td>1,638(11.6)</td>
<td>1.357</td>
<td>1.199–1.536*</td>
</tr>
<tr>
<td><strong>Types of focal infections</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UFI</td>
<td>1,637(11.6)</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>CVI</td>
<td>110(0.8)</td>
<td>1.220</td>
<td>0.791–1.882</td>
</tr>
<tr>
<td>GTI</td>
<td>1,328(9.4)</td>
<td>2.759</td>
<td>2.336–3.257*</td>
</tr>
<tr>
<td>LRTI</td>
<td>3,932(27.9)</td>
<td>2.520</td>
<td>2.200–2.887*</td>
</tr>
<tr>
<td>NMI</td>
<td>368(2.6)</td>
<td>2.140</td>
<td>1.658–2.763*</td>
</tr>
<tr>
<td>UTI</td>
<td>1,348(9.6)</td>
<td>1.016</td>
<td>0.839–1.231</td>
</tr>
<tr>
<td>2 focal infections</td>
<td>3,873(9.6)</td>
<td>2.332</td>
<td>2.010–2.705*</td>
</tr>
<tr>
<td>3 or more focal infections</td>
<td>431(3.1)</td>
<td>3.247</td>
<td>2.529–4.169*</td>
</tr>
<tr>
<td>Having SSIs</td>
<td>2,138(15.2)</td>
<td>2.223</td>
<td>1.954–2.529*</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Neoplasm</td>
<td>2,123(15.1)</td>
<td>6.128</td>
<td>5.392–6.964*</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4,333(30.8)</td>
<td>2.098</td>
<td>1.919–2.292*</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>3,629(25.8)</td>
<td>4.455</td>
<td>4.044–4.907*</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>3,804(27.0)</td>
<td>1.134</td>
<td>1.019–1.263*</td>
</tr>
<tr>
<td>ICU</td>
<td>4,297(30.8)</td>
<td>2.658</td>
<td>2.438–2.898*</td>
</tr>
</tbody>
</table>

**Notes:** aOR = adjusted odds ratio, CVI = cardiovascular infection, GTI = gastrointestinal-tract infection, ICU = intensive care unit, LRTI = lower respiratory tract infection, NMI = neuromuscular infection, OR = odds ratio, UFI = unspecified focal infection, Ref: reference, UTI = urinary tract infection, WI = wound infection.

*Statistically significant.*
Figure 7.1 Kaplan-Meier plots depicting 30-day survival rates for sepsis with focal infections.

Note: CVI = cardiovascular infection, GII = gastrointestinal infection, LRTI = lower respiratory tract infection, NMI = neuromuscular infection, SSI = surgical site infection, and UTI = urinary tract infection

We endorse the Indonesian national guidelines, which state that patients who have started on empirical antimicrobial therapy and who show clinical improvement within the first three days should be switched from intravenous to oral antibiotics. The day 3 evaluation is a critical point at which to evaluate the efficacy of empirical treatment and to estimate patients’ risk of mortality. The assessment of clinical responses on day 4 of the treatment for patients with community-acquired bacterial pneumonia suggested in the guidance from the Food and Drug Administration (FDA) could also be implemented.\textsuperscript{31} We recommend a combination assessment of clinical response in the first three days to complement PSI scoring, where both assessments are investigated as independent risk factors for mortality among patients with pneumonia. If there is a successful response to empirical treatment, it could be useful to switch to oral antimicrobial treatment on day 3, as this will provide additional information in the form of culture and susceptibility data from the microbiology laboratory.

Future perspectives
Further work needs to focus on the current challenges in the use of non-guided treatments using prophylactic and empirical antibiotics so as to improve patient outcomes, especially in a resource-limited setting such as Indonesia. First, updated data on the local pattern of resistance to
antibiotics would be useful, although it may be more challenging to determine the definite cause of SSI and CAP, since both accurate hospital data and community data from primary healthcare are not always available. A multicenter qualitative study representing the 34 provinces of Indonesia is urgently needed, with a robust research methodology, to look at the antibiotic strategies used. Further research into patient characteristics is needed as well as studies to evaluate SSIs and CAP impacts at an individual level, inclusive quality-of-life assessments. A pharmacoeconomics analysis of screening for bacterial infections using gram staining from infected sites, which is more likely to produce fast results, should be undertaken to guide antibiotic use from an economic perspective as started in this thesis. Notably, all strategies and research need the full involvement of government, clinicians, infection control practitioners, clinical microbiologists, hospital and community pharmacists, nurses and nutritionists. Implementation of antimicrobial resistance and infection prevention measures within quintessential Antimicrobial, Infection Prevention, and Diagnostic (AID) stewardship, involving a multidisciplinary team in the resource-limited setting, could be considered by adapting the results of our study conducted in the Netherlands (Chapter 4) to the situation in Indonesian hospitals.
REFERENCES


